

Review

The hallmarks of cancer immune evasion

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SUMMARY

According to the widely accepted “three Es” model, the host immune system eliminates malignant cell precursors and contains microscopic neoplasms in a dynamic equilibrium, preventing cancer outgrowth until neoplastic cells acquire genetic or epigenetic alterations that enable immune escape. This immuno-evasive phenotype originates from various mechanisms that can be classified under a novel “three Cs” conceptual framework: (1) camouflage, which hides cancer cells from immune recognition, (2) coercion, which directly or indirectly interferes with immune effector cells, and (3) cytoprotection, which shields malignant cells from immune cytotoxicity. Blocking the ability of neoplastic cells to evade the host immune system is crucial for increasing the efficacy of modern immunotherapy and conventional therapeutic strategies that ultimately activate anticancer immunosurveillance. Here, we review key hallmarks of cancer immune evasion under the “three Cs” framework and discuss promising strategies targeting such immuno-evasive mechanisms.

INTRODUCTION

Contrary to the outdated view of cancer as an immune agnostic disease, malignant cell precursors can be efficiently eliminated by the immune system.^{1,2} Natural killer (NK) cells, which are activated by rather non-specific signals of distress exposed on the surface of cells experiencing perturbations of homeostasis, play a critical role in the elimination of recently transformed cells.^{3,4} In some cases however, malignant cell precursors can form microscopic neoplasms that display accelerated proliferation, but such lesions exist in a dynamic equilibrium with the host immune system, which prevents outgrowth and hence both local and metastatic dissemination.^{1,2} CD8⁺ cytotoxic T lymphocytes (CTLs), which are activated by antigenic determinants presented on the surface of malignant cells in complex with major histocompatibility complex (MHC) class I molecules, are essential to confine the growth of microscopic tumors,^{5,6} but at the same time they edit them through Darwinian mechanisms, ultimately favoring the selection of cancer cell clones with genetic or epigenetic alterations that enable overt immuno-escape.^{7,8}

According to this conceptual framework, which is commonly referred to as the “three Es” model, progressing neoplasms become clinically manifest only when malignant cells develop the ability to evade immune recognition and elimination,² a process that—similar to the pathogen-host co-evolution— involves the acquisition of specific features by malignant cells under the selective pressure of the host immune system.⁹ Importantly, ma-

lignant cells can acquire overtly immuno-evasive properties by a number of different mechanisms, which is fundamental not only for them to form locally invasive and metastatic lesions, but also for established tumors to resist therapeutic challenges and relapse.^{10,11} While this may seem trivial for modern immunotherapy, which purposely aims at (re)activating tumor-targeting immunity,¹ immuno-evasion also contributes to the resistance of some tumors to treatments that mediate clinically relevant immunostimulatory effects even though they have been developed in an immune agnostic manner, including some chemotherapeutics,¹² targeted anticancer agents,¹³ and (at least in some settings) radiotherapy.¹⁴ In line with this notion, considerable efforts are being dedicated to the development of clinically viable strategies that prevent or reverse immuno-evasion to be employed either as standalone therapeutic approaches or in combination with established treatments.^{15–17}

Inspired by the “three Es” model, we propose that the mechanisms through which cancer cells evade tumor-targeting immunity can be interpreted under a “three Cs” conceptual framework involving camouflage, coercion, and cytoprotection, which refer to the ability of some malignant cells to evade recognition by the immune system (i.e., not be found by immune effector cells or not be identified as malignant), directly or indirectly interfere with immune effector cells (i.e., once found by immune effector cells and identified as malignant, prevent immune cell activation), and protect themselves from immune cytotoxicity (i.e., resist effector molecules normally released upon immune cell activation),

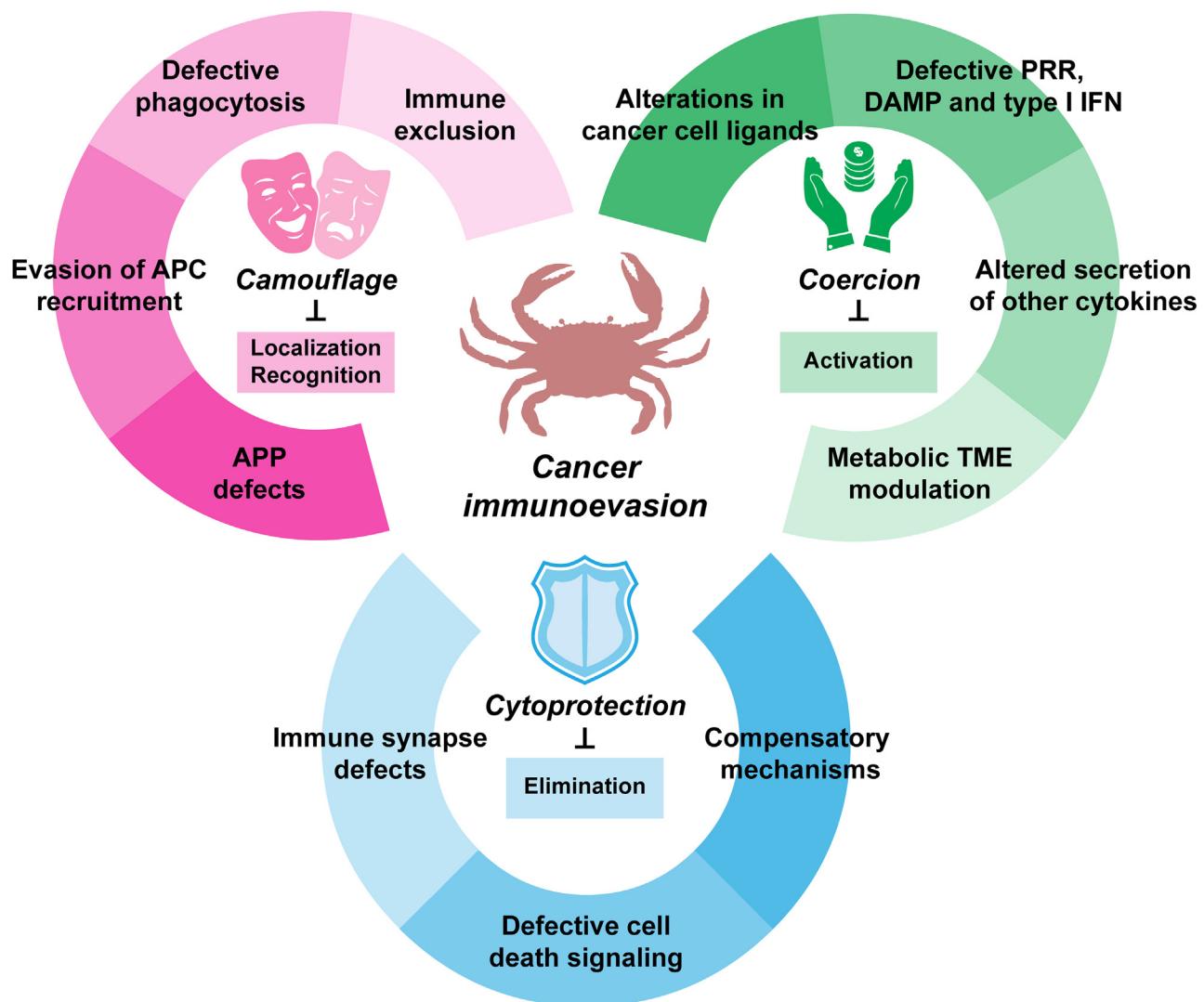


Figure 1. The “three Cs” of cancer immune evasion

Malignant cells can evade immune surveillance by (1) avoiding being localized by immune effector cells or being recognized as neoplastic (camouflage), (2) preventing immune cell activation despite being localized and recognized as neoplastic (coercion), or (3) protecting themselves from immune cytotoxicity in the context of normal immune cell activation (cytoprotection). APC, antigen-presenting cell; APP, antigen processing and presentation; DAMP, damage-associated molecular pattern; IFN, interferon; PRR, pattern recognition receptor; TME, tumor microenvironment.

respectively (Figure 1). In addition to reviewing these hallmarks of cancer immuno-evasion under the “three Cs” paradigm, here, we discuss promising strategies to prevent or reverse such immuno-evasive mechanisms for therapeutic purposes. Importantly, host alterations related to these hallmarks, including (1) polymorphisms in genes encoding key receptors, (2) immunological alterations of the tumor microenvironment (TME) driven by non-malignant cells, (3) defects in the whole-body ecosystem that are not elicited by neoplastic cells, go beyond the scope of the present review and hence will not be discussed.

CAMOUFLAGE

One major strategy for malignant cells to evade immunosurveillance relies on their ability to hide from immune effector cells,

i.e., to avoid being localized by immune effector cells or being recognized as transformed. Such a camouflage can result from defects in antigen processing and presentation, from the limited secretion of chemotactic factors associated or not with immunogenic cell death (ICD), or from the creation of stromal barriers preventing immune infiltration (Figure 2).

Antigen processing and presentation defects

Both mutational and non-mutational events provide cancer cells with a distinct antigenic landscape compared to their normal counterparts, at least theoretically increasing their visibility CD8⁺ CTLs.^{18,19} However, the molecular machinery underlying the proper processing and exposure of such neoantigens on the cell surface is often defective in malignant cells, allowing them to avoid immune recognition.¹⁸ Supporting the clinical

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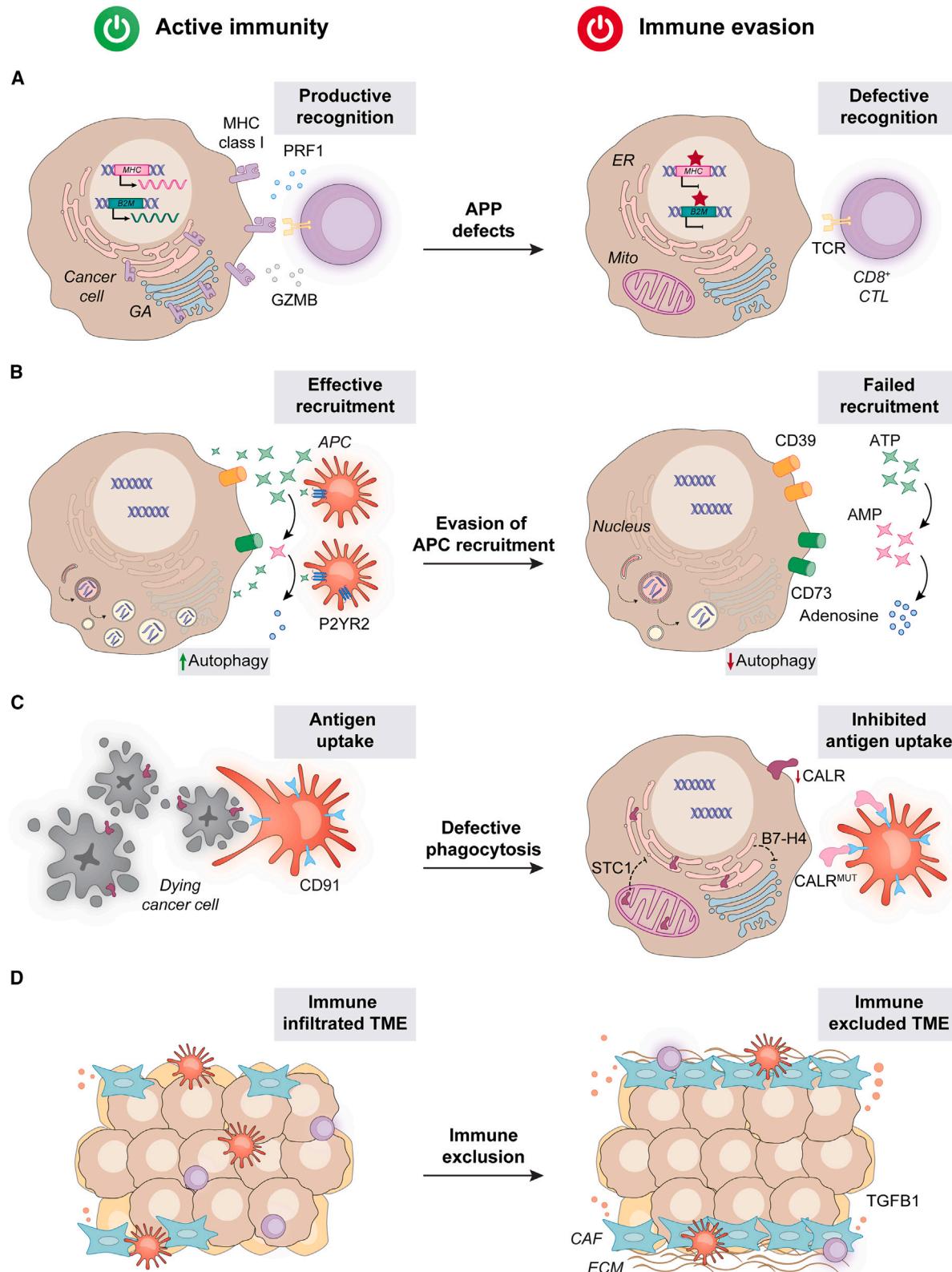


Figure 2. Camouflage in cancer immune evasion

Neoplastic cells can avert tumor-targeting immunity through multiple alterations that ultimately prevent them from being detected or contacted by immune effector cells. These include (but may not be limited to) (1) defects in the antigen and presentation (APP) machinery, as exemplified by mutations in genes

relevance of such a camouflage strategy, a reduced mutational or neoantigen burden has been correlated with inferior disease outcome in various cohorts of patients with cancer receiving immune checkpoint inhibitor (ICI)-based immunotherapy.^{20–23}

Neoplastic cells can acquire defects in the antigen processing and presentation (APP) machinery via genetic mechanisms, including mutations in genes encoding MHC molecules or the obligate MHC class I interactor beta-2 microglobulin (B2M) as observed across a variety of tumors,²⁴ as well as loss of heterozygosity (LOH) at chromosome 6p, which encompasses the MHC locus, as documented in patients with non-small cell lung carcinoma (NSCLC) and homologous recombination-deficient (HRD) high-grade serous ovarian cancer (HGSOC).^{25–27} Moreover, defective antigen presentation in malignant cells can emerge from epigenetic mechanisms. This can occur via the accumulation of repressive histone acetylation marks as consequent downregulation of APP component including proteasome 20S subunit beta 8 (PSMB8, best known as LMP7), PSMB9 (best known as LMP2), transporter associated with antigen processing 1 (TAP1), and TAP2, which is frequent in Merkel cell carcinoma (MCC),²⁸ as well as through the establishment of repressive histone 3 trimethylation marks (namely H3K9me3 and H3K27me3) at the promoter region of MHC-encoding genes, an immuno-evasive mechanism that is common in hematological malignancies and is initiated by enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2) and SET domain bifurcated histone lysine methyltransferase 1 (SETDB1).^{29,30} A similar epigenetic camouflage has also been observed in other solid tumors.^{31–34} Of note, immuno-evasive malignancies often exhibit reduced DNA methylation in specific genomic regions that promote the formation of transcriptional inactive heterochromatic structures known as partial methylation domains (PMDs). Such PMDs have been associated with the silencing of various immunomodulatory genes, including APP-related genes.³⁵

Additional examples of epigenetic camouflage have been reported in advanced prostate cancer, a setting in which downregulation of melanocyte inducing transcription factor (MITF) results in MHC class I silencing upon expression of eukaryotic translation initiation factor 3 subunit B (EIF3B),³⁶ as well as in melanoma, which can limit MHC class I expression upon transactivating the embryonic transcription factor double homeobox 4 (DUX4).³⁷ Moreover, the epigenetic repression of APP is frequent among cancer stem cells (CSCs), a small population of malignant cells with superior tumor-repopulating potential that can self-renew while generating a more differentiated progeny.³⁸ While some of these mechanisms are *de facto* shared with normal stem cells from the hair follicle and muscle, suggesting that the normal stem cell compartment also benefits from immuno-evasion,³⁹ others appear to be specific for CSCs, and hence potentially relevant for therapeutic purposes. As a standalone

example, melanoma- and breast cancer-initiating cells have been shown to repress APP-relevant genes upon the epigenetic upregulation of the RNA-binding protein cold shock domain-containing protein E1 (CSDE1) and consequent inactivating dephosphorylation of signal transducer and activator of transcription 1 (STAT1) (see in the following text).⁴⁰

Of note, post-translational mechanisms have also been shown to cause APP defects in cancer cells. Specifically, NBR1 autophagy cargo receptor (NBR1) has been shown to cause the degradation of MHC class I molecules via autophagy (a catabolic pathways that is generally upregulated in cancer cells),⁴¹ at least in pancreatic malignancies.^{42,43} Similarly, proprotein convertase subtilisin/kexin type 9 (PCSK9), a key regulator of cholesterol metabolism, reportedly inhibits MHC class I molecule expression by favoring their lysosomal degradation via a cholesterol-independent mechanism.⁴⁴ Moreover, acute myeloid leukemia (AML) cells appear to degrade MHC class I molecules via the ubiquitin-proteasome system, through a mechanism that depends on sushi domain containing 6 (SUSD6), transmembrane protein 127 (TMEM127), and WW domain containing E3 ubiquitin protein ligase 2 (WWP2).⁴⁵

Corroborating the importance of APP-related camouflage for immune evasion, the downregulation of MHC class I molecules is a common mechanism of acquired resistance to immunotherapy. For instance, late relapse in patients with metastatic MCC treated with adoptive cell therapy (ACT) plus ICI-based immunotherapy has been associated with the transcriptional repression of MHC genes presenting the ACT target.⁴⁶ Along similar lines, early treatment biopsies from melanoma patients refractory to ICIs have revealed an enrichment of malignant cells characterized by transcriptional reprogramming toward a mesenchymal-like state with suppressed APP that depended on transcription factor 4 (TCF4).⁴⁷

Another camouflage strategy harnessed by cancer cells involves the genetic or epigenetic downregulation of dominant neoantigens driving immune recognition.¹⁸ While this is particularly frequent when one or a few antigens drive anticancer immunity, such as in patients with hematological malignancies receiving chimeric antigen receptor (CAR) T cells,⁴⁸ it has also been documented in patients with melanoma undergoing ICI-based immunotherapy,^{49,50} as well as in patients with treatment-naïve NSCLC, a setting in which neoantigen-expressing genes appeared to be silenced upon promoter hypermethylation.²⁵ A similar mechanism has been recapitulated in a syngeneic mouse model of melanoma receiving ACT.⁵¹ In this latter setting, epigenetic modifiers such as azacitidine and decitabine partially restored neoantigen expression and immunological disease control.⁵¹

Collectively, these observations suggest that genetic and epigenetic mechanisms affecting APP are a major source of

encoding MHC molecules or the obligate MHC class I interactor beta-2 microglobulin (B2M), which prevents the recognition of malignant cells by CD8⁺ cytotoxic T lymphocytes (CTLs) (A); (2) a defective recruitment of antigen-presenting cells (APCs) or the precursors thereof to the tumor bed, as exemplified by the up-regulation of enzymes that convert extracellular ATP into adenosine, such as ectonucleoside triphosphate diphosphohydrolase 1 (ENTPD1, best known as CD39), ectonucleotidase 5'-nucleotidase ecto 5NT (best known as CD73) as well as the downregulation of autophagy (B); (3) defects in the engagement of phagocytosis by APCs, as exemplified by a variety of mechanisms preventing the immunogenic cell death (ICD)-associated exposure of the endoplasmic reticulum (ER) chaperone calreticulin (CALR) on the cell surface (C); and (4) the physical exclusion of immune effector cells from cancer cell nests, as exemplified by the cancer-associated fibroblast (CAF)-driven and transforming growth factor β 1 (TGFB1)-dependent establishment of a dense, collagen-rich stromal reaction (D). B7-H4 (official name: VTCN1), V-set domain containing T cell activation inhibitor 1; CD91 (official name: LRP1), LDL receptor-related protein 1; ECM, extracellular matrix; GA, Golgi apparatus; GZMB, granzyme B; P2RY2; purinergic receptor P2Y2; PRF1, perforin 1; STC1, stanniocalcin 1; TCR, T cell receptor.

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camouflage for cancer cells. Importantly, these defects can emerge both in the context of natural immunoevasion (and hence be potential sources of innate resistance to immunotherapy) or as a result of a selective pressure imposed by immunotherapy (acquired resistance). Of note, APP is upregulated by both type I interferon (IFN) and interferon gamma (IFNG) signaling.⁵² However, given the broader impact these factors have on the TME, we will discuss them as part of coercion (see in the following text). Along similar lines, considerable defects in APP as those elicited by *B2M* loss are expected to generate a potent activatory signal for NK cells,⁵³ which requires the acquisition of coercive mechanisms based on NK cell-inhibitory ligands (NKILs, also discussed in the following sections).

Evasion of APC recruitment

Malignant cells can succumb to various therapeutic agents via a variant of cell death that is sufficient to elicit antigen-specific immune responses associated with an effector phase and immunological memory, i.e., ICD.⁵⁴ ICD relies on the pre-mortem activation of stress response pathways including (but not limited to) autophagy and the integrated stress response (ISR)—a cellular mechanism of protection from endoplasmic reticulum stress⁵⁵—that culminate with the production of chemotactic, pro-phagocytic, and immunostimulatory signals for antigen-presenting cells (APCs) or the precursors thereof that are cumulatively referred to as damage-associated molecular patterns (DAMPs).⁵⁴ Of note, while both preclinical and clinical data suggest that multiple malignancies benefit from defects in the molecular machinery underlying ICD-associated DAMP emission, fully harnessing ICD induction as a means to increase ICI sensitivity in clinical settings remains challenging.^{14,54} Whereas defects in ICD-related immunostimulation are a source of coercion (see in the following text), the lack of interaction between cancer cells and APCs as promoted by defective chemoattraction or exposure of pro-phagocytic signals constitutes a common mechanism of camouflage.

Defective release of chemoattractants

Malignant cells undergoing ICD release ATP and ANXA1, which operate as mid-range and short-range chemoattractants for APCs upon binding to purinergic receptor P2Y2 (P2RY2) and formyl peptide receptor 1 (FPR1), respectively.^{56–58} Corroborating the importance of these signals for the initiation of anti-cancer immunity, cancer cells generally acquire several mechanisms to suppress ICD-related ATP and ANXA1 release.

Specifically, multiple cancer cells appear to express increased levels of ectonucleoside triphosphate diphosphohydrolase 1 (ENTPD1, best known as CD39) and/or 5'-nucleotidase ecto (NT5E, best known as CD73), which sequentially convert extracellular ATP into ADP, AMP and the potent immunosuppressive metabolite adenosine.⁵⁹ In line with this notion, CD39 overexpression as well as the pharmacological or genetic blockage of purinergic receptors has been shown to abolish APC recruitment and ICD-driven antitumor immunity as induced by administration of ICD-inducing anthracyclines in syngeneic mouse models of fibrosarcoma.⁶⁰ Similar results have been obtained by the genetic inactivation of autophagy in malignant cells, knowing that optimal autophagic responses to stress ensure proper ATP secretion during ICD.⁶¹ Conversely, pharmacological or nutritional whole-body hyperactivation of autophagy has been shown

to boost the efficacy of ICD-inducing therapeutic regimens in a variety of syngeneic tumor models.^{62,63} In line with these observations, the expression of the autophagic marker microtubule-associated protein 1 light chain 3 beta (MAP1LC3B, best known as LC3B) has been positively correlated with abundant immune infiltration and improved disease outcome in patients with breast carcinoma.⁶⁴ Similar to defects in ATP release, the deletion of *Anxa1* from mouse fibrosarcomas, colorectal cancers (CRCs) and mammary cancers compromises their ability to respond to immunogenic chemotherapy *in vivo*.^{58,65} Moreover, higher-than-median levels of ANXA1 have been associated with an improved recruitment of APCs and T cells in patients with CRC, NSCLC as well as breast and kidney cancer.⁶⁶

ICD is also associated with the release of chemokines that recruit immune effector cells to the TME, notably C-X-C motif chemokine ligand 10 (CXCL10) and (at least in some settings) C-C motif chemokine ligand 2 (CCL2).⁵⁴ Defects in CXCL10 release downstream of failed type I IFN signaling in cancer cells succumbing to ICD induction by anthracyclines have been mechanistically linked to decreased disease control in syngeneic mouse models of fibrosarcoma.⁶⁷ Along similar lines, both CXCL10 and CXCL9 are transcriptionally repressed by epigenetic modifiers such as EZH2 and DNA methyltransferase 1 (DNMT1) in ovarian cancer, resulting in poor recruitment of effector T cells to the tumor site.⁶⁸ Decreased CXCL10 secretion also appears to promote camouflage and immuno-evasion in melanomas with elevated glycolytic activity.⁶⁹ Finally, genetic defects in ICD-associated CCL2 release or sensing have been associated with reduced APC recruitment and compromised anticancer immunity in preclinical models of fibrosarcoma.⁷⁰ That said, CCL2 also appears to mediate robust coercive effects (see in the following text).

Activation of the ISR by a low-protein diet reportedly elicits therapeutically relevant tumor-targeting immune responses in immunocompetent mice bearing CT26 CRCs via a mechanism that (at least in part) involves CXCL10-dependent chemoattraction.⁷¹ Similar results have been obtained by genetically activating the ISR via ADP ribosylation factor 1 (*Arf1*) deletion in preclinical models of CRC.⁷² Moreover, signs of ISR activation in malignant cells, notably the pathognomonic activating phosphorylation of eukaryotic translation initiation factor 2 subunit alpha (EIF2S1, best known as eIF2α), have been correlated with improved disease outcome in various cohorts of patients with cancer.⁷³ However, it is likely that such an advantage may also relate to the critical role of the ISR in exposure of calreticulin (CALR), an ER chaperone with pro-phagocytic activity once translocated to the outer leaflet of the plasma membrane (see in the following text).⁷⁴ Activation of the ISR (or at least modules thereof) has also been associated with detrimental cancer cell phenotypes including (1) the inhibition of antigen presentation on MHC class I molecules downstream of mitochondrial fragmentation⁷⁵; (2) the outgrowth of disseminated cancer cells despite MHC class I expression; (3) the survival of glioblastoma (GBM) CSCs exposed to adverse microenvironmental conditions⁷⁶; as well as (4) the generation of drug-tolerant colorectal and lung cancer cells.⁷⁷ Whether the immune system is involved in these latter two phenotypes, however, remains to be elucidated.

Of note, the release of ICD-unrelated chemoattractants can also be defective in some tumors, which also represents a

camouflage mechanism. For instance, histone deacetylase 8 (HDAC8) reportedly promotes the transcriptional repression of CCL4, a potent T cell chemoattractant, in models of hepatocellular carcinoma (HCC), *de facto* limiting anticancer immunity.⁷⁸ Along similar lines, in breast, colorectal, and lung cancer, defects in the secretion of CCL20 hamper the recruitment CCR6⁺ type 3 innate lymphoid cells (ILC3s) to the tumor site, resulting in decreased tumor infiltration by CD4⁺ and CD8⁺ T cells and limited responsiveness to ICIs.⁷⁹

In summary, defects in chemoattraction promote camouflage in variety of cancer types, resulting in limited tumor infiltration by immune effector cells and hence poor disease outcome.

Defective ICD-driven phagocytosis

The ICD-associated exposure of CALR on the surface of cancer cells, which mechanistically impinges on the ISR and eIF2 α phosphorylation, provides a potent pro-phagocytic signal to APC upon binding to LDL receptor-related protein 1 (LRP1, also known as CD91).⁷⁴ Besides explaining at least some facets of camouflage as emerging in the context of suboptimal ISRs (see mentioned previously), this accounts for multiple instances of camouflage related to suppressed phagocytosis. Malignant cells have indeed been shown to avoid CALR-mediated phagocytosis by APCs by: (1) downregulating CALR expression, which reportedly has negative prognostic value in hematological malignancies like AML,^{80,81} as well as in some solid tumors including NSCLC;⁸² (2) trapping CALR at mitochondria upon overexpression of stanniocalcin 1 (STC1), which is common across cancer types;⁸³ (3) upregulating V-set domain containing T cell activation inhibitor 1 (VTCN1, best known as B7-H4), which, besides being a potent co-inhibitory ligand for T cells (see in the following text), also inhibits eIF2 α phosphorylation;⁸⁴ and (4) secreting a truncated forms of CALR, competitively inhibiting the interaction between surface-exposed CALR and CD91.⁸⁵

In line with these observations, pharmacological and genetic strategies that block CALR exposure on cancer cells experiencing immunogenic stress and death have been linked to immuno-evasion in a variety of syngeneic tumor models.^{86–89} Conversely, improving the (otherwise suboptimal) externalization of CALR has been associated with improved immunogenicity in preclinical models of fibrosarcoma and multiple myeloma.^{90,91} Of note, defects in CALR exposure also endow cancer cells with the ability to inhibit NK cells, reflecting the notion that CALR can bind natural cytotoxicity triggering receptor 1 (NCR1, an NK cell-activating receptor [NKAR] best known as NKp46).⁹² While an implication for NK cells in the clinical benefits experienced by patients with AML exposing abundant CALR at the blast surface has been reported,⁹³ the actual contribution of this latter mechanism to camouflage as elicited by defects in CALR exposure remains to be investigated. Finally, it should be noted that defective CALR exposure also promotes coercion by enabling the phosphatidylserine (PS)-driven clearance of dying cells by macrophages, an immunologically silent process commonly known as efferocytosis (see in the following text).^{94–97}

Collectively, these observations highlight several mechanisms that camouflage cancer cells from the immune system by interfering with chemoattraction and APC-dependent phagocytosis.

Exclusion

At least in some instance, malignant cells evade immunosurveillance by generating a physical barrier that impedes immune effector cell recruitment to the TME. Such a camouflage mechanism mainly stems from TME remodeling as mediated by specific immune and stromal cells or from the reconfiguration of the extracellular matrix (ECM).

Three major cell populations of the TME that actively promote exclusion and consequently resistance to ICI-based immunotherapy⁹⁸ are cancer-associated fibroblasts (CAFs), tumor-associated macrophages (TAMs), and tumor-associated neutrophils (TANs). Specifically, CAFs have been involved in the excluded phenotype and resistance to ICIs in patients with metastatic urothelial cancer and CRC, two settings in which CAF-derived transforming growth factor β 1 (TGFB1) promotes the confinement of CD8⁺ CTLs inside CAF- and collagen-enriched peritumoral stromal regions.^{99,100} Importantly, in syngeneic mouse models of these tumors, pharmacologically blocking TGFB1 resulted in unleashed CTL responses and improved sensitivity to ICI-based immunotherapy,^{99,100} suggesting that TGFB1 and/or its receptors may constitute targets for the development of therapeutic strategies to limit exclusion-based camouflage. Similar findings, although without a clear implication for CAFs, have been obtained in patients with HGSOC bearing a specific mutational signature linked to foldback-inversion.²⁷ Along similar lines, patients with lung squamous-cell carcinomas exhibiting an excluded phenotype have been shown to experience inferior disease outcome as compared to patients with abundant tumor infiltration by CD8⁺ CTLs.¹⁰¹ In this latter setting, though, TAMs were the major contributors to exclusion, and blocking them with a small molecule specific for colony stimulating factor 1 receptor (CSF1R) restored the CD8⁺ CTLs to tumor islets and ICI sensitivity, at least in a syngeneic mouse model of the disease.¹⁰¹ However, in none of the aforementioned setting the mechanisms through which neoplastic cells educate CAFs or TAMs to establish exclusion have been clearly elucidated. Conversely, cancer cell-derived chitinase-3-like protein 1 (CHI3L1) has been shown to promote exclusion in triple negative breast cancer (TNBC), at least in part by favoring the recruitment of TANs to the TME and their ability to produce neutrophil extracellular traps (NETs),¹⁰² i.e., extracellular protrusions containing chromatin and granule proteins that are generally involved in antimicrobial defense.¹⁰³ Similar findings have been obtained in preclinical models of melanoma and CRC, although in these settings TANs were reportedly recruited to the TME by cancer cell-derived CXCL8,¹⁰⁴ as well as in pancreatic ductal adenocarcinoma (PDAC) models, a setting in which immature and overall immunosuppressive neutrophil-like cells commonly known as polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs) appeared to infiltrate neoplastic lesions via CXCL1 secretion by malignant cells and to establish exclusion upon the secretion of tumor necrosis factor (TNF).¹⁰⁵

In melanoma, at least two mechanisms of exclusion have been documented. On the one hand, preclinical and clinical findings indicate that catenin beta 1 (CTNNB1) overexpression and consequent hyperactivation of WNT signaling promotes the establishment of an excluded phenotype in melanoma upon failed recruitment of CD103⁺ conventional type I dendritic cells (cDC1s),¹⁰⁶ which are central orchestrators of anticancer

Box 1. Hypoxia and metabolic coercion

Vasculature defects causing at least some degree of hypoxia are common to most (if not all) solid tumors and have been consistently associated with immunosuppression.^{276,439} Hypoxia promotes indeed the transcriptional activity of hypoxia inducible factor 1 subunit alpha (HIF1A) in malignant cells, which has multiple immunosuppressive consequences (detailed in the main text), including (1) a pronounced shift from oxidative mitochondrial metabolism to glycolysis coupled with abundant lactate secretion; (2) the secretion of vascular endothelial growth factor A (VEGFA); (3) the upregulation of ectonucleoside triphosphate diphosphohydrolase 1 (ENTPD1, best known as CD39), ectonucleotidase 5'-nucleotidase ecto (5NT, best known as CD73) and adenosinergic receptors^{279,439}; as well as (4) the release of chemokines that either recruit immunosuppressive cells to the TME or sequester immune effector cells in hypoxic tumor regions while promoting their functional inhibition.^{247,248} Of note, hypoxia has also direct inhibitory effects on tumor-infiltrating immune cells. For instance, hypoxic conditions have been associated with the upregulation of CD39 on intratumoral CD8⁺ CTLs, resulting in accrued adenosinergic signaling and consequent immunosuppression.⁴⁴⁰ Along similar lines, hypoxia reportedly promotes mitochondrial fragmentation in NK cells, hence compromising their effector functions, via a mechanism involving mechanistic target of rapamycin (MTOR) and dynamin 1 like (DNM1L).⁴⁴¹ Finally, tumor-targeting $\gamma\delta$ T cells have been shown to be particularly sensitive to hypoxia, at least in preclinical models of glioblastoma (GBM).⁴⁴² Thus, hypoxia is a major factor underlying immune evasion in solid tumors, reflecting not only the activation of immunosuppressive mechanisms in malignant cells, but also the direct inhibition of intratumoral immune effectors.

immunity.^{107,108} On the other hand, single-cell RNA sequencing studies suggested that melanoma cells can drive exclusion by a mechanism centered on cyclin-dependent kinase 4/6 (CDK4/6) signaling.¹⁰⁹ However, while in patients with melanoma a signature of CDK4/6 activation has been correlated with sensitivity to ICIs targeting programmed cell death 1 (PDCD1, best known as PD-1),¹⁰⁹ CDK4/6 inhibitors currently available for clinical use are only approved for advanced/metastatic hormone receptor (HR)-positive breast cancer,¹¹⁰ implying that the value of these agents combined with ICIs remains to be established. Moreover, whether any exclusion-relevant link exists between WNT and CDK4/6 signaling has not been formally investigated.

Recent data indicate that phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta (PIK3CB), which is often hyperactivated in HR⁺ breast cancer,¹¹¹ is also involved in the reclusion of CD8⁺ CTLs to the periphery of mouse mammary carcinomas elicited by the loss of two phosphatase and tensin homolog (*Pten*) and transformation related protein 53 (*Trp53*), at least in part through a mechanism that involves suppressed STAT3 signaling.¹¹² Whether these observations are relevant for human HR⁺ BC, however, remains to be clarified. Along similar lines, whether the ability of receptor-interacting protein kinase 2 (RIPK2) and proline isomerase (PIN1) to favor the establishment of a desmoplastic stroma coupled with limited ICI sensitivity in syngeneic models of PDAC^{42,113} can be targeted for the development of novel therapeutic strategies against exclusion that can be translated to clinical testing is unclear.

Besides alterations in collagen abundance (as mediated by CAFs, mentioned previously), changes in its spatial arrangement also participate in exclusion. For instance, discoidin domain receptor 1 (DDR1) expression by TNBC cells has been shown to favor a parallel orientation of collagen fibers, *de facto* reducing the accessibility of the TME to immune effector cells.¹¹⁴ Interestingly, in the same disease setting, T cell infiltration exhibits at least some degree of spatial heterogeneity, with subsets of quiescent stem-like cancer cells escaping immune recognition through the formation of immunosuppressive hypoxic niches enriched in CAFs that exhibit signatures of collagen-deposition pathways and an excluded phenotype.¹¹⁵ That said, hypoxia is a major mechanism of coercion (Box 1) implying that the actual

contribution of collagen deposition and physical CTL exclusion to these observations requires direct experimental verification.

Altogether, exclusion stands out as a major mechanism through which malignant cells camouflage from the host immune system. That said, whether exclusion can be targeted therapeutically in support of restored immunosurveillance and improved ICI sensitivity remains to be clinically demonstrated.

COERCION

Malignant cells that fail at camouflage (and hence are found and identified as transformed by the immune system) can evade anticancer immunity by suppressing the activity of immune effector cells including (but potentially not limited to) DCs, NK cells, T_H1-polarized CD4⁺ T cells, and CD8⁺ CTLs, as well as by promoting the activity of immunosuppressive cells such as CD4⁺CD25⁺FOXP3⁺ regulatory T (T_{REG}) cells, specific TAM subsets, and MDSCs. Such a coercive activity can be the result of numerous alterations that involve shifts in the expression of immunomodulatory ligands on the cancer cell surface, defects in DAMP or pro-inflammatory cytokine signaling and/or the release of immunomodulatory metabolites in the TME (Figure 3).

Alterations in immunomodulatory ligands

Most neoplastic cells are characterized by an altered surface phenotype that encompasses reduced MHC levels in support of camouflage (mentioned previously) as well as changes in the expression of ligands for immune cell receptors with immunostimulatory or immunosuppressive effects.

PD-L1

CD274 (best known as PD-L1) is arguably the best characterized surface molecule that cancer cells harness in support of direct coercion, largely reflecting its ability to suppress the effector functions of CD8⁺ CTLs,¹¹⁶ NK cells,¹¹⁷ and at least some myeloid cells¹¹⁸ upon interaction with the co-inhibitory receptor PD-1, which is normally expressed in the context of immune activation. PD-L1 is also abundantly expressed by tumor-infiltrating myeloid cells, which also contribute to local immunosuppression.¹¹⁹ As most normal cells, cancer cells upregulate PD-L1 in response to (mostly CTL-derived) IFNG, as part of a

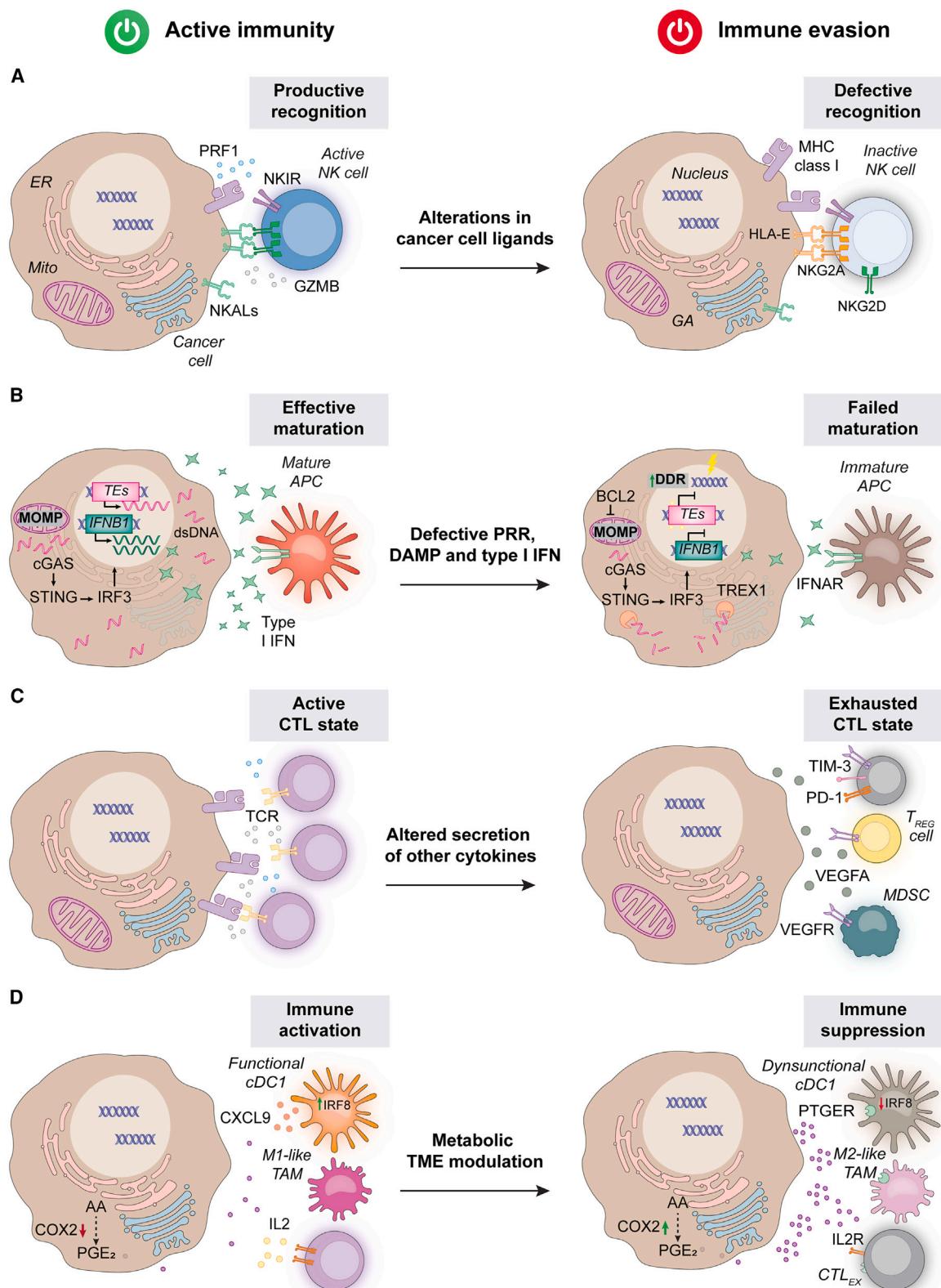


Figure 3. Coercion in cancer immune evasion

Developing neoplasms often acquire a number of alterations that actively inhibit tumor-targeting immune responses, either directly—by quenching the activity of immune effector cells, such as CD8⁺ cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells—or indirectly—by promoting the regulatory functions of their

(legend continued on next page)

physiological mechanism that ensures the resolution of immune responses,¹¹⁹ which is in line with the notion that most malignancies with an abundant CD8⁺ CTL infiltrate are sensitive to ICIs targeting PD-1 or PD-L1.¹²⁰ Moreover, not only genetic variants structurally disrupting the 3'-untranslated region (UTR) of *CD274* are frequent in hematological malignancies, culminating with increased mRNA levels of *CD274* in support of immune evasion,¹²¹ but *CD274* is often amplified across a variety of solid tumors, correlating with increased PD-L1 expression on the surface of malignant cells.¹²²

PD-L1-mediated immunoevasion by breast CSCs has also been associated with increased transcription at the *CD274* locus upon removal of repressing marks from DNA and histone in the promoter region.¹²³ Importantly, such an epigenetic regulation of *CD274* expression can be targeted with Food and Drug Administration (FDA)-approved epigenetic modifiers such as azacitidine and decitabine, at least preclinically, resulting in increased PD-L1 expression and restored ICI sensitivity across cancer types.^{124,125} Moreover, SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a like 1 (SMARCAL1, a DNA damage response [DDR] factor) promotes PD-L1 expression by enhancing chromatin accessibility at the *CD274* locus with a mechanism involving Jun proto-oncogene, AP-1 transcription factor subunit (JUN).¹²⁶ Of note, PD-L1 expression levels can also be controlled at translation. Specifically, malignant cells can boost *CD274* translation by a mechanism involving eukaryotic translation initiation factor 4E (EIF4E) activation, as shown in MYC- and KRAS-driven liver cancer,¹²⁷ or impaired heme synthesis and consequent ISR signaling, as shown in lung cancer.¹²⁸

At least in some tumor types, PD-L1 expression is also regulated by protein stabilization. For instance, the interleukin 6 (IL6)-dependent activation of Janus kinase 1 (JAK1) in liver cancer cells has been shown to result in PD-L1 phosphorylation and stabilization upon N-glycosylation as catalyzed by STT3 oligosaccharyltransferase complex catalytic subunit A (STT3A).¹²⁹ A similar mechanism has been shown to operate in breast cancer cells undergoing the epithelial-to-mesenchymal transition (EMT)—a dedifferentiation process associated with increased stemness and metastatic potential—upon increased WNT signaling.¹³⁰ Moreover, PD-L1 is stabilized in multiple tumor types by CKLF-like MARVEL transmembrane domain containing protein 6 (CMTM6), which directly binds PD-L1 at the plasma membrane and in recycling endosomes to prevent its lysosomal degradation.^{131,132} Of note, at least in melanoma, PD-L1 has

been shown to compete with CD58 (a ligand for the co-stimulatory receptor CD2) for CMTM6, with defects in CD58-CD2 axis promoting immune evasion.¹³² PIN1 inhibition also appears to promote PD-L1 stabilization in PDAC, presumably through a mechanism that involves suppressed lysosomal degradation.¹¹³

Finally, PD-L1 appears to respond to a variety of stress conditions. For instance, reduced adenosine signaling via adenosine receptor A1 (ADORA1) reportedly promotes PD-L1 expression on melanoma cells via the stress-responsive transcription factor activating transcription factor 3 (ATF3).¹³³ Moreover, a switch to increased glucose consumption (as occurring in hypoxic tumor area) has been linked to PD-L1 upregulation in GBM cells, through a mechanism involving hexokinase 1 (HK2) and nuclear factor kappa B (NF- κ B).¹³⁴

In summary, while various ICIs targeting PD-L1 or PD-1 are currently available for clinical use, additional targets may exist to regulate this coercion mechanism via small molecules rather than monoclonal antibodies.

NK cell-interacting ligands

Neoplastic cells can evade elimination NK cells by downregulating a number of NK cell-activating ligands (NKALs) such as MHC class I polypeptide-related sequence A (MICA), MHC class I polypeptide-related sequence B (MICB), and UL16 binding proteins (ULBPs).³ This is particularly relevant for cancer cells expressing reduced MHC class I levels to camouflage from CD8⁺ CTLs, knowing that MHC class I is major NK cell-inhibitory ligand (NKIL).³ Thus, MCC cells can avoid NK cell cytotoxicity through epigenetic silencing of *MICA* and *MICB* upon histone hypoacetylation at their promoter region, a process that could be reverted upon pharmacological inhibition of histone deacetylases (HDACs).¹³⁵ Likewise, GBM cells have been shown to epigenetically silence MICA, MICB, and ULBPs in an EZH2-dependent manner,¹³⁶ while glioma cells appear to achieve a similar coercion via the histone demethylase lysine demethylase 1A (KDM1A, also known as LSD1).¹³⁷ In leukemic stem cells (LSCs) from patients with AML, the transcriptional repression of NKALs has been attributed to poly-ADP-ribose polymerase 1 (PARP1), a component of the DNA damage machinery that can be targeted by FDA approved inhibitors.¹³⁸ Finally, multiple cancer cells evade NK cell activation by promoting the proteolytic degradation or membrane shedding of NKALs upon overexpressing protein disulfide isomerase (PDI)^{139,140} or various matrix metalloproteinases.^{141,142}

Of note, malignant cells can coerce NK cells via the overexpression of various NKILs, notably canonical MHC class I

immunosuppressive counterparts, such as CD4⁺CD25⁺FOXP3⁺ regulatory T (T_{REG}) cells. The alterations encompass (1) shifts in the expression of immuno-modulatory ligands, as exemplified by changes in the expression pattern of NK cell-activating ligands (NKALs) or NK cell-inhibitory ligands (NKILs) (A); (2) defects in pattern recognition receptor (PRR), damage-associated molecular pattern (DAMP) or type I interferon (IFN) signaling, as exemplified by a variety of mechanisms that actively suppress viral mimicry (B); (3) alterations in the cancer cell secretome that affect cytokines other than type I IFN, as exemplified by the oversecretion of vascular endothelial growth factor A (VEGFA) (C); and (4) by a number of metabolic alterations that ultimately impact immune cell functions, such as the abundant secretion of prostaglandin E₂ (PGE₂; D). AA, arachidonic acid; APC, antigen-presenting cell; CALR^{MUT}, mutant CALR; CGAS, cyclic GMP-AMP synthase; cDC1, conventional type I dendritic cell; COX2 (official name: PTGS2) prostaglandin-endoperoxide synthase 2; CTLA4; cytotoxic T lymphocyte-associated protein 4; CXCL9, C-X-C motif chemokine ligand 9; CTL_{EX}, exhausted cytotoxic T lymphocyte; DDR, DNA damage response; dsDNA, double-stranded DNA; ER, endoplasmic reticulum; GA, Golgi apparatus; GZMB, granzyme B; IFNAR, interferon (alpha and beta) receptor; IFNB1, interferon beta 1; IL2, interleukin-2; IL2R, interleukin-2 receptor; IRF, interferon regulatory factor; MDSC, myeloid-derived suppressor cell; MOMP, mitochondrial outer membrane permeabilization; NKG2A (official name: KLRC1), killer cell lectin like receptor C1; NKG2D (official name: KLRK1), killer cell lectin like receptor K1; NKIR, NK cell-inhibitory receptor; PD-1 (official name: PDCD1), programmed cell death 1; PRF1, perforin 1; PTGER, prostaglandin E receptor; STING (official name: STING), stimulator of interferon response cGAMP interactor 1; TAM, tumor-associated macrophage; TCR, T cell receptor; TE, transposable element; TIM-3 (official name: HAVCR2), hepatitis A virus cellular receptor 2; TME, tumor microenvironment; TREX1, three prime repair exonuclease 1; VEGFR (official name: KDR), kinase insert domain receptor.

molecules as well as their non-canonical counterparts such as HLA-E,³ as reported for a variety of solid and hematological malignancies.^{143,144} Since this would come at the cost of potentially losing camouflage from CD8⁺ T cells, it is tempting to speculate that cancer cells may benefit from reduced MHC class I levels (to camouflage from adaptive immunity) but not absent (to coerce innate immunity as mediated by NK cells). Alternatively, it is plausible that different tumors (or different areas of the same malignant lesion) may preferentially develop camouflage vs. coercion strategy depending on the type of immune pressure they are facing. Despite these and other unknowns, it is worth noting that the interaction between HLA-E and its cognate NK cell-inhibitory receptor (NKIR), namely killer cell lectin like receptor C1 (KLRC1, best known as NKG2A) has been harnessed for the development of a monoclonal antibody (monalizumab)^{145,146} that is now under clinical development (see in the following text). Conversely, the development of pharmacological strategies targeting killer cell immunoglobulin like receptor, two Ig domains and long cytoplasmic tail 1 (KIR2DL1), KIR2DL2, and KIR2DL3 including the monoclonal antibody IPH2101 has been discontinued after early phase clinical trials pointing to a paradoxical reduction in NK cell activity.¹⁴⁷ The reasons for this unexpected finding remain to be formally elucidated.

In summary, targeting the mechanisms through which cancer cells coerce NK cells stands out as a promising strategy to circumvent immune evasion, especially for malignancies that exhibit superior sensitivity to NK cell-mediated immunosurveillance (e.g., hematological tumors).

Other immunomodulatory ligands

Several other surface proteins are harnessed by malignant cells to coerce CD8⁺ T cells, NK cells, and APCs. For instance, in PDAC models, overexpression of PVR cell adhesion molecule (PVR, also known as CD155) has been shown to promote and sustain immune escape upon inhibition of the T cell and NK cell co-inhibitory receptor T cell immunoreceptor with Ig and ITIM domains (TIGIT).¹⁴⁸ Moreover, a prolonged interaction between human type 2 innate lymphoid cells (ILC2s) and CD155⁺ AML cells impairs the lytic activity of the former by downregulating CD226 (also known as DNAM-1) and granzyme B (GZMB), *de facto* facilitating immune evasion.¹⁴⁹ In AML, LSCs display the epitranscriptomic activation of different co-inhibitory ligands for T cells, including leukocyte immunoglobulin-like receptor B4 (LILRB4), a process that is mediated by the RNA N6-methyladenosine (m6A) demethylase FTO alpha-ketoglutarate dependent dioxygenase (FTO).¹⁵⁰

In breast cancer cells, B7-H4 is stabilized via glycosylation, leading to immunosuppression and resistance to ICD inducers via a mechanism that also involves eIF2 α dephosphorylation (aforementioned).⁵⁴ Hypoxic liver cancer cells overexpress galectin 9 (LGALS9), which suppresses T cell responses via the co-inhibitory receptor hepatitis A virus cellular receptor 2 (HAVCR2, best known as TIM-3),¹⁵¹ through a mechanism involving the lysosomal degradation of the negative LGALS9 regulator nuclear transcription factor, X-box binding 1 (NFX1) by a carnosine synthase 2 (CARNS2) isoform.¹⁵²

Importantly, CD8⁺ CTLs and NK cells are not the sole targets for coercion by cancer cells via immunomodulatory surface ligands. Indeed, malignant cells actively evade phagocytosis by APCs including DCs by upregulating the expression of CD47

on the plasma membrane, which directly counteracts the pro-phagocytic activity of surface-exposed CALR.¹⁵³ More specifically, CD47 suppresses phagocytosis (and hence limits the initiation of antitumor immunity) by interacting with signal regulatory protein alpha (SIRPA) on APCs and masking the pro-phagocytic ligand SLAM family member 7 (SLAMF7) on cancer cells.^{154,155} CD47 is upregulated in GBM cells via a fatty acid-dependent mechanism that involves the acetylation of RELA proto-oncogene, NF- κ B subunit (RELA) and correlates with poor patient prognosis.¹⁵⁶ Likewise, elevated CD47 levels have been linked with dismal disease outcome in three independent cohorts of adult patients with AML.¹⁵⁷ Of note, CD47 appears to be particularly elevated in LSCs,^{157,158} potentially constituting an actionable target for this highly tumorigenic leukemia cell subpopulation. Moreover, CD47 can be upregulated in response to ICD induction. For instance, in syngeneic osteosarcoma models, treatment with ICD-inducing chemotherapy has been associated with upregulation of solute carrier family 7 member 8 (SLC7A8, best known as LAT2) coupled with enhanced uptake of leucine and glutamine, culminating with mechanistic target of rapamycin complex 1 (mTORC1) signaling and *Cd47* transactivation.¹⁵⁹ Of note, CD24 also appears to provide robust anti-phagocytic signals to myeloid cells upon interacting with sialic acid binding Ig like lectin 10 (SIGLEC10).¹⁶⁰ At least in part, the ability of CD24 and perhaps other surface proteins expressed by cancer cells to limit phagocytosis may explain why several clinical studies testing CD47-targeting agents in patients with cancer have failed to document consistent efficacy so far.¹⁶¹

Collectively, these observations exemplify the existence of multiple immunomodulatory ligands other than PD-L1 that cancer cells harness to coerce the immune system, some of which are being actively pursued for the development of novel therapeutic interventions (see in the following text).

Defective PRR, DAMP, and type I IFN signaling

In many malignant cells, the molecular mechanisms that underlie the emission of immunostimulatory DAMPs and cytokines, be them related to ICD or not, are dysfunctional or actively counterbalanced, resulting in the establishment of microenvironmental conditions that are not permissive for anticancer immunity.

Defective CGAS-STING1 signaling

Cyclic GMP-AMP synthase (CGAS) is a sensor of cytosolic double-stranded DNA (dsDNA) that elicits pro-inflammatory transcriptional programs executed by interferon regulatory factor 3 (IRF3), IRF7, and NF- κ B upon activation of stimulator of interferon response cGAMP interactor 1 (STING1, best known as STING) and consequent TANK binding kinase 1 (TBK1) signaling.¹⁶² Defects in CGAS-STING signaling considerably impair the ability of stressed and dying cancer cells to attract and activate immune effector cells downstream of IRF3-, IRF7-, and NF- κ B-dependent cytokines, notably interferon beta 1 (IFNB1).¹⁶³

A number of common oncogenic events have been associated with compromised CGAS-STING signaling in malignant cells, largely corroborating the importance of immuno-evasion for overt tumor progression. For instance, loss of kelch like ECH associated protein 1 (KEAP1) promotes lung cancer resistance to immunotherapy by stabilizing EMSY transcriptional repressor, BRCA2 interacting (EMSY), hence suppressing CGAS-STING

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signaling by a mechanism that can be reverted upon administration of pharmacological STING agonists.¹⁶⁴ Moreover, in mammary tumors, mutant tumor protein p53 (TP53, best known as p53) has been shown to physically interfere with the interaction between STING and TBK1, *de facto* promoting immunoevasion via defective IRF3 signaling.¹⁶⁵

Several epigenetic mechanisms through which malignant cells suppress CGAS-STING signaling have also been documented. For instance, loss of serine/threonine kinase 11 (STK11, best known as LKB1) enhances immunoevasion and resistance to ICIs in KRAS-driven lung cancer by promoting the hyperactivation of DNMT1 and EZH2, resulting in epigenetic *STING1* silencing.¹⁶⁶ Along similar lines, hypermethylation of the *STING1* promoter and enhancers has been shown to promote immune evasion in dormant lung cancer cells.¹⁶⁷ Moreover, in melanoma and head and neck squamous cell carcinoma (HNSCC), CGAS expression is epigenetically regulated by histone methylases, including protein arginine methyltransferase 5 (PRMT5) and SUV39H1 histone lysine methyltransferase (SUV39H1), or components of supramolecular histone ubiquitin transferases complexes, such as BMI1 proto-oncogene, polycomb ring finger (BMI1), a core constituent of the polycomb repressive complex 1 (PRC1).^{168–170} Lung cancer cells appear to silence *IRF3* and *IRF7* by promoter hypermethylation, resulting in decreased type I IFN signaling and reduced sensitivity to ICIs, an immuno-evasive mechanism that can be at least in part reverted with hypomethylating agents.¹²⁵ Along similar lines, both lung and breast malignancies have been shown to exhibit defects in the type I IFN signal transducers STAT1 and STAT2,^{171,172} which—at least in the latter cancer type—are epigenetically established by EZH2 and hence can be effectively targeted with pharmacological EZH2 inhibitors.¹⁷² Finally, melanoma-initiating cells appear to promote the inhibitory dephosphorylation of STAT1 through a mechanism mediated by the epitranscriptomic stabilization of T cell protein tyrosine phosphatase (TCPTP).⁴⁰

Post-translational CGAS and STING modifications have also been shown to endow malignant cells with immuno-evasive properties. For instance, melanoma cells reportedly coerce immune effector cells upon losing expression of the oncosuppressor death-associated protein kinase 3 (DAPK3), which—among other functions—stabilizes STING via polyubiquitination.¹⁷³ Along similar lines, the non-enzymatic, inactivating acetylation of CGAS as promoted by aspirin,¹⁷⁴ as well as the degradation of the CGAS-derived STING activator 2'3'-cyclic GMP-AMP (cGAMP) as mediated by sphingomyelin phosphodiesterase acid like 3A (SMPDL3A),¹⁷⁵ or ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1),^{176–178} have all been linked to reduced CGAS signaling, although only the latter has been formally associated with suppressed antitumor immunity.

These observations indicate that the direct repression of CGAS and STING signaling endow malignant cells with immuno-evasive properties. Importantly, the same signaling pathway can also be disrupted by numerous indirect mechanisms, as described here in the following text.

Impaired viral mimicry

CGAS signaling is elicited by the ectopic accumulation of dsDNA in the cytosol, a process that is considerably more effective when dsDNA is naked (i.e., does not contain histones), and hence originates from mitochondria as a consequence

of apoptotic mitochondrial outer membrane permeabilization (MOMP) (or viral infection).^{182–185} Cancer cells often evolve strategies to avoid or compensate for the cytosolic accumulation of endogenous dsDNA, including (but not limited to) an increased propensity to repair nuclear DNA damage in the absence of potentially interferogenic side products, to repress endogenous retroviruses (ERVs) and other transposable elements (TEs), to preserve mitochondrial integrity and to actively degrade cytosolic nucleic acids.

Several components of the DDR, apparatus have been shown to prevent CGAS-STING signaling.¹⁸⁶ These include various proteins that have already been established or are being actively investigated as targets for (novel) anticancer (immuno)therapy, such as PARP1 (for which several inhibitors have already been approved for use in humans), as well as ATR serine/threonine kinase (ATR), and ATM serine/threonine kinase (ATM).¹⁸⁶ An abundant preclinical literature indicates indeed that inhibiting PARP1, ATM, and ATR results in the accumulation of interferogenic nucleic acids in the cytosol of malignant cells, culminating with the STING-dependent restoration of ICI sensitivity across a number of cancer types.^{187–190} While similar observations have recently been extended to SMARCAL1 and DExD/H-box helicase 9 (DHX9),^{126,191} pharmacological strategies to target these two DDR components to avert immune evasion downstream suppressed CGAS activation by cytosolic dsDNA have not entered clinical development yet. Moreover, at least in some settings including skin cancer, some epigenetic modifiers like KDM4A have been shown to limit the accumulation of potentially interferogenic nucleic acids in the cytosol of malignant cells by strengthening the DDR,¹⁹² but the precise molecular mechanisms remain to be elucidated.

Malignant cells, especially CSCs, silence the expression of ERVs and other TEs that may not only drive robust type I IFN responses via CGAS or cytosolic RNA sensors like RNA sensor RIG-I (RIGI) or interferon induced with helicase C domain 1 (IFIH1) but may also generate neoantigens.^{193,194} In multiple solid and hematological malignancies, both DNA and histone methyltransferases contribute to TE silencing, including DNMT1, SETDB1, and HDACs, which deposit repressive DNA methylation, histone methylation, and histone acetylation marks within TE regions, *de facto* limiting type I IFN responses.^{195–199} A similar ERV-repressing role has been ascribed to KDM1A and PHD finger protein 8 (PHF8, also known as KDM7B).^{200,201} That said, the histone methyltransferase nuclear receptor binding SET domain protein 1 (NSD1) appears to transactivate, rather than repress, ERVs in skin cancer,²⁰² indicating that—at least in some settings—coercion as promoted by TE repression is driven by an unbalanced activity of epigenetic modifiers. Along similar lines, GBM CSCs appear to repress interferogenic TEs by a unique mechanism involving increased histone H4 lysine crotonylation arising from reprogrammed lysine catabolism, which also results in changes on histone acetylation and methylation marks on TEs.²⁰³ Moreover, both p53 and CDK4/6 have been involved in the transcriptional regulation of ERVs and consequent type I IFN responses,^{204,205} hence representing promising targets for the development of pharmacological strategies to avert coercion, especially since no less than three distinct CDK4/6 inhibitors are currently approved for use in patients with advanced or metastatic HR⁺ breast cancer.¹¹⁰

A major mechanism through which neoplastic cells avert the cytosolic accumulation of potentially interferogenic dsDNA is by ensuring a tight mitochondrial checkpoint. This is achieved not only upon the overexpression of endogenous inhibitors of the BCL2 apoptosis regulator (BCL2) family, which is common across a variety of tumors,²⁰⁶ but also upon the proficient degradation of permeabilized mitochondria via a specialized variant of autophagy called mitophagy.²⁰⁷ In line with this notion, both pharmacological and genetic strategies targeting the BCL2 system have been associated with increased CGAS-STING signaling in malignant cells, especially (but not exclusively) in the context of caspase inhibition (see in the following text).^{183,184,208,209} Intriguingly, at least in some settings, MOMP does not only promote CGAS activation via cytosolic DNA but also initiates a ubiquitin-dependent pro-inflammatory pathway that involves inhibitor of nuclear factor kappa B kinase regulatory subunit gamma (IKBKG, best known as NEMO) and culminates with NF-κB signaling.²¹⁰ Further corroborating the importance of the mitochondrial checkpoint for malignant cells to coerce their immune counterparts, both pharmacological and genetic inhibition of autophagy at large or mitophagy have been associated with accrued CGAS-STING signaling and superior disease control in preclinical models of breast cancer,¹⁸³ lung cancer,²¹¹ and CRC.²¹² Moreover, intact serine metabolism appears to be critical for the preservation of the mitochondrial immune checkpoint (see in the following text).¹⁸² Interestingly, in macrophages the mitophagic degradation of permeabilized mitochondria has been involved in a negative feedback loop to extinguish NF-κB responses.²¹³ Whether this mechanism is operational in cancer cells, however, remains to be formally investigated.

Finally, neoplastic cells express some cytosolic nucleases that efficiently degrade potentially interferogenic nucleic acids. For instance, three prime repair exonuclease 1 (TREX1) has been shown to degrade cytosolic mtDNA,²¹⁴ as well as cytosolic dsDNA originating from ruptured micronuclei (which are common in tumors with elevated chromosomal instability [CIN]).²¹⁵ In line with this notion, TREX1 overexpression has been associated with suppressed CGAS-STING signaling and resistance to treatment in syngeneic preclinical models of breast cancer exposed to focal radiotherapy,²¹⁶ and lung cancer exposed to ICIs.²¹⁷ Ribonuclease H2 also limits the cytosolic accumulation of potentially interferogenic nucleic acids, especially so-called “R-loops” (three-stranded nucleic acids composed of a DNA:RNA hybrid and the associated non-template single-stranded DNA).²¹⁸ While it is likely that—at least in some settings—ribonuclease H2 may operate similar to TREX1 in promoting coercion and resistance to immunotherapy, this possibility remains to be explored. Intriguingly, it has recently been shown that MRE11 homolog, double-strand break repair nuclease (MRE11), a DNA double-strand break sensor, promotes CGAS activation by dsDNA upon favoring its dissociation from nucleosomes.²¹⁹ In this context, malignant cells appear to take advantage from reduced MRE11 levels, resulting in increased genome instability and immune suppression.²¹⁹ Supporting the clinical relevance of this coercion mechanism, reduced levels of the MRE11 signal transducer Z-DNA binding protein 1 (ZBP1) appear to correlate with poor disease outcome in a cohort of patients with TNBC.²¹⁹

In summary, malignant cells not only can directly subvert CGAS-STING signaling but also can adopt a variety of strategies to minimize the availability of interferogenic nucleic acids, *de facto* limiting viral mimicry.

Defective DAMP signaling

The non-histone chromatin-binding protein high-mobility group box 1 (HMGB1) is one of the major ICD-associated DAMPs, and its microenvironmental accumulation mediates immunostimulatory effects upon binding to Toll-like receptor 4 (TLR4) and advanced glycosylation end-product specific receptor (AGER) on the surface of APCs or their precursors.^{220,221} Experimental evidence indicates that neoplastic cells lose the expression of HMGB1 and other DAMPs during tumor progression, at least in the breast cancer setting.⁶⁴ Moreover, cancer cells engineered to lack HMGB1 fail to elicit anticancer immune responses upon exposure to ICD inducers in immunocompetent syngeneic host, largely via a coercion mechanism that could be reverted by intratumoral injection of a synthetic TLR4 agonist.^{220,222} Along similar lines, human bladder cancer cells undergoing ICD upon exposure gemcitabine fail to release HMGB1 in the supernatant, hence failing to endow DCs with CD8⁺ T cell cross-priming functions, at least in part owing to the release of the bioactive lipid prostaglandin E₂ (PGE₂) (see in the following text).²²³ Intriguingly, it appears that the ISR-relevant kinase eukaryotic translation initiation factor 2 alpha kinase 3 (EIF2AK3, best known as PERK) restricts anticancer immunity in melanoma cells at least in part by inhibiting the release of HMGB1 and other DAMPs as a consequence of blocked paraptosis (which appears to be immunogenic).²²⁴ Thus, PERK inhibitors may constitute promising tool to promote immunogenic paraptosis, at least in melanoma.

Coercion via defective DAMP signaling can also emerge from the secretion of immunosuppressive DAMPs. For instance, mouse melanoma and fibrosarcoma cells have been shown to avert antitumor immunity downstream of ICD by secreting gel-solin (GSN), which inhibits the binding of F-actin exposed on dying malignant cells to C-type lectin domain containing 9A (CLEC9A) on cDC1s, thereby preventing CD8⁺ T cell cross-priming.²²⁵ Similarly, fibrinogen-like protein 1 (FGL1) released by CRC cells reportedly binds the co-inhibitory receptor lymphocyte activating 3 (LAG3) on the CD8⁺ CTL surface, hence suppressing their activation.²²⁶ Importantly, the ICD-associated release of ATP provides chemotactic cues (mentioned previously) as well as immunostimulatory signals to APCs and their precursors, implying that defects in this pathway also constitute a source of coercion (see in the following text).

These observations exemplify the ability of malignant cells to coerce immune effector cells by altering DAMP signaling.

Apoptotic signaling

Neoplastic cells often succumb to unrecoverable perturbations of homeostasis via apoptosis, a caspase-regulated form of cell death with major physiological functions.²²⁷ In line with the critical role of apoptosis in embryonic development and the maintenance of adult tissue architecture, though, caspase activation has multipronged immunosuppressive effects, even when apoptotic cell death ensues MOMP and hence is potentially associated with the abundant cytosolic accumulation of interferogenic mtDNA. Indeed, post-mitochondrial caspases including caspase 3 (CASP3) and its major activator CASP9

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have been shown to suppress MOMP-driven type I IFN secretion in a variety of experimental models, including preclinical models of breast and CRC.^{208,209,228–230}

Such a coercion mechanism has been attributed to the ability of CASP3 to (1) catalyze the proteolytic inactivation of CGAS, IRF3 and mitochondrial antiviral signaling protein (MAVS), a signal transducer involved in RIGI-dependent RNA sensing²³¹ and (2) accelerate the terminal inactivation of otherwise still metabolically active (and hence type I IFN-secreting) dying cancer cells.²³² Moreover, CASP3 promotes the apoptosis-associated exposure of PS on the surface of dying cells coupled with the secretion of the macrophage chemoattractant lysophosphatidylcholine (LPC), hence facilitating the rapid efferocytic removal of dying cells and their corpses by macrophages.^{94–97} The immunologically silent nature of efferocytosis is further enforced by CASP3 activation in dying cancer cells as a consequence of PGE₂ secretion (see in the following text).²³³

Thus, developing tumors harness apoptotic cell death to prevent the initiation of anticancer immunity by dying malignant cells. Along with the ever more accepted notion that post-mitochondrial caspases are dispensable for cell death after widespread MOMP—but only control its kinetic and immunological manifestations²³⁴—these observations point to caspases as to potential target to promote therapeutically relevant anticancer immunity.

Chronic type I interferon signaling

At least some neoplastic cells can coerce type I interferon signaling in support of local immunosuppression and accelerated disease progression, most likely reflecting the fundamental difference between acute and resolving inflammatory processes (which generally promote immunosurveillance) versus chronic and indolent inflammation (which generally supports immunoevasion).²³⁵ For instance, malignant cells with elevated CIN levels have been shown to evade immunosurveillance despite high levels of cytosolic DNA by rewiring the CGAS-STING pathway from abundant type I IFN production to low-grade inflammation, resulting in the EMT and accrued metastatic dissemination.^{236–239} Along similar lines, chronic and indolent type I IFN signaling has been shown to promote stemness, disease progression, and immune evasion in preclinical models of CRC, TNBC, and melanoma.^{240,241} Consistent with this notion, genetic signatures of type I IFN signaling have been associated to cancer stemness, immunosuppression, and poor patient outcomes across multiple cohorts of patients with cancer.^{228,242}

Thus, while robust and acute type I IFN signaling is fundamental for tumor-targeting immune responses (see previously), malignant cells normally benefit from weak and chronic type I IFN signaling, at least in part reflecting the establishment of a low-grade inflammatory milieu associated with immunosuppression.

Altered secretion of other cytokines

Multiple tumors evade anticancer immunity by alterations in their secretome that involve an accrued production of anti-inflammatory cytokines and/or a defective release of pro-inflammatory factors other than type I IFN.

Secretion of anti-inflammatory cytokines

Multiple cancer types can secrete cytokines that favor the establishment of local and/or systemic immunosuppression. For instance, prostate cancer cells have been shown to secrete

CCL2 downstream of PRC1-dependent epigenetic alterations, culminating with the recruitment of immunosuppressive M2-like TAMs and T_{REG} cells, which facilitate tumor dissemination.²⁴³ Similarly, in mammary tumors, the loss of the tumor suppressor G protein subunit alpha 13 (GNA13) promotes CCL2 expression and secretion, attracting M2-like TAMs.²⁴⁴ Moreover, PDAC cells have been shown to secrete abundant levels of CCL5 upon STAT1 activation in response to microenvironmental adenosine (see in the following text), resulting in the establishment of local immunosuppression upon T_{REG} cell recruitment.²⁴⁵ A similar CCL5-dependent mechanism has been documented to promote M2-like TAM recruitment in CRCs producing kynurenone (see in the following text).²⁴⁶ Finally, ovarian cancer cells have been shown to recruit T_{REG} cells via CCL28, a mechanism that is elicited by hypoxia (Box 1).²⁴⁷ Likewise, hypoxic GBM niches appear to secrete increased levels of CCL8, resulting in the sequestration of TAMs and tumor-infiltrating CD8⁺ CTLs and their reprogramming toward an immunosuppressive state.²⁴⁸

Besides being a major player in exclusion-based camouflage (mentioned previously), TGFB1 also mediates potent immunosuppressive effects, *de facto* promoting coercion, across a variety of tumor types. For instance, MFSD2 lysolipid transporter A, lysophospholipid (MFSD2A) overexpression in gastric cancer cells has been shown to promote anticancer immune responses downstream of reduced PGE₂-driven TGFB1 secretion, hence increasing tumor sensitivity to ICIs.²⁴⁹ Moreover, TGFB1 signaling in CD4⁺ (but not CD8⁺) T cells potently suppresses therapeutically relevant immune responses in preclinical models of breast carcinoma, at least in part reflecting an IL4-dependent (but not IFNG-dependent) tissue remodeling mechanism that culminates with cancer cell death.²⁵⁰ Along similar lines, both TGFB1 and its relative inhibin subunit beta A (INHBA) have been implicated in the ability of irradiated breast cancer cells to coerce the TME in favor of suppressed anticancer immunity.^{251,252} Accordingly, combining focal radiotherapy with a monoclonal antibody targeting multiple members of the TGFB1 family was well tolerated and demonstrated some clinical activity in a cohort of patients with metastatic breast cancer,²⁵³ and strategies to inhibit this pathway are currently being investigated in clinical trials (see in the following text).

CXCL8 and IL33 are also harnessed by some cancer cells to promote local immunosuppression. For instance, tumor-derived CXCL8 has been implicated in the recruitment of both monocytic (M-) and PMN-MDSCs to the TME, resulting in suppressed T cell responses.²⁵⁴ At least in some settings including preclinical models of cervical carcinoma, such an effect is mediated by serpin family B member 3 (SERPINB3),²⁵⁵ which is frequently mutated in patients with melanoma responding to cytotoxic T lymphocyte-associated protein 4 (CTLA4) blockers.²⁵⁶ The immunosuppressive role of IL33 has been documented in syngeneic models of lung cancer, breast cancer and melanoma exposed to an IL33 blocker.^{257,258} That said, the transgene enforced overexpression of IL33 has also been associated with improved anticancer immunity in models of breast cancer and melanoma.²⁵⁹ In line with this notion, IL33 expression as driven in mouse CRC and melanoma cells by the deletion of fragile X mental retardation protein (*Fmrp*), encoding an RNA binding protein, has been associated with restored tumor infiltration by CD8⁺ CTLs and recovered ICI sensitivity (also involving a

Box 2. T cell exhaustion

In a number of pathophysiological settings, including (but not limited to) chronic viral infection and cancer, the sustained antigenic stimulation of CD8⁺ cytotoxic T lymphocytes (CTLs), as occurring in the absence of target cell eradication, can promote terminal CTL dysfunction.⁴⁴³ In cancer, such a dysfunctional state, which is commonly referred to as “exhaustion”, is associated with the progressive loss of CTL cytotoxic and secretory functions, *de facto* enabling immune evasion, accelerated disease progression and resistance to a variety of therapeutic agents that operate (at least in part) by (re)instating immunosurveillance, including (but not limited to) immune checkpoint inhibitors (ICIs).⁴⁴⁴ While *sensu stricto* exhaustion does not emerge from cancer cells but rather reflects chronic TCR signaling, developing neoplasms harness multiple phenotypic T cell changes associated with this process, notably the overexpression of co-inhibitory receptors including programmed cell death 1 (PDCD1, best known as PD-1), hepatitis A virus cellular receptor 2 (HAVCR2, best known as TIM-3) and T cell immunoreceptor with Ig and ITIM domains (TIGIT), to maximize immunosuppression in the tumor microenvironment upon the overexpression of their cognate ligands (see main text).^{390,445,446} While exhaustion is largely dictated by epigenetic modifications encompassing the downregulation of transcription factor 7 (TCF7), a master regulator of T cell effector functions whose expression generally identifies CTL subsets that are sensitive to ICIs,⁴⁴⁷ accumulating evidence suggests that terminal T cell exhaustion can be prevented, but most often not reverted.⁴⁴³ This suggests that (immuno)therapeutic agents targeting exhaustion may need to be administered as early as possible during disease progression to effectively restore immunosurveillance. In line with this notion, neoadjuvant immunotherapy with ICIs has demonstrated superior efficacy in a number of oncological indications.¹

CCL7-dependent camouflage mechanism).²⁶⁰ Together, these observations potentially indicate that indolent IL33 signaling may be detrimental, while robust IL33 signaling beneficial, for anticancer immune responses, as in the case of type I IFN (mentioned previously).

Importantly, while vascular endothelial growth factor (VEGFA), which is the target of the FDA-approved monoclonal antibody bevacizumab,²⁶¹ has long been considered a purely angiogenic cytokine, it is now clear that VEGFA also mediates considerable immunosuppressive functions. For instance, VEGFA reportedly promotes the expansion of T_{REG} cells in syngeneic models of CRC and patients with metastatic CRC, as demonstrated by the T_{REG} cell-depleting effects of blocking VEGFA in either setting.^{262,263} Similar findings have been documented in patients with glioblastoma receiving radiotherapy, temozolomide and bevacizumab.²⁶⁴ Moreover, VEGFA (which is actively secreted by malignant cells especially in hypoxic tumor areas, see below) appears to promote T cell exhaustion (Box 2) by favoring the expression of co-inhibitory receptors including PD-1, TIM-3, and CTLA4 on their surface, at least in preclinical CRC models.²⁶⁵ In line with this finding, combined VEGFA, PD-1, and angiopoietin 2 (ANGPT2) inhibition has been associated with a therapeutically relevant reprogramming of the TME involving increased CD8⁺ CTL infiltration and reduced intratumoral MDSC levels in preclinical GBM models.²⁶⁶ The therapeutic value of concomitantly blocking VEGFA and PD-1 signaling has already been confirmed in multiple phase III clinical trials enrolling patients with renal cell carcinoma (RCC).^{267,268}

Defective release of pro-inflammatory cytokines other than type I IFN

Besides defects in the release of chemoattractants in support of camouflage and type I IFN-related cytokines in support of coercion (mentioned previously), some malignant cells often secrete limited amounts of other pro-inflammatory cytokines to promote local immunosuppression. For instance, breast, colorectal, and lung cancer cells release limited levels of interleukin 1B (IL1B), which inhibits the activation of tumor-infiltrating ILC3s in support of immune evasion.⁷⁹ Along similar lines, it is plausible that the detrimental effects of reduced ZBP1 levels in patients with

TNBC²¹⁹ (mentioned previously) may impinge on limited inflammasome activation and IL1B secretion, knowing that ZBP1 promotes an inflammatory cell death modality commonly known as necroptosis.^{269,270} That said, IL1B (and TNF) secretion by tumor-infiltrating immune cells has also been shown to elicit immunosuppressive CXCL8 secretion in a broad panel of human cancer cell lines,²⁷¹ pointing to at least some degree of context dependency in the immunomodulatory effects of IL1B.

Similar results have been documented for IL10. Indeed, while the presence of IL10-secreting macrophages as elicited by GABA-producing B cells has been associated with impaired anticancer immunity in preclinical models of CRC,²⁷² the administration of a half-life-extended IL10-Fc fusion protein considerably boosts the antitumor functions of CD8⁺ CTLs via metabolic reprogramming, offering a potential combinatorial partner for ICI- and ACT-based immunotherapy.²⁷³ In line with this notion, recombinant IL10 has been shown to improve CD8⁺ CTL secretory and cytotoxic functions.²⁷⁴ Similar observations have been obtained in a cohort of patients with advanced solid tumors receiving PEGylated IL-10 (pegilodecakin).²⁷⁵ Specifically, pegilodecakin improved tumor infiltration by CD8⁺ CTLs and their IFNG and GZMB expression levels while causing the expansion of previously undetectable circulating CD8⁺ CTL clones up to 1%–10% of the total peripheral T cell repertoire.²⁷⁵ These observations are reminiscent of the type I IFN and IL33 scenarios, pointing to a divergent immunomodulatory activity for indolent vs. robust signaling, at least in the TME.

In summary, malignant cells often acquire secretory alterations that endow them with the ability to coerce immune cells and establish robust immunosuppression in favor of disease progression.

Metabolic modulation of the TME

All cancer cells exhibit a considerable metabolic rewiring as compared to their normal counterparts.²⁷⁶ While for long such metabolic alterations were interpreted as a pure consequence of the accrued trophic needs of malignant cells, it is now clear that several metabolic pathways that are altered in cancer actively promote immunosuppression.²⁷⁷

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ATP and adenosine

Besides being a powerful chemoattractant (mentioned previously), extracellular ATP mediates immunostimulatory functions upon binding to purinergic receptor P2X 7 (P2RX7) on APCs or their precursors, which results in IL1B secretion upon inflammasome activation.²⁷⁸ Thus, most of the immunological defects caused by defective ATP release by cancer cells (mentioned previously) may involve coercion (rather than camouflage only). That said, extracellular ATP hydrolysis and consequent adenosine accumulation mediates immunosuppressive effects that are mostly based on coercion. In line with this notion, most human tumors expressed increased levels of CD39 and CD73, resulting in prominent adenosinergic signaling on tumor-infiltrating immune cells.²⁷⁹ This is particularly true for hypoxic tumor regions (Box 1), at least in part reflecting the ability of hypoxia inducible factor 1 subunit alpha (HIF1A) to transactivate ENTPD1 and NT5E.²⁷⁹ By binding to adenosine A2a receptor (ADORA2A) on the T cell surface, adenosine potently limits TCR signaling and IFNG production.²⁸⁰

Adenosine signaling has been consistently linked with disease progression and resistance to (immuno)therapy in a variety of preclinical tumor models. For instance, radiotherapy has been shown to drive the upregulation of CD73 on the surface of mouse breast cancer cells, an effect that could be circumvented in support of restored cDC1 tumor infiltration and recovered anticancer immunity with a CD73-targeting monoclonal antibody.²⁸¹ A similar immunosuppressive upregulation of CD73 (and PD-L1) has been documented in GBM CSCs exposed to repeated immunological pressure, resulting in the acquisition of a myeloid-like transcriptional profile dominated by IRF8 upregulation.²⁸² ADORA2A also appears to be upregulated on CAR T cells responding to mouse PDACs *in vivo*, resulting in limited efficacy owing to microenvironmental adenosine levels, a compensatory mechanism that can be circumvent by both genetic and pharmacological strategies targeting ADORA2A or CD73, also as a result of decreased CCL5-driven T_{REG} cell recruitment (mentioned previously).²⁴⁵ Interestingly, the dual inhibition of CD73 and ADORA2A has proven more effective than either approach in promoting anticancer immunity in syngeneic mouse models of mammary cancer and melanoma.²⁸³ This suggest that the global immunosuppressive effects of CD73 and ADORA2A do not only emerge from suppressed adenosinergic signaling via the latter, potentially involving (1) decreased ATP availability or (2) adenosinergic signaling via adenosine A2b receptor (ADORA2B).⁵⁹

In summary, both extracellular ATP degradation and consequent adenosinergic signaling mediate robust coercive effects on the TME in various oncological settings. That said, various clinical studies have been performed to investigate the therapeutic potential of agents that limit adenosinergic signaling in patients with cancer, so far with limited success.²⁸⁴

Kynurenine

Tryptophan degradation is a prominent mechanism of immunosuppression within the TME, as primarily driven by the indoleamine 2,3-dioxygenase 1 (IDO1)- or tryptophan 2,3-dioxygenase (TDO2)-catalyzed conversion of tryptophan into kynurenine, a potently immunosuppressive metabolite.²⁸⁵ While IDO1 is mostly expressed by myeloid cells of the TME,²⁸⁵ some neoplastic cells can also produce kynurenine in support of local

immunosuppression. For instance, CRC cells can secrete kynurenine through a mechanism that involves the upregulation of ubiquitin specific peptidase 14 (USP14), resulting in deubiquitination-dependent IDO1 stabilization.²⁸⁶ In this setting, genetic or pharmacological inhibition of USP14 restored CTL activation and tumor sensitivity to ICIs targeting PD-1.²⁸⁶ Immuno-evasive CRCs have also been shown to exhibit TDO2 upregulation as driven by transcription factor 4 (TCF4) and WNT signaling, resulting in elevated kynurenine production and consequent recruitment of M2-like TAMs via an aryl hydrocarbon receptor (AHR)-dependent mechanism promoting CCL5 secretion.²⁴⁶ Similarly, the secretion of kynurenine by glioma cells has been shown to inhibit the proliferation and functionality of CD4⁺ and CD8⁺ T cells via paracrine AHR signaling.²⁸⁷

Intriguingly, in preclinical melanoma models, IFNG release by tumor-infiltrating CD8⁺ CTLs appears to upregulate the neutral amino acid transporter solute carrier family 1 member 5 (SLC1A5) on the surface of tumor repopulating cells (TRCs), resulting in increased tryptophan uptake and consequent kynurenine production.²⁸⁸ In this context, TRCs overexpress both IDO1 and AHR, which endow them with capacity to evade cell death as initiated by IFNG and instead undergo dormancy (see in the following text).²⁸⁸ Despite considerable expectations as set by the encouraging results of multiple phase II clinical trials, however, combining the IDO1 inhibitor epacadostat with the PD-1 blocker pembrolizumab failed to provide a clinical advantage as compared to pembrolizumab alone to patients with advanced melanoma enrolled in a large, randomized phase III clinical study.²⁸⁹ While the precise reasons underlying these negative results remain to be understood, the enthusiasm around the use of IDO1 inhibitors as combinatorial partners for ICI-based immunotherapy in patients with cancer has considerably reduced as a consequence thereof.^{290,291}

Of note, other IDO1-derived metabolites have been attributed potent immunomodulatory functions, including quinolinic, which accumulates in GBM to promoting TAM polarization toward an M1-like phenotype through glutamate ionotropic receptor NMDA type subunit 2B (GRIN2B), forkhead box O1 (FOXO1), and peroxisome proliferator activated receptor gamma (PPARG) signaling,²⁹² as well 3-hydroxy-L-kynurenamine (3-HKA), which, at least in non-oncological settings, inhibits the STAT1 and NF-κB signaling in DCs, thereby limiting their release of pro-inflammatory cytokines.²⁹³ Whether these metabolites or the signaling pathways they elicit can be harnessed therapeutically to circumvent metabolic immune coercion remains to be determined.

Despite this unexplored possibility, tryptophan catabolism remains a core mechanism through which malignant lesions establish local immunosuppression. That said, additional work is required to understand the actual therapeutic potential of this pathway.

Glucose and glutamine

Anticancer immune responses are highly influenced by the metabolic competition for nutritional substrates, notably glucose and glutamine, in the TME.²⁷⁷ For example, glucose consumption by ovarian cancer cells has been shown to limit its availability to CD8⁺ CTLs, resulting in impaired glycolytic flux and effector functions.²⁹⁴ A similar coercion mechanism has been observed in a syngeneic model of sarcoma, a setting in which ICI administration restored glucose availability in the TME, resulting in

increased glycolytic flux in T cells and therapeutically relevant IFNG secretion,²⁹⁵ and lymphoma, in a scenario in which acetate supplementation was sufficient to restore CD8⁺ CTL effector functions.²⁹⁶ Moreover, a robust flux through glycolysis in malignant cells—which at least in some settings results from FTO-dependent epitranscriptomic mechanisms.²⁹⁷—has been associated with an increased threshold for TNF sensitivity (see in the following text),²⁹⁸ as well as to a reduced sensitivity to CTLA4 inhibition.²⁹⁹

That said, it has recently been demonstrated that distinct cellular compartment of TME preferentially take up different nutrients, with immune and malignant cells relying on glucose and glutamine as the major fuel source, respectively.³⁰⁰ Moreover, antagonizing glutamine metabolism has been attributed a cell-specific impact on distinct TME compartments, largely affecting energy metabolism and survival in malignant cells while promoting activation and proliferation of effector T cells, altogether driving robust anticancer immunity.³⁰¹ Corroborating the critical role of glutamine metabolism in cancer immune evasion, the cancer cell-specific loss of glutaminase (GLS), a key enzyme for glutamine metabolism, improved effector T cell activation in multiple breast cancer models.³⁰² Similarly, in a syngeneic model of CRC inhibition of glutamine uptake or metabolism reportedly promoted the expression of Fas cell surface death receptor (FAS) and PD-L1 on the surface of malignant cells, *de facto* favoring their sensitivity to CD8⁺ CTLs in an ICI-dependent manner.³⁰³ That said, cDC1 functions also depend on glutamine, and, at least in preclinical model of CRC, glutamine supplementation inhibits (rather than boosting) disease progression in the context of restored cDC1 activity.³⁰⁴

Taken together, these observations point to glutamine more so than glucose as a potential target for the development of therapeutic strategies to circumvent metabolic coercion. That said, targeted approaches may be required to spare immune effector cells from the detrimental effects of glutamine restriction and hence achieve superior therapeutic activity.

Lactate

Most malignant cells produce abundant lactate levels, largely reflecting their increased uptake of glucose compared to their normal counterparts and/or overexpression of proteins involved in lactate generation or export, namely lactate dehydrogenase A (LDHA).³⁰⁵ Extracellular lactate favors immuno-evasion by promoting the acidification of the TME and by inhibiting the proliferation and function of immune effector cells including CD8⁺ CTLs and NK cells.^{305,306} In melanoma and CRC, lactate as secreted by neoplastic cells exhibiting increased glycolytic flux has been shown to impair the cytotoxicity of CD8⁺ T cells by a metabolic reprogramming involving reduced pyruvate carboxylase (PC) activity and consequent depletion of tricarboxylic acid (TCA) cycle intermediates.³⁰⁷ Indeed, melanoma cells often express high LDHA levels and the consequent hypersecretion of lactate has been shown to promote the downregulation of nuclear factor of activated T cells 1 (NFATC1) in CD8⁺ CTLs and NK cells, leading to decreased synthesis of IFNG and immune escape.³⁰⁸ Moreover, the loss of LKB1 is reported to enhance lactate secretion by KRAS-driven lung cancer cells upon the upregulation of lactate transporters such as solute carrier family 16 member 4 (SLC16A4, best known as MCT4), resulting in M2-like TAM repolarization and dysfunctional T cell accumulation.³⁰⁹ In line with

this notion, MCT4 inhibition has been shown to reverse lactate-driven immunosuppression in syngeneic CRC models, *de facto* restoring their sensitivity to ICI-based immunotherapy.³¹⁰ Similar results have been obtained in preclinical models of multiple myeloma exposed to pharmacological inhibitors of SLC16A1 (best known MCT1) in combination with CAR T cells.³¹¹

Supporting its broad immunosuppressive effects, extracellular lactate has also been reported to promote (1) M2-like TAM repolarization in breast cancer and melanoma models, at least in part through the acidification of the TME^{312,313} as well as (2) T_{REG} cell functions in various cancers with high glycolytic activity.^{314–316} Specifically, lactate appears to boost T_{REG} cell activity not only by providing metabolic support³¹⁵ but also by upregulating signal transduction cascades involved in immunosuppression, including TGFB1 and PD-1 signaling.^{314,316}

Thus, lactate mediates multipronged immunosuppressive effects either upon uptake by immune cells or via local acidification. Drug development efforts targeting lactate to restore cancer immuno-surveillance, though, appear to stand at an impasse.²⁷⁷

Other TCA cycle intermediates

Transformed cells often exhibit a considerable rewiring of the TCA cycle, at least in some cases owing to oncogenic mutations in TCA cycle enzymes such as isocitrate dehydrogenase (NADP(+)) 1 (IDH1),³¹⁷ which is generally accompanied by the accumulation of immunosuppressive metabolites.²⁷⁷ For instance, fumarate hydratase (FH) defects lead to an increased secretion of fumarate, which suppresses the cytotoxic activity of tumor infiltrating CD8⁺ CTLs by promoting the inhibitory succination of zeta chain of T cell receptor associated protein kinase 70 (ZAP70).^{318,319} Accordingly, fumarate depletion has been shown to potentiate the efficacy of CD19-targeting CAR T cells in preclinical models of lymphoma.³¹⁹ Apparently at odds with these observations, the loss of FH in the healthy kidney reportedly results in intracellular fumarate accumulation and increased immunogenicity via a mechanism that involves the vesicular release of mtDNA and consequent activation of CGAS-STING signaling.³¹⁸ Given that FH mutations predispose for RCC,³²⁰ it is tempting to speculate that an early and indolent inflammatory response as driven by the loss of FH in healthy cells of the renal epithelium may initiate an oncogenic program that at some stage would also benefit from the fumarate-dependent inhibition of immune effector functions. This possibility remains to be experimentally validated.

The inhibition of acetyl-CoA synthetase 2 (ACSS2) in breast cancer cells results in the microenvironmental accumulation of acetate, which intratumoral CD8⁺ CTLs have been shown to utilize in support of proliferation and effector functions.³²¹ Accordingly, pharmacological ACSS2 inhibitors reportedly synergize with immunogenic chemotherapy in preclinical breast cancer models.³²¹ Gain-of-function mutations in IDH1 drive the accumulation of D-2-hydroxyglutarate (D-2HG), a byproduct of the TCA cycle that acts as an oncometabolite by inhibiting various epigenetic regulators that depend on α -ketoglutarate, including DNA demethylases of the TET family.³²² Studies in CRC and melanoma have revealed that tumor-derived D-2HG exerts immunosuppressive functions by inhibiting LDHA and glycolysis in CD8⁺ CTLs, resulting in decreased IFNG signaling and compromised antitumor immunity.³²³ Of note, L-2HG (which is not produced

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by mutant IDH1 but accumulates in response to hypoxia via a promiscuous LDHA activity) also appears to mediate oncogenic effects, at least in the renal setting,³²⁴ and to promote immuno-evasion in preclinical PDAC models, although the underlying mechanisms remain to be explored.³²⁵

These observations are aligned with the notion that oncogenic events, including tumor-promoting alterations of intermediate metabolism, do not only provide cancer cells with a growth advantage but also render them immuno-evasive.

Ketone bodies

Human CRCs often exhibit reduced ketogenesis, which is the biochemical pathway through which cells produce alternative fuel sources (ketone bodies) in the absence of sufficient carbohydrate supplies.³²⁶ In this context, a limited metabolic flux though ketogenesis has been associated with the release of CXCL12 from CAFs via a KLF transcription factor 5 (KLF5)-dependent mechanisms, resulting in the recruitment of M2-like TAMs, MDSCs, and T_{REG} cells to the TME and accelerated disease progression.³²⁷ Accordingly, subjecting CRC-bearing immunocompetent mice to a ketogenic diet (i.e., a high-fat and low-carbohydrate dietary regimen), administering them with the ketone body β-hydroxybutyrate or genetically, and promoting ketogenesis upon the overexpression of 3-hydroxy-3-methylglutaryl-CoA synthase 2 (HMGC2) in malignant cells have all been reported to restore immuno-surveillance and elevate ICI sensitivity.³²⁷ Similar results have recently been obtained in syngeneic models of prostate cancer.³²⁸

These observations suggest that dietary interventions such as ketogenic diets may constitute promising tools to circumvent metabolic coercion in at least some tumor types.

Methionine and serine

Cancer cells can evade immunity by overconsuming methionine upon the upregulation of the methionine transporter solute carrier family 43 member 2 (SLC43A2, best known as LAT4), thus restricting the availability of this essential amino acid for immune cells.³²⁹ Decreased methionine availability in T cells results indeed in reduced levels of S-adenosylmethionine (SAM, a donor of methyl groups for DNA and histone methyltransferases), culminating with the epigenetic repression of genes critically involved in effector functions such as STAT5.³²⁹ Apparently at odds with the aforementioned, the accumulation of SAM and other methionine metabolism byproducts such as 5-methylthioadenosine (MTA) has also been reported to mediate immuno-suppressive effects by favoring T cell exhaustion (Box 2), at least in preclinical models of HCC and melanoma.^{330,331} Interestingly, such an accumulation may emerge from the hyperactivation of methionine adenosyltransferase 2A (MAT2A), which produces SAM, as well as from defects in methylthioadenosine phosphorylase (MTAP), which catabolizes MTA,^{330,331} perhaps offering novel targets to circumvent the metabolic coercion of anticancer immunity in these oncological settings.

Methionine restriction has also been shown to promote CGAS activation by interfering with its inactivating methylation by SUV39H1.¹⁷⁰ Similar results have been reported in CRC cells deprived of both endogenous and exogenous sources of the non-essential amino acid serine, resulting in restored sensitivity to ICIs.¹⁸² In this latter scenario, though, CGAS activation appears to be largely driven by the ability of serine restriction to compromise the mitochondrial checkpoint (mentioned previ-

ously), resulting in the MOMP-dependent accumulation of intergenic mtDNA in the cytosol of malignant cells.^{182,332}

These observations exemplify the ability of transformed cells to coerce immune effector cells via metabolic pathways stemming from both essential and non-essential amino acids.

Lipids

Neoplastic cells exhibit a major rewiring of lipid metabolism in support of accelerated proliferation,³³³ which—at least in some tumors—also promotes immuno-evasion. The accumulation of lipids in ovarian cancer cells as driven by the upregulation of fatty acid synthase (FASN) has been shown to impair the cross-priming activity of tumor-infiltrating DCs.³³⁴ Accordingly, FASN inhibition partially restores DC functionality in this setting, leading to improved immunological disease control.³³⁴ Moreover, enhanced fatty acid catabolism in GBM cells as caused by an increased flux of lipid through fatty acid oxidation (FAO) leads to radioresistance and immuno-evasion by promoting the upregulation of CD47 (see above).¹⁵⁶ However, whether this mechanism of immuno evasion stems from the accumulation of TCA cycle intermediate with immunosuppressive effects (mentioned previously) has not been formally investigated. Deregulated lipid metabolism also seems to drive immune evasion in the CSC compartment. Specifically, in preclinical models of HCC, the ablation of Arf1—which encodes a core regulator of fatty acid metabolism³³⁵—reportedly fosters the immunogenicity of CSCs, leading to increased tumor infiltration by DCs and restored anticancer immunity.⁷² At least in part, however, these observations reflect the ability of ARF1 to preserve the mitochondrial checkpoint and inhibit ISR signaling (mentioned previously).⁷²

A major player in immunosuppression as driven by deregulated lipid metabolism in cancer cells is CD36, a broadly expressed long-chain fatty acid transporter.³³⁶ Indeed, CD36 is upregulated by both CD8⁺ CTLs and T_{REG} cells exposed to fatty acid accumulation in the TME but mediates diametrically divergent effects on these immune cells. On the one hand, CD8⁺ CTLs respond to CD36-dependent fatty acid uptake by experiencing widespread oxidative stress coupled with the impaired secretion of effector molecular such as IFNG, TNF, and perforin 1 (PRF1).^{337,338} On the other hand, CD36 favors the metabolic adaptation of intratumoral T_{REG} cells to a lactate-enriched microenvironment, *de facto* promoting their immunosuppressive functions.³³⁹ In line with this notion, the T_{REG} cell-specific ablation of Cd36 has been shown to restore immuno-surveillance and ICI sensitivity in a syngeneic mouse model of melanoma.³³⁹

While targeting lipid metabolism to counteract coercion may pose obstacles, notably specificity, these observations point to microenvironmental fatty acids as to potent immunosuppressive factors.

Bioactive lipids

Cancer cells can evade immunity by releasing bioactive lipids into the TME, including PGE₂ and lysoglycerophospholipids. PGE₂—which derives from the sequential catalysis of membrane-released arachidonic acid by prostaglandin-endoperoxide synthase 2 (PTGS2, best now as COX2) and prostaglandin E synthase 2 (PTGES2)²⁷⁷—is involved in metabolic coercion in variety of tumors.^{340–345}

In some of these settings, increased PGE₂ signaling via prostaglandin E receptor 2 (PTGER2) and/or PTGER4 has been

shown to reduce the functionality of intratumoral cDC1s in support of immune evasion.^{340–342} Specifically, PGE₂ has been reported to (1) promote the downregulation of IRF8 and hence reprograms cDC1s toward a dysfunctional state³⁴⁰; (2) limit CXCL9 release by cDC1s, hence impeding intratumoral CD8⁺ CTL differentiation and expansion³⁴²; and (3) indirectly compromise cDC1 recruitment and activation by limiting NK cell survival, resulting in the suppressed release of the cDC1 chemoattractants CCL5 and X-C motif chemokine ligand 1 (XCL1).³⁴⁵

Recently, it has also been shown that PGE₂ promotes immune escape by directly affecting the function and survival of tumor-infiltrating CD8⁺ CTLs.^{343,344} In this setting, PGE₂ signaling via PTGER2 and PTGER4 not only impairs IL2 sensing by CD8⁺ CTLs, hence limiting their expansion and effector differentiation of CD8⁺ CTLs³⁴³ but also exposes them to widespread oxidative stress coupled with ferroptotic cell death.³⁴⁴ Finally, PGE₂ has been reported to favor immunoescape during pancreatic tumorigenesis by driving the differentiation of tumor-infiltrating monocytes into M2-like TAMs.³⁴⁶

LPC does not only mediate immunosuppressive effects by promoting the silent efferocytic removal of dying cells and their corpses by macrophages (mentioned previously)⁹⁷ but also as a substrate for the ENPP2-mediated synthesis of lysophosphatidic acid (LPA).³⁴⁷ ENPP2 is overexpressed in some malignancies including ovarian cancer, promoting the LPA-driven release of PGE₂ from DCs and the consequent autocrine and paracrine suppression of anticancer immunity.³⁴⁷

These few observations exemplify the multipronged immunosuppressive effects enabled by the LPC-LPA-PGE₂ axis. While this axis can be efficiently targeted by a number of clinically available COX2 inhibitors (e.g., celecoxib and aspirin), past efforts to combine COX2 blockers with chemotherapy or radiotherapy have generally failed to demonstrate a superiority for the combinatorial regimen over standard-of-care (SOC).³⁴⁸

Vitamins and retinoic acid

Vitamins and their derivatives can modulate anticancer immunity by affecting various immune effector cells. For instance, pancreatic cancer cells restrict vitamin B₆ availability to NK cells, which require this metabolite for activation, at least in part by regulating glycogen metabolism.³⁴⁹ Similar results have been obtained with the vitamin B₃ precursors nicotinamide (NAM), at least in preclinical models of mammary carcinoma and PDAC.^{350–352} In line with these observations, vitamin B₆ or NAM supplementation has been shown to promote NK cell functions, both in syngeneic PDAC models³⁴⁹ or in ex vivo settings prior to ACT.³⁵³ Conversely, sarcoma cells reportedly coerce immune effectors by overproducing retinoic acid (RA).³⁵⁴ RA appears to inhibit the transcriptional activity of IRF4 in intratumoral monocytes, thus promoting the accumulation of immunosuppressive TAMs over DCs.³⁵⁴

In summary, at least some cancer types alter the local abundance of vitamins and their precursors in support of immunosuppression. While some attempts at utilizing specific vitamins, notably vitamin C, as anticancer agents in the clinic are underway,³⁵⁵ most of them were developed in an immune-agnostic manner.

Potassium

Ion channels, and in particular potassium channels, regulate T cell functionality.³⁵⁶ Accordingly, elevated concentrations of

extracellular potassium as released by dying melanoma cells have been shown to compromise the functionality of intratumoral CD8⁺ CTLs by suppressing mTORC1 signaling.³⁵⁷ Moreover, increased environmental levels of potassium have been reported to inhibit nutrient uptake by effector T cells, resulting in the activation of an autophagic response coupled with decreased availability of histone acetylation donors (e.g., acetyl-CoA) and consequent downregulation of effector molecules.³⁵⁸ At least in preclinical models of melanoma, such an ionic coercion has been associated with decreased tumor control by adoptively transferred CD8⁺ CTLs.³⁵⁸

These observations indicate that the ionic balance of the TME is important for immunosurveillance, opening the possibility to genetically engineer (CAR) T cells prior to infusion to circumvent ionic coercion. To the best of our knowledge, this possibility is not being explored.

CYTOPROTECTION

Both CD8⁺ CTLs and NK cells kill malignant cells upon the establishment of the so-called “immunological synapse”, a highly organized structure that physically connects immune effector cells with their targets and enables the polarized (1) release of cytotoxic molecules including GZMB and PRF1; (2) expression of death receptor ligands, such as Fas ligand (FASLG); and (3) release of tumor-targeting cytokines, notably IFNG.³⁵⁹ Neoplastic cells can evade immune elimination by effector cells that normally recognize them as transformed and hence normally engage in cytotoxic and secretory functions through a variety of cytoprotective mechanisms that either involve defects in the formation of the immunological synapse or the activation of cell death pathways downstream thereof, or rely on the initiation of compensatory responses such as autophagy (Figure 4).

Alterations of the immunological synapse

At least in some cases, cancer cells evade immune cytotoxicity via mechanical properties that result in decreased sensitivity to GZMB and PRF1. For instance, TRCs appear to evade immune attack due to their unique cellular softness as compared to their more differentiated counterparts, resulting in insufficient contractile force for PRF1 pore formation at the immunological synapse, at least in preclinical melanoma and breast cancer models.³⁶⁰ Similar findings have been documented in models of T cell leukemia, at least in part emerging from the downregulation of the cytoskeletal component filamin A (FLNA), a process that also appears to protect CTL themselves from PRF1-mediated lysis.³⁶¹ Moreover, breast cancer cells resisting NK cell killing appear to display extensive actin remodeling at the immunologic synapse, resulting in decreased access of GZMB to the cytosol and hence robust cytoprotection.³⁶² Finally, it has been shown that insufficient target cell contraction (which is mediated by the actin cytoskeleton) prevents the rapid dissolution of the immunological synapse, resulting in effector cell retention and limited engagement of additional targets.³⁶³

Along similar lines, malignant cells can actively compensate for PRF1 and GZMB killing at the immunological synapse. For instance, melanoma cells have been shown to react to the formation of the immunological synapse with an increased

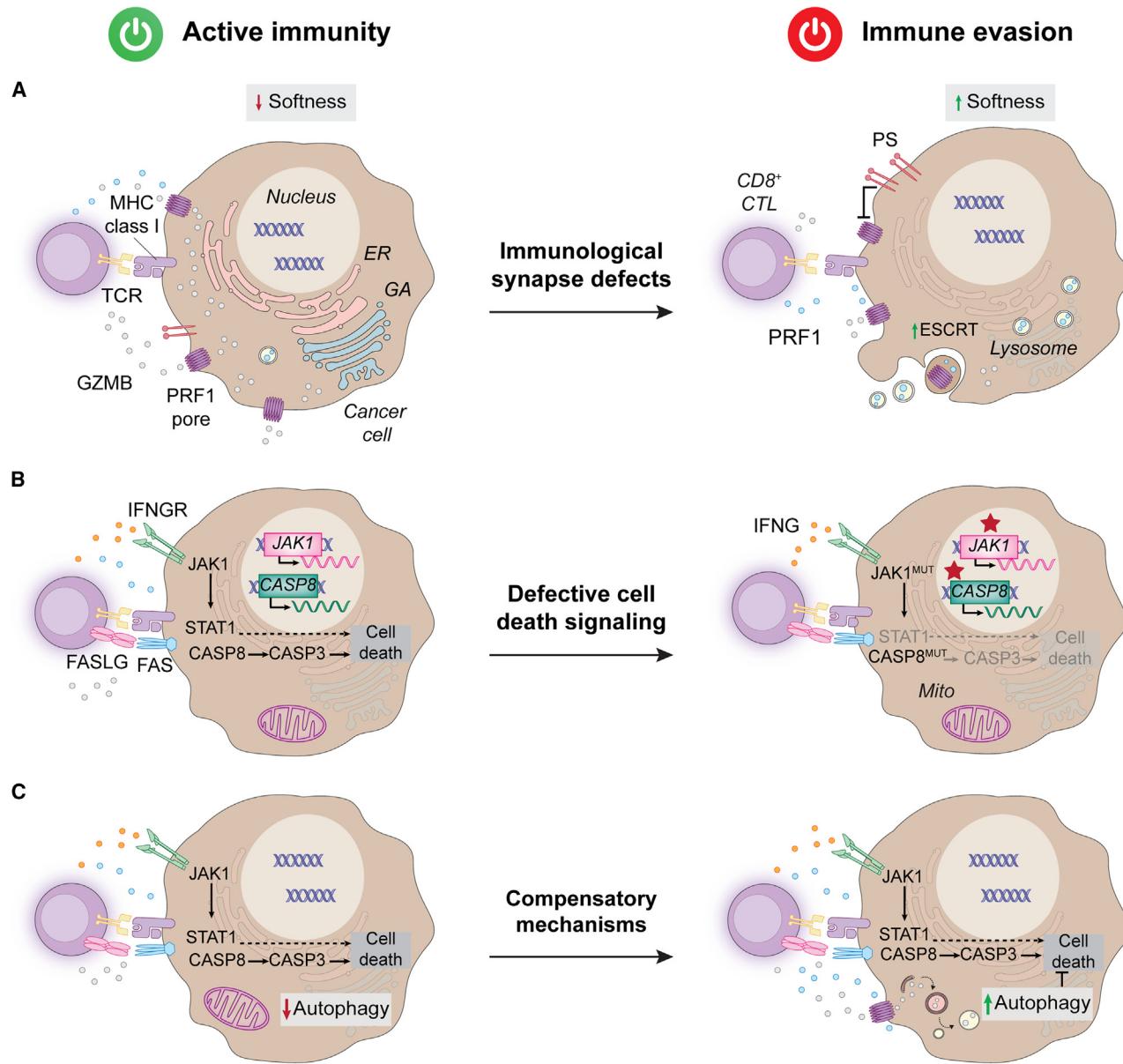


Figure 4. Cytoprotection in cancer immune evasion

Cancer cells of different histology can evade tumor-targeting immune responses by acquiring an increased resistance to immune effector molecules such as perforin 1 (PRF1), granzyme B (GZMB), tumor necrosis factor (TNF), or interferon gamma (IFNG). Such a decreased sensitivity to cytotoxicity by immune effector cells can involve (1) mechanical defects of the immune synapse, generally resulting in inhibited PRF1-mediated pore formation or improved endosomal sorting complexes required for transport (ESCRT)-dependent membrane repair (A); (2) defects in Fas cell surface death receptor (FAS) and IFNG signal transduction, at least in some cases linked to caspase 8 (CASP8) and Janus kinase 1 (JAK1) mutations (B); and (3) the activation of compensatory cytoprotective pathways including (but not limited to) autophagy (C). CASP, caspase; CASP8^{MUT}, mutant caspase 8; CTL, cytotoxic T lymphocyte; ER, endoplasmic reticulum; FASLG, Fas ligand; GA, Golgi apparatus; GZMB, granzyme B; JAK1^{MUT}, mutant Janus kinase 1; PRF1, perforin 1; PS, phosphatidylserine; STAT1, signal transducer and activator of transcription 1; TCR, T cell receptor.

vesicular trafficking and secretion, resulting in degradation of PRF1 by lysosomal cathepsins and cytoprotection.³⁶⁴ Moreover, both melanoma and CRC cells have been reported to harness endosomal sorting complexes required for transport (ESCRT) factors at the immunological synapse to actively repair PRF1 pores and consequently limit cytosolic GZMB entry.³⁶⁵ Moreover, irradiated cancer cells appear to acquire transient resis-

tance to NK cell killing by a mechanism involving PRF1 inhibition by surface-exposed PS.³⁶⁶

Altogether, these observations exemplify mechanical and biological processes through which malignant cells achieve cytoprotection from immune effector cells. Pharmacological inhibitors of these mechanisms may result in superior cancer cell elimination by CD8⁺ CTLs and NK cells and hence superior ICI

sensitivity across a variety of neoplasms, a possibility that has just begun to be explored.

Defective cell death signaling

Genomic studies on biopsies from patients with solid tumors have revealed frequent mutations in *CASP8*,²⁴ which encodes for an apoptotic caspase activated by FAS.²²⁷ In line with this notion, malignant cells have been shown to frequently downregulate FAS by epigenetic mechanisms, resulting in accrued resistance to NK cell cytotoxicity.³⁶⁷ Similar observations have been made in preclinical models of CRC and lung carcinoma, although in this setting glutamine metabolism appeared to suppress FAS expression.³⁰³ Moreover, the sensitivity of melanoma and CRC cells to immune effectors including CD8⁺ CTLs and NK cells appears to rely on intact TNF signaling, as demonstrated by a CRISPR screen that identified multiple TNF signal transducers involved in cytotoxicity.³⁶⁸ Similar observations have been made in syngeneic PDAC models, although in this setting decreased TNF sensitivity appeared to emerge from the EMT-driven repression of *IRF6*.³⁶⁹ Melanoma cells also display frequent genetic defects in IFNG signal transducers, resulting in limited activation of JAK-STAT signaling and consequent cytoprotection from IFNG-mediated killing.³⁷⁰ Along similar lines, SRY-box transcription factor 17 (*SOX17*) overexpression has recently been shown to increase the resistance of CRC cells to IFNG,³⁷¹ although the precise mechanisms underlying this observation remains to be characterized.

Corroborating the importance of operational cell death signaling in cancer cells for efficient immunosurveillance, defects in TNF and IFNG signaling have been consistently associated with resistance to immunotherapy. For instance, ICI-unresponsive tumors have been reported to display an increased cytotoxicity threshold to effector cytokines including TNF.^{372,373} In line with this notion, lowering the threshold for efficient TNF signaling in melanoma cells by TNF receptor associated factor 2 (*Traf2*) ablation or pharmacological inhibition of TBK1 has been shown to restore ICI sensitivity by a mechanism involving the induction of receptor interacting serine/threonine kinase 1 (*RIPK1*)- and caspase-dependent cancer cell death.^{372,373} Similar observations linking lowered TNF signaling threshold to improved disease control and restored ICI sensitivity have been made in preclinical models of highly glycolytic lung and pancreatic cancer subjected to the depletion of solute carrier family 2 member 1 (*SLC2A1*, a glucose transporter best known as GLUT1) (mentioned previously).²⁹⁸ Finally, a rewiring of IFNG signaling from STAT1 activation to the upregulation of the endogenous cell cycle inhibitor cyclin dependent kinase inhibitor 1B (*CDKN1B*, best known as p27^{KIP1}) and consequent acquisition of a dormant state has been linked with IFNG resistance in melanoma-repopulating cells.²⁸⁸

Corroborating the key role of cell death defects in immune evasion, in patients with refractory/relapsed B-cell non-Hodgkin lymphoma, resistance to CD19-targeting CAR T cells has been associated with *BCL2* amplifications.³⁷⁴ Accordingly, the FDA-approved *BCL2* inhibitor venetoclax has been shown to sensitize CAR T cell-refractory lymphoma cells to therapy.³⁷⁴ Of note, IFNG has recently been reported to promote ferroptotic lipid oxidation in malignant cells, by a dual mechanism involving (1) downregulation of solute carrier family 3 member 2 (*SLC3A2*)

and solute carrier family 7 member 11 (*SLC7A11*) and consequent decrease of intracellular cysteine (which mediates robust antioxidative effects); and/or (2) activation of acyl-CoA synthetase long chain family member 4 (*ACSL4*) and consequent reprogramming in lipid metabolism.^{375,376} Of note, at least in some malignant cells, *GZMB* has also been shown to promote a gasdermin E (*GSDME*)-dependent regulated variant of necrosis commonly known as pyroptosis.³⁷⁷ Whether malignant cells can harness *CASP7* and sphingomyelin phosphodiesterase 1 (*SMPD1*) to repair *PRF1* and *GSDME* pores as demonstrated in preclinical models of bacterial infection,³⁷⁸ however, remains to be clarified.

Collectively, these observations indicate that cytoprotection as a consequence of common defects in cell death signal transduction is beneficial to malignant cells not only by virtue of an increased resistance to stress, but also because of immunoevasion.

Compensatory mechanisms

Malignant cells can activate a number of cell-wide pathways that protect them from the cytotoxicity of immune effectors. For instance, multiple tumor types have been shown to respond to CD8⁺ CTL activation by overexpressing *SERPINB9*,^{379,380} which is generally harnessed by immune effectors themselves including CD8⁺ CTLs and DCs to avoid *GZMB* cytotoxicity.^{381,382} Especially under hypoxic conditions (Box 1), cancer cells of different histological derivation can also achieve increased resistance to immune effector molecules including IFNG, TNF, and *GZMB* upon activation of autophagy,³⁸³ via a mechanism that appears to involve the activating phosphorylation of STAT3,³⁸⁴ as well as lysosomal *GZMB* degradation.³⁸⁵

That said, autophagy in malignant cells is critically involved in the ICD-associated release of ATP (mentioned previously), and immune effector cells have been shown to kill their malignant counterparts in an immunogenic manner.^{386,387} Moreover, autophagy has been reported to promote the degradation of tenascin C (*TNC*)—an extracellular matrix glycoprotein contributing to immune evasion—in preclinical TNBC models, *de facto* favoring tumor-targeting immune responses.³⁸⁸ Thus, at least hypothetically, autophagic defects may result in the inhibition of CTL cytotoxicity and the ATP-dependent feedforward amplificatory loops it may elicit.

In summary, various compensatory mechanisms can be utilized by transformed cells to resist killing by TNF, IFNG, and the *PRF1*-*GZMB* system.

Other mechanisms

TFGB1 has also been reported to promote cytoprotection by limiting the sensitivity of malignant cells to CD8⁺ CTLs, via a mechanism involving *SOX4*.³⁸⁹ While the precise link between *SOX4* expression and the increased resistance of cancer cells to lysis by CD8⁺ CTLs remains to be formally established, *SOX17* has also been shown to provide CRC cells with cytoprotection, at least in part reflecting decreased sensitivity to IFNG (mentioned previously),³⁷¹ potentially suggesting the implication of a similar mechanism. An accrued resistance to immune cytotoxicity has also been associated with the acquisition of a quiescence phenotype characterized by transcriptional features of hypoxic responses by transformed cells,¹¹⁵ but the molecular

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underpinnings of this process have not yet been thoroughly dissected.

NOVEL PHARMACOLOGICAL STRATEGIES TO TARGET IMMUNE EVASION IN THE CLINIC

Over the past two decades, multiple clinically relevant pharmacological strategies have been conceived to target camouflage, coercion and cytoprotection, and some of these *bona fide* immunotherapies have already entered routine clinical use. The latter include (1) a number of ICIs targeting PD-1, PD-L1, CTLA4, or LAG3, which operate by inhibiting coercion as driven by co-inhibitory ligands expressed by cancer cells³⁹⁰; (2) CAR T cells and bispecific antibodies, which circumvent camouflage^{391,392}; and (3) some recombinant cytokines and TLR agonists,³⁹³ which operate by targeting coercion as driven by immunosuppressive shifts in cytokine and DAMP signaling. Moreover, a number of FDA approved anticancer treatments that have been developed in an immune agnostic manner have been found to inhibit immune evasion (by a multitude of mechanisms), *de facto* promoting the (re)instatement of tumor-targeting immunity. These include (1) some cytotoxicants such as anthracyclines and oxaliplatin¹²; (2) some targeted anticancer agents encompassing a variety of tyrosine kinase inhibitors (TKIs), tumor-targeting antibodies, epigenetic modifiers and the BCL2 inhibitor venetoclax¹³; and (3) at least in some settings, focal radiotherapy.¹⁴

Besides these established approaches, numerous clinical trials—including a few phase III studies (Table 1)—are now open to investigate hitherto experimental strategies to inhibit immune evasion, which generally aim at (1) inhibiting coercion by co-inhibitory ligands; (2) inhibiting metabolic coercion and suppressed cytokine signaling; or (3) simultaneously targeting multiple “Cs”.

Inhibiting coercion by co-inhibitory ligands

Considerable attention is being devoted to blocking the coercive effects of co-inhibitory receptors other than PD-1, CTLA4, and LAG3, notably TIM-3, TIGIT, VISTA, and NKG2A, generally in combination with FDA-approved PD-1 or PD-L1 blockers.²⁸⁴ Combinations of this type that are currently being investigated in clinical trials enrolling patients with advanced solid tumors (unless specified) include (1) pembrolizumab plus the VISTA inhibitor KVA12123³⁹⁴; (2) the PD-1 blocker dostarlimab plus the TIM-3 inhibitor TSR-022,³⁹⁵ or the TIGIT inhibitor EOS-448³⁹⁶ (in patients with lung cancer); (3) the PD-1 inhibitor nivolumab plus the TIGIT-targeting antibodies BMS-986207³⁹⁷ or etigilimab (both in patients with ovarian carcinoma); (4) the PD-1 blocker tisilizumab plus the anti-TIGIT monoclonal antibody ociperlimab³⁹⁸ (in subjects with lung cancer, biliary tract carcinoma, or lymphoma); (5) the PD-1 blocker toripalimab plus the TIGIT blocker JS006; and (6) the PD-L1 inhibitor avelumab plus the TIGIT-targeting agent M6223³⁹⁹ (in individuals with urothelial carcinoma). Along similar lines, the NKG2A blocker monalizumab¹⁴⁵ with or without SOC chemotherapy is being investigated in combination with the FDA-approved PD-L1 inhibitor durvalumab (in patients with lung cancer or head and neck carcinoma), optionally along with the experimental CD73 inhibitor oleclumab⁴⁰⁰ (in subjects with lung cancer), as well as with the dual CTLA4 and PD-1 blocker MEDI5752⁴⁰¹ (in individuals with

CRC). Finally, two dual TIGIT and PD-L1 inhibitors, namely HB0036⁴⁰² and HLX301,⁴⁰³ are currently being tested in patients with advanced solid tumors as standalone therapeutic agents (source www.clinicaltrials.gov).

Two CD47 blockers are currently being investigated in clinical trials: (1) magrolimab⁴⁰⁴ is being tested—invariably along with SOC chemotherapy and/or one or more ICI(s)—in multiple cohorts of patients with solid and hematological malignancies; and (2) lemzoparlimab,⁴⁰⁵ which is being tested for safety and efficacy in combination with azacytidine in individuals with myelodysplastic syndromes (MDSs). Finally, a number of SIRPA-Fc fusion proteins are under clinical evaluation, including (1) TTI-622,⁴⁰⁶ which is being tested along with pembrolizumab in patients with lymphoma; (2) evorpacept,⁴⁰⁷ which is being investigated as a combinatorial partner for venetoclax and azacytidine in patients with hematological malignancies, or for ICIs in subjects with CRC and gastric cancer; and (3) IMM001, whose safety and efficacy are being assessed in combination with tisilizumab in patients with Hodgkin’s lymphoma, or with azacitidine in individuals with AML and MDS (source www.clinicaltrials.gov).

Collectively, these studies testify the considerable interest raised among clinical and pharmaceutical companies by the possibility to effectively target the immunosuppressive pathways elicited by co-inhibitory receptors other than PD-1, CTLA4, and LAG3 and anti-phagocytic receptors.

Inhibiting metabolic coercion and suppressed cytokine signaling

An attractive area of clinical investigation is focusing on agents that target coercion as driven by metabolic cancer cell rewiring.²⁷⁷ For instance, the glutamine antagonist DRP-104⁴⁰⁸ is being explored in combination with durvalumab in patients with fibrolamellar carcinoma. The safety and efficacy of the MCT1 inhibitor AZD3965⁴⁰⁹ optionally combined with the FDA approved CD20-targeting agent rituximab are currently being evaluated in individuals with B-cell malignancies and advanced solid tumors. Restoring methionine metabolism in CD8⁺ CTLs via SAM administration along with PD-1 inhibition and optional VEGF signaling blockage is also under clinical evaluation in patients with HCC or RCC. The FASN inhibitor TVB-2640 is being assessed as stand-alone therapeutic intervention or combined with endocrine therapy in patients with CRC as well as prostate and breast cancer. Finally, while the ADORA2A antagonists ciforadenant⁴¹⁰ and inupadenant are being tested in combination with ICIs or chemotherapy in individuals with solid tumors, including NSCLC and RCC, the dual ADORA2A and ADORA2B blocker etrumadenant⁴¹¹ is being assessed combined with immunotherapy, chemotherapy, and/or radiotherapy in subjects with solid tumors including NSCLC, prostate cancer, and CRC (source www.clinicaltrials.gov).

Considerable attention also remains around the possibility to boost immunostimulatory cytokine signaling via DDR inhibitors and pattern recognition receptor (PRR) agonists, notably STING agonists.⁴¹² In line with this notion, a number of ATR inhibitors including (but not limited to) ceralasertib,⁴¹³ berzofertib,⁴¹⁴ and camosertib,⁴¹⁵ as well as the WEE1 G2 checkpoint kinase (WEE1) inhibitor adavosertib⁴¹⁶ are currently being investigated as monotherapies or combined with ICIs across various oncological indications. Similar considerations apply to inhibitors of ATR and ATM signal transducers, such as the checkpoint

Table 1. Advanced clinical trials investigating conceptually novel approaches to target cancer immune evasion in patients with cancer

Target ^a	Drug	Indication	Phase	Status	Notes	Reference
ATR	Ceralasertib	Non-small cell lung carcinoma	III	Active, not recruiting	In combination with durvalumab	NCT05450692
CD36	VT1021	Glioblastoma	II/III	Recruiting	In combination with standard-of-care chemoradiation	NCT03970447
CD47	Evorpacept	Gastric carcinoma	II/III	Recruiting	In combination with multimodal chemoimmunotherapy	NCT05002127
	Lemzoparlimab	Myelodysplastic syndrome	III	Recruiting	In combination with azacytidine	NCT05709093
CD73	Oleclumab	Non-small cell lung carcinoma	III	Recruiting	In combination with durvalumab	NCT05221840
FASN	TVB-2640	Glioblastoma	III	Recruiting	In combination with bevacizumab	NCT05118776
TGFB1 (PD-L1)	Bintrafusp alfa	Non-small cell lung carcinoma	III	Active, not recruiting	As standalone therapeutic agent	NCT05061823

^aSource: www.clinicaltrials.gov, current as of June 24th, 2024. Restricted to Phase II/III or higher studies with status “Active, not recruiting”, “Not yet recruiting” and “Recruiting”, and investigating pharmacological agents with no FDA-approved target.

kinase 1 (CHEK1) blocker BBI-355 as well as the CHEK2-targeting agent PHI-101.⁴¹⁷ Moreover, the pharmacological STING activators IMSA101⁴¹⁸ and TAK-676⁴¹⁹ are being tested in combination with personalized ultrafractionated stereotactic adaptive radiation therapy (PULSAR) plus ICIs or pembrolizumab, respectively, in patients with advanced solid tumors (source www.clinicaltrials.gov). That said, STING agonists have previously been shown to exert robust antiproliferative and cytotoxic effects on CD8⁺ CTLs,^{420,421} potentially limiting the therapeutic effects of this approach.

In summary, while some pharmacological inhibitors of metabolic coercion and suppressed cytokine signaling remain under clinical investigation, targeting metabolic and immunomodulatory pathways with systemic interventions has considerable limitations linked to specificity that have not yet been circumvented.^{393,422}

Simultaneously targeting multiple “Cs”

A number of novel pharmacological regimens under clinical evaluation simultaneously (at least hypothetically) inhibit different mechanisms of immuno-evasion, potentially offering clinical advantages in the context of highly heterogeneous tumors that may harness multiple pathways to evade anticancer immunity in different intratumoral areas.¹¹ As mentioned previously, a number of clinically employed anticancer agents inhibit immune evasion, including a number of drugs like FDA-approved epigenetic modifiers that simultaneously target camouflage and coercion, like azacytidine, decitabine, and multiple HDAC inhibitors.⁴²³ In this context, novel approaches involve PRMT5 inhibitors, which are being investigated mostly as standalone therapeutic agents in early-phase clinical studies enrolling patients with solid tumors deficient for methylthioadenosine phosphorylase (MTAP) or non-Hodgkin’s lymphoma, as well as the KDM1A inhibitors bomedemstat and seclidemstat, which are being tested in combination with ICIs in subjects with lung cancer, or with azacytidine in patients with MDS and chronic myelomonocytic leukemia (source www.clinicaltrials.gov). That said, most (if not all) immune cells also rely on epigenetic mechanisms for their survival, proliferation, and effector functions,⁴²³ implying that pharmacological epigenetic modifiers may have unwanted immunosuppressive effects unless precise targeting strategies are developed.

Additional strategies targeting conceptually distinct mechanisms of immune evasion (notably camouflage and coercion, see aforementioned) include (1) VT1021 (a dual CD36 and CD47 inhibitor, hence targeting both camouflage and coercion)⁴²⁴ which is being assessed in patients along with SOC temozolamide-based chemoradiation in subjects with GBM; (2) the CD73 antagonists quemliclustat and oleclumab, which are being tested along with ICIs and (at least in some settings) other (immuno)therapeutic agents in patients with a variety of solid tumors; (3) the dual BCL2 and BCL2-like 1 (BCL2L1, best known as BCL-X_L) inhibitors (and hence MOMP inducers) navitoclax and pelcitoclax and R-(–)-gossypol acetic acid (AT-101),⁴²⁵ which are being investigated as combinatorial partners for SOC chemotherapy and/or immunotherapy most often in patients hematological malignancies; as well as (4) the transforming growth factor β receptor 1 (TGFBR1) inhibitor vactosertib⁴²⁶ which is being tested along with ICIs in patients with NSCLC, CRC, or gastric cancer, an autologous cancer vaccine encompassing genetic engineering for TGFB1 and TGFB2 inhibition (gemogenovatucel-T) which is being investigated as adjuvant therapy for women with ovarian carcinoma, and the dual TGFB1 and PD-L1 blocker bintrafusp alfa⁴²⁷ which is being evaluated alone or in combination with additional drugs in patients with solid tumors including NSCLC patients (source www.clinicaltrials.gov). Previously reported clinical studies have shown that blocking TGFB1 is safe and mediates at least some efficacy when combined with SOC therapeutic strategies.²⁵³ Whether this strategy will soon receive regulatory approval for use in humans, however, remains unclear.

Despite this and other unknowns, simultaneously targeting camouflage and coercion stands out as a promising approach to avert immuno-evasion in a variety of tumors as it potentially addresses elevated degree of intratumoral heterogeneity that may be associated with the acquisition of different immuno-evasive properties by malignant cells in different tumor areas.

CONCLUDING REMARKS

Here, we propose a novel conceptual framework to classify cancer immuno-evasion by suggesting that most mechanisms through which malignant cells escape immune recognition and

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elimination involve either of “three Cs”: camouflage, coercion, or cytoprotection. Such a framework is obviously not devoid of limitations. For instance, some malignant cells exhibit genetic or epigenetic defects that simultaneously engage more than one “C”. As a standalone example, EZH2 has been shown to promote both camouflage and coercion, downstream of the epigenetic silencing of MHC class I molecules, STING, and pro-inflammatory cytokines.^{30,68,166} Along similar lines, some pathways of immunoevasion are difficult to precisely classify as a single “C” or may be framed as different “Cs” in a context-dependent manner. For instance, whereas accrued ATP degradation may *a priori* underlie both camouflage and coercion,⁵⁹ the latter would be the predominant mechanism of immunoevasion in tumors that exhibit robust infiltration by immune effector cells at baseline. Some malignant cells have also been shown to utilize mechanisms of immunoevasion that are difficult to frame within the “three Cs” paradigm. For instance, HCC-infiltrating NK cells appear to exhibit surface defects due to altered sphingomyelin (SM) content that prevent them from recognizing and lysing tumor cells,⁴²⁸ but (1) the precise molecular mechanisms causing such alterations remain to be determined, and (2) whether this is a form of coercion or cytoprotection is unclear. Along similar lines, disseminated dormant cancer cells appear to be so rare that their likelihood to interact with the host immune system in support of active immunosurveillance is extraordinarily low,⁴²⁹ a mechanism of immune evasion that is difficult to reconcile to conventional camouflage, coercion, or cytoprotection. Finally, the loss of the Y chromosome (LOY)—which is frequent across tumor types—has been linked to an increased propensity of host CD8⁺ CTLs for exhaustion, resulting in immunoevasion and accelerated disease progression by a hitherto poorly defined mechanism.⁴³⁰

At least hypothetically, malignant cells evading anticancer immunity through a specific “C” (e.g., camouflage) may not need to acquire additional immuno-evasive mechanisms (e.g., coercion or cytoprotection), as *de facto* no longer exposed to a selective immune pressure. While some clinical data in support of this possibility exists,^{25,431–434} (1) passenger alterations potentially generating extra immuno-evasive phenotypes, as far as non-detrimental for cancer cells, remain possible; and (2) most importantly, as most neoplasms exhibit considerable degree of intratumoral heterogeneity (both across distinct lesions in the same patient, and within a single lesion), it is likely that malignant cells populating different tumor areas may evade immunity by different mechanisms.¹¹ This implies that, at least in some cases, simultaneously inhibiting distinct mechanisms of immuno evasion may have superior therapeutic effects as compared to targeting only one “C”. That said, whether a specific “C” would be hierarchically superior to others (and hence represent a preferential target for therapy) not only remains to be experimentally demonstrated but also may exhibit a considerable degree of context dependency and hence vary in different oncological settings.

Importantly, at least some manifestations of the “three Cs” have been successfully employed to guide clinical decision making in a variety of oncological indications.⁴³⁵ For instance, an elevated tumor mutational burden (TMB) as assessed on diagnostic biopsies by FDA-approved detection kits are currently being employed to allocate patients with cancer to pembrolizumab irrespective of disease histology.²⁰ Along similar lines, PD-L1

expression levels on malignant and/or immune cells are routinely employed to direct the use of PD-1 or PD-L1 blockers in numerous oncological settings.⁴³⁶ That said, a fraction of PD-L1-positive tumors fails to respond to ICI as standalone therapeutics,⁴³⁶ which (1) potentially points to the existence of PD-L1-independent mechanisms of immuno-evasion, and (2) calls for the identification of complementary (if not alternative) predictive biomarkers of response. In this setting, an expanding clinical literature suggests that assessing the proficiency of IFNG signaling in malignant cells may convey additional predictive information as compared to the quantification of PD-L1 expression alone.^{314,370,437,438} Whether diagnostic tests assessing IFNG signaling in malignant cells as a predictor of ICI sensitivity will soon enter the clinical routine, however, is unclear.

Despite these and other unknowns, we believe that the “three Cs” framework proposed herein may facilitate the understanding of a complex phenomenon such as immune evasion, and potentially guide the discovery of novel, clinically relevant strategies to circumvent it.

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AUTHOR CONTRIBUTIONS

T.A.C. conceived the article. C.G., I.V., and L.G. wrote the first version of the manuscript with critical input from T.A.C. C.G. designed display items under supervision from L.G. All authors approve the submitted version of the article.

DECLARATION OF INTERESTS

T.A.C. is a co-founder of Gritstone Oncology and holds equity in Gritstone Oncology and An2H, is/has been holding research contracts with Bristol-Myers Squibb, AstraZeneca, Illumina, Pfizer, An2H, and Eisai, has served as an advisor for Bristol-Myers, MedImmune, Squibb, Illumina, Eisai, AstraZeneca, and An2H, and is an inventor on intellectual property and a patent held by MSKCC on using tumor mutation burden to predict immunotherapy response, which has been licensed to PGDx. L.G. is/has been holding research contracts with Lytix Biopharma, Promontory, and Onxeo, has received consulting/advisory honoraria from Boehringer Ingelheim, AstraZeneca, AbbVie, OmniSEQ, Onxeo, The Longevity Labs, Inzen, Imvax,

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REFERENCES

- Kroemer, G., Chan, T.A., Eggermont, A.M.M., and Galluzzi, L. (2024). Immunosurveillance in clinical cancer management. *CA: Cancer J. Clin.* 74, 187–202. <https://doi.org/10.3322/caac.21818>.
- Dunn, G.P., Bruce, A.T., Ikeda, H., Old, L.J., and Schreiber, R.D. (2002). Cancer immunoediting: from immunosurveillance to tumor escape. *Nat. Immunol.* 3, 991–998. <https://doi.org/10.1038/ni1102-991>.
- Wolf, N.K., Kissiov, D.U., and Raulet, D.H. (2023). Roles of natural killer cells in immunity to cancer, and applications to immunotherapy. *Nat. Rev. Immunol.* 23, 90–105. <https://doi.org/10.1038/s41577-022-00732-1>.
- Huntington, N.D., Cursons, J., and Rautela, J. (2020). The cancer-natural killer cell immunity cycle. *Nat. Rev. Cancer* 20, 437–454. <https://doi.org/10.1038/s41568-020-0272-z>.
- Koebel, C.M., Vermi, W., Swann, J.B., Zerafa, N., Rodig, S.J., Old, L.J., Smyth, M.J., and Schreiber, R.D. (2007). Adaptive immunity maintains occult cancer in an equilibrium state. *Nature* 450, 903–907. <https://doi.org/10.1038/nature06309>.
- Shankaran, V., Ikeda, H., Bruce, A.T., White, J.M., Swanson, P.E., Old, L.J., and Schreiber, R.D. (2001). IFNgamma and lymphocytes prevent primary tumour development and shape tumour immunogenicity. *Nature* 410, 1107–1111. <https://doi.org/10.1038/35074122>.
- Dunn, G.P., Bruce, A.T., Sheehan, K.C.F., Shankaran, V., Uppaluri, R., Bui, J.D., Diamond, M.S., Koebel, C.M., Arthur, C., White, J.M., and Schreiber, R.D. (2005). A critical function for type I interferons in cancer immunoediting. *Nat. Immunol.* 6, 722–729. <https://doi.org/10.1038/ni1213>.
- O'Sullivan, T., Saddawi-Konefka, R., Vermi, W., Koebel, C.M., Arthur, C., White, J.M., Uppaluri, R., Andrews, D.M., Ngiow, S.F., Teng, M.W.L., et al. (2012). Cancer immunoediting by the innate immune system in the absence of adaptive immunity. *J. Exp. Med.* 209, 1869–1882. <https://doi.org/10.1084/jem.20112738>.
- Hausser, J., and Alon, U. (2020). Tumour heterogeneity and the evolutionary trade-offs of cancer. *Nat. Rev. Cancer* 20, 247–257. <https://doi.org/10.1038/s41568-020-0241-6>.
- Spranger, S., and Gajewski, T.F. (2018). Impact of oncogenic pathways on evasion of antitumour immune responses. *Nat. Rev. Cancer* 18, 139–147. <https://doi.org/10.1038/nrc.2017.117>.
- Vitale, I., Shema, E., Loi, S., and Galluzzi, L. (2021). Intratumoral heterogeneity in cancer progression and response to immunotherapy. *Nat. Med.* 27, 212–224. <https://doi.org/10.1038/s41591-021-01233-9>.
- Galluzzi, L., Humeau, J., Buqué, A., Zitvogel, L., and Kroemer, G. (2020). Immunostimulation with chemotherapy in the era of immune checkpoint inhibitors. *Nat. Rev. Clin. Oncol.* 17, 725–741. <https://doi.org/10.1038/s41571-020-0413-z>.
- Petroni, G., Buqué, A., Zitvogel, L., Kroemer, G., and Galluzzi, L. (2021). Immunomodulation by targeted anticancer agents. *Cancer Cell* 39, 310–345. <https://doi.org/10.1016/j.ccr.2020.11.009>.
- Galluzzi, L., Aryankalayil, M.J., Coleman, C.N., and Formenti, S.C. (2023). Emerging evidence for adapting radiotherapy to immunotherapy. *Nat. Rev. Clin. Oncol.* 20, 543–557. <https://doi.org/10.1038/s41571-023-00782-x>.
- Tauriello, D.V.F., Sancho, E., and Batlle, E. (2022). Overcoming TGFβ-mediated immune evasion in cancer. *Nat. Rev. Cancer* 22, 25–44. <https://doi.org/10.1038/s41568-021-00413-6>.
- Dersh, D., Hollý, J., and Yewdell, J.W. (2021). A few good peptides: MHC class I-based cancer immunosurveillance and immuno-evasion. *Nat. Rev. Immunol.* 21, 116–128. <https://doi.org/10.1038/s41577-020-0390-6>.
- Offringa, R., Kötzner, L., Huck, B., and Urbahns, K. (2022). The expanding role for small molecules in immuno-oncology. *Nat. Rev. Drug Discov.* 21, 821–840. <https://doi.org/10.1038/s41573-022-00538-9>.
- Yang, K., Halima, A., and Chan, T.A. (2023). Antigen presentation in cancer - mechanisms and clinical implications for immunotherapy. *Nat. Rev. Clin. Oncol.* 20, 604–623. <https://doi.org/10.1038/s41571-023-00789-4>.
- Stern, L.J., Clement, C., Galluzzi, L., and Santambrogio, L. (2024). Non-mutational neoantigens in disease. *Nat. Immunol.* 25, 29–40. <https://doi.org/10.1038/s41590-023-01664-1>.
- Anagnostou, V., Bardelli, A., Chan, T.A., and Turajlic, S. (2022). The status of tumor mutational burden and immunotherapy. *Nat. Cancer* 3, 652–656. <https://doi.org/10.1038/s43018-022-00382-1>.
- Chan, T.A., Yarchoan, M., Jaffee, E., Swanton, C., Quezada, S.A., Stenzinger, A., and Peters, S. (2019). Development of tumor mutation burden as an immunotherapy biomarker: utility for the oncology clinic. *Ann. Oncol.* 30, 44–56. <https://doi.org/10.1093/annonc/mdy495>.
- Rizvi, N.A., Hellmann, M.D., Snyder, A., Kvistborg, P., Makarov, V., Havel, J.J., Lee, W., Yuan, J., Wong, P., Ho, T.S., et al. (2015). Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science* 348, 124–128. <https://doi.org/10.1126/science.aaa1348>.
- Samstein, R.M., Lee, C.H., Shoushtari, A.N., Hellmann, M.D., Shen, R., Janjigian, Y.Y., Barron, D.A., Zehir, A., Jordan, E.J., Omuro, A., et al. (2019). Tumor mutational load predicts survival after immunotherapy across multiple cancer types. *Nat. Genet.* 51, 202–206. <https://doi.org/10.1038/s41588-018-0312-8>.
- Rooney, M.S., Shukla, S.A., Wu, C.J., Getz, G., and Hacohen, N. (2015). Molecular and genetic properties of tumors associated with local immune cytolytic activity. *Cell* 160, 48–61. <https://doi.org/10.1016/j.cell.2014.12.033>.
- Rosenthal, R., Cadieux, E.L., Salgado, R., Bakir, M.A., Moore, D.A., Hiley, C.T., Lund, T., Tanić, M., Reading, J.L., Joshi, K., et al. (2019). Neoantigen-directed immune escape in lung cancer evolution. *Nature* 567, 479–485. <https://doi.org/10.1038/s41586-019-1032-7>.
- McGranahan, N., Rosenthal, R., Hiley, C.T., Rowan, A.J., Watkins, T.B.K., Wilson, G.A., Birkbak, N.J., Veeriah, S., Van Loo, P., Herrero, J., et al. (2017). Allele-Specific HLA Loss and Immune Escape in Lung Cancer Evolution. *Cell* 171, 1259–1271.e11. <https://doi.org/10.1016/j.cell.2017.10.001>.
- Vázquez-García, I., Uhlietz, F., Ceglia, N., Lim, J.L.P., Wu, M., Mohibullah, N., Niyazov, J., Ruiz, A.E.B., Boehm, K.M., Bojilova, V., et al. (2022). Ovarian cancer mutational processes drive site-specific immune evasion. *Nature* 612, 778–786. <https://doi.org/10.1038/s41586-022-05496-1>.
- Ritter, C., Fan, K., Paschen, A., Reker Hardrup, S., Ferrone, S., Nghiem, P., Ugurel, S., Schrama, D., and Becker, J.C. (2017). Epigenetic priming restores the HLA class-I antigen processing machinery expression in Merkel cell carcinoma. *Sci. Rep.* 7, 2290. <https://doi.org/10.1038/s41598-017-02608-0>.
- Gambacorta, V., Beretta, S., Ciccarella, M., Zito, L., Giannetti, K., Andriani, A., Gnani, D., Zanotti, L., Oliveira, G., Carrabba, M.G., et al. (2022). Integrated Multiomic Profiling Identifies the Epigenetic Regulator PRC2 as a Therapeutic Target to Counteract Leukemia Immune Escape and Relapse. *Cancer Discov.* 12, 1449–1461. <https://doi.org/10.1158/2159-8290.CD-21-0980>.
- Ennishi, D., Takata, K., Béguelin, W., Duns, G., Mottok, A., Farinha, P., Bashashati, A., Saberi, S., Boyle, M., Meissner, B., et al. (2019). Molecular and Genetic Characterization of MHC Deficiency Identifies EZH2 as Therapeutic Target for Enhancing Immune Recognition. *Cancer Discov.* 9, 546–563. <https://doi.org/10.1158/2159-8290.CD-18-1090>.
- Burr, M.L., Sparbier, C.E., Chan, K.L., Chan, Y.C., Kersbergen, A., Lam, E.Y.N., Azidis-Yates, E., Vassiliadis, D., Bell, C.C., Gilan, O., et al. (2019). An Evolutionarily Conserved Function of Polycomb Silences the MHC Class I Antigen Presentation Pathway and Enables Immune Evasion in Cancer. *Cancer Cell* 36, 385–401.e8. <https://doi.org/10.1016/j.ccr.2019.08.008>.
- Mangalhara, K.C., Varanasi, S.K., Johnson, M.A., Burns, M.J., Rojas, G.R., Esparza Molto, P.B., Sainz, A.G., Tadepalie, N., Abbott, K.L., Mendiratta, G., et al. (2023). Manipulating mitochondrial electron flow enhances tumor immunogenicity. *Science* 381, 1316–1323. <https://doi.org/10.1126/science.abq1053>.

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33. Zingg, D., Arenas-Ramirez, N., Sahin, D., Rosalia, R.A., Antunes, A.T., Haesel, J., Sommer, L., and Boyman, O. (2017). The Histone Methyltransferase Ezh2 Controls Mechanisms of Adaptive Resistance to Tumor Immunotherapy. *Cell Rep.* 20, 854–867. <https://doi.org/10.1016/j.celrep.2017.07.007>.
34. Zhang, S.M., Cai, W.L., Liu, X., Thakral, D., Luo, J., Chan, L.H., McGahey, M.K., Song, E., Blenman, K.R.M., Micevic, G., et al. (2021). KDM5B promotes immune evasion by recruiting SETDB1 to silence retroelements. *Nature* 598, 682–687. <https://doi.org/10.1038/s41586-021-03994-2>.
35. Jung, H., Kim, H.S., Kim, J.Y., Sun, J.M., Ahn, J.S., Ahn, M.J., Park, K., Esteller, M., Lee, S.H., and Choi, J.K. (2019). DNA methylation loss promotes immune evasion of tumours with high mutation and copy number load. *Nat. Commun.* 10, 4278. <https://doi.org/10.1038/s41467-019-12159-9>.
36. Santasusagna, S., Zhu, S., Jawalagatti, V., Carceles-Cordon, M., Ertel, A., Garcia-Longarte, S., Song, W.M., Fujiwara, N., Li, P., Mendizabal, I., et al. (2023). Master Transcription Factor Reprogramming Unleashes Selective Translation Promoting Castration Resistance and Immune Evasion in Lethal Prostate Cancer. *Cancer Discov.* 13, 2584–2609. <https://doi.org/10.1158/2159-8290.CD-23-0306>.
37. Chew, G.L., Campbell, A.E., De Neef, E., Sutliff, N.A., Shadie, S.C., Tapscott, S.J., and Bradley, R.K. (2019). DUX4 Suppresses MHC Class I to Promote Cancer Immune Evasion and Resistance to Checkpoint Blockade. *Dev. Cell* 50, 658–671.e7. <https://doi.org/10.1016/j.devcel.2019.06.011>.
38. Bayik, D., and Lathia, J.D. (2021). Cancer stem cell-immune cell crosstalk in tumour progression. *Nat. Rev. Cancer* 21, 526–536. <https://doi.org/10.1038/s41568-021-00366-w>.
39. Agudo, J., Park, E.S., Rose, S.A., Alibo, E., Sweeney, R., Dhainaut, M., Kobayashi, K.S., Sachidanandam, R., Baccarini, A., Merad, M., and Brown, B.D. (2018). Quiescent Tissue Stem Cells Evade Immune Surveillance. *Immunity* 48, 271–285.e5. <https://doi.org/10.1016/j.immuni.2018.02.001>.
40. Lv, J., Zhou, Y., Zhou, N., Wang, Z., Chen, J., Chen, H., Wang, D., Zhou, L., Wei, K., Zhang, H., et al. (2023). Epigenetic modification of CSDE1 locus dictates immune recognition of nascent tumorigenic cells. *Sci. Transl. Med.* 15, eabq6024. <https://doi.org/10.1126/scitranslmed.abq6024>.
41. Rybstein, M.D., Bravo-San Pedro, J.M., Kroemer, G., and Galluzzi, L. (2018). The autophagic network and cancer. *Nat. Cell Biol.* 20, 243–251. <https://doi.org/10.1038/s41556-018-0042-2>.
42. Sang, W., Zhou, Y., Chen, H., Yu, C., Dai, L., Liu, Z., Chen, L., Fang, Y., Ma, P., Wu, X., et al. (2024). Receptor-interacting Protein Kinase 2 Is an Immunotherapy Target in Pancreatic Cancer. *Cancer Discov.* 14, 326–347. <https://doi.org/10.1158/2159-8290.CD-23-0584>.
43. Yamamoto, K., Venida, A., Yano, J., Biancur, D.E., Kakiuchi, M., Gupta, S., Sohn, A.S.W., Mukhopadhyay, S., Lin, E.Y., Parker, S.J., et al. (2020). Autophagy promotes immune evasion of pancreatic cancer by degrading MHC-I. *Nature* 581, 100–105. <https://doi.org/10.1038/s41586-020-2229-5>.
44. Liu, X., Bao, X., Hu, M., Chang, H., Jiao, M., Cheng, J., Xie, L., Huang, Q., Li, F., and Li, C.Y. (2020). Inhibition of PCSK9 potentiates immune checkpoint therapy for cancer. *Nature* 588, 693–698. <https://doi.org/10.1038/s41586-020-2911-7>.
45. Chen, X., Lu, Q., Zhou, H., Liu, J., Nadorp, B., Lasry, A., Sun, Z., Lai, B., Rona, G., Zhang, J., et al. (2023). A membrane-associated MHC-I inhibitory axis for cancer immune evasion. *Cell* 186, 3903–3920.e21. <https://doi.org/10.1016/j.cell.2023.07.016>.
46. Paulson, K.G., Voillet, V., McAfee, M.S., Hunter, D.S., Wagener, F.D., Perdicchio, M., Valente, W.J., Koelle, S.J., Church, C.D., Vandeven, N., et al. (2018). Acquired cancer resistance to combination immunotherapy from transcriptional loss of class I HLA. *Nat. Commun.* 9, 3868. <https://doi.org/10.1038/s41467-018-06300-3>.
47. Pozniak, J., Pedri, D., Landeloos, E., Van Herck, Y., Antoranz, A., Vanwynsberghe, L., Nowosad, A., Roda, N., Makhzami, S., Bervoets, G., et al. (2024). A TCF4-dependent gene regulatory network confers resistance to immunotherapy in melanoma. *Cell* 187, 166–183.e25. <https://doi.org/10.1016/j.cell.2023.11.037>.
48. Ruella, M., Korell, F., Porazzi, P., and Maus, M.V. (2023). Mechanisms of resistance to chimeric antigen receptor-T cells in haematological malignancies. *Nat. Rev. Drug Discov.* 22, 976–995. <https://doi.org/10.1038/s41573-023-00807-1>.
49. Verdegaard, E.M.E., de Miranda, N.F.C.C., Visser, M., Harryvan, T., van Buuren, M.M., Andersen, R.S., Hadrup, S.R., van der Minne, C.E., Schotte, R., Spits, H., et al. (2016). Neoantigen landscape dynamics during human melanoma-T cell interactions. *Nature* 536, 91–95. <https://doi.org/10.1038/nature18945>.
50. Riaz, N., Havel, J.J., Makarov, V., Desrichard, A., Urba, W.J., Sims, J.S., Hodin, F.S., Martín-Algarra, S., Mandal, R., Sharfman, W.H., et al. (2017). Tumor and Microenvironment Evolution during Immunotherapy with Nivolumab. *Cell* 171, 934–949.e16. <https://doi.org/10.1016/j.cell.2017.09.028>.
51. Wylie, B., Chee, J., Forbes, C.A., Booth, M., Stone, S.R., Buzzai, A., Abad, A., Foley, B., Cruickshank, M.N., and Waithman, J. (2019). Acquired resistance during adoptive cell therapy by transcriptional silencing of immunogenic antigens. *Oncolimmunology* 8, 1609874. <https://doi.org/10.1080/2162402X.2019.1609874>.
52. Jhunjhunwala, S., Hammer, C., and Delamarre, L. (2021). Antigen presentation in cancer: insights into tumour immunogenicity and immune evasion. *Nat. Rev. Cancer* 21, 298–312. <https://doi.org/10.1038/s41568-021-00339-z>.
53. Chiassone, L., Dumas, P.Y., Vienne, M., and Vivier, E. (2018). Natural killer cells and other innate lymphoid cells in cancer. *Nat. Rev. Immunol.* 18, 671–688. <https://doi.org/10.1038/s41577-018-0061-z>.
54. Galluzzi, L., Guilbaud, E., Schmidt, D., Kroemer, G., and Marincola, F.M. (2024). Targeting immunogenic cell stress and death for cancer therapy. *Nat. Rev. Drug Discov.* 23, 445–460. <https://doi.org/10.1038/s41573-024-00920-9>.
55. Kroemer, G., Mariño, G., and Levine, B. (2010). Autophagy and the integrated stress response. *Mol. Cell* 40, 280–293. <https://doi.org/10.1016/j.molcel.2010.09.023>.
56. Elliott, M.R., Chekeni, F.B., Trampont, P.C., Lazarowski, E.R., Kadl, A., Walk, S.F., Park, D., Woodson, R.I., Ostankovich, M., Sharma, P., et al. (2009). Nucleotides released by apoptotic cells act as a find-me signal to promote phagocytic clearance. *Nature* 461, 282–286. <https://doi.org/10.1038/nature08296>.
57. Chekeni, F.B., Elliott, M.R., Sandilos, J.K., Walk, S.F., Kinchen, J.M., Lazarowski, E.R., Armstrong, A.J., Penuela, S., Laird, D.W., Salvesen, G.S., et al. (2010). PanneXin 1 channels mediate ‘find-me’ signal release and membrane permeability during apoptosis. *Nature* 467, 863–867. <https://doi.org/10.1038/nature09413>.
58. Vacchelli, E., Ma, Y., Baracco, E.E., Sistigu, A., Enot, D.P., Pietrocola, F., Yang, H., Adjeman, S., Chaba, K., Semeraro, M., et al. (2015). Chemotherapy-induced antitumor immunity requires formyl peptide receptor 1. *Science* 350, 972–978. <https://doi.org/10.1126/science.aad0779>.
59. Kepp, O., Bezu, L., Yamazaki, T., Di Virgilio, F., Smyth, M.J., Kroemer, G., and Galluzzi, L. (2021). ATP and cancer immuno-surveillance. *EMBO J.* 40, e108130. <https://doi.org/10.1525/embj.2021108130>.
60. Ma, Y., Adjeman, S., Mattarollo, S.R., Yamazaki, T., Aymeric, L., Yang, H., Portela Catani, J.P., Hannani, D., Duret, H., Steegh, K., et al. (2013). Anticancer chemotherapy-induced intratumoral recruitment and differentiation of antigen-presenting cells. *Immunity* 38, 729–741. <https://doi.org/10.1016/j.jimuni.2013.03.003>.
61. Michaud, M., Martins, I., Sukkurwala, A.Q., Adjeman, S., Ma, Y., Pellegratti, P., Shen, S., Kepp, O., Scoazec, M., Mignot, G., et al. (2011). Autophagy-dependent anticancer immune responses induced by chemotherapeutic agents in mice. *Science* 334, 1573–1577. <https://doi.org/10.1126/science.1208347>.
62. Pietrocola, F., Pol, J., Vacchelli, E., Rao, S., Enot, D.P., Baracco, E.E., Levesque, S., Castoldi, F., Jacquemet, N., Yamazaki, T., et al. (2016). Caloric Restriction Mimetics Enhance Anticancer Immuno-surveillance. *Cancer Cell* 30, 147–160. <https://doi.org/10.1016/j.ccr.2016.05.016>.
63. Wu, Q., Tian, A.L., Li, B., Leduc, M., Forveille, S., Hamley, P., Galloway, W., Xie, W., Liu, P., Zhao, L., et al. (2021). IGF1 receptor inhibition amplifies the effects of cancer drugs by autophagy and immune-dependent

- mechanisms. *J. Immunother. Cancer* 9, e002722. <https://doi.org/10.1136/jtc-2021-002722>.
64. Ladoire, S., Enot, D., Senovilla, L., Ghiringhelli, F., Poirier-Colame, V., Chaba, K., Semeraro, M., Chaix, M., Penault-Llorca, F., Arnould, L., et al. (2016). The presence of LC3B puncta and HMGB1 expression in malignant cells correlate with the immune infiltrate in breast cancer. *Autophagy* 12, 864–875. <https://doi.org/10.1080/15548627.2016.1154244>.
65. Le Naour, J., Liu, P., Zhao, L., Adjemian, S., Sztypinszki, Z., Taieb, J., Mullet, C., Silvin, A., Dutertre, C.A., Ginhoux, F., et al. (2021). A TLR3 Ligand Reestablishes Chemotherapeutic Responses in the Context of FPR1 Deficiency. *Cancer Discov.* 11, 408–423. <https://doi.org/10.1158/2159-8290.Cd-20-0465>.
66. Baracco, E.E., Stoll, G., Van Endert, P., Zitvogel, L., Vacchelli, E., and Kroemer, G. (2019). Contribution of annexin A1 to anticancer immuno-surveillance. *Oncolimmunology* 8, e1647760. <https://doi.org/10.1080/2162402x.2019.1647760>.
67. Sistigu, A., Yamazaki, T., Vacchelli, E., Chaba, K., Enot, D.P., Adam, J., Vitale, I., Goubar, A., Baracco, E.E., Remédios, C., et al. (2014). Cancer cell-autonomous contribution of type I interferon signaling to the efficacy of chemotherapy. *Nat. Med.* 20, 1301–1309. <https://doi.org/10.1038/nm.3708>.
68. Peng, D., Kryczek, I., Nagarsheth, N., Zhao, L., Wei, S., Wang, W., Sun, Y., Zhao, E., Vatan, L., Szeliga, W., et al. (2015). Epigenetic silencing of TH1-type chemokines shapes tumour immunity and immunotherapy. *Nature* 527, 249–253. <https://doi.org/10.1038/nature15520>.
69. Cascone, T., McKenzie, J.A., Mbafung, R.M., Punt, S., Wang, Z., Xu, C., Williams, L.J., Wang, Z., Bristow, C.A., Carugo, A., et al. (2018). Increased Tumor Glycolysis Characterizes Immune Resistance to Adoptive T Cell Therapy. *Cell Metab.* 27, 977–987.e4. <https://doi.org/10.1016/j.cmet.2018.02.024>.
70. Ma, Y., Mattarollo, S.R., Adjemian, S., Yang, H., Aymeric, L., Hannani, D., Portela Catani, J.P., Duret, H., Teng, M.W.L., Kepp, O., et al. (2014). CCL2/CCR2-dependent recruitment of functional antigen-presenting cells into tumors upon chemotherapy. *Cancer Res.* 74, 436–445. <https://doi.org/10.1158/0008-5472.CAN-13-1265>.
71. Rubio-Patiño, C., Bossowski, J.P., De Donatis, G.M., Mondragón, L., Villa, E., Aira, L.E., Chiche, J., Mhaidly, R., Lebeaupin, C., Marchetti, S., et al. (2018). Low-Protein Diet Induces IRE1 α -Dependent Anticancer Immunosurveillance. *Cell Metab.* 27, 828–842.e7. <https://doi.org/10.1016/j.cmet.2018.02.009>.
72. Wang, G., Xu, J., Zhao, J., Yin, W., Liu, D., Chen, W., and Hou, S.X. (2020). Arf1-mediated lipid metabolism sustains cancer cells and its ablation induces anti-tumor immune responses in mice. *Nat. Commun.* 11, 220. <https://doi.org/10.1038/s41467-019-14046-9>.
73. Fucikova, J., Moserova, I., Urbanova, L., Bezu, L., Kepp, O., Cremer, I., Salek, C., Strnad, P., Kroemer, G., Galluzzi, L., and Spisek, R. (2015). Prognostic and Predictive Value of DAMPs and DAMP-Associated Processes in Cancer. *Front. Immunol.* 6, 402. <https://doi.org/10.3389/fimmu.2015.00402>.
74. Fucikova, J., Spisek, R., Kroemer, G., and Galluzzi, L. (2021). Calreticulin and cancer. *Cell Res.* 31, 5–16. <https://doi.org/10.1038/s41422-020-0383-9>.
75. Lei, X., Lin, H., Wang, J., Ou, Z., Ruan, Y., Sadagopan, A., Chen, W., Xie, S., Chen, B., Li, Q., et al. (2022). Mitochondrial fission induces immunoevasion in solid tumors through decreasing MHC-I surface expression. *Nat. Commun.* 13, 3882. <https://doi.org/10.1038/s41467-022-31417-x>.
76. Faletti, S., Osti, D., Ceccacci, E., Richichi, C., Costanza, B., Nicosia, L., Noberini, R., Marotta, G., Furia, L., Fareta, M.R., et al. (2021). LSD1-directed therapy affects glioblastoma tumorigenicity by deregulating the protective ATF4-dependent integrated stress response. *Sci. Transl. Med.* 13, eabf7036. <https://doi.org/10.1126/scitranslmed.abf7036>.
77. Kalkavan, H., Chen, M.J., Crawford, J.C., Quarato, G., Fitzgerald, P., Tait, S.W.G., Goding, C.R., and Green, D.R. (2022). Sublethal cytochrome c release generates drug-tolerant persister cells. *Cell* 185, 3356–3374.e22. <https://doi.org/10.1016/j.cell.2022.07.025>.
78. Yang, W., Feng, Y., Zhou, J., Cheung, O.K.W., Cao, J., Wang, J., Tang, W., Tu, Y., Xu, L., Wu, F., et al. (2021). A selective HDAC8 inhibitor potentiates antitumor immunity and efficacy of immune checkpoint blockade in hepatocellular carcinoma. *Sci. Transl. Med.* 13, eaaz6804. <https://doi.org/10.1126/scitranslmed.aaz6804>.
79. Bruchard, M., Geindreau, M., Perrichet, A., Truntzer, C., Ballot, E., Boisot, R., Racoeur, C., Barsac, E., Chalmin, F., Hibos, C., et al. (2022). Recruitment and activation of type 3 innate lymphoid cells promote anti-tumor immune responses. *Nat. Immunol.* 23, 262–274. <https://doi.org/10.1038/s41590-021-01120-y>.
80. Fucikova, J., Truxova, I., Hensler, M., Becht, E., Kasikova, L., Moserova, I., Vosahlikova, S., Klouckova, J., Church, S.E., Cremer, I., et al. (2016). Calreticulin exposure by malignant blasts correlates with robust anti-cancer immunity and improved clinical outcome in AML patients. *Blood* 128, 3113–3124. <https://doi.org/10.1182/blood-2016-08-731737>.
81. Wemeau, M., Kepp, O., Tesnière, A., Panaretakis, T., Flament, C., De Botton, S., Zitvogel, L., Kroemer, G., and Chaput, N. (2010). Calreticulin exposure on malignant blasts predicts a cellular anticancer immune response in patients with acute myeloid leukemia. *Cell Death Dis.* 1, e104. <https://doi.org/10.1038/cddis.2010.82>.
82. Fucikova, J., Becht, E., Iribarren, K., Goc, J., Remark, R., Damotte, D., Alifano, M., Devi, P., Biton, J., Germain, C., et al. (2016). Calreticulin Expression in Human Non-Small Cell Lung Cancers Correlates with Increased Accumulation of Antitumor Immune Cells and Favorable Prognosis. *Cancer Res.* 76, 1746–1756. <https://doi.org/10.1158/0008-5472.Can-15-1142>.
83. Lin, H., Kryczek, I., Li, S., Green, M.D., Ali, A., Hamasha, R., Wei, S., Vatan, L., Szeliga, W., Grove, S., et al. (2021). Stanniocalcin 1 is a phagocytosis checkpoint driving tumor immune resistance. *Cancer Cell* 39, 480–493.e6. <https://doi.org/10.1016/j.ccr.2020.12.023>.
84. Song, X., Zhou, Z., Li, H., Xue, Y., Lu, X., Bahar, I., Kepp, O., Hung, M.C., Kroemer, G., and Wan, Y. (2020). Pharmacologic Suppression of B7-H4 Glycosylation Restores Antitumor Immunity in Immune-Cold Breast Cancers. *Cancer Discov.* 10, 1872–1893. <https://doi.org/10.1158/2159-8290.Cd-20-0402>.
85. Liu, P., Zhao, L., Loos, F., Marty, C., Xie, W., Martins, I., Lachkar, S., Qu, B., Waackel-Énée, E., Plo, I., et al. (2020). Immunosuppression by Mutated Calreticulin Released from Malignant Cells. *Mol. Cell* 77, 748–760.e9. <https://doi.org/10.1016/j.molcel.2019.11.004>.
86. Obeid, M., Tesnière, A., Ghiringhelli, F., Firmino, G.M., Apetoh, L., Perfettini, J.L., Castedo, M., Mignot, G., Panaretakis, T., Casares, N., et al. (2007). Calreticulin exposure dictates the immunogenicity of cancer cell death. *Nat. Med.* 13, 54–61. <https://doi.org/10.1038/nm1523>.
87. Tatsuno, K., Yamazaki, T., Hanlon, D., Han, P., Robinson, E., Sobolev, O., Yurter, A., Rivera-Molina, F., Arshad, N., Edelson, R.L., and Galluzzi, L. (2019). Extracorporeal photochemotherapy induces bona fide immunogenic cell death. *Cell Death Dis.* 10, 578. <https://doi.org/10.1038/s41419-019-1819-3>.
88. Panaretakis, T., Kepp, O., Brockmeier, U., Tesnière, A., Bjorklund, A.C., Chapman, D.C., Durchschlag, M., Joza, N., Pierron, G., van Endert, P., et al. (2009). Mechanisms of pre-apoptotic calreticulin exposure in immunogenic cell death. *EMBO J.* 28, 578–590. <https://doi.org/10.1038/emboj.2009.1>.
89. Garg, A.D., Krysko, D.V., Verfaillie, T., Kaczmarek, A., Ferreira, G.B., Maruya, T., Rubio, N., Firczuk, M., Mathieu, C., Roebroek, A.J.M., et al. (2012). A novel pathway combining calreticulin exposure and ATP secretion in immunogenic cancer cell death. *EMBO J.* 31, 1062–1079. <https://doi.org/10.1038/emboj.2011.497>.
90. Martins, I., Kepp, O., Schlemmer, F., Adjemian, S., Tailler, M., Shen, S., Michaud, M., Menger, L., Gdoura, A., Tajeddine, N., et al. (2011). Restoration of the immunogenicity of cisplatin-induced cancer cell death by endoplasmic reticulum stress. *Oncogene* 30, 1147–1158. <https://doi.org/10.1038/onc.2010.500>.
91. De Beck, L., Melhaoui, S., De Veirman, K., Menu, E., De Bruyne, E., Vanderkerken, K., Breckpot, K., and Maes, K. (2018). Epigenetic treatment of multiple myeloma mediates tumor intrinsic and extrinsic immunomodulatory effects. *Oncolimmunology* 7, e1484981. <https://doi.org/10.1080/2162402X.2018.1484981>.

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92. Sen Santara, S., Lee, D.J., Crespo, Á., Hu, J.J., Walker, C., Ma, X., Zhang, Y., Chowdhury, S., Meza-Sosa, K.F., Lewandrowski, M., et al. (2023). The NK cell receptor NKp46 recognizes ecto-calreticulin on ER-stressed cells. *Nature* 616, 348–356. <https://doi.org/10.1038/s41586-023-05912-0>.
93. Truxova, I., Kasikova, L., Salek, C., Hensler, M., Lysak, D., Holicek, P., Bilkova, P., Holubova, M., Chen, X., Mikyskova, R., et al. (2020). Calreticulin exposure on malignant blasts correlates with improved natural killer cell-mediated cytotoxicity in acute myeloid leukemia patients. *Haematologica* 105, 1868–1878. <https://doi.org/10.3324/haematol.2019.223933>.
94. Fadok, V.A., Bratton, D.L., Rose, D.M., Pearson, A., Ezekowitz, R.A., and Henson, P.M. (2000). A receptor for phosphatidylserine-specific clearance of apoptotic cells. *Nature* 405, 85–90. <https://doi.org/10.1038/35011084>.
95. Li, M.O., Sarkisian, M.R., Mehal, W.Z., Rakic, P., and Flavell, R.A. (2003). Phosphatidylserine receptor is required for clearance of apoptotic cells. *Science* 302, 1560–1563. <https://doi.org/10.1126/science.1087621>.
96. Segawa, K., Kurata, S., Yanagihashi, Y., Brummelkamp, T.R., Matsuda, F., and Nagata, S. (2014). Caspase-mediated cleavage of phospholipid flippase for apoptotic phosphatidylserine exposure. *Science* 344, 1164–1168. <https://doi.org/10.1126/science.1252809>.
97. Lauber, K., Bohn, E., Kröber, S.M., Xiao, Y.J., Blumenthal, S.G., Linde-mann, R.K., Marini, P., Wiedig, C., Zobaywalski, A., Baksh, S., et al. (2003). Apoptotic cells induce migration of phagocytes via caspase-3-mediated release of a lipid attraction signal. *Cell* 113, 717–730. [https://doi.org/10.1016/s0092-8674\(03\)00422-7](https://doi.org/10.1016/s0092-8674(03)00422-7).
98. Galluzzi, L., Chan, T.A., Kroemer, G., Wolchok, J.D., and López-Soto, A. (2018). The hallmarks of successful anticancer immunotherapy. *Sci. Transl. Med.* 10, eaat7807. <https://doi.org/10.1126/scitranslmed.aat7807>.
99. Mariathasan, S., Turley, S.J., Nickles, D., Castiglioni, A., Yuen, K., Wang, Y., Kadel, E.E., III, Koeppen, H., Astarita, J.L., Cubas, R., et al. (2018). TGF β attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells. *Nature* 554, 544–548. <https://doi.org/10.1038/nature25501>.
100. Tauriello, D.V.F., Palomo-Ponce, S., Stork, D., Berenguer-Llergo, A., Badia-Ramentol, J., Iglesias, M., Sevillano, M., Ibiza, S., Cañellas, A., Hernando-Momblon, X., et al. (2018). TGF β drives immune evasion in genetically reconstituted colon cancer metastasis. *Nature* 554, 538–543. <https://doi.org/10.1038/nature25492>.
101. Peranzoni, E., Lemoine, J., Vimeux, L., Feuillet, V., Barrin, S., Kantari-Mimoun, C., Bercovici, N., Guérin, M., Biton, J., Ouakrim, H., et al. (2018). Macrophages impede CD8 T cells from reaching tumor cells and limit the efficacy of anti-PD-1 treatment. *Proc. Natl. Acad. Sci. USA* 115, E4041–E4050. <https://doi.org/10.1073/pnas.1720948115>.
102. Taifour, T., Attalla, S.S., Zuo, D., Gu, Y., Sanguin-Gendreau, V., Proud, H., Solymoss, E., Bui, T., Kuasne, H., Papavasiliou, V., et al. (2023). The tumor-derived cytokine Chi3l1 induces neutrophil extracellular traps that promote T cell exclusion in triple-negative breast cancer. *Immunity* 56, 2755–2772.e8. <https://doi.org/10.1016/j.immuni.2023.11.002>.
103. Papayannopoulos, V. (2018). Neutrophil extracellular traps in immunity and disease. *Nat. Rev. Immunol.* 18, 134–147. <https://doi.org/10.1038/nri.2017.105>.
104. Teijeira, Á., Garasa, S., Gato, M., Alfaro, C., Migueliz, I., Cirella, A., de Andrea, C., Ochoa, M.C., Otano, I., Etxeberria, I., et al. (2020). CXCR1 and CXCR2 Chemokine Receptor Agonists Produced by Tumors Induce Neutrophil Extracellular Traps that Interfere with Immune Cytotoxicity. *Immunity* 52, 856–871.e8. <https://doi.org/10.1016/j.immuni.2020.03.001>.
105. Bianchi, A., De Castro Silva, I., Deshpande, N.U., Singh, S., Mehra, S., Garrido, V.T., Guo, X., Nivelo, L.A., Kolonias, D.S., Saigh, S.J., et al. (2023). Cell-Autonomous Cxcl1 Sustains Tolerogenic Circuitries and Stromal Inflammation via Neutrophil-Derived TNF in Pancreatic Cancer. *Cancer Discov.* 13, 1428–1453. <https://doi.org/10.1158/2159-8290.Cd-22-1046>.
106. Spranger, S., Bao, R., and Gajewski, T.F. (2015). Melanoma-intrinsic β -catenin signalling prevents anti-tumour immunity. *Nature* 523, 231–235. <https://doi.org/10.1038/nature14404>.
107. Hildner, K., Edelson, B.T., Purtha, W.E., Diamond, M., Matsushita, H., Kohyama, M., Calderon, B., Schraml, B.U., Unanue, E.R., Diamond, M.S., et al. (2008). Batf3 deficiency reveals a critical role for CD8alpha+ dendritic cells in cytotoxic T cell immunity. *Science* 322, 1097–1100. <https://doi.org/10.1126/science.1164206>.
108. Theisen, D.J., Davidson, J.T., 4th, Briseño, C.G., Gargaro, M., Lauron, E.J., Wang, Q., Desai, P., Durai, V., Bagadia, P., Brickner, J.R., et al. (2018). WDFY4 is required for cross-presentation in response to viral and tumor antigens. *Science* 362, 694–699. <https://doi.org/10.1126/science.aat5030>.
109. Jerby-Arnon, L., Shah, P., Cuoco, M.S., Rodman, C., Su, M.J., Melms, J.C., Leeson, R., Kanodia, A., Mei, S., Lin, J.R., et al. (2018). A Cancer Cell Program Promotes T Cell Exclusion and Resistance to Checkpoint Blockade. *Cell* 175, 984–997.e24. <https://doi.org/10.1016/j.cell.2018.09.006>.
110. Morrison, L., Loibl, S., and Turner, N.C. (2024). The CDK4/6 inhibitor revolution - a game-changing era for breast cancer treatment. *Nat. Rev. Clin. Oncol.* 21, 89–105. <https://doi.org/10.1038/s41571-023-00840-4>.
111. Harbeck, N., Penault-Llorca, F., Cortes, J., Gnant, M., Houssami, N., Poortmans, P., Ruddy, K., Tsang, J., and Cardoso, F. (2019). Breast cancer. *Nat. Rev. Dis. Primers* 5, 66. <https://doi.org/10.1038/s41572-019-0111-2>.
112. Bergholz, J.S., Wang, Q., Wang, Q., Ramseier, M., Prakadan, S., Wang, W., Fang, R., Kabraji, S., Zhou, Q., Gray, G.K., et al. (2023). PI3K β controls immune evasion in PTEN-deficient breast tumours. *Nature* 617, 139–146. <https://doi.org/10.1038/s41586-023-05940-w>.
113. Koikawa, K., Kibe, S., Suizu, F., Sekino, N., Kim, N., Manz, T.D., Pinch, B.J., Akshinthala, D., Verma, A., Gaglia, G., et al. (2021). Targeting Pin1 renders pancreatic cancer eradicable by synergizing with immunochemotherapy. *Cell* 184, 4753–4771.e27. <https://doi.org/10.1016/j.cell.2021.07.020>.
114. Sun, X., Wu, B., Chiang, H.C., Deng, H., Zhang, X., Xiong, W., Liu, J., Rozeboom, A.M., Harris, B.T., Blommaert, E., et al. (2021). Tumour DDR1 promotes collagen fibre alignment to instigate immune exclusion. *Nature* 599, 673–678. <https://doi.org/10.1038/s41586-021-04057-2>.
115. Baldominos, P., Barbera-Mourelle, A., Barreiro, O., Huang, Y., Wight, A., Cho, J.W., Zhao, X., Estivill, G., Adam, I., Sanchez, X., et al. (2022). Quiescent cancer cells resist T cell attack by forming an immunosuppressive niche. *Cell* 185, 1694–1708.e19. <https://doi.org/10.1016/j.cell.2022.03.033>.
116. Freeman, G.J., Long, A.J., Iwai, Y., Bourque, K., Chernova, T., Nishimura, H., Fitz, L.J., Malenkovich, N., Okazaki, T., Byrne, M.C., et al. (2000). Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. *J. Exp. Med.* 192, 1027–1034. <https://doi.org/10.1084/jem.192.7.1027>.
117. Bellucci, R., Martin, A., Bommarito, D., Wang, K., Hansen, S.H., Freeman, G.J., and Ritz, J. (2015). Interferon- γ -induced activation of JAK1 and JAK2 suppresses tumor cell susceptibility to NK cells through upregulation of PD-L1 expression. *Oncolimmunology* 4, e1008824. <https://doi.org/10.1080/2162402x.2015.1008824>.
118. Klement, J.D., Redd, P.S., Lu, C., Merting, A.D., Poschel, D.B., Yang, D., Savage, N.M., Zhou, G., Munn, D.H., Fallon, P.G., and Liu, K. (2023). Tumor PD-L1 engages myeloid PD-1 to suppress type I interferon to impair cytotoxic T lymphocyte recruitment. *Cancer Cell* 41, 620–636.e9. <https://doi.org/10.1016/j.ccr.2023.02.005>.
119. Yamaguchi, H., Hsu, J.M., Yang, W.H., and Hung, M.C. (2022). Mechanisms regulating PD-L1 expression in cancers and associated opportunities for novel small-molecule therapeutics. *Nat. Rev. Clin. Oncol.* 19, 287–305. <https://doi.org/10.1038/s41571-022-00601-9>.
120. Holder, A.M., Dedeilia, A., Sierra-Davidson, K., Cohen, S., Liu, D., Parikh, A., and Boland, G.M. (2024). Defining clinically useful biomarkers of immune checkpoint inhibitors in solid tumours. *Nat. Rev. Cancer* 24, 498–512. <https://doi.org/10.1038/s41568-024-00705-7>.
121. Kataoka, K., Shiraishi, Y., Takeda, Y., Sakata, S., Matsumoto, M., Naganou, S., Maeda, T., Nagata, Y., Kitanaka, A., Mizuno, S., et al. (2016). Aberrant PD-L1 expression through 3'-UTR disruption in multiple cancers. *Nature* 534, 402–406. <https://doi.org/10.1038/nature18294>.

122. Huang, R.S.P., Murugesan, K., Montesion, M., Pavlick, D.C., Mata, D.A., Hiemenz, M.C., Decker, B., Frampton, G., Albacker, L.A., and Ross, J.S. (2021). Pan-cancer landscape of CD274 (PD-L1) copy number changes in 244–584 patient samples and the correlation with PD-L1 protein expression. *J. Immunother. Cancer* 9, e002680. <https://doi.org/10.1136/jtc-2021-002680>.
123. Darvin, P., Sasidharan Nair, V., and Elkord, E. (2019). PD-L1 Expression in Human Breast Cancer Stem Cells Is Epigenetically Regulated through Posttranslational Histone Modifications. *J. Oncol.* 2019, 3958908. <https://doi.org/10.1155/2019/3958908>.
124. Zhang, Y., Xiang, C., Wang, Y., Duan, Y., Liu, C., and Zhang, Y. (2017). PD-L1 promoter methylation mediates the resistance response to anti-PD-1 therapy in NSCLC patients with EGFR-TKI resistance. *Oncotarget* 8, 101535–101544. <https://doi.org/10.18632/oncotarget.21328>.
125. Lai, Q., Wang, H., Li, A., Xu, Y., Tang, L., Chen, Q., Zhang, C., Gao, Y., Song, J., and Du, Z. (2018). Decitabine improve the efficiency of anti-PD-1 therapy via activating the response to IFN/PD-L1 signal of lung cancer cells. *Oncogene* 37, 2302–2312. <https://doi.org/10.1038/s41388-018-0125-3>.
126. Leuzzi, G., Vasciaveo, A., Tagliafata, A., Chen, X., Firestone, T.M., Hickman, A.R., Mao, W., Thakar, T., Vaitišankova, A., Huang, J.W., et al. (2024). SMARCAL1 is a dual regulator of innate immune signaling and PD-L1 expression that promotes tumor immune evasion. *Cell* 187, 861–881.e32. <https://doi.org/10.1016/j.cell.2024.01.008>.
127. Xu, Y., Poggio, M., Jin, H.Y., Shi, Z., Forester, C.M., Wang, Y., Stumpf, C.R., Xue, L., Devericks, E., So, L., et al. (2019). Translation control of the immune checkpoint in cancer and its therapeutic targeting. *Nat. Med.* 25, 301–311. <https://doi.org/10.1038/s41591-018-0321-2>.
128. Suresh, S., Chen, B., Zhu, J., Golden, R.J., Lu, C., Evers, B.M., Novaresi, N., Smith, B., Zhan, X., Schmid, V., et al. (2020). eIF5B drives integrated stress response-dependent translation of PD-L1 in lung cancer. *Nat. Cancer* 1, 533–545. <https://doi.org/10.1038/s43018-020-0056-0>.
129. Chan, L.C., Li, C.W., Xia, W., Hsu, J.M., Lee, H.H., Cha, J.H., Wang, H.L., Yang, W.H., Yen, E.Y., Chang, W.C., et al. (2019). IL-6/JAK1 pathway drives PD-L1 Y112 phosphorylation to promote cancer immune evasion. *J. Clin. Invest.* 129, 3324–3338. <https://doi.org/10.1172/JCI126022>.
130. Hsu, J.M., Xia, W., Hsu, Y.H., Chan, L.C., Yu, W.H., Cha, J.H., Chen, C.T., Liao, H.W., Kuo, C.W., Khoo, K.H., et al. (2018). STT3-dependent PD-L1 accumulation on cancer stem cells promotes immune evasion. *Nat. Commun.* 9, 1908. <https://doi.org/10.1038/s41467-018-04313-6>.
131. Burr, M.L., Sparbier, C.E., Chan, Y.C., Williamson, J.C., Woods, K., Beavis, P.A., Lam, E.Y.N., Henderson, M.A., Bell, C.C., Stolzenburg, S., et al. (2017). CMTM6 maintains the expression of PD-L1 and regulates anti-tumour immunity. *Nature* 549, 101–105. <https://doi.org/10.1038/nature23643>.
132. Ho, P., Melms, J.C., Rogava, M., Frangieh, C.J., Poźniak, J., Shah, S.B., Walsh, Z., Kyrysyuk, O., Amin, A.D., Caprio, L., et al. (2023). The CD58-CD2 axis is co-regulated with PD-L1 via CMTM6 and shapes anti-tumor immunity. *Cancer Cell* 41, 1207–1221.e12. <https://doi.org/10.1016/j.ccr.2023.05.014>.
133. Liu, H., Kuang, X., Zhang, Y., Ye, Y., Li, J., Liang, L., Xie, Z., Weng, L., Guo, J., Li, H., et al. (2020). ADORA1 Inhibition Promotes Tumor Immune Evasion by Regulating the ATF3-PD-L1 Axis. *Cancer Cell* 37, 324–339.e8. <https://doi.org/10.1016/j.ccr.2020.02.006>.
134. Guo, D., Tong, Y., Jiang, X., Meng, Y., Jiang, H., Du, L., Wu, Q., Li, S., Luo, S., Li, M., et al. (2022). Aerobic glycolysis promotes tumor immune evasion by hexokinase2-mediated phosphorylation of IκB α . *Cell Metab.* 34, 1312–1324.e6. <https://doi.org/10.1016/j.cmet.2022.08.002>.
135. Ritter, C., Fan, K., Paulson, K.G., Nghiem, P., Schrama, D., and Becker, J.C. (2016). Reversal of epigenetic silencing of MHC class I chain-related protein A and B improves immune recognition of Merkel cell carcinoma. *Sci. Rep.* 6, 21678. <https://doi.org/10.1038/srep21678>.
136. Zhong, J., Yang, X., Chen, J., He, K., Gao, X., Wu, X., Zhang, M., Zhou, H., Xiao, F., An, L., et al. (2022). Circular EZH2-encoded EZH2-92aa mediates immune evasion in glioblastoma via inhibition of surface NKG2D ligands. *Nat. Commun.* 13, 4795. <https://doi.org/10.1038/s41467-022-32311-2>.
137. Bailey, C.P., Figueiroa, M., Gangadharan, A., Yang, Y., Romero, M.M., Kennis, B.A., Yadavalli, S., Henry, V., Collier, T., Monje, M., et al. (2020). Pharmacologic inhibition of lysine-specific demethylase 1 as a therapeutic and immune-sensitization strategy in pediatric high-grade glioma. *Neuro Oncol.* 22, 1302–1314. <https://doi.org/10.1093/neuonc/noaa058>.
138. Paczulla, A.M., Rothfelder, K., Raffel, S., Konantz, M., Steinbacher, J., Wang, H., Tandler, C., Mbarga, M., Schaefer, T., Falcone, M., et al. (2019). Absence of NKG2D ligands defines leukaemia stem cells and mediates their immune evasion. *Nature* 572, 254–259. <https://doi.org/10.1038/s41586-019-1410-1>.
139. Kaiser, B.K., Yim, D., Chow, I.T., Gonzalez, S., Dai, Z., Mann, H.H., Strong, R.K., Groh, V., and Spies, T. (2007). Disulphide-isomerase-enabled shedding of tumour-associated NKG2D ligands. *Nature* 447, 482–486. <https://doi.org/10.1038/nature05768>.
140. Singh, S., and Banerjee, S. (2020). Downregulation of HLA-ABC expression through promoter hypermethylation and downmodulation of MIC/A/B surface expression in LMP2A-positive epithelial carcinoma cell lines. *Sci. Rep.* 10, 5415. <https://doi.org/10.1038/s41598-020-62081-0>.
141. Salih, H.R., Rammensee, H.G., and Steinle, A. (2002). Cutting edge: down-regulation of MICA on human tumors by proteolytic shedding. *J. Immunol.* 169, 4098–4102. <https://doi.org/10.4049/jimmunol.169.8.4098>.
142. Wu, J.D., Higgins, L.M., Steinle, A., Cosman, D., Haugk, K., and Plymate, S.R. (2004). Prevalent expression of the immunostimulatory MHC class I chain-related molecule is counteracted by shedding in prostate cancer. *J. Clin. Invest.* 114, 560–568. <https://doi.org/10.1172/jci22206>.
143. Dubrot, J., Du, P.P., Lane-Reticker, S.K., Kessler, E.A., Muscato, A.J., Mehta, A., Freeman, S.S., Allen, P.M., Olander, K.E., Ockerman, K.M., et al. (2022). In vivo CRISPR screens reveal the landscape of immune evasion pathways across cancer. *Nat. Immunol.* 23, 1495–1506. <https://doi.org/10.1038/s41590-022-01315-x>.
144. Liu, X., Song, J., Zhang, H., Liu, X., Zuo, F., Zhao, Y., Zhao, Y., Yin, X., Guo, X., Wu, X., et al. (2023). Immune checkpoint HLA-E:CD94-NKG2A mediates evasion of circulating tumor cells from NK cell surveillance. *Cancer Cell* 41, 272–287.e9. <https://doi.org/10.1016/j.ccr.2023.01.001>.
145. André, P., Denis, C., Soulas, C., Bourbon-Caillet, C., Lopez, J., Arnoux, T., Bléry, M., Bonnafous, C., Gauthier, L., Morel, A., et al. (2018). Anti-NKG2A mAb Is a Checkpoint Inhibitor that Promotes Anti-tumor Immunity by Unleashing Both T and NK Cells. *Cell* 175, 1731–1743.e13. <https://doi.org/10.1016/j.cell.2018.10.014>.
146. Salomé, B., Sfakianos, J.P., Ranti, D., Daza, J., Bieber, C., Charap, A., Hammer, C., Banchereau, R., Farkas, A.M., Ruan, D.F., et al. (2022). NKG2A and HLA-E define an alternative immune checkpoint axis in bladder cancer. *Cancer Cell* 40, 1027–1043.e9. <https://doi.org/10.1016/j.ccr.2022.08.005>.
147. Carlsten, M., Korde, N., Kotecha, R., Reger, R., Bor, S., Kazandjian, D., Landgren, O., and Childs, R.W. (2016). Checkpoint Inhibition of KIR2D with the Monoclonal Antibody IPH2101 Induces Contraction and Hyporesponsiveness of NK Cells in Patients with Myeloma. *Clin. Cancer Res.* 22, 5211–5222. <https://doi.org/10.1158/1078-0432.Ccr-16-1108>.
148. Freed-Pastor, W.A., Lambert, L.J., Ely, Z.A., Pattada, N.B., Bhutkar, A., Eng, G., Mercer, K.L., Garcia, A.P., Lin, L., Rideout, W.M., 3rd, et al. (2021). The CD155/TIGIT axis promotes and maintains immune evasion in neoantigen-expressing pancreatic cancer. *Cancer Cell* 39, 1342–1360.e14. <https://doi.org/10.1016/j.ccr.2021.07.007>.
149. Li, Z., Ma, R., Tang, H., Guo, J., Shah, Z., Zhang, J., Liu, N., Cao, S., Maruccia, G., Artis, D., et al. (2024). Therapeutic application of human type 2 innate lymphoid cells via induction of granzyme B-mediated tumor cell death. *Cell* 187, 624–641.e23. <https://doi.org/10.1016/j.cell.2023.12.015>.
150. Su, R., Dong, L., Li, Y., Gao, M., Han, L., Wunderlich, M., Deng, X., Li, H., Huang, Y., Gao, L., et al. (2020). Targeting FTO Suppresses Cancer Stem Cell Maintenance and Immune Evasion. *Cancer Cell* 38, 79–96.e11. <https://doi.org/10.1016/j.ccr.2020.04.017>.
151. Zhu, C., Anderson, A.C., Schubart, A., Xiong, H., Imitola, J., Khouri, S.J., Zheng, X.X., Strom, T.B., and Kuchroo, V.K. (2005). The Tim-3 ligand galectin-9 negatively regulates T helper type 1 immunity. *Nat. Immunol.* 6, 1245–1252. <https://doi.org/10.1038/ni1271>.

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152. Yan, R., Zhang, P., Shen, S., Zeng, Y., Wang, T., Chen, Z., Ma, W., Feng, J., Suo, C., Zhang, T., et al. (2024). Carnosine regulation of intracellular pH homeostasis promotes lysosome-dependent tumor immuno-evasion. *Nat. Immunol.* 25, 483–495. <https://doi.org/10.1038/s41590-023-01719-3>.
153. Chao, M.P., Jaiswal, S., Weissman-Tsukamoto, R., Alizadeh, A.A., Gentles, A.J., Volkmer, J., Weiskopf, K., Willingham, S.B., Raveh, T., Park, C.Y., et al. (2010). Calreticulin is the dominant pro-phagocytic signal on multiple human cancers and is counterbalanced by CD47. *Sci. Transl. Med.* 2, 63ra94. <https://doi.org/10.1126/scitranslmed.3001375>.
154. Gardai, S.J., McPhillips, K.A., Frasch, S.C., Janssen, W.J., Starefeldt, A., Murphy-Ullrich, J.E., Bratton, D.L., Oldenborg, P.A., Michalak, M., and Henson, P.M. (2005). Cell-surface calreticulin initiates clearance of viable or apoptotic cells through trans-activation of LRP on the phagocyte. *Cell* 123, 321–334. <https://doi.org/10.1016/j.cell.2005.08.032>.
155. Tang, Z., Zhong, M.C., Qian, J., Galindo, C.C., Davidson, D., Li, J., Zhao, Y., Hui, E., and Veillette, A. (2023). CD47 masks pro-phagocytic ligands in cis on tumor cells to suppress antitumor immunity. *Nat. Immunol.* 24, 2032–2041. <https://doi.org/10.1038/s41590-023-01671-2>.
156. Jiang, N., Xie, B., Xiao, W., Fan, M., Xu, S., Duan, Y., Hamsafar, Y., Evans, A.C., Huang, J., Zhou, W., et al. (2022). Fatty acid oxidation fuels glioblastoma radioresistance with CD47-mediated immune evasion. *Nat. Commun.* 13, 1511. <https://doi.org/10.1038/s41467-022-29137-3>.
157. Majeti, R., Chao, M.P., Alizadeh, A.A., Pang, W.W., Jaiswal, S., Gibbs, K.D., Jr., van Rooijen, N., and Weissman, I.L. (2009). CD47 is an adverse prognostic factor and therapeutic antibody target on human acute myeloid leukemia stem cells. *Cell* 138, 286–299. <https://doi.org/10.1016/j.cell.2009.05.045>.
158. Jaiswal, S., Jamieson, C.H.M., Pang, W.W., Park, C.Y., Chao, M.P., Majeti, R., Traver, D., van Rooijen, N., and Weissman, I.L. (2009). CD47 is up-regulated on circulating hematopoietic stem cells and leukemia cells to avoid phagocytosis. *Cell* 138, 271–285. <https://doi.org/10.1016/j.cell.2009.05.046>.
159. Wang, Z., Li, B., Li, S., Lin, W., Wang, Z., Wang, S., Chen, W., Shi, W., Chen, T., Zhou, H., et al. (2022). Metabolic control of CD47 expression through LAT2-mediated amino acid uptake promotes tumor immune evasion. *Nat. Commun.* 13, 6308. <https://doi.org/10.1038/s41467-022-34064-4>.
160. Barkal, A.A., Brewer, R.E., Markovic, M., Kowarsky, M., Barkal, S.A., Zaro, B.W., Krishnan, V., Hatakeyama, J., Dorigo, O., Barkal, L.J., and Weissman, I.L. (2019). CD24 signalling through macrophage Siglec-10 is a target for cancer immunotherapy. *Nature* 572, 392–396. <https://doi.org/10.1038/s41586-019-1456-0>.
161. Jiang, C., Sun, H., Jiang, Z., Tian, W., Cang, S., and Yu, J. (2024). Targeting the CD47/SIRPalpha pathway in malignancies: recent progress, difficulties and future perspectives. *Front. Oncol.* 14, 1378647. <https://doi.org/10.3389/fonc.2024.1378647>.
162. Galluzzi, L., Vanpouille-Box, C., Bakhoum, S.F., and Demaria, S. (2018). SnapShot: CGAS-STING Signaling. *Cell* 173, 276–276.e1. <https://doi.org/10.1016/j.cell.2018.03.015>.
163. Ritchie, C., Carozza, J.A., and Li, L. (2022). Biochemistry, Cell Biology, and Pathophysiology of the Innate Immune cGAS-cGAMP-STING Pathway. *Annu. Rev. Biochem.* 91, 599–628. <https://doi.org/10.1146/annurev-biochem-040320-101629>.
164. Marzio, A., Kurz, E., Sahni, J.M., Di Feo, G., Puccini, J., Jiang, S., Hirsch, C.A., Arbini, A.A., Wu, W.L., Pass, H.I., et al. (2022). EMSY inhibits homologous recombination repair and the interferon response, promoting lung cancer immune evasion. *Cell* 185, 169–183.e19. <https://doi.org/10.1016/j.cell.2021.12.005>.
165. Ghosh, M., Saha, S., Bettke, J., Nagar, R., Parrales, A., Iwakuma, T., van der Velden, A.W.M., and Martinez, L.A. (2021). Mutant p53 suppresses innate immune signaling to promote tumorigenesis. *Cancer Cell* 39, 494–508.e5. <https://doi.org/10.1016/j.ccell.2021.01.003>.
166. Kitajima, S., Ivanova, E., Guo, S., Yoshida, R., Campisi, M., Sundararaman, S.K., Tange, S., Mitsuishi, Y., Thai, T.C., Masuda, S., et al. (2019). Suppression of STING Associated with LKB1 Loss in KRAS-Driven Lung Cancer. *Cancer Discov.* 9, 34–45. <https://doi.org/10.1158/2159-8290.CD-18-0689>.
167. Hu, J., Sánchez-Rivera, F.J., Wang, Z., Johnson, G.N., Ho, Y.J., Ganesh, K., Umeda, S., Gan, S., Mujal, A.M., Delconte, R.B., et al. (2023). STING inhibits the reactivation of dormant metastasis in lung adenocarcinoma. *Nature* 616, 806–813. <https://doi.org/10.1038/s41586-023-05880-5>.
168. Kim, H., Kim, H., Feng, Y., Li, Y., Tamiya, H., Tocci, S., and Ronai, Z.A. (2020). PRMT5 control of cGAS/STING and NLRC5 pathways defines melanoma response to antitumor immunity. *Sci. Transl. Med.* 12, eaaz5683. <https://doi.org/10.1126/scitranslmed.aaz5683>.
169. Jia, L., Zhang, W., and Wang, C.Y. (2020). BMI1 Inhibition Eliminates Residual Cancer Stem Cells after PD1 Blockade and Activates Antitumor Immunity to Prevent Metastasis and Relapse. *Cell Stem Cell* 27, 238–253.e6. <https://doi.org/10.1016/j.stem.2020.06.022>.
170. Fang, L., Hao, Y., Yu, H., Gu, X., Peng, Q., Zhuo, H., Li, Y., Liu, Z., Wang, J., Chen, Y., et al. (2023). Methionine restriction promotes cGAS activation and chromatin untethering through demethylation to enhance anti-tumor immunity. *Cancer Cell* 41, 1118–1133.e12. <https://doi.org/10.1016/j.ccell.2023.05.005>.
171. Govindan, R., Ding, L., Griffith, M., Subramanian, J., Dees, N.D., Kanchi, K.L., Maher, C.A., Fulton, R., Fulton, L., Wallis, J., et al. (2012). Genomic landscape of non-small cell lung cancer in smokers and never-smokers. *Cell* 150, 1121–1134. <https://doi.org/10.1016/j.cell.2012.08.024>.
172. Hong, J., Lee, J.H., Zhang, Z., Wu, Y., Yang, M., Liao, Y., de la Rosa, R., Scheirer, J., Pechacek, D., Zhang, N., et al. (2022). PRC2-Mediated Epigenetic Suppression of Type I IFN-STAT2 Signaling Impairs Antitumor Immunity in Luminal Breast Cancer. *Cancer Res.* 82, 4624–4640. <https://doi.org/10.1158/0008-5472.CAN-22-0736>.
173. Takahashi, M., Lio, C.W.J., Campeau, A., Steger, M., Ay, F., Mann, M., Gonzalez, D.J., Jain, M., and Sharma, S. (2021). The tumor suppressor kinase DAPK3 drives tumor-intrinsic immunity through the STING-IFN- β pathway. *Nat. Immunol.* 22, 485–496. <https://doi.org/10.1038/s41590-021-00896-3>.
174. Dai, J., Huang, Y.J., He, X., Zhao, M., Wang, X., Liu, Z.S., Xue, W., Cai, H., Zhan, X.Y., Huang, S.Y., et al. (2019). Acetylation Blocks cGAS Activity and Inhibits Self-DNA-Induced Autoimmunity. *Cell* 176, 1447–1460.e14. <https://doi.org/10.1016/j.cell.2019.01.016>.
175. Hou, Y., Wang, Z., Liu, P., Wei, X., Zhang, Z., Fan, S., Zhang, L., Han, F., Song, Y., Chu, L., and Zhang, C. (2023). SMPDL3A is a cGAMP-degrading enzyme induced by LXR-mediated lipid metabolism to restrict cGAS-STING DNA sensing. *Immunity* 56, 2492–2507.e10. <https://doi.org/10.1016/j.immuni.2023.10.001>.
176. Wang, S., Böhner, V., Joseph, A.J., Sudaryo, V., Skariah, G., Swinderman, J.T., Yu, F.B., Subramanyam, V., Wolf, D.M., Lyu, X., et al. (2023). ENPP1 is an innate immune checkpoint of the anticancer cGAMP-STING pathway in breast cancer. *Proc. Natl. Acad. Sci. USA* 120, e2313693120. <https://doi.org/10.1073/pnas.2313693120>.
177. Carozza, J.A., Cordova, A.F., Brown, J.A., AlSaif, Y., Böhner, V., Cao, X., Mardjuki, R.E., Skariah, G., Fernandez, D., and Li, L. (2022). ENPP1's regulation of extracellular cGAMP is a ubiquitous mechanism of attenuating STING signaling. *Proc. Natl. Acad. Sci. USA* 119, e2119189119. <https://doi.org/10.1073/pnas.2119189119>.
178. Carozza, J.A., Böhner, V., Nguyen, K.C., Skariah, G., Shaw, K.E., Brown, J.A., Rafat, M., von Eyben, R., Graves, E.E., Glenn, J.S., et al. (2020). Extracellular cGAMP is a cancer cell-produced immunotransmitter involved in radiation-induced anti-cancer immunity. *Nat. Cancer* 1, 184–196. <https://doi.org/10.1038/s43018-020-0028-4>.
179. Takaki, T., Millar, R., Hiley, C.T., and Boulton, S.J. (2024). Micronuclei induced by radiation, replication stress, or chromosome segregation errors do not activate cGAS-STING. *Mol. Cell* 84, 2203–2213.e5. <https://doi.org/10.1016/j.molcel.2024.04.017>.
180. Zierhut, C., Yamaguchi, N., Paredes, M., Luo, J.D., Carroll, T., and Funabiki, H. (2019). The Cytoplasmic DNA Sensor cGAS Promotes Mitotic Cell Death. *Cell* 178, 302–315.e23. <https://doi.org/10.1016/j.cell.2019.05.035>.
181. Kujirai, T., Zierhut, C., Takizawa, Y., Kim, R., Negishi, L., Uruma, N., Hirai, S., Funabiki, H., and Kurumizaka, H. (2020). Structural basis for the inhibition of cGAS by nucleosomes. *Science* 370, 455–458. <https://doi.org/10.1126/science.abd0237>.

182. Saha, S., Ghosh, M., Li, J., Wen, A., Galluzzi, L., Martinez, L.A., and Montrose, D.C. (2024). Serine Depletion Promotes Anti-Tumor Immunity by Activating Mitochondrial DNA-mediated cGAS-STING Signaling. *Cancer Res.* 84, 2645–2659. <https://doi.org/10.1158/0008-5472.CAN-23-1788>.
183. Yamazaki, T., Kirchmair, A., Sato, A., Buqué, A., Rybstein, M., Petroni, G., Bloy, N., Finotello, F., Stafford, L., Navarro Manzano, E., et al. (2020). Mitochondrial DNA drives abscopal responses to radiation that are inhibited by autophagy. *Nat. Immunol.* 21, 1160–1171. <https://doi.org/10.1038/s41590-020-0751-0>.
184. Riley, J.S., Quarato, G., Cloix, C., Lopez, J., O'Prey, J., Pearson, M., Chapman, J., Sesaki, H., Carlin, L.M., Passos, J.F., et al. (2018). Mitochondrial inner membrane permeabilisation enables mtDNA release during apoptosis. *EMBO J.* 37, e99238. <https://doi.org/10.1525/embj.201899238>.
185. West, A.P., Khouri-Hanold, W., Staron, M., Tal, M.C., Pineda, C.M., Lang, S.M., Bestwick, M., Duguay, B.A., Raimundo, N., MacDuff, D.A., et al. (2015). Mitochondrial DNA stress primes the antiviral innate immune response. *Nature* 520, 553–557. <https://doi.org/10.1038/nature14156>.
186. Klapp, V., Álvarez-Abril, B., Leuzzi, G., Kroemer, G., Ciccia, A., and Galluzzi, L. (2023). The DNA Damage Response and Inflammation in Cancer. *Cancer Discov.* 13, 1521–1545. <https://doi.org/10.1158/2159-8290.CD-22-1220>.
187. Ding, L., Kim, H.J., Wang, Q., Kearns, M., Jiang, T., Ohlson, C.E., Li, B.B., Xie, S., Liu, J.F., Stover, E.H., et al. (2018). PARP Inhibition Elicits STING-Dependent Antitumor Immunity in Brca1-Deficient Ovarian Cancer. *Cell Rep.* 25, 2972–2980.e5. <https://doi.org/10.1016/j.celrep.2018.11.054>.
188. Pantelidou, C., Sonzogni, O., De Oliveria Taveira, M., Mehta, A.K., Kothari, A., Wang, D., Visal, T., Li, M.K., Pinto, J., Castrillon, J.A., et al. (2019). PARP Inhibitor Efficacy Depends on CD8(+) T-cell Recruitment via Intratumoral STING Pathway Activation in BRCA-Deficient Models of Triple-Negative Breast Cancer. *Cancer Discov.* 9, 722–737. <https://doi.org/10.1158/2159-8290.CD-18-1218>.
189. Dillon, M.T., Bergerhoff, K.F., Pedersen, M., Whittock, H., Crespo-Rodríguez, E., Patin, E.C., Pearson, A., Smith, H.G., Paget, J.T.E., Patel, R.R., et al. (2019). ATR Inhibition Potentiates the Radiation-induced Inflammatory Tumor Microenvironment. *Clin. Cancer Res.* 25, 3392–3403. <https://doi.org/10.1158/1078-0432.CCR-18-1821>.
190. Hu, M., Zhou, M., Bao, X., Pan, D., Jiao, M., Liu, X., Li, F., and Li, C.Y. (2021). ATM inhibition enhances cancer immunotherapy by promoting mtDNA leakage and cGAS/STING activation. *J. Clin. Invest.* 131, e139333. <https://doi.org/10.1172/JCI139333>.
191. Murayama, T., Nakayama, J., Jiang, X., Miyata, K., Morris, A.D., Cai, K.Q., Prasad, R.M., Ma, X., Efimov, A., Belani, N., et al. (2024). Targeting DHX9 Triggers Tumor-Intrinsic Interferon Response and Replication Stress in Small Cell Lung Cancer. *Cancer Discov.* 14, 468–491. <https://doi.org/10.1158/2159-8290.CD-23-0486>.
192. Zhang, W., Liu, W., Jia, L., Chen, D., Chang, I., Lake, M., Bentolila, L.A., and Wang, C.Y. (2021). Targeting KDM4A epigenetically activates tumor-cell-intrinsic immunity by inducing DNA replication stress. *Mol. Cell* 81, 2148–2165.e9. <https://doi.org/10.1016/j.molcel.2021.02.038>.
193. Doplaks, N., and Nixon, D.F. (2024). Activation of human endogenous retroviruses and its physiological consequences. *Nat. Rev. Mol. Cell Biol.* 25, 212–222. <https://doi.org/10.1038/s41580-023-00674-z>.
194. Saw, P.E., Liu, Q., Wong, P.P., and Song, E. (2024). Cancer stem cell mimicry for immune evasion and therapeutic resistance. *Cell Stem Cell* 31, 1101–1112. <https://doi.org/10.1016/j.stem.2024.06.003>.
195. Chiappinelli, K.B., Strissel, P.L., Desrichard, A., Li, H., Henke, C., Akman, B., Hein, A., Rote, N.S., Cope, L.M., Snyder, A., et al. (2015). Inhibiting DNA Methylation Causes an Interferon Response in Cancer via dsRNA Including Endogenous Retroviruses. *Cell* 162, 974–986. <https://doi.org/10.1016/j.cell.2015.07.011>.
196. Roulois, D., Loo Yau, H., Singhania, R., Wang, Y., Danesh, A., Shen, S.Y., Han, H., Liang, G., Jones, P.A., Pugh, T.J., et al. (2015). DNA-Demethylating Agents Target Colorectal Cancer Cells by Inducing Viral Mimicry by Endogenous Transcripts. *Cell* 162, 961–973. <https://doi.org/10.1016/j.cell.2015.07.056>.
197. Topper, M.J., Vaz, M., Chiappinelli, K.B., DeStefano Shields, C.E., Niknafs, N., Yen, R.W.C., Wenzel, A., Hicks, J., Ballew, M., Stone, M., et al. (2017). Epigenetic Therapy Ties MYC Depletion to Reversing Immune Evasion and Treating Lung Cancer. *Cell* 171, 1284–1300.e21. <https://doi.org/10.1016/j.cell.2017.10.022>.
198. Griffin, G.K., Wu, J., Iracheta-Vellve, A., Patti, J.C., Hsu, J., Davis, T., Dele-Oni, D., Du, P.P., Halawi, A.G., Ishizuka, J.J., et al. (2021). Epigenetic silencing by SETDB1 suppresses tumour intrinsic immunogenicity. *Nature* 595, 309–314. <https://doi.org/10.1038/s41586-021-03520-4>.
199. Kong, Y., Rose, C.M., Cass, A.A., Williams, A.G., Darwish, M., Lianoglou, S., Haverty, P.M., Tong, A.J., Blanchette, C., Albert, M.L., et al. (2019). Transposable element expression in tumors is associated with immune infiltration and increased antigenicity. *Nat. Commun.* 10, 5228. <https://doi.org/10.1038/s41467-019-13035-2>.
200. Liu, Y., Hu, L., Wu, Z., Yuan, K., Hong, G., Lian, Z., Feng, J., Li, N., Li, D., Wong, J., et al. (2023). Loss of PHF8 induces a viral mimicry response by activating endogenous retrotransposons. *Nat. Commun.* 14, 4225. <https://doi.org/10.1038/s41467-023-39943-y>.
201. Sheng, W., LaFleur, M.W., Nguyen, T.H., Chen, S., Chakravarthy, A., Conway, J.R., Li, Y., Chen, H., Yang, H., Hsu, P.H., et al. (2018). LSD1 Ablation Stimulates Anti-tumor Immunity and Enables Checkpoint Blockade. *Cell* 174, 549–563.e19. <https://doi.org/10.1016/j.cell.2018.05.052>.
202. Li, Y., Goldberg, E.M., Chen, X., Xu, X., McGuire, J.T., Leuzzi, G., Karagiannis, D., Tate, T., Farhangdoost, N., Horth, C., et al. (2022). Histone methylation antagonism drives tumor immune evasion in squamous cell carcinomas. *Mol. Cell* 82, 3901–3918.e7. <https://doi.org/10.1016/j.molcel.2022.09.007>.
203. Yuan, H., Wu, X., Wu, Q., Chatoff, A., Megill, E., Gao, J., Huang, T., Duan, T., Yang, K., Jin, C., et al. (2023). Lysine catabolism reprograms tumour immunity through histone crotonylation. *Nature* 617, 818–826. <https://doi.org/10.1038/s41586-023-06061-0>.
204. Zhou, X., Singh, M., Sanz Santos, G., Guerlavais, V., Carvajal, L.A., Aviavado, M., Zhan, Y., Oliveira, M.M.S., Westerberg, L.S., Annis, D.A., et al. (2021). Pharmacologic Activation of p53 Triggers Viral Mimicry Response Thereby Abolishing Tumor Immune Evasion and Promoting Antitumor Immunity. *Cancer Discov.* 11, 3090–3105. <https://doi.org/10.1158/2159-8290.CD-20-1741>.
205. Goel, S., DeCristo, M.J., Watt, A.C., BrinJones, H., Scneay, J., Li, B.B., Khan, N., Ubellacker, J.M., Xie, S., Metzger-Filho, O., et al. (2017). CDK4/6 inhibition triggers anti-tumour immunity. *Nature* 548, 471–475. <https://doi.org/10.1038/nature23465>.
206. Singh, R., Letai, A., and Sarosiek, K. (2019). Regulation of apoptosis in health and disease: the balancing act of BCL-2 family proteins. *Nat. Rev. Mol. Cell Biol.* 20, 175–193. <https://doi.org/10.1038/s41580-018-0089-8>.
207. Vargas, J.N.S., Hamasaki, M., Kawabata, T., Youle, R.J., and Yoshimori, T. (2023). The mechanisms and roles of selective autophagy in mammals. *Nat. Rev. Mol. Cell Biol.* 24, 167–185. <https://doi.org/10.1038/s41580-022-00542-2>.
208. White, M.J., McArthur, K., Metcalf, D., Lane, R.M., Cambier, J.C., Herold, M.J., van Delft, M.F., Bedoui, S., Lessene, G., Ritchie, M.E., et al. (2014). Apoptotic caspases suppress mtDNA-induced STING-mediated type I IFN production. *Cell* 159, 1549–1562. <https://doi.org/10.1016/j.cell.2014.11.036>.
209. Rongvaux, A., Jackson, R., Harman, C.C.D., Li, T., West, A.P., de Zoete, M.R., Wu, Y., Yordy, B., Lakhani, S.A., Kuan, C.Y., et al. (2014). Apoptotic caspases prevent the induction of type I interferons by mitochondrial DNA. *Cell* 159, 1563–1577. <https://doi.org/10.1016/j.cell.2014.11.037>.
210. Vringer, E., Heilig, R., Riley, J.S., Black, A., Cloix, C., Skalka, G., Montes-Gómez, A.E., Aguado, A., Lilla, S., Walczak, H., et al. (2024). Mitochondrial outer membrane integrity regulates a ubiquitin-dependent and NF-κB-mediated inflammatory response. *EMBO J.* 43, 904–930. <https://doi.org/10.1038/s44318-024-00044-1>.
211. Zhao, X., Hu, S., Zeng, L., Liu, X., Song, Y., Zhang, Y., Chen, Q., Bai, Y., Zhang, J., Zhang, H., et al. (2022). Irradiation combined with PD-L1(-) and autophagy inhibition enhances the antitumor effect of lung cancer

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- via cGAS-STING-mediated T cell activation. *iScience* 25, 104690. <https://doi.org/10.1101/2022.10.05.504690>.
212. Jena, K.K., Mehto, S., Nath, P., Chauhan, N.R., Sahu, R., Dhar, K., Das, S.K., Kolapalli, S.P., Murmu, K.C., Jain, A., et al. (2020). Autoimmunity gene IRGM suppresses cGAS-STING and RIG-I-MAVS signaling to control interferon response. *EMBO Rep.* 21, e50051. <https://doi.org/10.15252/embr.202050051>.
213. Zhong, Z., Umemura, A., Sanchez-Lopez, E., Liang, S., Shalapour, S., Wong, J., He, F., Boassa, D., Perkins, G., Ali, S.R., et al. (2016). NF- κ B Restricts Inflammasome Activation via Elimination of Damaged Mitochondria. *Cell* 164, 896–910. <https://doi.org/10.1016/j.cell.2015.12.057>.
214. King, C.R., Liu, Y., Amato, K.A., Schaack, G.A., Mickelson, C., Sanders, A.E., Hu, T., Gupta, S., Langlois, R.A., Smith, J.A., and Mehle, A. (2023). Pathogen-driven CRISPR screens identify TREX1 as a regulator of DNA self-sensing during influenza virus infection. *Cell Host Microbe* 31, 1552–1567.e8. <https://doi.org/10.1016/j.chom.2023.08.001>.
215. Mohr, L., Toufektchan, E., von Morgen, P., Chu, K., Kapoor, A., and Maciejowski, J. (2021). ER-directed TREX1 limits cGAS activation at micro-nuclei. *Mol. Cell* 81, 724–738.e9. <https://doi.org/10.1016/j.molcel.2020.12.037>.
216. Vanpouille-Box, C., Alard, A., Aryankalayil, M.J., Sarfraz, Y., Diamond, J.M., Schneider, R.J., Inghirami, G., Coleman, C.N., Formenti, S.C., and Demaria, S. (2017). DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity. *Nat. Commun.* 8, 15618. <https://doi.org/10.1038/ncomms15618>.
217. Tani, T., Mathsyyaraja, H., Campisi, M., Li, Z.H., Haratani, K., Fahey, C.G., Ota, K., Mahadevan, N.R., Shi, Y., Saito, S., et al. (2024). TREX1 Inactivation Unleashes Cancer Cell STING-Interferon Signaling and Promotes Antitumor Immunity. *Cancer Discov.* 14, 752–765. <https://doi.org/10.1158/2159-8290.CD-23-0700>.
218. Cristini, A., Tellier, M., Constantinescu, F., Accalai, C., Albulescu, L.O., Heringhoff, R., Bery, N., Sordet, O., Murphy, S., and Gromak, N. (2022). RNase H2, mutated in Aicardi-Goutières syndrome, resolves co-transcriptional R-loops to prevent DNA breaks and inflammation. *Nat. Commun.* 13, 2961. <https://doi.org/10.1038/s41467-022-30604-0>.
219. Cho, M.G., Kumar, R.J., Lin, C.C., Boyer, J.A., Shahir, J.A., Fagan-Solis, K., Simpson, D.A., Fan, C., Foster, C.E., Goddard, A.M., et al. (2024). MRE11 liberates cGAS from nucleosome sequestration during tumorigenesis. *Nature* 625, 585–592. <https://doi.org/10.1038/s41586-023-06889-6>.
220. Apetoh, L., Ghiringhelli, F., Tesniere, A., Obeid, M., Ortiz, C., Criollo, A., Mignot, G., Maiuri, M.C., Ullrich, E., Saulnier, P., et al. (2007). Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. *Nat. Med.* 13, 1050–1059. <https://doi.org/10.1038/nm1622>.
221. Scaffidi, P., Misteli, T., and Bianchi, M.E. (2002). Release of chromatin protein HMGB1 by necrotic cells triggers inflammation. *Nature* 418, 191–195. <https://doi.org/10.1038/nature00858>.
222. Yamazaki, T., Hannani, D., Poirier-Colame, V., Ladoire, S., Locher, C., Sistigu, A., Prada, N., Adjemian, S., Catani, J.P.P., Freudenberg, M., et al. (2014). Defective immunogenic cell death of HMGB1-deficient tumors: compensatory therapy with TLR4 agonists. *Cell Death Differ.* 21, 69–78. <https://doi.org/10.1038/cdd.2013.72>.
223. Hayashi, K., Nikolos, F., Lee, Y.C., Jain, A., Tsouko, E., Gao, H., Kasabyan, A., Leung, H.E., Osipov, A., Jung, S.Y., et al. (2020). Tipping the immunostimulatory and inhibitory DAMP balance to harness immunogenic cell death. *Nat. Commun.* 11, 6299. <https://doi.org/10.1038/s41467-020-19970-9>.
224. Mandula, J.K., Chang, S., Mohamed, E., Jimenez, R., Sierra-Mondragon, R.A., Chang, D.C., Obermayer, A.N., Moran-Segura, C.M., Das, S., Vazquez-Martinez, J.A., et al. (2022). Ablation of the endoplasmic reticulum stress kinase PERK induces paraptosis and type I interferon to promote anti-tumor T cell responses. *Cancer Cell* 40, 1145–1160.e9. <https://doi.org/10.1101/2022.08.016>.
225. Giampazolias, E., Schulz, O., Lim, K.H.J., Rogers, N.C., Chakravarty, P., Srinivasan, N., Gordon, O., Cardoso, A., Buck, M.D., Poirier, E.Z., et al. (2021). Secreted gelsolin inhibits DNGR-1-dependent cross-presentation and cancer immunity. *Cell* 184, 4016–4031.e22. <https://doi.org/10.1016/j.cell.2021.05.021>.
226. Wang, J., Sanmamed, M.F., Datar, I., Su, T.T., Ji, L., Sun, J., Chen, L., Chen, Y., Zhu, G., Yin, W., et al. (2019). Fibrinogen-like Protein 1 Is a Major Immune Inhibitory Ligand of LAG-3. *Cell* 176, 334–347.e12. <https://doi.org/10.1016/j.cell.2018.11.010>.
227. Vitale, I., Pietrocola, F., Guilbaud, E., Aaronson, S.A., Abrams, J.M., Adam, D., Agostini, M., Agostinis, P., Alnemri, E.S., Altucci, L., et al. (2023). Apoptotic cell death in disease—Current understanding of the NCCD 2023. *Cell Death Differ.* 30, 1097–1154. <https://doi.org/10.1038/s41418-023-01153-w>.
228. Rodriguez-Ruiz, M.E., Buqué, A., Hensler, M., Chen, J., Bloy, N., Petroni, G., Sato, A., Yamazaki, T., Fucikova, J., and Galluzzi, L. (2019). Apoptotic caspases inhibit abscopal responses to radiation and identify a new prognostic biomarker for breast cancer patients. *Oncolimmunology* 8, e1655964. <https://doi.org/10.1080/2162402X.2019.1655964>.
229. Han, C., Liu, Z., Zhang, Y., Shen, A., Dong, C., Zhang, A., Moore, C., Ren, Z., Lu, C., Cao, X., et al. (2020). Tumor cells suppress radiation-induced immunity by hijacking caspase 9 signaling. *Nat. Immunol.* 21, 546–554. <https://doi.org/10.1038/s41590-020-0641-5>.
230. Giampazolias, E., Zunino, B., Dhayade, S., Bock, F., Cloix, C., Cao, K., Roca, A., Lopez, J., Ichim, G., Proïcs, E., et al. (2017). Mitochondrial permeabilization engages NF- κ B-dependent anti-tumour activity under caspase deficiency. *Nat. Cell Biol.* 19, 1116–1129. <https://doi.org/10.1038/ncb3596>.
231. Ning, X., Wang, Y., Jing, M., Sha, M., Lv, M., Gao, P., Zhang, R., Huang, X., Feng, J.M., and Jiang, Z. (2019). Apoptotic Caspases Suppress Type I Interferon Production via the Cleavage of cGAS, MAVS, and IRF3. *Mol. Cell* 74, 19–31.e7. <https://doi.org/10.1016/j.molcel.2019.02.013>.
232. Buqué, A., Rodriguez-Ruiz, M.E., Fucikova, J., and Galluzzi, L. (2019). Apoptotic caspases cut down the immunogenicity of radiation. *Oncolimmunology* 8, e1655364. <https://doi.org/10.1080/2162402X.2019.1655364>.
233. Huang, Q., Li, F., Liu, X., Li, W., Shi, W., Liu, F.F., O'Sullivan, B., He, Z., Peng, Y., Tan, A.C., et al. (2011). Caspase 3-mediated stimulation of tumor cell repopulation during cancer radiotherapy. *Nat. Med.* 17, 860–866. <https://doi.org/10.1038/nm.2385>.
234. Galluzzi, L., Bravo-San Pedro, J.M., Vitale, I., Aaronson, S.A., Abrams, J.M., Adam, D., Alnemri, E.S., Altucci, L., Andrews, D., Annicchiarico-Petrusselli, M., et al. (2015). Essential versus accessory aspects of cell death: recommendations of the NCCD 2015. *Cell Death Differ.* 22, 58–73. <https://doi.org/10.1038/cdd.2014.137>.
235. Vanpouille-Box, C., Demaria, S., Formenti, S.C., and Galluzzi, L. (2018). Cytosolic DNA Sensing in Organismal Tumor Control. *Cancer Cell* 34, 361–378. <https://doi.org/10.1016/j.ccr.2018.05.013>.
236. Bakhour, S.F., Ngo, B., Laughney, A.M., Cavallo, J.A., Murphy, C.J., Ly, P., Shah, P., Sriram, R.K., Watkins, T.B.K., Taunk, N.K., et al. (2018). Chromosomal instability drives metastasis through a cytosolic DNA response. *Nature* 553, 467–472. <https://doi.org/10.1038/nature25432>.
237. Venkatesan, S., Angelova, M., Puttick, C., Zhai, H., Caswell, D.R., Lu, W.T., Dietzen, M., Galanos, P., Evangelou, K., Bellelli, R., et al. (2021). Induction of APOBEC3 Exacerbates DNA Replication Stress and Chromosomal Instability in Early Breast and Lung Cancer Evolution. *Cancer Discov.* 11, 2456–2473. <https://doi.org/10.1158/2159-8290.CD-20-0725>.
238. Martinez-Ruiz, C., Black, J.R.M., Puttick, C., Hill, M.S., Demeuilemeester, J., Larose Cadieux, E., Thol, K., Jones, T.P., Veeriah, S., Naceur-Lombardelli, C., et al. (2023). Genomic-transcriptomic evolution in lung cancer and metastasis. *Nature* 616, 543–552. <https://doi.org/10.1038/s41586-023-05706-4>.
239. Liu, Q., Zhang, J., Guo, C., Wang, M., Wang, C., Yan, Y., Sun, L., Wang, D., Zhang, L., Yu, H., et al. (2024). Proteogenomic characterization of small cell lung cancer identifies biological insights and subtype-specific therapeutic strategies. *Cell* 187, 184–203.e28. <https://doi.org/10.1016/j.cell.2023.12.004>.
240. Musella, M., Guaraccino, A., Manduca, N., Galassi, C., Ruggiero, E., Potenza, A., Maccagno, E., Manic, G., Mattiello, L., Soliman Abdel Rehim, S., et al. (2022). Type I IFNs promote cancer cell stemness by triggering

- the epigenetic regulator KDM1B. *Nat. Immunol.* 23, 1379–1392. <https://doi.org/10.1038/s41590-022-01290-3>.
241. Li, J., Hubisz, M.J., Earlie, E.M., Duran, M.A., Hong, C., Varela, A.A., Lettner, E., Deyell, M., Tavora, B., Havel, J.J., et al. (2023). Non-cell-autonomous cancer progression from chromosomal instability. *Nature* 620, 1080–1088. <https://doi.org/10.1038/s41586-023-06464-z>.
242. Weichselbaum, R.R., Ishwaran, H., Yoon, T., Nuyten, D.S.A., Baker, S.W., Khodarev, N., Su, A.W., Shaikh, A.Y., Roach, P., Kreike, B., et al. (2008). An interferon-related gene signature for DNA damage resistance is a predictive marker for chemotherapy and radiation for breast cancer. *Proc. Natl. Acad. Sci. USA* 105, 18490–18495. <https://doi.org/10.1073/pnas.0809242105>.
243. Su, W., Han, H.H., Wang, Y., Zhang, B., Zhou, B., Cheng, Y., Rumandla, A., Gurrapu, S., Chakraborty, G., Su, J., et al. (2019). The Polycomb Repressor Complex 1 Drives Double-Negative Prostate Cancer Metastasis by Coordinating Stemness and Immune Suppression. *Cancer Cell* 36, 139–155.e10. <https://doi.org/10.1016/j.ccr.2019.06.009>.
244. Martin, T.D., Patel, R.S., Cook, D.R., Choi, M.Y., Patil, A., Liang, A.C., Li, M.Z., Haigis, K.M., and Elledge, S.J. (2021). The adaptive immune system is a major driver of selection for tumor suppressor gene inactivation. *Science* 373, 1327–1335. <https://doi.org/10.1126/science.abg5784>.
245. Tang, T., Huang, X., Lu, M., Zhang, G., Han, X., and Liang, T. (2023). Transcriptional control of pancreatic cancer immunosuppression by metabolic enzyme CD73 in a tumor-autonomous and -autocrine manner. *Nat. Commun.* 14, 3364. <https://doi.org/10.1038/s41467-023-38578-3>.
246. Lee, R., Li, J., Li, J., Wu, C.J., Jiang, S., Hsu, W.H., Chakravarti, D., Chen, P., LaBella, K.A., Li, J., et al. (2022). Synthetic Essentiality of Tryptophan 2,3-Dioxygenase 2 in APC-Mutated Colorectal Cancer. *Cancer Discov.* 12, 1702–1717. <https://doi.org/10.1158/2159-8290.CD-21-0680>.
247. Facciabene, A., Peng, X., Hagemann, I.S., Balint, K., Barchetti, A., Wang, L.P., Gimotty, P.A., Gilks, C.B., Lal, P., Zhang, L., and Coukos, G. (2011). Tumour hypoxia promotes tolerance and angiogenesis via CCL28 and T(reg) cells. *Nature* 475, 226–230. <https://doi.org/10.1038/nature10169>.
248. Sattiraju, A., Kang, S., Giotti, B., Chen, Z., Marallano, V.J., Brusco, C., Ramakrishnan, A., Shen, L., Tsankov, A.M., Hambardzumyan, D., et al. (2023). Hypoxic niches attract and sequester tumor-associated macrophages and cytotoxic T cells and reprogram them for immunosuppression. *Immunity* 56, 1825–1843.e6. <https://doi.org/10.1016/j.jimmuni.2023.06.017>.
249. Zhang, B., Wang, C.M., Wu, H.X., Wang, F., Chai, Y.Y., Hu, Y., Wang, B.J., Yu, Z., Xia, R.H., Xu, R.H., and Cao, X.T. (2023). MFS2A potentiates gastric cancer response to anti-PD-1 immunotherapy by reprogramming the tumor microenvironment to activate T cell response. *Cancer Commun.* 43, 1097–1116. <https://doi.org/10.1002/cac2.12476>.
250. Liu, M., Kuo, F., Capistrano, K.J., Kang, D., Nixon, B.G., Shi, W., Chou, C., Do, M.H., Stamatopoulos, E.G., Gao, S., et al. (2020). TGF-beta suppresses type 2 immunity to cancer. *Nature* 587, 115–120. <https://doi.org/10.1038/s41586-020-2836-1>.
251. Vanpouille-Box, C., Diamond, J.M., Pilones, K.A., Zavadil, J., Babb, J.S., Formenti, S.C., Barcellos-Hoff, M.H., and Demaria, S. (2015). TGF β Is a Master Regulator of Radiation Therapy-Induced Antitumor Immunity. *Cancer Res.* 75, 2232–2242. <https://doi.org/10.1158/0008-5472.CAN-14-3511>.
252. De Martino, M., Daviaud, C., Diamond, J.M., Kraynak, J., Alard, A., Formenti, S.C., Miller, L.D., Demaria, S., and Vanpouille-Box, C. (2021). Activin A Promotes Regulatory T-cell-Mediated Immunosuppression in Irradiated Breast Cancer. *Cancer Immunol. Res.* 9, 89–102. <https://doi.org/10.1158/2326-6066.CIR-19-0305>.
253. Formenti, S.C., Lee, P., Adams, S., Goldberg, J.D., Li, X., Xie, M.W., Ratikan, J.A., Felix, C., Hwang, L., Faull, K.F., et al. (2018). Focal Irradiation and Systemic TGF β Blockade in Metastatic Breast Cancer. *Clin. Cancer Res.* 24, 2493–2504. <https://doi.org/10.1158/1078-0432.CCR-17-3322>.
254. Alfaro, C., Teijeira, A., Oñate, C., Pérez, G., Sanmamed, M.F., Andueza, M.P., Alignani, D., Labiano, S., Azpilikueta, A., Rodriguez-Paulete, A., et al. (2016). Tumor-Produced Interleukin-8 Attracts Human Myeloid-Derived Suppressor Cells and Elicits Extrusion of Neutrophil Extracellular Traps (NETs). *Clin. Cancer Res.* 22, 3924–3936. <https://doi.org/10.1158/1078-0432.CCR-15-2463>.
255. Chen, L., Shi, V., Wang, S., Sun, L., Freeman, R., Yang, J., Inkman, M.J., Ghosh, S., Ruiz, F., Jayachandran, K., et al. (2023). SCCA1/SERPINB3 suppresses antitumor immunity and blunts therapy-induced T cell responses via STAT-dependent chemokine production. *J. Clin. Invest.* 133, e163841. <https://doi.org/10.1172/JCI163841>.
256. Riaz, N., Havel, J.J., Kendall, S.M., Makarov, V., Walsh, L.A., Desrichard, A., Weinhold, N., and Chan, T.A. (2016). Recurrent SERPINB3 and SERPINB4 mutations in patients who respond to anti-CTLA4 immunotherapy. *Nat. Genet.* 48, 1327–1329. <https://doi.org/10.1038/ng.3677>.
257. Yue, J., Guo, H., Xu, P., Ma, J., Shi, W., and Wu, Y. (2024). Combination of IL-33 with PD-1 blockade augment mILC2s-mediated anti-tumor immunity. *Cancer Immunol. Immunother.* 73, 65. <https://doi.org/10.1007/s00262-023-03580-7>.
258. Jovanovic, M.Z., Geller, D.A., Gajovic, N.M., Jurisevic, M.M., Arsenijevic, N.N., Jovanovic, M.M., Supic, G.M., Vojvodic, D.V., and Jovanovic, I.P. (2022). Dual blockage of PD-L/PD-1 and IL33/ST2 axes slows tumor growth and improves antitumor immunity by boosting NK cells. *Life Sci.* 289, 120214. <https://doi.org/10.1016/j.lfs.2021.120214>.
259. Gao, X., Wang, X., Yang, Q., Zhao, X., Wen, W., Li, G., Lu, J., Qin, W., Qi, Y., Xie, F., et al. (2015). Tumoral expression of IL-33 inhibits tumor growth and modifies the tumor microenvironment through CD8+ T and NK cells. *J. Immunol.* 194, 438–445. <https://doi.org/10.4049/jimmunol.1401344>.
260. Zeng, Q., Saghafinia, S., Chrystlewich, A., Fournier, N., Christe, L., Xie, Y.Q., Guillot, J., Yucel, S., Li, P., Galván, J.A., et al. (2022). Aberrant hyperexpression of the RNA binding protein FMRP in tumors mediates immune evasion. *Science* 378, eabl7207. <https://doi.org/10.1126/science.abl7207>.
261. Ferrara, N., Hillan, K.J., Gerber, H.P., and Novotny, W. (2004). Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. *Nat. Rev. Drug Discov.* 3, 391–400. <https://doi.org/10.1038/nrd1381>.
262. Terme, M., Pernot, S., Marcheteau, E., Sandoval, F., Benhamouda, N., Colussi, O., Dubreuil, O., Carpentier, A.F., Tartour, E., and Taieb, J. (2013). VEGFA-VEGFR pathway blockade inhibits tumor-induced regulatory T-cell proliferation in colorectal cancer. *Cancer Res.* 73, 539–549. <https://doi.org/10.1158/0008-5472.CAN-12-2325>.
263. Tanchot, C., Terme, M., Pere, H., Tran, T., Benhamouda, N., Strioga, M., Banissi, C., Galluzzi, L., Kroemer, G., and Tartour, E. (2013). Tumor-infiltrating regulatory T cells: phenotype, role, mechanism of expansion *in situ* and clinical significance. *Cancer Microenviron.* 6, 147–157. <https://doi.org/10.1007/s12307-012-0122-y>.
264. Thomas, A.A., Fisher, J.L., Hampton, T.H., Christensen, B.C., Tsongalis, G.J., Rahme, G.J., Whipple, C.A., Steel, S.E., Davis, M.C., Gaur, A.B., et al. (2017). Immune modulation associated with vascular endothelial growth factor (VEGF) blockade in patients with glioblastoma. *Cancer Immunol. Immunother.* 66, 379–389. <https://doi.org/10.1007/s00262-016-1941-3>.
265. Voron, T., Colussi, O., Marcheteau, E., Pernot, S., Nizard, M., Pointet, A.L., Latreche, S., Bergaya, S., Benhamouda, N., Tanchot, C., et al. (2015). VEGF-A modulates expression of inhibitory checkpoints on CD8+ T cells in tumors. *J. Exp. Med.* 212, 139–148. <https://doi.org/10.1084/jem.20140559>.
266. Di Tacchio, M., Macas, J., Weissenberger, J., Sommer, K., Bähr, O., Steinbach, J.P., Senft, C., Seifert, V., Glas, M., Herrlinger, U., et al. (2019). Tumor Vessel Normalization, Immunostimulatory Reprogramming, and Improved Survival in Glioblastoma with Combined Inhibition of PD-1, Angiopoietin-2, and VEGF. *Cancer Immunol. Res.* 7, 1910–1927. <https://doi.org/10.1158/2326-6066.CIR-18-0865>.
267. Choueiri, T.K., Eto, M., Motzer, R., De Giorgi, U., Buchler, T., Basappa, N.S., Méndez-Vidal, M.J., Tjulandin, S., Hoon Park, S., Melichar, B., et al. (2023). Lenvatinib plus pembrolizumab versus sunitinib as first-line treatment of patients with advanced renal cell carcinoma (CLEAR): extended follow-up from the phase 3, randomised, open-label study. *Lancet Oncol.* 24, 228–238. [https://doi.org/10.1016/S1470-2045\(23\)00049-9](https://doi.org/10.1016/S1470-2045(23)00049-9).
268. Powles, T., Plimack, E.R., Soulières, D., Waddell, T., Stus, V., Gafanov, R., Nosov, D., Pouliot, F., Melichar, B., Vynnychenko, I., et al. (2020). Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended

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- follow-up from a randomised, open-label, phase 3 trial. *Lancet Oncol.* 21, 1563–1573. [https://doi.org/10.1016/S1470-2045\(20\)30436-8](https://doi.org/10.1016/S1470-2045(20)30436-8).
269. Thapa, R.J., Ingram, J.P., Ragan, K.B., Nogusa, S., Boyd, D.F., Benitez, A.A., Sridharan, H., Kosoff, R., Shubina, M., Landsteiner, V.J., et al. (2016). DAI Senses Influenza A Virus Genomic RNA and Activates RIPK3-Dependent Cell Death. *Cell Host Microbe* 20, 674–681. <https://doi.org/10.1016/j.chom.2016.09.014>.
270. Kuriakose, T., Man, S.M., Malireddi, R.K.S., Karki, R., Kesavardhana, S., Place, D.E., Neale, G., Vogel, P., and Kanneganti, T.D. (2016). ZBP1/DAI is an innate sensor of influenza virus triggering the NLRP3 inflammasome and programmed cell death pathways. *Sci. Immunol.* 1, aag2045. <https://doi.org/10.1126/scimmunol.aag2045>.
271. Olivera, I., Sanz-Pamplona, R., Bolaños, E., Rodriguez, I., Etxeberria, I., Cirella, A., Egea, J., Garasa, S., Migueliz, I., Eguren-Santamaría, I., et al. (2022). A Therapeutically Actionable Protumoral Axis of Cytokines Involving IL-8, TNF α , and IL-1 β . *Cancer Discov.* 12, 2140–2157. <https://doi.org/10.1158/2159-8290.Cd-21-1115>.
272. Zhang, B., Vogelzang, A., Miyajima, M., Sugiura, Y., Wu, Y., Chamoto, K., Nakano, R., Hatae, R., Menzies, R.J., Sonomura, K., et al. (2021). B cell-derived GABA elicits IL-10(+) macrophages to limit anti-tumour immunity. *Nature* 599, 471–476. <https://doi.org/10.1038/s41586-021-04082-1>.
273. Guo, Y., Xie, Y.Q., Gao, M., Zhao, Y., Franco, F., Wenes, M., Siddiqui, I., Bevilacqua, A., Wang, H., Yang, H., et al. (2021). Metabolic reprogramming of terminally exhausted CD8(+) T cells by IL-10 enhances anti-tumor immunity. *Nat. Immunol.* 22, 746–756. <https://doi.org/10.1038/s41590-021-00940-2>.
274. Mumm, J.B., Emmerich, J., Zhang, X., Chan, I., Wu, L., Mauze, S., Blaisdell, S., Basham, B., Dai, J., Grein, J., et al. (2011). IL-10 elicits IFN γ -dependent tumor immune surveillance. *Cancer Cell* 20, 781–796. <https://doi.org/10.1016/j.ccr.2011.11.003>.
275. Naing, A., Infante, J.R., Papadopoulos, K.P., Chan, I.H., Shen, C., Ratti, N.P., Rojo, B., Autio, K.A., Wong, D.J., Patel, M.R., et al. (2018). PEGylated IL-10 (Pegilodecakin) Induces Systemic Immune Activation, CD8(+) T Cell Invigoration and Polyclonal T Cell Expansion in Cancer Patients. *Cancer Cell* 34, 775–791.e3. <https://doi.org/10.1016/j.ccell.2018.10.007>.
276. Hanahan, D. (2022). Hallmarks of Cancer: New Dimensions. *Cancer Discov.* 12, 31–46. <https://doi.org/10.1158/2159-8290.Cd-21-1059>.
277. De Martino, M., Rathmell, J.C., Galluzzi, L., and Vanpouille-Box, C. (2024). Cancer cell metabolism and antitumour immunity. *Nat. Rev. Immunol.* 24, 654–669. <https://doi.org/10.1038/s41577-024-01026-4>.
278. Ghiringhelli, F., Apetoh, L., Tesniere, A., Aymeric, L., Ma, Y., Ortiz, C., Vermaelen, K., Panaretakis, T., Mignot, G., Ullrich, E., et al. (2009). Activation of the NLRP3 inflammasome in dendritic cells induces IL-1beta-dependent adaptive immunity against tumors. *Nat. Med.* 15, 1170–1178. <https://doi.org/10.1038/nm.2028>.
279. Allard, B., Allard, D., Buisseret, L., and Stagg, J. (2020). The adenosine pathway in immuno-oncology. *Nat. Rev. Clin. Oncol.* 17, 611–629. <https://doi.org/10.1038/s41571-020-0382-2>.
280. Ohta, A., Gorelik, E., Prasad, S.J., Ronchese, F., Lukashev, D., Wong, M.K.K., Huang, X., Caldwell, S., Liu, K., Smith, P., et al. (2006). A2A adenosine receptor protects tumors from antitumor T cells. *Proc. Natl. Acad. Sci. USA* 103, 13132–13137. <https://doi.org/10.1073/pnas.0605251103>.
281. Wennerberg, E., Spada, S., Rudqvist, N.P., Lhuillier, C., Gruber, S., Chen, Q., Zhang, F., Zhou, X.K., Gross, S.S., Formenti, S.C., and Demaria, S. (2020). CD73 Blockade Promotes Dendritic Cell Infiltration of Irradiated Tumors and Tumor Rejection. *Cancer Immunol. Res.* 8, 465–478. <https://doi.org/10.1158/2326-6066.Cir-19-0449>.
282. Gangoso, E., Southgate, B., Bradley, L., Rus, S., Galvez-Cancino, F., McGivern, N., Güç, E., Kapourani, C.A., Byron, A., Ferguson, K.M., et al. (2021). Glioblastomas acquire myeloid-affiliated transcriptional programs via epigenetic immunoediting to elicit immune evasion. *Cell* 184, 2454–2470.e26. <https://doi.org/10.1016/j.cell.2021.03.023>.
283. Young, A., Ngiow, S.F., Barkauskas, D.S., Sult, E., Hay, C., Blake, S.J., Huang, Q., Liu, J., Takeda, K., Teng, M.W.L., et al. (2016). Co-inhibition of CD73 and A2AR Adenosine Signaling Improves Anti-tumor Immune Responses. *Cancer Cell* 30, 391–403. <https://doi.org/10.1016/j.ccel.2016.06.025>.
284. Krahenbuehl, L., Weng, C.H., Eghbali, S., Wolchock, J.D., and Merghoub, T. (2022). Enhancing immunotherapy in cancer by targeting emerging immunomodulatory pathways. *Nat. Rev. Clin. Oncol.* 19, 37–50. <https://doi.org/10.1038/s41571-021-00552-7>.
285. Lemos, H., Huang, L., Prendergast, G.C., and Mellor, A.L. (2019). Immune control by amino acid catabolism during tumorigenesis and therapy. *Nat. Rev. Cancer* 19, 162–175. <https://doi.org/10.1038/s41568-019-0106-z>.
286. Shi, D., Wu, X., Jian, Y., Wang, J., Huang, C., Mo, S., Li, Y., Li, F., Zhang, C., Zhang, D., et al. (2022). USP14 promotes tryptophan metabolism and immune suppression by stabilizing IDO1 in colorectal cancer. *Nat. Commun.* 13, 5644. <https://doi.org/10.1038/s41467-022-33285-x>.
287. Opitz, C.A., Litzenburger, U.M., Sahm, F., Ott, M., Tritschler, I., Trump, S., Schumacher, T., Jestaedt, L., Schrenk, D., Weller, M., et al. (2011). An endogenous tumour-promoting ligand of the human aryl hydrocarbon receptor. *Nature* 478, 197–203. <https://doi.org/10.1038/nature10491>.
288. Liu, Y., Liang, X., Yin, X., Lv, J., Tang, K., Ma, J., Ji, T., Zhang, H., Dong, W., Jin, X., et al. (2017). Blockade of IDO-kynurenone-AhR metabolic circuitry abrogates IFN γ -induced immunologic dormancy of tumor-repopulating cells. *Nat. Commun.* 8, 15207. <https://doi.org/10.1038/ncomms15207>.
289. Long, G.V., Dummer, R., Hamid, O., Gajewski, T.F., Caglevic, C., Dalle, S., Arance, A., Carlini, M.S., Grob, J.J., Kim, T.M., et al. (2019). Epacadostat plus pembrolizumab versus placebo plus pembrolizumab in patients with unresectable or metastatic melanoma (ECHO-301/KEYNOTE-252): a phase 3, randomised, double-blind study. *Lancet Oncol.* 20, 1083–1097. <https://doi.org/10.1016/j.lane.2019.30274-8>.
290. Le Naour, J., Galluzzi, L., Zitvogel, L., Kroemer, G., and Vacchelli, E. (2020). Trial watch: IDO inhibitors in cancer therapy. *Oncolimmunology* 9, 1777625. <https://doi.org/10.1080/2162402X.2020.1777625>.
291. Vacchelli, E., Aranda, F., Eggermont, A., Sautès-Fridman, C., Tartour, E., Kennedy, E.P., Platten, M., Zitvogel, L., Kroemer, G., and Galluzzi, L. (2014). Trial watch: IDO inhibitors in cancer therapy. *Oncolimmunology* 3, e957994. <https://doi.org/10.4161/21624011.2014.957994>.
292. Kesarwani, P., Kant, S., Zhao, Y., Prabhu, A., Buelow, K.L., Miller, C.R., and Chinnaiyan, P. (2023). Quinolinolate promotes macrophage-induced immune tolerance in glioblastoma through the NMDAR/PPAR γ signaling axis. *Nat. Commun.* 14, 1459. <https://doi.org/10.1038/s41467-023-37170-z>.
293. Clement, C.C., D'Alessandro, A., Thangaswamy, S., Chalmers, S., Furtado, R., Spada, S., Mondanelli, G., Ianni, F., Gehrke, S., Gargaro, M., et al. (2021). 3-hydroxy-L-kynurenamine is an immunomodulatory biogenic amine. *Nat. Commun.* 12, 4447. <https://doi.org/10.1038/s41467-021-24785-3>.
294. Zhao, E., Maj, T., Kryczek, I., Li, W., Wu, K., Zhao, L., Wei, S., Crespo, J., Wan, S., Vatan, L., et al. (2016). Cancer mediates effector T cell dysfunction by targeting microRNAs and EZH2 via glycolysis restriction. *Nat. Immunol.* 17, 95–103. <https://doi.org/10.1038/ni.3313>.
295. Chang, C.H., Qiu, J., O'Sullivan, D., Buck, M.D., Noguchi, T., Curtis, J.D., Chen, Q., Gindin, M., Gubin, M.M., van der Windt, G.J.W., et al. (2015). Metabolic Competition in the Tumor Microenvironment Is a Driver of Cancer Progression. *Cell* 162, 1229–1241. <https://doi.org/10.1016/j.cell.2015.08.016>.
296. Qiu, J., Villa, M., Sanin, D.E., Buck, M.D., O'Sullivan, D., Ching, R., Matsushita, M., Grzes, K.M., Winkler, F., Chang, C.H., et al. (2019). Acetate Promotes T Cell Effector Function during Glucose Restriction. *Cell Rep.* 27, 2063–2074.e5. <https://doi.org/10.1016/j.celrep.2019.04.022>.
297. Liu, Y., Liang, G., Xu, H., Dong, W., Dong, Z., Qiu, Z., Zhang, Z., Li, F., Huang, Y., Li, Y., et al. (2021). Tumors exploit FTO-mediated regulation of glycolytic metabolism to evade immune surveillance. *Cell Metab.* 33, 1221–1233.e11. <https://doi.org/10.1016/j.cmet.2021.04.001>.
298. Wu, L., Jin, Y., Zhao, X., Tang, K., Zhao, Y., Tong, L., Yu, X., Xiong, K., Luo, C., Zhu, J., et al. (2023). Tumor aerobic glycolysis confers immune evasion through modulating sensitivity to T cell-mediated bystander

- killing via TNF- α . *Cell Metab.* 35, 1580–1596.e9. <https://doi.org/10.1016/j.cmet.2023.07.001>.
299. Zappasodi, R., Serganova, I., Cohen, I.J., Maeda, M., Shindo, M., Senba-baoglu, Y., Watson, M.J., Leftin, A., Maniyar, R., Verma, S., et al. (2021). CTLA-4 blockade drives loss of T(reg) stability in glycolysis-low tumours. *Nature* 597, 652–658. <https://doi.org/10.1038/s41586-021-03326-4>.
300. Reinfeld, B.I., Madden, M.Z., Wolf, M.M., Chytil, A., Bader, J.E., Patterson, A.R., Sugiura, A., Cohen, A.S., Ali, A., Do, B.T., et al. (2021). Cell-programmed nutrient partitioning in the tumour microenvironment. *Nature* 593, 282–288. <https://doi.org/10.1038/s41586-021-03442-1>.
301. Leone, R.D., Zhao, L., Englert, J.M., Sun, I.M., Oh, M.H., Sun, I.H., Arwood, M.L., Bettencourt, I.A., Patel, C.H., Wen, J., et al. (2019). Glutamine blockade induces divergent metabolic programs to overcome tumor immune evasion. *Science* 366, 1013–1021. <https://doi.org/10.1126/science.aav2588>.
302. Edwards, D.N., Ngwa, V.M., Raybuck, A.L., Wang, S., Hwang, Y., Kim, L.C., Cho, S.H., Paik, Y., Wang, Q., Zhang, S., et al. (2021). Selective glutamine metabolism inhibition in tumor cells improves antitumor T lymphocyte activity in triple-negative breast cancer. *J. Clin. Invest.* 131, e140100. <https://doi.org/10.1172/JCI140100>.
303. Byun, J.K., Park, M., Lee, S., Yun, J.W., Lee, J., Kim, J.S., Cho, S.J., Jeon, H.J., Lee, I.K., Choi, Y.K., and Park, K.G. (2020). Inhibition of Glutamine Utilization Synergizes with Immune Checkpoint Inhibitor to Promote Antitumor Immunity. *Mol. Cell* 80, 592–606.e8. <https://doi.org/10.1016/j.molcel.2020.10.015>.
304. Guo, C., You, Z., Shi, H., Sun, Y., Du, X., Palacios, G., Guy, C., Yuan, S., Chapman, N.M., Lim, S.A., et al. (2023). SLC38A2 and glutamine signaling in cDC1s dictate anti-tumour immunity. *Nature* 620, 200–208. <https://doi.org/10.1038/s41586-023-06299-8>.
305. Claps, G., Faouzi, S., Quidville, V., Chehade, F., Shen, S., Vagner, S., and Robert, C. (2022). The multiple roles of LDH in cancer. *Nat. Rev. Clin. Oncol.* 19, 749–762. <https://doi.org/10.1038/s41571-022-00686-2>.
306. Swietach, P., Boedtkjer, E., and Pedersen, S.F. (2023). How protons pave the way to aggressive cancers. *Nat. Rev. Cancer* 23, 825–841. <https://doi.org/10.1038/s41568-023-00628-9>.
307. Elia, I., Rowe, J.H., Johnson, S., Joshi, S., Notarangelo, G., Kurmi, K., Weiss, S., Freeman, G.J., Sharpe, A.H., and Haigis, M.C. (2022). Tumor cells dictate anti-tumor immune responses by altering pyruvate utilization and succinate signaling in CD8(+) T cells. *Cell Metab.* 34, 1137–1150.e6. <https://doi.org/10.1016/j.cmet.2022.06.008>.
308. Brand, A., Singer, K., Koehl, G.E., Kolitzus, M., Schoenhammer, G., Thiel, A., Matos, C., Bruss, C., Klobuch, S., Peter, K., et al. (2016). LDHA-Associated Lactic Acid Production Blunts Tumor Immunosurveillance by T and NK Cells. *Cell Metab.* 24, 657–671. <https://doi.org/10.1016/j.cmet.2016.08.011>.
309. Qian, Y., Galan-Cobo, A., Guijarro, I., Dang, M., Molkentin, D., Poteete, A., Zhang, F., Wang, Q., Wang, J., Parra, E., et al. (2023). MCT4-dependent lactate secretion suppresses antitumor immunity in LKB1-deficient lung adenocarcinoma. *Cancer Cell* 41, 1363–1380.e7. <https://doi.org/10.1016/j.ccell.2023.05.015>.
310. Babl, N., Decking, S.M., Voll, F., Althammer, M., Sala-Hojman, A., Ferretti, R., Korf, C., Schmidl, C., Schmidleithner, L., Nerb, B., et al. (2023). MCT4 blockade increases the efficacy of immune checkpoint blockade. *J. Immunother. Cancer* 11, e007349. <https://doi.org/10.1136/jitc-2023-007349>.
311. Lopez, E., Karattil, R., Nannini, F., Weng-Kit Cheung, G., Denzler, L., Galvez-Cancino, F., Quezada, S., and Pule, M.A. (2023). Inhibition of lactate transport by MCT-1 blockade improves chimeric antigen receptor T-cell therapy against B-cell malignancies. *J. Immunother. Cancer* 11, e006287. <https://doi.org/10.1136/jitc-2022-006287>.
312. Bohn, T., Rapp, S., Luther, N., Klein, M., Bruehl, T.J., Kojima, N., Aranda Lopez, P., Hahlbrock, J., Muth, S., Endo, S., et al. (2018). Tumor immunevasion via acidosis-dependent induction of regulatory tumor-associated macrophages. *Nat. Immunol.* 19, 1319–1329. <https://doi.org/10.1038/s41590-018-0226-8>.
313. Chen, P., Zuo, H., Xiong, H., Kolar, M.J., Chu, Q., Saghatelyan, A., Siegwart, D.J., and Wan, Y. (2017). Gpr132 sensing of lactate mediates tumor-macrophage interplay to promote breast cancer metastasis. *Proc. Natl. Acad. Sci. USA* 114, 580–585. <https://doi.org/10.1073/pnas.1614035114>.
314. Gu, J., Zhou, J., Chen, Q., Xu, X., Gao, J., Li, X., Shao, Q., Zhou, B., Zhou, H., Wei, S., et al. (2022). Tumor metabolite lactate promotes tumorigenesis by modulating MOESIN lactylation and enhancing TGF- β signaling in regulatory T cells. *Cell Rep.* 39, 110986. <https://doi.org/10.1016/j.celrep.2022.110986>.
315. Watson, M.J., Vignali, P.D.A., Mullett, S.J., Overacre-Delgoffe, A.E., Peralta, R.M., Grebinoski, S., Menk, A.V., Rittenhouse, N.L., DePeaux, K., Whetstone, R.D., et al. (2021). Metabolic support of tumour-infiltrating regulatory T cells by lactic acid. *Nature* 591, 645–651. <https://doi.org/10.1038/s41586-020-03045-2>.
316. Kumagai, S., Koyama, S., Itashiki, K., Tanegashima, T., Lin, Y.T., Togashi, Y., Kamada, T., Irie, T., Okumura, G., Kono, H., et al. (2022). Lactic acid promotes PD-1 expression in regulatory T cells in highly glycolytic tumor microenvironments. *Cancer Cell* 40, 201–218.e9. <https://doi.org/10.1016/j.ccel.2022.01.001>.
317. Pirozzi, C.J., and Yan, H. (2021). The implications of IDH mutations for cancer development and therapy. *Nat. Rev. Clin. Oncol.* 18, 645–661. <https://doi.org/10.1038/s41571-021-00521-0>.
318. Zecchinelli, V., Paupe, V., Herranz-Montoya, I., Janssen, J., Wortel, I.M.N., Morris, J.L., Ferguson, A., Chowdury, S.R., Segarra-Mondejar, M., Costa, A.S.H., et al. (2023). Fumarate induces vesicular release of mtDNA to drive innate immunity. *Nature* 615, 499–506. <https://doi.org/10.1038/s41586-023-05770-w>.
319. Cheng, J., Yan, J., Liu, Y., Shi, J., Wang, H., Zhou, H., Zhou, Y., Zhang, T., Zhao, L., Meng, X., et al. (2023). Cancer-cell-derived fumarate suppresses the anti-tumor capacity of CD8(+) T cells in the tumor microenvironment. *Cell Metab.* 35, 961–978.e10. <https://doi.org/10.1016/j.cmet.2023.04.017>.
320. Tomlinson, I.P.M., Alam, N.A., Rowan, A.J., Barclay, E., Jaeger, E.E.M., Kelsell, D., Leigh, I., Gorman, P., Lamium, H., Rahman, S., et al. (2002). Germline mutations in FH predispose to dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cell cancer. *Nat. Genet.* 30, 406–410. <https://doi.org/10.1038/ng849>.
321. Miller, K.D., O'Connor, S., Pniewski, K.A., Kannan, T., Acosta, R., Mirji, G., Papp, S., Hulse, M., Mukha, D., Hlavaty, S.I., et al. (2023). Acetate acts as a metabolic immunomodulator by bolstering T-cell effector function and potentiating antitumor immunity in breast cancer. *Nat. Cancer* 4, 1491–1507. <https://doi.org/10.1038/s43018-023-00636-6>.
322. Xu, W., Yang, H., Liu, Y., Yang, Y., Wang, P., Kim, S.H., Ito, S., Yang, C., Wang, P., Xiao, M.T., et al. (2011). Oncometabolite 2-hydroxyglutarate is a competitive inhibitor of α -ketoglutarate-dependent dioxygenases. *Cancer Cell* 19, 17–30. <https://doi.org/10.1016/j.ccr.2010.12.014>.
323. Notarangelo, G., Spinelli, J.B., Perez, E.M., Baker, G.J., Kurmi, K., Elia, I., Stopka, S.A., Baquer, G., Lin, J.R., Golby, A.J., et al. (2022). Oncometabolite d-2HG alters T cell metabolism to impair CD8(+) T cell function. *Science* 377, 1519–1529. <https://doi.org/10.1126/science.abj5104>.
324. Shim, E.H., Livi, C.B., Rakheja, D., Tan, J., Benson, D., Parekh, V., Kho, E.Y., Ghosh, A.P., Kirkman, R., Velu, S., et al. (2014). L-2-Hydroxyglutarate: an epigenetic modifier and putative oncometabolite in renal cancer. *Cancer Discov.* 4, 1290–1298. <https://doi.org/10.1158/2159-8290.CD-13-0696>.
325. Gupta, V.K., Sharma, N.S., Durden, B., Garrido, V.T., Kesh, K., Edwards, D., Wang, D., Myer, C., Mateo-Victoriano, B., Kollala, S.S., et al. (2021). Hypoxia-Driven Oncometabolite L-2HG Maintains Stemness-Differentiation Balance and Facilitates Immune Evasion in Pancreatic Cancer. *Cancer Res.* 81, 4001–4013. <https://doi.org/10.1158/0008-5472.CAN-20-2562>.
326. Puchalska, P., and Crawford, P.A. (2021). Metabolic and Signaling Roles of Ketone Bodies in Health and Disease. *Annu. Rev. Nutr.* 41, 49–77. <https://doi.org/10.1146/annurev-nutr-111120-111518>.
327. Wei, R., Zhou, Y., Li, C., Rychahou, P., Zhang, S., Titlow, W.B., Bauman, G., Wu, Y., Liu, J., Wang, C., et al. (2022). Ketogenesis Attenuates KLF5-Dependent Production of CXCL12 to Overcome the Immunosuppressive Tumor Microenvironment in Colorectal Cancer. *Cancer Res.* 82, 1575–1588. <https://doi.org/10.1158/0008-5472.CAN-21-2778>.

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Review



328. Murphy, S., Rahmy, S., Gan, D., Liu, G., Zhu, Y., Manyak, M., Duong, L., He, J., Schofield, J.H., Schafer, Z.T., et al. (2024). Ketogenic Diet Alters the Epigenetic and Immune Landscape of Prostate Cancer to Overcome Resistance to Immune Checkpoint Blockade Therapy. *Cancer Res.* 84, 1597–1612. <https://doi.org/10.1158/0008-5472.Can-23-2742>.
329. Bian, Y., Li, W., Kremer, D.M., Sajjakulnukit, P., Li, S., Crespo, J., Nwosu, Z.C., Zhang, L., Czerwonka, A., Pawłowska, A., et al. (2020). Cancer SLC43A2 alters T cell methionine metabolism and histone methylation. *Nature* 585, 277–282. <https://doi.org/10.1038/s41586-020-2682-1>.
330. Hung, M.H., Lee, J.S., Ma, C., Diggs, L.P., Heinrich, S., Chang, C.W., Ma, L., Forgues, M., Budhu, A., Chaisaingmongkol, J., et al. (2021). Tumor methionine metabolism drives T-cell exhaustion in hepatocellular carcinoma. *Nat. Commun.* 12, 1455. <https://doi.org/10.1038/s41467-021-21804-1>.
331. Henrich, F.C., Singer, K., Poller, K., Bernhardt, L., Strobl, C.D., Limm, K., Ritter, A.P., Gottfried, E., Völkl, S., Jacobs, B., et al. (2016). Suppressive effects of tumor cell-derived 5'-deoxy-5'-methylthiadenosine on human T cells. *Oncol Immunol* 5, e1184802. <https://doi.org/10.1080/2162402X.2016.1184802>.
332. Montrose, D.C., Saha, S., Foronda, M., McNally, E.M., Chen, J., Zhou, X.K., Ha, T., Krumsiek, J., Buyukozkan, M., Verma, A., et al. (2021). Exogenous and Endogenous Sources of Serine Contribute to Colon Cancer Metabolism, Growth, and Resistance to 5-Fluorouracil. *Cancer Res.* 81, 2275–2288. <https://doi.org/10.1158/0008-5472.Can-20-1541>.
333. Röhrig, F., and Schulze, A. (2016). The multifaceted roles of fatty acid synthesis in cancer. *Nat. Rev. Cancer* 16, 732–749. <https://doi.org/10.1038/nrc.2016.89>.
334. Jiang, L., Fang, X., Wang, H., Li, D., and Wang, X. (2018). Ovarian Cancer-Intrinsic Fatty Acid Synthase Prevents Anti-tumor Immunity by Disrupting Tumor-Infiltrating Dendritic Cells. *Front. Immunol.* 9, 2927. <https://doi.org/10.3389/fimmu.2018.02927>.
335. Enkler, L., Szentgyörgyi, V., Pennauer, M., Prescianotto-Baschong, C., Riezman, I., Wiesyk, A., Avraham, R.E., Spiess, M., Zalckvar, E., Kurcharczyk, R., et al. (2023). Arf1 coordinates fatty acid metabolism and mitochondrial homeostasis. *Nat. Cell Biol.* 25, 1157–1172. <https://doi.org/10.1038/s41556-023-01180-2>.
336. Samovski, D., Jacome-Sosa, M., and Abumrad, N.A. (2023). Fatty Acid Transport and Signaling: Mechanisms and Physiological Implications. *Annu. Rev. Physiol.* 85, 317–337. [https://doi.org/10.1146/annurev-physiol-032122-030352](https://doi.org/10.1146/annurevophysiol-032122-030352).
337. Ma, X., Xiao, L., Liu, L., Ye, L., Su, P., Bi, E., Wang, Q., Yang, M., Qian, J., and Yi, Q. (2021). CD36-mediated ferroptosis dampens intratumoral CD8(+) T cell effector function and impairs their antitumor ability. *Cell Metab.* 33, 1001–1012.e5. <https://doi.org/10.1016/j.cmet.2021.02.015>.
338. Xu, S., Chaudhary, O., Rodríguez-Morales, P., Sun, X., Chen, D., Zappasodi, R., Xu, Z., Pinto, A.F.M., Williams, A., Schulze, I., et al. (2021). Uptake of oxidized lipids by the scavenger receptor CD36 promotes lipid peroxidation and dysfunction in CD8(+) T cells in tumors. *Immunity* 54, 1561–1577.e7. <https://doi.org/10.1016/j.jimmuni.2021.05.003>.
339. Wang, H., Franco, F., Tsui, Y.C., Xie, X., Trefny, M.P., Zappasodi, R., Mohmood, S.R., Fernández-García, J., Tsai, C.H., Schulze, I., et al. (2020). CD36-mediated metabolic adaptation supports regulatory T cell survival and function in tumors. *Nat. Immunol.* 21, 298–308. <https://doi.org/10.1038/s41590-019-0589-5>.
340. Bayerl, F., Meiser, P., Donakonda, S., Hirschberger, A., Lacher, S.B., Pedde, A.M., Hermann, C.D., Elewaut, A., Knolle, M., Ramsauer, L., et al. (2023). Tumor-derived prostaglandin E2 programs cDC1 dysfunction to impair intratumoral orchestration of anti-cancer T cell responses. *Immunity* 56, 1341–1358.e11. <https://doi.org/10.1016/j.jimmuni.2023.05.011>.
341. Zelenay, S., van der Veen, A.G., Böttcher, J.P., Snelgrove, K.J., Rogers, N., Acton, S.E., Chakravarty, P., Girotti, M.R., Marais, R., Quezada, S.A., et al. (2015). Cyclooxygenase-Dependent Tumor Growth through Evasion of Immunity. *Cell* 162, 1257–1270. <https://doi.org/10.1016/j.cell.2015.08.015>.
342. Meiser, P., Knolle, M.A., Hirschberger, A., de Almeida, G.P., Bayerl, F., Lacher, S., Pedde, A.M., Flommersfeld, S., Hönniger, J., Stark, L., et al. (2023). A distinct stimulatory cDC1 subpopulation amplifies CD8(+) T cell responses in tumors for protective anti-cancer immunity. *Cancer Cell* 41, 1498–1515.e10. <https://doi.org/10.1016/j.ccell.2023.06.008>.
343. Lacher, S.B., Dörr, J., de Almeida, G.P., Hönniger, J., Bayerl, F., Hirschberger, A., Pedde, A.M., Meiser, P., Ramsauer, L., Rudolph, T.J., et al. (2024). PGE(2) limits effector expansion of tumour-infiltrating stem-like CD8(+) T cells. *Nature* 629, 417–425. <https://doi.org/10.1038/s41586-024-07254-x>.
344. Morotti, M., Grimm, A.J., Hope, H.C., Arnaud, M., Desbuissson, M., Rayroux, N., Barras, D., Masid, M., Murgues, B., Chap, B.S., et al. (2024). PGE(2) inhibits TIL expansion by disrupting IL-2 signalling and mitochondrial function. *Nature* 629, 426–434. <https://doi.org/10.1038/s41586-024-07352-w>.
345. Böttcher, J.P., Bonavita, E., Chakravarty, P., Blees, H., Cabeza-Cabrerizo, M., Sammiceli, S., Rogers, N.C., Sahai, E., Zelenay, S., and Reis e Sousa, C. (2018). NK Cells Stimulate Recruitment of cDC1 into the Tumor Microenvironment Promoting Cancer Immune Control. *Cell* 172, 1022–1037.e14. <https://doi.org/10.1016/j.cell.2018.01.004>.
346. Caronni, N., La Terza, F., Vittoria, F.M., Barbiera, G., Mezzanzanica, L., Cuzzola, V., Barresi, S., Pellegratta, M., Canevazzi, P., Dunsmore, G., et al. (2023). IL-1β(+) macrophages fuel pathogenic inflammation in pancreatic cancer. *Nature* 623, 415–422. <https://doi.org/10.1038/s41586-023-06685-2>.
347. Chae, C.S., Sandoval, T.A., Hwang, S.M., Park, E.S., Giovanelli, P., Awasthi, D., Salvagno, C., Ermanuelli, A., Tan, C., Chaudhary, V., et al. (2022). Tumor-Derived Lysophosphatidic Acid Blunts Protective Type I Interferon Responses in Ovarian Cancer. *Cancer Discov.* 12, 1904–1921. <https://doi.org/10.1158/2159-8290.CD-21-1181>.
348. Ye, S.Y., Li, J.Y., Li, T.H., Song, Y.X., Sun, J.X., Chen, X.W., Zhao, J.H., Li, Y., Wu, Z.H., Gao, P., and Huang, X.Z. (2022). The Efficacy and Safety of Celecoxib in Addition to Standard Cancer Therapy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Curr. Oncol.* 29, 6137–6153. <https://doi.org/10.3390/croncol29090482>.
349. He, C., Wang, D., Shukla, S.K., Hu, T., Thakur, R., Fu, X., King, R.J., Koliala, S.S., Attri, K.S., Murthy, D., et al. (2024). Vitamin B6 Competition in the Tumor Microenvironment Hampers Antitumor Functions of NK Cells. *Cancer Discov.* 14, 176–193. <https://doi.org/10.1158/2159-8290.CD-23-0334>.
350. Buqué, A., Bloy, N., Perez-Lanzón, M., Iribarren, K., Humeau, J., Pol, J.G., Levesque, S., Mondragon, L., Yamazaki, T., Sato, A., et al. (2020). Immunoprophylactic and immunotherapeutic control of hormone receptor-positive breast cancer. *Nat. Commun.* 11, 3819. <https://doi.org/10.1038/s41467-020-17644-0>.
351. Selvanesan, B.C., Meena, K., Beck, A., Meheus, L., Lara, O., Rooman, I., and Gravekamp, C. (2020). Nicotinamide combined with gemcitabine is an immunomodulatory therapy that restrains pancreatic cancer in mice. *J. Immunother. Cancer* 8, e001250. <https://doi.org/10.1136/jitc-2020-001250>.
352. Galluzzi, L., Vacchelli, E., Michels, J., Garcia, P., Kepp, O., Senovilla, L., Vitale, I., and Kroemer, G. (2013). Effects of vitamin B6 metabolism on oncogenesis, tumor progression and therapeutic responses. *Oncogene* 32, 4995–5004. <https://doi.org/10.1038/onc.2012.623>.
353. Cichocki, F., Zhang, B., Wu, C.Y., Chiu, E., Day, A., O'Connor, R.S., Yackoubov, D., Simantov, R., McKenna, D.H., Cao, Q., et al. (2023). Nicotinamide enhances natural killer cell function and yields remissions in patients with non-Hodgkin lymphoma. *Sci. Transl. Med.* 15, eade3341. <https://doi.org/10.1126/scitranslmed.ad3341>.
354. Devalaraja, S., To, T.K.J., Folkert, I.W., Natesan, R., Alam, M.Z., Li, M., Tada, Y., Budagyan, K., Dang, M.T., Zhai, L., et al. (2020). Tumor-Derived Retinoic Acid Regulates Intratumoral Monocyte Differentiation to Promote Immune Suppression. *Cell* 180, 1098–1114.e16. <https://doi.org/10.1016/j.cell.2020.02.042>.
355. Ngo, B., Van Riper, J.M., Cantley, L.C., and Yun, J. (2019). Targeting cancer vulnerabilities with high-dose vitamin C. *Nat. Rev. Cancer* 19, 271–282. <https://doi.org/10.1038/s41588-019-0135-7>.
356. Feske, S., Wulff, H., and Skolnik, E.Y. (2015). Ion channels in innate and adaptive immunity. *Annu. Rev. Immunol.* 33, 291–353. <https://doi.org/10.1146/annurev-immunol-032414-112212>.

357. Eil, R., Vodnala, S.K., Clever, D., Klebanoff, C.A., Sukumar, M., Pan, J.H., Palmer, D.C., Gros, A., Yamamoto, T.N., Patel, S.J., et al. (2016). Ionic immune suppression within the tumour microenvironment limits T cell effector function. *Nature* 537, 539–543. <https://doi.org/10.1038/nature19364>.
358. Vodnala, S.K., Eil, R., Kishton, R.J., Sukumar, M., Yamamoto, T.N., Ha, N.H., Lee, P.H., Shin, M., Patel, S.J., Yu, Z., et al. (2019). T cell stemness and dysfunction in tumors are triggered by a common mechanism. *Science* 363, eaau0135. <https://doi.org/10.1126/science.aau0135>.
359. Dustin, M.L., and Choudhuri, K. (2016). Signaling and Polarized Communication Across the T Cell Immunological Synapse. *Annu. Rev. Cell Dev. Biol.* 32, 303–325. <https://doi.org/10.1146/annurev-cellbio-100814-125330>.
360. Liu, Y., Zhang, T., Zhang, H., Li, J., Zhou, N., Fiskesund, R., Chen, J., Lv, J., Ma, J., Zhang, H., et al. (2021). Cell Softness Prevents Cytolytic T-cell Killing of Tumor-Rep populating Cells. *Cancer Res.* 81, 476–488. <https://doi.org/10.1158/0008-5472.Can-20-2569>.
361. Zhou, Y., Wang, D., Zhou, L., Zhou, N., Wang, Z., Chen, J., Pang, R., Fu, H., Huang, Q., Dong, F., et al. (2024). Cell softness renders cytotoxic T lymphocytes and T leukemic cells resistant to perforin-mediated killing. *Nat. Commun.* 15, 1405. <https://doi.org/10.1038/s41467-024-45750-w>.
362. Al Absi, A., Wurzer, H., Guerin, C., Hoffmann, C., Moreau, F., Mao, X., Brown-Clay, J., Petrolini, R., Casellas, C.P., Dieterle, M., et al. (2018). Actin Cytoskeleton Remodeling Drives Breast Cancer Cell Escape from Natural Killer-Mediated Cytotoxicity. *Cancer Res.* 78, 5631–5643. <https://doi.org/10.1158/0008-5472.Can-18-0441>.
363. Sanchez, E.E., Tello-Lafoz, M., Guo, A.J., de Jesus, M., Elbanna, Y.A., Winer, B.Y., Budhu, S., Chan, E., Rosiek, E., Kondo, T., et al. (2023). Apoptotic contraction drives target cell release by cytotoxic T cells. *Nat. Immunol.* 24, 1434–1442. <https://doi.org/10.1038/s41590-023-01572-4>.
364. Khazen, R., Müller, S., Gaudenzio, N., Espinosa, E., Puissegur, M.P., and Valtutti, S. (2016). Melanoma cell lysosome secretory burst neutralizes the CTL-mediated cytotoxicity at the lytic synapse. *Nat. Commun.* 7, 10823. <https://doi.org/10.1038/ncomms10823>.
365. Ritter, A.T., Shtengel, G., Xu, C.S., Weigel, A., Hoffman, D.P., Freeman, M., Iyer, N., Alivodej, N., Ackerman, D., Voskoboinik, I., et al. (2022). ESCRT-mediated membrane repair protects tumor-derived cells against T cell attack. *Science* 376, 377–382. <https://doi.org/10.1126/science.abi3855>.
366. Tuomela, K., Mukherjee, D., Ambrose, A.R., Harikrishnan, A., Mole, H., Hurlstone, A., Önfelt, B., Honeychurch, J., and Davis, D.M. (2022). Radiotherapy transiently reduces the sensitivity of cancer cells to lymphocyte cytotoxicity. *Proc. Natl. Acad. Sci. USA* 119, e2111900119. <https://doi.org/10.1073/pnas.2111900119>.
367. Maecker, H.L., Yun, Z., Maecker, H.T., and Giaccia, A.J. (2002). Epigenetic changes in tumor Fas levels determine immune escape and response to therapy. *Cancer Cell* 2, 139–148. [https://doi.org/10.1016/s1535-6108\(02\)00095-8](https://doi.org/10.1016/s1535-6108(02)00095-8).
368. Kearney, C.J., Vervoort, S.J., Hogg, S.J., Ramsbottom, K.M., Freeman, A.J., Lalaoui, N., Pijpers, L., Michie, J., Brown, K.K., Knight, D.A., et al. (2018). Tumor immune evasion arises through loss of TNF sensitivity. *Sci. Immunol.* 3, eaar3451. <https://doi.org/10.1126/sciimmunol.aar3451>.
369. Kim, I.K., Diamond, M.S., Yuan, S., Kemp, S.B., Kahn, B.M., Li, Q., Lin, J.H., Li, J., Norgard, R.J., Thomas, S.K., et al. (2024). Plasticity-induced repression of Irf6 underlies acquired resistance to cancer immunotherapy in pancreatic ductal adenocarcinoma. *Nat. Commun.* 15, 1532. <https://doi.org/10.1038/s41467-024-46048-7>.
370. Gao, J., Shi, L.Z., Zhao, H., Chen, J., Xiong, L., He, Q., Chen, T., Roszik, J., Bernatchez, C., Woodman, S.E., et al. (2016). Loss of IFN- γ Pathway Genes in Tumor Cells as a Mechanism of Resistance to Anti-CTLA-4 Therapy. *Cell* 167, 397–404.e9. <https://doi.org/10.1016/j.cell.2016.08.069>.
371. Goto, N., Westcott, P.M.K., Goto, S., Imada, S., Taylor, M.S., Eng, G., Braverman, J., Deshpande, V., Jacks, T., Agudo, J., and Yilmaz, O.H. (2024). SOX17 enables immune evasion of early colorectal adenomas and cancers. *Nature* 627, 636–645. <https://doi.org/10.1038/s41586-024-07135-3>.
372. Vredevoogd, D.W., Kuilman, T., Ligtenberg, M.A., Boshuizen, J., Stecker, K.E., de Brujin, B., Krijgsman, O., Huang, X., Kenski, J.C.N., Lacroix, R., et al. (2019). Augmenting Immunotherapy Impact by Lowering Tumor TNF Cytotoxicity Threshold. *Cell* 178, 585–599.e15. <https://doi.org/10.1016/j.cell.2019.06.014>.
373. Sun, Y., Revach, O.Y., Anderson, S., Kessler, E.A., Wolfe, C.H., Jenney, A., Mills, C.E., Robitschek, E.J., Davis, T.G.R., Kim, S., et al. (2023). Targeting TBK1 to overcome resistance to cancer immunotherapy. *Nature* 615, 158–167. <https://doi.org/10.1038/s41586-023-05704-6>.
374. Lee, Y.G., Guruprasad, P., Ghilardi, G., Pajarillo, R., Sauter, C.T., Patel, R., Ballard, H.J., Hong, S.J., Chun, I., Yang, N., et al. (2022). Modulation of BCL-2 in Both T Cells and Tumor Cells to Enhance Chimeric Antigen Receptor T-cell Immunotherapy against Cancer. *Cancer Discov.* 12, 2372–2391. <https://doi.org/10.1158/2159-8290.CD-21-1026>.
375. Wang, W., Green, M., Choi, J.E., Gijón, M., Kennedy, P.D., Johnson, J.K., Liao, P., Lang, X., Kryczek, I., Sell, A., et al. (2019). CD8(+) T cells regulate tumour ferroptosis during cancer immunotherapy. *Nature* 569, 270–274. <https://doi.org/10.1038/s41586-019-1170-y>.
376. Liao, P., Wang, W., Wang, W., Kryczek, I., Li, X., Bian, Y., Sell, A., Wei, S., Grove, S., Johnson, J.K., et al. (2022). CD8(+) T cells and fatty acids orchestrate tumor ferroptosis and immunity via ACSL4. *Cancer Cell* 40, 365–378.e6. <https://doi.org/10.1016/j.ccr.2022.02.003>.
377. Zhang, Z., Zhang, Y., Xia, S., Kong, Q., Li, S., Liu, X., Junqueira, C., Meza-Sosa, K.F., Mok, T.M.Y., Ansara, J., et al. (2020). Gasdermin E suppresses tumour growth by activating anti-tumour immunity. *Nature* 579, 415–420. <https://doi.org/10.1038/s41586-020-2071-9>.
378. Nozaki, K., Maltez, V.I., Rayamajhi, M., Tubbs, A.L., Mitchell, J.E., Lacey, C.A., Harvest, C.K., Li, L., Nash, W.T., Larson, H.N., et al. (2022). Caspase-7 activates ASM to repair gasdermin and perforin pores. *Nature* 606, 960–967. <https://doi.org/10.1038/s41586-022-04825-8>.
379. Medema, J.P., de Jong, J., Peltensburg, L.T., Verdegaaal, E.M., Gorter, A., Bres, S.A., Franken, K.L., Hahne, M., Albar, J.P., Melief, C.J., and Offringa, R. (2001). Blockade of the granzyme B/perforin pathway through overexpression of the serine protease inhibitor PI-9/SPI-6 constitutes a mechanism for immune escape by tumors. *Proc. Natl. Acad. Sci. USA* 98, 11515–11520. <https://doi.org/10.1073/pnas.201398198>.
380. Jiang, L., Wang, Y.J., Zhao, J., Uehara, M., Hou, Q., Kasinath, V., Ichimura, T., Banouni, N., Dai, L., Li, X., et al. (2020). Direct Tumor Killing and Immunotherapy through Anti-SerpinB9 Therapy. *Cell* 183, 1219–1233.e18. <https://doi.org/10.1016/j.cell.2020.10.045>.
381. Sun, J., Bird, C.H., Sutton, V., McDonald, L., Coughlin, P.B., De Jong, T.A., Trapani, J.A., and Bird, P.I. (1996). A cytosolic granzyme B inhibitor related to the viral apoptotic regulator cytokine response modifier A is present in cytotoxic lymphocytes. *J. Biol. Chem.* 271, 27802–27809. <https://doi.org/10.1074/jbc.271.44.27802>.
382. Bladergroen, B.A., Strik, M.C., Bovenschen, N., van Berkum, O., Scheffer, G.L., Meijer, C.J., Hack, C.E., and Kummer, J.A. (2001). The granzyme B inhibitor, protease inhibitor 9, is mainly expressed by dendritic cells and at immune-privileged sites. *J. Immunol.* 166, 3218–3225. <https://doi.org/10.4049/jimmunol.166.5.3218>.
383. Lawson, K.A., Sousa, C.M., Zhang, X., Kim, E., Akther, R., Caumanns, J.J., Yao, Y., Mikolajewicz, N., Ross, C., Brown, K.R., et al. (2020). Functional genomic landscape of cancer-intrinsic evasion of killing by T cells. *Nature* 586, 120–126. <https://doi.org/10.1038/s41586-020-2746-2>.
384. Norman, M.Z., Janji, B., Kaminska, B., Van Moer, K., Pierson, S., Prznowski, P., Buart, S., Berchem, G., Romero, P., Mami-Chouaib, F., and Chouaib, S. (2011). Blocking hypoxia-induced autophagy in tumors restores cytotoxic T-cell activity and promotes regression. *Cancer Res.* 71, 5976–5986. <https://doi.org/10.1158/0008-5472.Can-11-1094>.
385. Baginska, J., Viry, E., Berchem, G., Poli, A., Norman, M.Z., van Moer, K., Medves, S., Zimmer, J., Oudin, A., Niclou, S.P., et al. (2013). Granzyme B degradation by autophagy decreases tumor cell susceptibility to natural killer-mediated lysis under hypoxia. *Proc. Natl. Acad. Sci. USA* 110, 17450–17455. <https://doi.org/10.1073/pnas.1304790110>.
386. Minute, L., Teijeira, A., Sanchez-Paulete, A.R., Ochoa, M.C., Alvarez, M., Otano, I., Etxeberria, I., Bolaños, E., Azpilikueta, A., Garasa, S., et al. (2020). Cellular cytotoxicity is a form of immunogenic cell death. <https://doi.org/10.1038/s41586-020-05704-6>.

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- J. Immunother. Cancer 8, e000325. <https://doi.org/10.1136/jitc-2019-000325>.
387. Jaime-Sanchez, P., Uranga-Murillo, I., Aguiló, N., Khouili, S.C., Arias, M.A., Sancho, D., and Pardo, J. (2020). Cell death induced by cytotoxic CD8⁺T cells is immunogenic and primes caspase-3-dependent spread immunity against endogenous tumor antigens. *J. Immunother. Cancer* 8, e000528. <https://doi.org/10.1136/jitc-2020-000528>.
388. Li, Z.L., Zhang, H.L., Huang, Y., Huang, J.H., Sun, P., Zhou, N.N., Chen, Y.H., Mai, J., Wang, Y., Yu, Y., et al. (2020). Autophagy deficiency promotes triple-negative breast cancer resistance to T cell-mediated cytotoxicity by blocking tenascin-C degradation. *Nat. Commun.* 11, 3806. <https://doi.org/10.1038/s41467-020-17395-y>.
389. Bagati, A., Kumar, S., Jiang, P., Pyrdol, J., Zou, A.E., Godicelj, A., Mathewson, N.D., Cartwright, A.N.R., Cejas, P., Brown, M., et al. (2021). Integrin $\alpha\beta$ -TGF β -SOX4 Pathway Drives Immune Evasion in Triple-Negative Breast Cancer. *Cancer Cell* 39, 54–67.e9. <https://doi.org/10.1016/j.ccr.2020.12.001>.
390. Sharma, P., and Allison, J.P. (2020). Dissecting the mechanisms of immune checkpoint therapy. *Nat. Rev. Immunol.* 20, 75–76. <https://doi.org/10.1038/s41577-020-0275-z>.
391. Goebeler, M.E., and Bargou, R.C. (2020). T cell-engaging therapies - BiTEs and beyond. *Nat. Rev. Clin. Oncol.* 17, 418–434. <https://doi.org/10.1038/s41571-020-0347-5>.
392. Larson, R.C., and Maus, M.V. (2021). Recent advances and discoveries in the mechanisms and functions of CAR T cells. *Nat. Rev. Cancer* 21, 145–161. <https://doi.org/10.1038/s41568-020-00323-z>.
393. Propper, D.J., and Balkwill, F.R. (2022). Harnessing cytokines and chemokines for cancer therapy. *Nat. Rev. Clin. Oncol.* 19, 237–253. <https://doi.org/10.1038/s41571-021-00588-9>.
394. Iadonato, S., Ovechkina, Y., Lustig, K., Cross, J., Eyde, N., Frazier, E., Kabi, N., Katz, C., Lance, R., Peckham, D., et al. (2023). A highly potent anti-VISTA antibody KVA12123 - a new immune checkpoint inhibitor and a promising therapy against poorly immunogenic tumors. *Front. Immunol.* 14, 1311658. <https://doi.org/10.3389/fimmu.2023.1311658>.
395. Klaibmon, P., Luanpitpong, S., Kang, X., and Issaragrisil, S. (2023). Anti-TIM3 chimeric antigen receptor-natural killer cells from engineered induced pluripotent stem cells effectively target acute myeloid leukemia cells. *Cancer Cell Int.* 23, 297. <https://doi.org/10.1186/s12935-023-03153-9>.
396. Preillon, J., Cuende, J., Rabolli, V., Garnero, L., Mercier, M., Wald, N., Pappalardo, A., Denies, S., Jamart, D., Michaux, A.C., et al. (2021). Restoration of T-cell Effector Function, Depletion of Tregs, and Direct Killing of Tumor Cells: The Multiple Mechanisms of Action of a-TIGIT Antagonist Antibodies. *Mol. Cancer Ther.* 20, 121–131. <https://doi.org/10.1158/1535-7163.Mct-20-0464>.
397. Diong, S.J., Jashnani, A., Drake, A.W., Bee, C., Findeisen, F., Dollinger, G., Wang, F., Rajpal, A., Strop, P., and Lee, P.S. (2023). Biophysical characterization of PVR family interactions and therapeutic antibody recognition to TIGIT. *mAbs* 15, 2253788. <https://doi.org/10.1080/19420862.2023.2253788>.
398. Chen, X., Xue, L., Ding, X., Zhang, J., Jiang, L., Liu, S., Hou, H., Jiang, B., Cheng, L., Zhu, Q., et al. (2022). An Fc-Competent Anti-Human TIGIT Blocking Antibody Ociperlimab (BGB-A1217) Elicits Strong Immune Responses and Potent Anti-Tumor Efficacy in Pre-Clinical Models. *Front. Immunol.* 13, 828319. <https://doi.org/10.3389/fimmu.2022.828319>.
399. Hoffman-Censits, J., Grivas, P., Powles, T., Hawley, J., Tyroller, K., Seeger, S., Guenther, S., Jacob, N., Mehr, K.T., and Hahn, N.M. (2024). The JAVELIN Bladder Medley trial: avelumab-based combinations as first-line maintenance in advanced urothelial carcinoma. *Future Oncol.* 20, 179–190. <https://doi.org/10.2217/fon-2023-0492>.
400. Herbst, R.S., Majem, M., Barlesi, F., Carcereny, E., Chu, Q., Monnet, I., Sanchez-Hernandez, A., Dakhlil, S., Camidge, D.R., Winzer, L., et al. (2022). COAST: An Open-Label, Phase II, Multidrug Platform Study of Durvalumab Alone or in Combination With Oleclumab or Monalizumab in Patients With Unresectable, Stage III Non-Small-Cell Lung Cancer. *J. Clin. Oncol.* 40, 3383–3393. <https://doi.org/10.1200/jco.22.00227>.
401. Dovedi, S.J., Elder, M.J., Yang, C., Sitnikova, S.I., Irving, L., Hansen, A., Hair, J., Jones, D.C., Hasani, S., Wang, B., et al. (2021). Design and Efficacy of a Monovalent Bispecific PD-1/CTLA4 Antibody That Enhances CTLA4 Blockade on PD-1(+) Activated T Cells. *Cancer Discov.* 11, 1100–1117. <https://doi.org/10.1158/2159-8290.Cd-20-1445>.
402. Sun, Y., Yu, J., Tolcher, A.W., Albany, C., Chaudhry, A., Dang, Q., Ye, L., Yang, F., Liu, B., Sun, L., et al. (2024). A phase I/II, open-label, multicenter study to evaluate the safety, pharmacokinetics, pharmacodynamics, and efficacy of HB0036 in patients with advanced solid tumors. *J. Clin. Oncol.* 42, e14504. https://doi.org/10.1200/JCO.2024.42.16_suppl.e14504.
403. Geng, Q., and Jiao, P. (2024). Anti-PD-L1-Based Bispecific Antibodies Targeting Co-Inhibitory and Co-Stimulatory Molecules for Cancer Immunotherapy. *Molecules* 29, 454. <https://doi.org/10.3390/molecules29020454>.
404. Sikic, B.I., Lakhani, N., Patnaik, A., Shah, S.A., Chandana, S.R., Rasco, D., Colevas, A.D., O'Rourke, T., Narayanan, S., Papadopoulos, K., et al. (2019). First-in-Human, First-in-Class Phase I Trial of the Anti-CD47 Antibody Hu5F9-G4 in Patients With Advanced Cancers. *J. Clin. Oncol.* 37, 946–953. <https://doi.org/10.1200/jco.18.02018>.
405. Berlin, J., Harb, W., Adjei, A., Xing, Y., Swiecicki, P., Seetharam, M., Nandagopal, L., Gopal, A., Xu, C., Meng, Y., et al. (2020). A First-in-Human Study of Lemzoparilimab, a Differentiated Anti-Cd47 Antibody, in Subjects with Relapsed/Refractory Malignancy: Initial Monotherapy Results. *J. Immunother. Cancer* 8, A233–A234. <https://doi.org/10.1136/jitc-2020-SITC2020.0385>.
406. Lin, G.H.Y., Villar, N.N., Chabonneau, M., Brinen, L., Mutukura, T., Dodge, K., Helke, S., Chai, V., House, V., Lee, V., et al. (2018). TTI-622 (SIRP α -IgG4 Fc), a CD47-blocking innate immune checkpoint inhibitor, suppresses tumor growth and demonstrates enhanced efficacy in combination with antitumor antibodies in both hematologic and solid tumor models. *Cancer Res.* 78, 2709. <https://doi.org/10.1158/1538-7445.Am2018-2709>.
407. Lakhani, N.J., Chow, L.Q.M., Gainor, J.F., LoRusso, P., Lee, K.W., Chung, H.C., Lee, J., Bang, Y.J., Hodi, F.S., Kim, W.S., et al. (2021). Evopacept alone and in combination with pembrolizumab or trastuzumab in patients with advanced solid tumours (ASPEN-01): a first-in-human, open-label, multicentre, phase 1 dose-escalation and dose-expansion study. *Lancet Oncol.* 22, 1740–1751. [https://doi.org/10.1016/S1470-2045\(21\)00584-2](https://doi.org/10.1016/S1470-2045(21)00584-2).
408. Yokoyama, Y., Estok, T.M., and Wild, R. (2022). Sirpiglenastat (DRP-104) Induces Antitumor Efficacy through Direct, Broad Antagonism of Glutamine Metabolism and Stimulation of the Innate and Adaptive Immune Systems. *Mol. Cancer Ther.* 21, 1561–1572. <https://doi.org/10.1158/1535-7163.Mct-22-0282>.
409. Polański, R., Hodgkinson, C.L., Fusi, A., Nonaka, D., Priest, L., Kelly, P., Trapani, F., Bishop, P.W., White, A., Critchlow, S.E., et al. (2014). Activity of the monocarboxylate transporter 1 inhibitor AZD3965 in small cell lung cancer. *Clin. Cancer Res.* 20, 926–937. <https://doi.org/10.1158/1078-0432.Ccr-13-2270>.
410. Leone, R.D., Sun, I.M., Oh, M.H., Sun, I.H., Wen, J., Englert, J., and Powell, J.D. (2018). Inhibition of the adenosine A2a receptor modulates expression of T cell coinhibitory receptors and improves effector function for enhanced checkpoint blockade and ACT in murine cancer models. *Cancer Immunol. Immunother.* 67, 1271–1284. <https://doi.org/10.1007/s00262-018-2186-0>.
411. Claff, T., Schlegel, J.G., Voss, J.H., Vaaßen, V.J., Weiße, R.H., Cheng, R.K.Y., Markovic-Mueller, S., Bucher, D., Sträter, N., and Müller, C.E. (2023). Crystal structure of adenosine A(2A) receptor in complex with clinical candidate Etrumadenant reveals unprecedented antagonist interaction. *Commun. Chem.* 6, 106. <https://doi.org/10.1038/s42004-023-00894-6>.
412. Vanpouille-Box, C., Hoffmann, J.A., and Galluzzi, L. (2019). Pharmacological modulation of nucleic acid sensors - therapeutic potential and persisting obstacles. *Nat. Rev. Drug Discov.* 18, 845–867. <https://doi.org/10.1038/s41573-019-0043-2>.
413. Kim, H., George, E., Ragland, R., Rafail, S., Zhang, R., Krepler, C., Morgan, M., Herlyn, M., Brown, E., and Simpkins, F. (2017). Targeting the ATR/CHK1 Axis with PARP Inhibition Results in Tumor Regression in BRCA-Mutant Ovarian Cancer Models. *Clin. Cancer Res.* 23, 3097–3108. <https://doi.org/10.1158/1078-0432.CCR-16-2273>.

414. Fokas, E., Prevo, R., Pollard, J.R., Reaper, P.M., Charlton, P.A., Cornelissen, B., Vallis, K.A., Hammond, E.M., Olcina, M.M., Gillies McKenna, W., et al. (2012). Targeting ATR *in vivo* using the novel inhibitor VE-822 results in selective sensitization of pancreatic tumors to radiation. *Cell Death Dis.* 3, e441. <https://doi.org/10.1038/cddis.2012.181>.
415. Roulston, A., Zimmermann, M., Papp, R., Skeldon, A., Pellerin, C., Dumas-Berube, É., Dumais, V., Dorich, S., Fader, L.D., Fournier, S., et al. (2022). RP-3500: A Novel, Potent, and Selective ATR Inhibitor that is Effective in Preclinical Models as a Monotherapy and in Combination with PARP Inhibitors. *Mol. Cancer Ther.* 21, 245–256. <https://doi.org/10.1158/1535-7163.MCT-21-0615>.
416. Hirai, H., Iwasawa, Y., Okada, M., Arai, T., Nishibata, T., Kobayashi, M., Kimura, T., Kaneko, N., Ohtani, J., Yamanaka, K., et al. (2009). Small-molecule inhibition of Wee1 kinase by MK-1775 selectively sensitizes p53-deficient tumor cells to DNA-damaging agents. *Mol. Cancer Ther.* 8, 2992–3000. <https://doi.org/10.1158/1535-7163.MCT-09-0463>.
417. Park, S.J., Chang, S.J., Suh, D.H., Kong, T.W., Song, H., Kim, T.H., Kim, J.W., Kim, H.S., and Lee, S.J. (2022). A phase I dose-escalation study of PHI-101, a new checkpoint kinase 2 inhibitor, for platinum-resistant recurrent ovarian cancer. *BMC Cancer* 22, 28. <https://doi.org/10.1186/s12885-021-09138-z>.
418. Uslu, U., Sun, L., Castelli, S., Finck, A.V., Assenmacher, C.A., Young, R.M., Chen, Z.J., and June, C.H. (2024). The STING agonist IMSA101 enhances chimeric antigen receptor T cell function by inducing IL-18 secretion. *Nat. Commun.* 15, 3933. <https://doi.org/10.1038/s41467-024-47692-9>.
419. Carideo Cunniff, E., Sato, Y., Mai, D., Appleman, V.A., Iwasaki, S., Kolev, V., Matsuda, A., Shi, J., Mochizuki, M., Yoshikawa, M., et al. (2022). TAK-676: A Novel Stimulator of Interferon Genes (STING) Agonist Promoting Durable IFN-dependent Antitumor Immunity in Preclinical Studies. *Cancer Res. Commun.* 2, 489–502. <https://doi.org/10.1158/2767-9764.Crc-21-0161>.
420. Gulen, M.F., Koch, U., Haag, S.M., Schuler, F., Apetoh, L., Villunger, A., Radtke, F., and Ablässer, A. (2017). Signalling strength determines pro-apoptotic functions of STING. *Nat. Commun.* 8, 427. <https://doi.org/10.1038/s41467-017-00573-w>.
421. Cerboni, S., Jeremiah, N., Gentili, M., Gehrmann, U., Conrad, C., Stolzenberg, M.C., Picard, C., Neven, B., Fischer, A., Amigorena, S., et al. (2017). Intrinsic antiproliferative activity of the innate sensor STING in T lymphocytes. *J. Exp. Med.* 214, 1769–1785. <https://doi.org/10.1084/jem.20161674>.
422. Stine, Z.E., Schug, Z.T., Salvino, J.M., and Dang, C.V. (2022). Targeting cancer metabolism in the era of precision oncology. *Nat. Rev. Drug Discov.* 21, 141–162. <https://doi.org/10.1038/s41573-021-00339-6>.
423. Hogg, S.J., Beavis, P.A., Dawson, M.A., and Johnstone, R.W. (2020). Targeting the epigenetic regulation of antitumour immunity. *Nat. Rev. Drug Discov.* 19, 776–800. <https://doi.org/10.1038/s41573-020-0077-5>.
424. Mahalingam, D., Harb, W., Patnaik, A., Bullock, A., Watnick, R.S., Vincent, M.Y., Chen, J.J., Wang, S., Pestana, H., Chao, J., et al. (2024). First-in-human phase I dose escalation trial of the first-in-class tumor microenvironment modulator VT1021 in advanced solid tumors. *Commun. Med.* 4, 10. <https://doi.org/10.1038/s43856-024-00433-x>.
425. Diepstraten, S.T., Anderson, M.A., Czabotar, P.E., Lessene, G., Strasser, A., and Kelly, G.L. (2022). The manipulation of apoptosis for cancer therapy using BH3-mimetic drugs. *Nat. Rev. Cancer* 22, 45–64. <https://doi.org/10.1038/s41568-021-00407-4>.
426. Naka, K., Ishihara, K., Jomen, Y., Jin, C.H., Kim, D.H., Gu, Y.K., Jeong, E.S., Li, S., Krause, D.S., Kim, D.W., et al. (2016). Novel oral transforming growth factor- β signaling inhibitor EW-7197 eradicates CML-initiating cells. *Cancer Sci.* 107, 140–148. <https://doi.org/10.1111/cas.12849>.
427. Vugmeyster, Y., Wilkins, J., Koenig, A., El Bawab, S., Dussault, I., Ojalvo, L.S., De Banerjee, S., Klopp-Schulze, L., and Khandelwal, A. (2020). Selection of the Recommended Phase 2 Dose for Bintrafusp Alfa, a Bifunctional Fusion Protein Targeting TGF- β and PD-L1. *Clin. Pharmacol. Ther.* 108, 566–574. <https://doi.org/10.1002/cpt.1776>.
428. Zheng, X., Hou, Z., Qian, Y., Zhang, Y., Cui, Q., Wang, X., Shen, Y., Liu, Z., Zhou, Y., Fu, B., et al. (2023). Tumors evade immune cytotoxicity by altering the surface topology of NK cells. *Nat. Immunol.* 24, 802–813. <https://doi.org/10.1038/s41590-023-01462-9>.
429. Goddard, E.T., Linde, M.H., Srivastava, S., Klug, G., Shabaneh, T.B., Iannone, S., Grzelak, C.A., Marsh, S., Riggio, A.I., Shor, R.E., et al. (2024). Immune evasion of dormant disseminated tumor cells is due to their scarcity and can be overcome by T cell immunotherapies. *Cancer Cell* 42, 119–134.e12. <https://doi.org/10.1016/j.ccr.2023.12.011>.
430. Abdel-Hafiz, H.A., Schafer, J.M., Chen, X., Xiao, T., Gauntner, T.D., Li, Z., and Theodorescu, D. (2023). Y chromosome loss in cancer drives growth by evasion of adaptive immunity. *Nature* 619, 624–631. <https://doi.org/10.1038/s41586-023-06234-x>.
431. Angelova, M., Mlecnik, B., Vasaturo, A., Bindea, G., Fredriksen, T., Lafontaine, L., Buttard, B., Morgand, E., Bruni, D., Jouret-Mourin, A., et al. (2018). Evolution of Metastases in Space and Time under Immune Selection. *Cell* 175, 751–765.e16. <https://doi.org/10.1016/j.cell.2018.09.018>.
432. Martinez-Jimenez, F., Priestley, P., Shale, C., Baber, J., Rozemuller, E., and Cuppen, E. (2023). Genetic immune escape landscape in primary and metastatic cancer. *Nat. Genet.* 55, 820–831. <https://doi.org/10.1038/s41588-023-01367-1>.
433. Mascaux, C., Angelova, M., Vasaturo, A., Beane, J., Hijazi, K., Anthoine, G., Buttard, B., Rothe, F., Willard-Gallo, K., Haller, A., et al. (2019). Immune evasion before tumour invasion in early lung squamous carcinogenesis. *Nature* 571, 570–575. <https://doi.org/10.1038/s41586-019-1330-0>.
434. Nguyen, P.H.D., Wasser, M., Tan, C.T., Lim, C.J., Lai, H.L.H., Seow, J.J.W., DasGupta, R., Phua, C.Z.J., Ma, S., Yang, J., et al. (2022). Trajectory of immune evasion and cancer progression in hepatocellular carcinoma. *Nat. Commun.* 13, 1441. <https://doi.org/10.1038/s41467-022-29122-w>.
435. Bruni, D., Angell, H.K., and Galon, J. (2020). The immune contexture and Immunoscore in cancer prognosis and therapeutic efficacy. *Nat. Rev. Cancer* 20, 662–680. <https://doi.org/10.1038/s41568-020-0285-7>.
436. Doroshow, D.B., Bhalla, S., Beasley, M.B., Sholl, L.M., Kerr, K.M., Gnajtic, S., Wistuba, I.I., Rimm, D.L., Tsao, M.S., and Hirsch, F.R. (2021). PD-L1 as a biomarker of response to immune-checkpoint inhibitors. *Nat. Rev. Clin. Oncol.* 18, 345–362. <https://doi.org/10.1038/s41571-021-00473-5>.
437. Grasso, C.S., Tsoi, J., Onyshchenko, M., Abril-Rodriguez, G., Ross-Macdonald, P., Wind-Rotolo, M., Champhekar, A., Medina, E., Torrejon, D.Y., Shin, D.S., et al. (2020). Conserved Interferon-gamma Signaling Drives Clinical Response to Immune Checkpoint Blockade Therapy in Melanoma. *Cancer Cell* 38, 500–515.e3. <https://doi.org/10.1016/j.ccr.2020.08.005>.
438. Benci, J.L., Johnson, L.R., Choa, R., Xu, Y., Qiu, J., Zhou, Z., Xu, B., Ye, D., Nathanson, K.L., June, C.H., et al. (2019). Opposing Functions of Interferon Coordinate Adaptive and Innate Immune Responses to Cancer Immune Checkpoint Blockade. *Cell* 178, 933–948.e14. <https://doi.org/10.1016/j.cell.2019.07.019>.
439. Lee, P., Chandel, N.S., and Simon, M.C. (2020). Cellular adaptation to hypoxia through hypoxia inducible factors and beyond. *Nat. Rev. Mol. Cell Biol.* 21, 268–283. <https://doi.org/10.1038/s41580-020-0227-y>.
440. Vignali, P.D.A., DePeaux, K., Watson, M.J., Ye, C., Ford, B.R., Lontos, K., McGaa, N.K., Scharping, N.E., Menk, A.V., Robson, S.C., et al. (2023). Hypoxia drives CD39-dependent suppressor function in exhausted T cells to limit antitumor immunity. *Nat. Immunol.* 24, 267–279. <https://doi.org/10.1038/s41590-022-01379-9>.
441. Zheng, X., Qian, Y., Fu, B., Jiao, D., Jiang, Y., Chen, P., Shen, Y., Zhang, H., Sun, R., Tian, Z., and Wei, H. (2019). Mitochondrial fragmentation limits NK cell-based tumor immunosurveillance. *Nat. Immunol.* 20, 1656–1667. <https://doi.org/10.1038/s41590-019-0511-1>.
442. Park, J.H., Kim, H.J., Kim, C.W., Kim, H.C., Jung, Y., Lee, H.S., Lee, Y., Ju, Y.S., Oh, J.E., Park, S.H., et al. (2021). Tumor hypoxia represses $\gamma\delta$ T cell-mediated antitumor immunity against brain tumors. *Nat. Immunol.* 22, 336–346. <https://doi.org/10.1038/s41590-020-00860-7>.
443. Baessler, A., and Vignali, D.A.A. (2024). T Cell Exhaustion. *Annu. Rev. Immunol.* 42, 179–206. <https://doi.org/10.1146/annurev-immunol-090222-110914>.
444. Chow, A., Perica, K., Klebanoff, C.A., and Wolchok, J.D. (2022). Clinical implications of T cell exhaustion for cancer immunotherapy. *Nat. Rev. Clin. Oncol.* 19, 775–790. <https://doi.org/10.1038/s41571-022-00689-z>.

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445. Galletti, G., De Simone, G., Mazza, E.M.C., Puccio, S., Mezzanotte, C., Bi, T.M., Davydov, A.N., Metsger, M., Scamardella, E., Alvisi, G., et al. (2020). Two subsets of stem-like CD8(+) memory T cell progenitors with distinct fate commitments in humans. *Nat. Immunol.* 21, 1552–1562. <https://doi.org/10.1038/s41590-020-0791-5>.
446. Brummelman, J., Mazza, E.M.C., Alvisi, G., Colombo, F.S., Grilli, A., Mikulak, J., Mavilio, D., Alloisio, M., Ferrari, F., Lopci, E., et al. (2018). High-dimensional single cell analysis identifies stem-like cytotoxic CD8(+) T cells infiltrating human tumors. *J. Exp. Med.* 215, 2520–2535. <https://doi.org/10.1084/jem.20180684>.
447. Sade-Feldman, M., Yizhak, K., Bjorgaard, S.L., Ray, J.P., de Boer, C.G., Jenkins, R.W., Lieb, D.J., Chen, J.H., Frederick, D.T., Barzily-Rokni, M., et al. (2018). Defining T Cell States Associated with Response to Checkpoint Immunotherapy in Melanoma. *Cell* 175, 998–1013.e20. <https://doi.org/10.1016/j.cell.2018.10.038>.