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Review

Impact of cancer cell-intrinsic features on neutrophil behavior

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ABSTRACT

Neutrophils are multifaceted innate immune cells that play a significant role in the progression of cancer by exerting both pro- and anti-tumorigenic functions. The crosstalk between cancer cells and neutrophils is complex and emerging evidence is pointing at cancer cell-intrinsic programs regulating neutrophil abundance, phenotype and function. Cancer cell-derived soluble mediators are key players in modulating the interaction with neutrophils. Here, we review how intrinsic features of cancer cells, including cancer cell genetics, epigenetics, signaling, and metabolism, manipulate neutrophil behavior and how to target these processes to impact cancer progression. A molecular understanding of cancer cell-intrinsic properties that shape the crosstalk with neutrophils will provide novel therapeutic strategies for personalized immunomodulation in cancer patients.

1. Introduction

In 1863, the German cellular pathologist Rudolf Virchow was the first to connect inflammation and cancer when he observed leukocytes in cancerous tissues [1]. He hypothesized that cancer originates at sites of inflammation. This observation was made even before the recognition of cancer being of genetic origin by Theodor Boveri and David von Hansemann [2,3]. For a long time, a functional role for immune cells in the progression of cancer was ignored. Although the notion of immune cells being present in tumors was first reported in the 19th century, it took over hundred years before immune cells were seen as important players underlying disease progression. At the end of the 1990s, the oncology field started to shift towards the recognition of immune cells having both favoring and opposing functions in shaping the tumor microenvironment (TME) and in impacting tumorigenesis and the metastatic cascade [4]. Recognition of the influential role of the immune system on cancer is now fully integrated into the oncology field and has changed clinical practice by laying the foundation for cancer immunotherapy [5–7].

Despite the clinical breakthrough of cancer immunotherapy, still many challenges have to be overcome to increase the number of cancer patients that benefit from immunomodulatory strategies. One of the major challenges in the field of onco-immunology is the largely unexplained inter-patient heterogeneity in immune composition and immune cell function. Why would two cancer patients with the same cancer type and cancer stage present with a completely different composition of immune cells in their tumors? It is critical to solve this question, since the immune landscape influences cancer behavior and how patients respond to anti-cancer therapies. Understanding how tumors influence the local and systemic immune landscape at the molecular level may contribute to the design of personalized immune intervention strategies. There is a growing realization that cancer cell-intrinsic mechanisms influence the composition and functionality of immune cells in the tumor microenvironment [8,9]. Here, we will specifically focus on how cancer cell-intrinsic processes impact the presence and functionality of neutrophils in cancer-bearing hosts.

Neutrophils are multifaceted innate immune cells that exert both promoting and opposing functions in cancer initiation and progression [10,11]. The nomenclature of cancer-associated neutrophils can be confusing, since some studies refer to neutrophils whereas others use the granulocytic or polymorphonuclear myeloid-derived suppressor cell (G-MDSC or PMN-MDSC, respectively) terminology that has been introduced about 15 years ago [12,13]. However, many studies have looked at the $CD11b^{+}Gr1^{+}$ MDSC population as a whole without distinguishing G-MDSCs from monocytic MDSCs (M-MDSCs). Moreover, the MDSC terminology implies that this cell population is immunosuppressive, yet still many studies do not proof the suppressive capacity of MDSCs. In this review, we will therefore refer to neutrophils when studies have referred to G-MDSCs or PMN-MDSCs or refer to $CD11b^{+}Gr1^{+}$ cells when studies have not characterized this population further, and their immunosuppressive nature will be explicitly mentioned if this was experimentally tested in the concurrent study.

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Better understanding of the underlying mechanisms causing abundance and distinct polarization states of neutrophils in cancer is needed to uncover novel actionable pathways that can be exploited to convert tumor-supportive states into those that favor anti-tumor immunity. In this review, the impact of cancer-cell intrinsic mechanisms on the crosstalk with neutrophils and how this influences the progression of cancer will be discussed.

2. Neutrophil complexity in cancer

A large body of clinical observations has correlated intratumoral and systemic neutrophil levels with poor prognosis of cancer patients [9,14,15], although in some cancer types neutrophils are associated with favorable outcome [16–18]. Moreover, dysregulation of the hematopoietic tree has been detected in cancer patients resulting in myeloid-biased skewing towards the generation of neutrophils [19]. More recently, neutrophils and neutrophil-associated mediators are emerging as adverse predictive factors for response to immunotherapy. Neutrophil-attractant IL-8 was identified as a strong adverse predictive marker for cancer patients treated with immune checkpoint inhibitors in two complementary retrospective studies that together represent over 2700 advanced cancer patients [20,21]. Elevated serum levels of IL-8 at baseline correlated with reduced overall survival and limited response to immune checkpoint blockade as a result of neutrophil- and monocyte-mediated immunosuppression. Apart from the systemic effect induced by myeloid cell-derived IL-8, tumor-intrinsic expression of *IL8* also correlated with neutrophil and monocyte recruitment into the TME [20,21]. These findings highlight the importance of understanding how neutrophils are modulated in cancer and raise the question what cancer cell determinants underlie the production of such a strong immunomodulatory factor to activate immunosuppressive polarization of myeloid cells.

In line with these clinical observations, preclinical studies have demonstrated that systemic accumulation of neutrophils promotes metastatic disease via blocking anti-tumor immune responses, by escorting circulating cancer cells, by facilitating cancer cell migration, by the formation of neutrophil extracellular traps (NETs) or by preparing the metastatic niche via other mechanisms [22–26]. Furthermore, neutrophils can counteract the efficacy of immunotherapy by influencing the adaptive immune system [27–31]. In contrast, in some preclinical models, neutrophils have been reported to exert anti-tumorigenic functions preventing cancer progression and cancer cell spreading by inducing cancer cell killing, by activating anti-tumor immune responses or by preventing cancer cell colonization in the pre-metastatic niche [18,32,33]. We still have a relatively poor understanding of which host- or tumor-parameters dictate whether neutrophils exert beneficial or detrimental functions. Interestingly, Ballesteros et al. demonstrated that the longevity and phenotypical state of neutrophils depend on the tissue they reside in during homeostasis [34]. Additionally, in recent studies, single-cell RNA-sequencing analysis of systemic and tumor-associated neutrophils from both murine and human cancer-bearing hosts uncovered distinct neutrophil subsets that were conserved between mouse and human, defined by differential gene expression patterns, diverse expression of cell surface markers, and varying immunosuppressive capacity [35–37]. Together, these studies highlight the plasticity of neutrophils, a feature that could serve as an attractive therapeutic target. Although neutrophil function has been strongly implicated in the progression of solid cancers, neutrophilia in cancer patients is not yet being deployed in therapeutic strategies. The challenge in finding suitable targeting strategies is due to several reasons, including but not limited to 1) adverse effects of neutrophil depletion given their essential role in the first line of immune defense, 2) inter-patient heterogeneity in terms of neutrophil expansion and their role in disease progression, 3) poorly understood mechanisms underlying neutrophil recruitment and polarization. Emerging evidence points at multiple tumor properties, including genetic make-up and downstream molecular networks, tumor stage, and cancer type or tissue context, being involved in shaping the immune system. Therefore, it is critical to find underlying cancer cell-intrinsic features that promote distinct immune phenotypes to be able to pave the way towards precision medicine for cancer patients.

3. The cancer secretome instructs crosstalk with neutrophils

Neutrophils have a remarkable ability to adapt in response to tumor-derived mediators. The different steps of neutrophil biology – their development in the bone marrow, mobilization into the blood, recruitment to tumors, and activation and systemic accumulation at (pre-) metastatic sites – can be manipulated by tumors through the secretion of mediators. Chemokine receptor CXCR2 expressed by neutrophils is known to mediate the mobilization of newly formed neutrophils from the bone marrow, which is activated by production of CXCR2-ligands including CXCL1, CXCL2 and CXCL5 [38,39]. Moreover, key growth factors, such as G-CSF and GM-CSF, skew hematopoiesis towards granulocyte production resulting in enhanced neutrophil mobilization into the circulation [40–42]. The IL-17–G-CSF axis – that is important for neutrophil expansion in homeostasis and infectious diseases [43] – has been reported to be involved in cancer-induced neutrophilic inflammation [22,44]. Common upstream mediators of IL-17 production are IL-1β and IL-23 [22,45–47], both frequently produced in the TME, that are able to indirectly instruct neutrophils via the induction of additional cytokines. Furthermore, TGF-β is able to dictate the pro-tumorigenic function of neutrophils in cancer [48,49]. Production of these cytokines, either by cancer cells or host cells in the TME, governs the interaction with and activation of neutrophils in cancer. Importantly, the secretion of cytokines into the TME can either directly lead to neutrophil recruitment or indirectly activate other immune or host cells to produce neutrophil attractants. The underlying mechanisms of direct or indirect neutrophil recruitment highly depend on the cancer cell features, the source of the cytokine and cancer-immune cell interactions.

Preclinical studies using mouse models of cancer are instrumental to mechanistically dissect how neutrophils are recruited and activated during tumor progression [50]. The importance of the secretome of cancer cells in shaping the crosstalk with immune cells is illustrated by a comprehensive study using multiple breast cancer cell line-based mouse models reflecting different molecular portraits of triple negative breast cancer (TNBC) [51]. This study demonstrated that these cell line-based breast tumors could be categorized into three subtypes depending on their differential ability to recruit intratumoral neutrophils and macrophages [51]. Neutrophil-enriched breast cancer models showed abundant systemic and intratumoral recruitment of immunosuppressive neutrophils rendering these tumors irresponsive to immune checkpoint blockade. Interestingly, the intratumoral immune profile was even maintained in the local tumor when breast tumors with different immune phenotypes, *i.e.* macrophage- or neutrophil-enriched, were transplanted into opposite mammary glands of the same animal. Exposure of bone marrow-derived neutrophils to the secretome of neutrophil-enriched models, which contained mediators like G-CSF, IL-6 and CXCL-ligands, resulted in neutrophil migration *in vitro* [51]. The authors found that epithelial-to-mesenchymal transition (EMT) of cancer cells modulated their secretome. This study illustrates a central role for cancer cell-intrinsic programs driving the secretome to promote local and systemic neutrophil infiltrate.

Besides well-known mediators of neutrophil behavior, a recent study demonstrated that secreted protease cathepsin C (CTSC) by breast cancer cells was associated with neutrophil-induced lung tropism of metastases [52]. Breast cancer cell-derived CTSC was found to attract neutrophils towards the lung metastatic niche by directly acting on neutrophil membrane-bound proteinase 3 (PR3). Activation of inflammatory signaling via NFκB in neutrophils led to the production of IL-6 and CCL3 providing a positive feedback loop to recruit more neutrophils and also led to ROS production providing NET formation [52].

Impairment of NET formation by inhibition of neutrophil elastase or DNase I reduced lung metastases illustrating the pro-metastatic capacity of CTSC-induced NETosis [52]. These findings highlight that the secretome of cancer cells directly instructs the pro-tumorigenic function of neutrophils.

The complexity of immune cell modulation by cancer cell-derived cytokines is illustrated by two studies that describe distinct functions of neutrophils in breast cancer, both involving the CCL2 chemokine [32,53]. Breast tumor-derived CCL2 was found to initiate a systemic cascade of events activating G-CSF-mediated neutrophil expansion in the transgenic *K14cre;Cdh1*$^{F/F}$*;Trp53*$^{F/F}$ breast cancer model [53]. In contrast, in the 4T1 metastatic breast cancer model, cancer cell-derived CCL2 was not an upstream mediator of G-CSF-induced systemic accumulation of neutrophils, but specifically dictated neutrophil education towards a cytotoxic phenotype preventing pulmonary metastases [32]. Although these findings highlight the functional plasticity of neutrophils dictated by cytokines, additional features are potentially involved in the polarization of neutrophils given that these two studies used different models of breast cancer recapitulating distinct breast cancer subtypes with diverse tumor characteristics. Notably, multiple studies using the 4T1 breast cancer model have shown that neutrophils are a driving force of metastatic disease [54–56]. Altogether, these controversial findings illustrate the complexity of cancer cell-neutrophil crosstalk that is most likely regulated by multiple characteristics of the tumor and its immune microenvironment. However, it is still largely unclear how cancer cells modulate cytokine secretion to guide neutrophil recruitment and phenotypical state. What are the cancer cell-intrinsic features that instruct immune cells? Which characteristics determine that some tumors produce certain cytokines that attract neutrophils, whereas others do not? Besides the secretion of soluble mediators, other mechanisms of intercellular communication are being exploited by cancer cells that influence immune cells, for instance the secretion of tumor-derived extracellular vesicles or direct cancer cell-neutrophil interactions [23,57–60]. The heterogeneity in the neutrophilic landscape of cancer that exists between cancer patients is conceivably defined by multiple parameters including patient characteristics such as age, the composition of the microbiome, and treatment history. In addition to many other variables that can dictate the immune composition of cancer, the characteristics of the tumor form an important basis for the crosstalk with neutrophils. We will focus on cancer cell-intrinsic processes, including

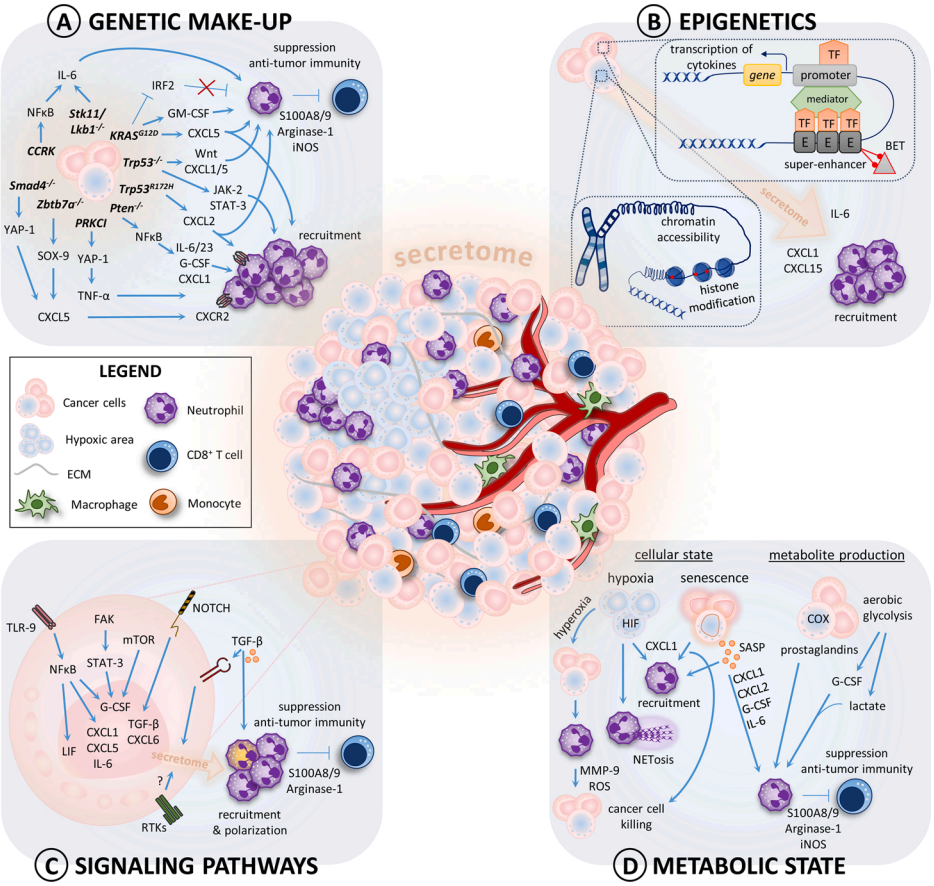

Fig. 1. Cancer cell-intrinsic processes influence neutrophil behavior in the tumor microenvironment. Schematic representation of how multiple cancer cell-intrinsic features, indicated in boxes A-D, modulate the recruitment, polarization and suppressive capacity of neutrophils. **A.** The genetic make-up of cancer plays a major role in tumorigenesis, but also impacts the crosstalk between cancer- and immune cells. Cancer cell-intrinsic loss of tumor suppressor genes (*Trp53*, *Pten*, *Zbtb7a*, *Smad4* or *Stk11/Lkb1*) [68–70,86–92,94], overexpression of kinases (PRKCI or CCRK) [93,95], or gene mutations (*Trp53*^{R172H} or *KRAS*^{G12D}) [78,80–85], dictate the expression pattern and secretion of immunomodulatory factors involved in the recruitment of neutrophils and neutrophil-mediated suppression of anti-tumor immune responses. Neutrophil accumulation occurs via cancer cell-derived factors including G-CSF, IL-6, and TNF-alpha, or CXCL-ligands for CXCR2-mediated recruitment. Immunosuppressive neutrophils block the anti-tumor immune response via S100A8, S100A9, Arginase-1, and iNOS. **B.** Gene expression of chemokines and cytokines that modulate neutrophil recruitment, such as CXCL1, CXCL15 and IL-6, is regulated at the epigenetic level [95,101–103]. Activation of transcription is dictated by chromatin accessibility, histone modification and transcription factor activity. Binding of transcription factors at (super) enhancer regions increases transcriptional activation. **C.** The signaling pathways involving NFκB, STAT3 and mTOR are frequently activated in cancer and lead to cancer cell secretion of factors that prompt the recruitment of immunosuppressive neutrophils [83,90,95,104,106,108,110,114]. Also, TGF-β is an important modulator of neutrophil polarization in cancer, dictating both pro- and anti-tumorigenic functions of neutrophils [48,116–120]. Whether tyrosine kinase receptors are involved in cancer cell-neutrophil crosstalk remains to be further elucidated. **D.** Multiple metabolic processes that occur in tumors, including cancer cell states and the availability of metabolites, can affect surrounding immune cells. Neutrophils recruited to hypoxic areas of tumors are more prone to form NETs [138,139], while enhanced oxygen availability (hyperoxia) induces neutrophil-mediated cancer cell killing [140,141]. The recruitment of neutrophils towards senescent tumors can also lead to tumor cell clearance [145], whereas the senescence-associated secretory phenotype (SASP) can mediate attraction of immunosuppressive neutrophils [146,147]. Besides cellular state, the production of metabolites, including lipid mediators (prostaglandins) and derivatives of aerobic glycolysis (lactate), promote immunosuppressive neutrophil recruitment in cancer [124–127,133–136]. Abbreviations used in this Figure: TF = transcription factor, E = enhancer, SE = super enhancer, BET = bromo- and extra-terminal domain, RTK = receptor tyrosine kinase, SASP = senescence-associated secretory phenotype.

cancer cell (epi)genetics, intracellular signaling molecules, and the metabolic state of the tumor, that impact neutrophil biology.

3.1. Genetic aberrations in cancer influencing neutrophil dynamics

Cancer-associated genetic aberrations that have been widely studied in the context of tumorigenesis are now also emerging as key regulators of cancer-induced inflammation. Multi-omics analyses, including computational deconvolution approaches on publicly available clinical datasets, have indicated a correlation between cancer genetics and the immune landscape of tumors [61–64]. Specific oncogenes and loss of tumor suppressor genes greatly influence the secretome of cancer cells involved in cancer-immune cell crosstalk. The relationship between the cancer genome and global immune infiltration in cancers has been reviewed elsewhere [8,65,66]. Below, we will highlight key genetic drivers of cancer that have been reported in multiple independent studies to directly influence the crosstalk between cancer and neutrophils (Fig. 1A).

3.1.1. Tumor suppressor p53

Tumor suppressor gene *TP53* is the most frequently mutated gene across human cancers and plays versatile roles in cancer processes, including dictating cancer-induced inflammation [67]. Both mutated and genetic loss of p53 lead to loss of tumor suppressor activity. In addition, mutations in p53 can lead to gain-of-functions (GOF) of the gene resulting in additional oncogenic functions for p53-mutated cancer cells. Several studies have demonstrated how cancer cell-intrinsic loss of p53, or mutant p53, modulates the crosstalk with neutrophils.

In a murine $Kras^{G12D};Trp53^{-/-}$ driven pancreatic cancer model, p53 deficiency led to infiltration of a $CD11b^{+}$ myeloid cell population, which includes monocytes, macrophages and neutrophils [68,69]. One study showed that p53 loss leads to activation of JAK2-STAT3 signaling that mediates neutrophil recruitment, as demonstrated by the strong reduction in neutrophil infiltration upon conditional deletion of *Stat3* in $Kras^{G12D};Trp53^{-/-}$ pancreatic tumors [68]. In another study, pancreatic cancer cell-intrinsic loss of p53 was reported to regulate the production of cytokines that are involved in neutrophil recruitment, such as CXCL1 and CXCL5 [69]. Using a co-culture setting of tumor-derived $CD11b^{+}$ myeloid cells and pre-activated splenic $CD4^{+}$ or $CD8^{+}$ T cells, the authors showed that $CD11b^{+}$ myeloid cells from p53-null tumors have a greater capability of suppressing T cell proliferation compared to myeloid cells from p53 wildtype tumors. Whether neutrophils are involved in this immunosuppressive phenotype has not been specified in this study [69]. These studies highlight the functional role of cancer cell-intrinsic loss of p53 in regulating the intratumoral myeloid compartment, although the functional significance of neutrophils in the context of p53-null cancers was not addressed here. To mechanistically understand inter-patient heterogeneity in the tumor-induced systemic immune landscape, we have previously utilized a unique panel of 16 transgenic mouse models of breast cancer driven by different genetic aberrations [70]. Interestingly, also from this extensive GEMM panel, loss of p53 emerged as the most dominant cancer cell-intrinsic genetic modifier driving neutrophil accumulation and polarization [70]. Here, loss of p53 resulted in secretion of Wnt ligands by cancer cells that activated IL-1β production in macrophages as kick-starter of systemic neutrophilia that promoted metastatic disease. Therapeutic targeting of Wnt ligand secretion using LGK974 – which blocks porcupine, the regulator of Wnt ligand secretion – led to abrogated neutrophil expansion and reduced metastasis formation [70]. The discovery that this therapeutic strategy was solely effective in p53-null tumor-bearing hosts and not in p53 wildtype tumor-bearing hosts [70], is setting the stage for personalized intervention strategies impacting neutrophil-driven disease progression.

Besides loss of p53 gene activity, mutated p53 has also been reported to modulate multiple processes involved in cancer-associated inflammation. Various studies have illustrated that p53 mutations can lead to an altered secretome via transcription of cytokines and chemokines [71,72], modulation of intracellular signaling pathways involved in inflammation including NFκB and STING signaling [71,73,74], and differential recruitment of macrophages, NK cells and T cells into the TME [73]. All of these steps could affect neutrophil recruitment and polarization in p53-mutated tumors, but this was not formally tested in these studies. Moreover, clinical data indicated mutated *TP53* as a predictive marker for response to immunotherapy for patients with breast or lung cancer [75–77], illustrating the clinical relevance of studying the role of p53-mutated cancers in immunomodulation. Although these studies have illustrated that p53 mutations in cancer can influence immune parameters, limited evidence exists on how neutrophils are shaped in the context of p53-mutated tumors. A recent study reported that the $p53^{R172H}$ mutation in pancreatic tumors mediates intratumoral neutrophil infiltration via cancer cell-derived CXCL2 in an orthotopic model using the $Kras^{G12D/+};p53^{R172H}$ pancreatic cancer cell line [78]. Neutrophils were shown not to be involved in cancer progression, given that primary tumor growth was not affected when neutrophils were depleted using an anti-Ly6G antibody [78]. Strikingly, neutrophil depletion during combination treatment of chemotherapy and immunotherapy enhanced treatment efficacy, illustrating a profound role for neutrophils in therapy resistance [78]. Given these insightful findings regarding the immune landscape in p53 mutant cancer, it would be interesting to further explore how neutrophils are affected when p53 is mutated in cancer cells.

3.1.2. Mutant KRAS

Another cancer driver that has been implicated to attract and activate neutrophils in tumors is mutant KRAS, which is often aberrantly expressed in cancer of the lungs, pancreas and colon. A recent analysis of a small cohort of patients with colorectal liver metastases showed increased levels of neutrophils in the peritumoral area of KRAS mutated tumors [79]. Interestingly, elevated levels of neutrophils that were found in the circulation of patients bearing KRAS-mutated colorectal liver metastases could potentially have a prognostic value once correlated with clinical and pathological outcome, yet this remains to be studied in more detail in additional patient cohorts. The underlying mechanism how mutant KRAS can affect neutrophil recruitment and behavior has been studied in multiple murine cancer models. Although more than one point mutation in KRAS can occur in solid tumors, the G12D-mutation has mainly been associated with cancer cell-neutrophil crosstalk. In a murine transplantation-based pancreatic cancer model, $KRAS^{G12D}$ was linked to GM-CSF release by cancer cells as mediator of neutrophil recruitment into the TME [80]. Interestingly, genetic downregulation of GM-CSF expression in pancreatic cancer cells resulted in the absence of neutrophils and in tumor control [80], suggesting that GM-CSF-induced neutrophils play a role in counteracting the anti-tumor response. Indeed, neutrophils isolated from these pancreatic tumors showed high capacity of T cell suppression *ex vivo* [80]. Also, control of pancreatic GM-CSF-knockdown tumors was attenuated by depletion of $CD8^{+}$ T cells [80], indicating an active function for $CD8^{+}$ T cells in tumor clearance in the absence of immunosuppressive neutrophils.

Mutant KRAS has also been associated with CXCR2-ligand secretion to recruit neutrophils into tumors of the lungs and pancreas [81–84]. When comparing $Kras^{G12D/+}$ to $Trp53^{R172H/+}$ pancreatic tumors, mutant KRAS was found to be the driver of cancer cell-specific expression of *Cxcl5* leading to pro-tumorigenic neutrophil infiltration [83]. Where most of the mentioned studies solely show the involvement of mutant KRAS in CXCL5-induced neutrophil homing, two studies in fact demonstrated how neutrophils influence the anti-tumor immune response. By utilizing full-body *Cxcr2*-knockout mice and $CD4^{+}$/$CD8^{+}$ T cell depleting antibodies in the context of $KRAS^{G12D}$ pancreatic cancer, CXCR2-mediated intratumoral neutrophil infiltration was demonstrated to enhance pancreatic cancer progression by blocking recruitment and activation of $CD4^{+}$ and $CD8^{+}$ T cells rendering them insensitive to

anti-PD-1 treatment [83,84]. Interestingly, these preclinical studies illustrate that one point mutation in KRAS in pancreatic cancer can induce multiple patterns of gene expression and protein secretion to modulate neutrophil recruitment and function.

CyTOF analysis of the immune landscape of transgenic mice developing $KRAS^{G12D}$ colorectal tumors revealed that $KRAS^{G12D}$ led to infiltration of neutrophils expressing immunosuppressive markers including S100A9, Arginase-1 and inducible nitric oxide synthase (iNOS) [85]. This study unraveled the KRAS-IRF2 axis to be underlying the immunosuppressive environment, where mutant KRAS inhibits IRF2 to relieve the repression of CXCL3-mediated neutrophil recruitment [85]. Indirect targeting of immunosuppressive neutrophils, either by activating IRF2 or by blocking CXCR2, sensitized colorectal tumors to anti-PD-1 treatment [85]. In conclusion, in different cancer types, one KRAS-mutation can exert distinct mechanisms to regulate neutrophil dynamics.

3.1.3. PTEN deficiency

Loss of the tumor suppressor gene PTEN leads to the downstream activation of the PI3K-Akt-mTOR signaling pathway resulting in accelerated cell proliferation, and is most often observed in human breast cancer, prostate cancer, and glioblastoma. Multiple studies have reported neutrophil infiltration in PTEN-deficient cancers [86–88]. However, limited studies have dissected the distinct role of PTEN in modulating neutrophil behavior. Here, we highlight a few studies that illustrate a potential role for PTEN in impacting neutrophils.

In synovial sarcoma, PTEN deficiency led to both systemic and intratumoral accumulation of neutrophils [89]. Since synovial sarcoma cells did not show differential expression of genes related to neutrophil recruitment, it was hypothesized that the infiltration of neutrophils into PTEN-null tumors was an indirect effect of PTEN loss in cancer cells. Indeed, intratumoral macrophages were found to be the main producers of neutrophil attractant IL-1β [89]. Another study illustrated that additional loss of PTEN in a pancreatic cancer model driven by mutant KRAS induced NFκB-mediated gene expression of cytokines that are known to be involved in neutrophil recruitment, including *Il6*, *Csf3*, *Cxcl1* and *Il23* [90]. Moreover, in the *Pb-Cre;*$Pten^{lox/lox}$ prostate cancer model, high number of $CD11b^{+}Gr1^{+}$ myeloid cells – a population of which the majority of cells was neutrophil – infiltrated prostate tumors [91]. Interestingly, no substantial systemic expansion of neutrophils was found in prostate tumor-bearing mice, suggesting that the neutrophil phenotype observed in PTEN-null prostate tumors is regulated locally. Upon PTEN deletion in murine prostate epithelial cells, gene expression of *Csf1* and *Il1b* was upregulated and this gene expression pattern was confirmed in human prostate tumors compared to healthy prostates [91]. Neutrophils isolated from murine prostate tumors – but not systemic neutrophils isolated from the spleen – had the capability to suppress T cells *ex vivo* [91]. Blocking of the CSF1 receptor reduced the recruitment of the immunosuppressive $CD11b^{+}Gr1^{+}$ myeloid cell population and resulted in attraction of activated T cells [91]. Likely, CSF1R blockade inhibited the infiltration of monocytic myeloid cells and not neutrophils, but the affected myeloid cell population was not specified further. Altogether, these findings suggest a profound role for PTEN loss-induced secretome alterations in modulating neutrophils. However, the functional characterization of neutrophils in the context of cancer cell-intrinsic loss of PTEN is subject for further investigation and will be specifically important for solid cancers of which the majority is driven by PTEN deficiency, such as prostate cancer.

3.1.4. Other genetic events in cancer affecting neutrophils

Besides aforementioned well-known genetic drivers of cancer, there is a growing number of other, sometimes less frequent, oncogenes and tumor suppressor genes that are involved in regulating the cancer cell secretome to modulate neutrophil dynamics.

3.1.4.1. Tumor suppressor genes. By utilizing transgenic mice with different genetic aberrations driving prostate cancer, Bezzi et al. demonstrated the role of distinct genetic drivers in the context of immune infiltrate [88]. In a PTEN-driven prostate cancer model, loss of three additional tumor suppressor genes, *Zbtb7a*, *Trp53* and *Pml,* were studied and each of these genes induced a distinct intratumoral immune composition [88]. Infiltration of $CD11b^{+}Gr1^{+}$ cells was specifically observed in models driven by loss of *Zbtb7a* or *Trp53*. Interestingly, *Zbtb7a* loss led to pro-tumorigenic neutrophil recruitment via cancer cell-intrinsic SOX9-induced CXCL5 expression, whereas *Trp53* loss induced upregulation of CXCL17 to attract monocytes [88]. Strikingly, both *Zbtb7a-Cxcl5* and *Trp53-Cxcl17* genetic links plus the high neutrophil signature of ZBTB7A-null prostate tumors were validated in a human prostate cancer dataset [88], illustrating the clinical relevance of cancer genotype-neutrophil relationships. Furthermore, by using CyTOF analysis of the same backbone model for prostate cancer ($Pten^{pc-/-}$), another study showed that additional loss of tumor suppressor SMAD4 induced CXCL5-mediated attraction of neutrophils into prostate tumors [92]. By comparing $Pten^{pc-/-}$ and $Pten^{pc-/-}Smad4^{pc-/-}$ prostate cancer models, the authors found the YAP1 protein to be enriched in $Pten^{pc-/-}Smad4^{pc-/-}$ prostate cancer and this protein directly regulated *Cxcl5* expression [92]. Impairment of neutrophil recruitment upon CXCR2-blockade or cancer cell-specific knockdown of YAP1 to abrogate *Cxcl5* expression reduced prostate cancer progression *in vivo* [92], illustrating the pro-tumorigenic function of neutrophils induced by SMAD4 loss. These studies demonstrate that distinct regulatory mechanisms underlie CXCL5-mediated neutrophil recruitment in different models of prostate cancer, depending on the genetic make-up of cancer cells.

3.1.4.2. Oncogenic kinases. Conditional overexpression of protein kinase C family member PRKCI in the fallopian tube epithelium leads to ovarian tumors enriched for neutrophils [93]. By assessing inducible overexpression of PRKCI in the $Tp53^{L/L}$;$Pten^{L/L}$;*Pax8-Cre* ovarian cancer model, PRKCI was demonstrated to induce YAP1-mediated TNF-α secretion by ovarian cancer cells to attract neutrophils into the TME [93]. Interestingly, the human TCGA dataset showed that PRKCI-expressing ovarian cancer correlated with a neutrophil gene signature and with low number of infiltrating T cells, confirming the immunosuppressive environment in ovarian tumors expressing PRKCI [93]. Additional studies addressed how aberrant expression of two different kinases in cancer cells affected neutrophils in influencing the anti-tumor $CD8^{+}$ T cell response. In human lung adenocarcinoma, mutant STK11 correlated with enrichment of neutrophils in the TME [76]. Likewise, loss of tumor suppressor kinase STK11/LKB1 in a murine KRAS-driven lung cancer model resulted in chemokine and cytokine production by cancer cells, including G-CSF, CXCL7 and IL-6, which are potentially involved in the observed recruitment of immunosuppressive neutrophils in LKB1-deficient lung tumors [94]. Immunosuppression was abrogated using an IL-6 neutralizing antibody that prompted $CD8^{+}$ T cells to proliferate and to express effector cytokine IFN-γ [94]. A similar IL-6-mediated neutrophil phenotype was reported in hepatocellular carcinoma driven by cell cycle-related kinase (CCRK). Cancer cell-intrinsic CCRK gene overexpression induced NFκB-dependent activation of IL-6-mediated recruitment of neutrophils [95]. Blockade of CCRK alone or in combination with anti-PD-L1 immunotherapy diminished neutrophil levels and activated IFN-γ/TNF-α producing $CD8^{+}$ T cell infiltration to eradicate the tumor [95]. Together, these findings highlight that aberrant expression of different kinases in cancer cells dictate similar mechanisms involved in modulating the recruitment and immunosuppressive features of neutrophils in multiple cancer types.

Altogether, these findings illustrate how distinct genetic programs in solid cancers of different origin can manipulate the extent of neutrophil recruitment and activation. These studies provide a mechanistic view on how genetic aberrations dictate the secretome of cancer cells to instruct

neutrophil functionality in cancer progression. By interfering with early steps in the cascade, through disruption of cancer cell intrinsic-processes or via blockade of secreted mediators, neutrophil accumulation or activation can be reduced preventing the suppression of the anti-tumor T cell response. Looking further than well-known genetic drivers of cancer is crucial to move a step closer to personalized medicine, as implied by the effect of less frequent genetic aberrations in cancer on neutrophil crosstalk that has detrimental consequences for cancer progression. Underlying mechanisms relating cancer genetics to immune phenotype are now being uncovered and will provide novel therapeutic options for precision medicine over the coming years.

3.2. Epigenetic regulation of the cancer secretome modulates neutrophils

Besides aberrations in the genetic code, cancer cells regulate intracellular molecular networks by modifying epigenetic programs. Epigenetic control of the transcriptome is mediated via histone modification, DNA methylation and non-coding RNAs. Alterations in the epigenome allow oncogenes and tumor suppressor genes to be aberrantly expressed without affecting the DNA code [96]. Epigenetic changes in cancer cells have been reported to control various immune parameters in the TME including the cancer cell secretome, T cell infiltration, and immunotherapy efficacy [97–100].

Apart from the impact on the adaptive immune system, the cancer epigenome is also involved in modulating the expression of genes that potentially affect neutrophil dynamics (Fig. 1B). Assessment of different clones derived from the *Kras*$^{LSL-G12D/+}$;*Trp53*$^{LSL-R172H/+}$;*Pdx1-Cre;Rosa26*$^{YFP/YFP}$ (KPCY) pancreatic cancer model gave rise to distinct immune phenotypes defining T cell- and neutrophil-enriched clones, of which the latter were resistant to immunotherapy [101]. Because the immune phenotype persisted after re-implantation of these clones, the authors asked which pancreatic cancer cell-derived factors could control this phenomenon. The neutrophil-enriched pancreatic cancer clones displayed upregulated *Cxcl1* expression that was controlled at the epigenetic level through a combination of greater accessibility of the promoter region, enrichment of the active H3K4me3 histone mark and activity of transcription factor MYC that governed *Cxcl1* expression [101]. In hepatocellular carcinoma, neutrophils were recruited towards the TME when transcription of *Il6* was activated by co-binding of histone methyl transferase EZH2 and NFκB to the promoter region of IL-6 [95]. Another study focused on neutrophil-driven metastatic disease of renal cell carcinoma in which an orthotopic transplantation-based mouse model of human RCC cell lines was used. Here, multiple CXCL chemokines were highly expressed by renal cancer cells due to binding of BRD4 to acetylated histones at super enhancers (SEs) formed at chemokine enhancer regions [102]. Epigenetic targeting using a BET inhibitor to block binding of BRD4 and SEs at genomic loci abrogated CXCL gene expression, neutrophil accumulation and pulmonary metastases *in vivo* [102]. Together, these studies demonstrate that cancer cell-intrinsic epigenetic control of neutrophil mediators shapes the neutrophil compartment of the TME. Therapeutic intervention of epigenetic processes can abrogate neutrophil-mediated cancer progression, illustrating that the epigenome is an attractive therapeutic target for anti-cancer therapies.

Whereas activating epigenetic signals often correlate with the induction of transcription, lack of repressing signals can also lead to activated gene expression. The androgen receptor is a nuclear receptor that directly acts as a transcription factor to regulate gene expression in prostate cells, where it represses the expression of murine *Cxcl15* or human *IL8* by competing with transcription activators [103]. This came to light during androgen deprivation therapy (ADT) in a transplantation-based prostate cancer cell line model, where reduced activation of the androgen receptor led to CXCR2-mediated enrichment of neutrophils in the TME that impaired the response to immune checkpoint blockade [103]. ADT allowed recruitment of active transcription marks such as phosphorylated RNA polymerase II and histone acetylation (H3K9ac), and released the brake of *Cxcl15* gene transcription [103]. Thus, antagonizing the androgen receptor – which is standard-of-care treatment for prostate cancer – actually promotes an immunosuppressive environment by attracting neutrophils into the tumor. These findings illustrate the need for additional therapies targeting immunosuppression in cancer. Although the use of epigenetic targeting as therapeutic strategy in cancer is coming up in the clinic [96], there are still limited insights into how the epigenetic control in cancer cells impacts communication in the TME. Various epigenetic molecules that are known to impact tumorigenesis, such as non-coding RNAs, are not yet coupled to cancer cell-immune cell interactions and are subject for future research. Deeper understanding how certain tumors impact neutrophils through modified epigenetics is crucial to be able to manipulate the cancer cell-neutrophil crosstalk and to design combinatorial therapies to improve efficacy of current therapies such as immunotherapy.

3.3. Cancer cell-intrinsic signaling pathways impacting neutrophil presence and function

Dysregulated signaling pathways lie at the basis of changes in cellular communication and behavior, and can be a consequence of both intrinsic signals (e.g. at the level of genetics or epigenetics) and extrinsic mediators (e.g. ligands binding to membrane receptors). Below, we discuss several frequently altered cancer cell-intrinsic signaling pathways that have been reported to directly affect the crosstalk with neutrophils (Fig. 1C).

3.3.1. Signaling of kinases and their receptors

Intracellular signaling pathways, such as the MAPK and PI3K-Akt signal transduction routes, can be affected in cancer as a consequence of mutations in or amplification of cell surface receptors or molecules in that particular pathway. This leads to aberrant activation of intracellular signaling, which renders the receptors and the kinases involved interesting therapeutic targets for many cancer types. Given their intrinsic role in regulating cellular state and behavior, kinases and their receptors likely also play a role in regulating the secretome of cancer cells, yet limited studies have focused on signaling molecules in the context of neutrophil dynamics in cancer. As an example, when cytosolic focal adhesion kinase (FAK) is highly active in pancreatic cancer, STAT3 phosphorylation and G-CSF expression are activated in cancer cells and attract neutrophils into the TME [104]. Either pharmacologic FAK inhibition in *p48-Cre;LSL-Kras*^{G12D};*Trp53*$^{flox/+}$ and *p48-Cre;LSL-Kras*^{G12D} mice or genetic knockdown of FAK in cell lines derived from these pancreatic cancer models reduced intratumoral neutrophil homing and rendered pancreatic tumors responsive to immunotherapy [104]. The tumor responsive phenotype during FAK inhibition was reverted by $CD4^+$/$CD8^+$ T cell depletion indicating the immunosuppressive nature of FAK-induced neutrophils [104]. However, anti-tumor control induced by pharmacological FAK inhibition could also be a consequence of direct targeting of myeloid cell function, since FAK has also been demonstrated to regulate the pro-tumorigenic function of myeloid cells during the invasive stage of breast cancer progression [105]. Interestingly, these data show that kinases that are known to regulate cancer-related processes such as cancer cell proliferation, migration, and invasion are indirectly contributing to an immunosuppressive environment in the tumor via downstream signaling, while they can also intrinsically regulate immune cell phenotype.

Another signaling route that is often activated in cancer and illustrates the crosstalk with immune cells involves mTOR, a member of the PI3K-related kinases family of protein kinases. The mTOR signaling pathway was enriched in mammary tumors with high content of neutrophils, an immune phenotype that was observed in transgenic *MMTV-Wnt1-iFGFR*, somatic *Trp53*$^{-/-}$*Pten*$^{-/-}$ and p53-null cell line-based mammary tumor models [106]. Activation of the mTOR pathway mediated G-CSF expression by breast cancer cells to attract neutrophils

[106]. Neutrophil infiltration into mammary tumors was abrogated when the mTOR–G-CSF axis was targeted using mTOR inhibitor rapamycin or breast cancer cell-specific genetic ablation of either Raptor (part of the mTORC1 complex) or G-CSF [106]. Interestingly, targeting FGFR – the receptor that signals upstream of mTOR – in Wnt1-FGFR-driven mammary tumors resulted in decreased G-CSF levels [106]. Since the mTOR–G-CSF axis was also found in mammary tumors not driven by FGFR [106], it is likely that there is another mechanism underlying mTOR activation in these breast cancer models. Still, this study shows that cancer cell-intrinsic mTOR signaling is evidently involved in recruiting immunosuppressive neutrophils contributing to disease progression [106]. Pharmacological targeting of mTOR signaling using rapamycin could also have directly affected neutrophils, as was shown for monocytic $CD11b^{+}Gr1^{+}$ cells in skin graft and lymphoma cell line models [107]. Notably, this may also be a consequence of other targeted therapies that are currently being used in the clinic to treat cancers with specific alterations, such as BRAF/MEK-inhibitors for BRAF mutant tumors.

Although limited evidence exists on the role of cancer cell surface receptors in modulating neutrophil crosstalk, some studies have indicated hints regarding how cell surface receptors contribute to neutrophil behavior. We anticipate that more insights will be generated over the coming years given the crucial function of such receptors in tumorigenesis across solid cancers. In human lung adenocarcinoma, mutant EGFR has been connected to an immune microenvironment consisting of a low number of neutrophils [76]. In contrast, EGFR activation in a human breast cancer cell line was reported to induce the production of cytokines including IL-8, IL-1β and CXCL1 – all neutrophil attractants [108]. Activation of another tyrosine kinase receptor, HER2, that is frequently amplified in epithelial cancers, has been shown to block the STING signaling pathway via Akt1 in the B16 melanoma model [109]. The HER2-Akt1 axis reduces the infiltration of $CD4^{+}$ and $CD8^{+}$ T cell populations to prevent anti-tumor immunity, but it is unknown whether neutrophils contributed to the immunosuppressive phenotype, as neutrophils were not included in the immune parameter analysis [109]. Moreover, activated signaling of the NOTCH1 cell surface receptor in the murine colorectal cancer model $villinCre^{ER}Kras^{G12D/+}Trp53^{fl/fl}Rosa26^{N1icd/+}$ led to secretion of TGF-β2 that regulated recruitment of neutrophils driving liver metastasis by suppressing T cell activation [110]. Interestingly, the signature of NOTCH1 and TGFB2 that was found in murine colorectal tumors resembled a subset of human colorectal carcinoma patients with poor prognosis [110].

These findings indicate that signaling pathways in cancer cells dictate the secretome of cancer cells, but also highlight the complexity of targeting these signaling routes, since they are also regulating immune cell states directly.

3.3.2. NFκB signaling pathway

The NFκB transcription factor family is a major regulator of inflammation and cancer by acting in various processes, including direct control of target gene expression, crosstalk with other signaling routes, and dictating cancer- and immune cell states [111–113]. For instance in a human dataset for pancreatic adenocarcinoma, elevated expression of CXCR2 ligands correlated with enrichment of both neutrophils and the NFκB signaling pathway in pancreatic tumors [83]. In *in vitro* cancer cell line-based assays, cancer cell-intrinsic NFκB signaling was shown to regulate gene expression of neutrophil attractants including *Cxcl5*, *Cxcl1*, *Csf3* and *Il6* [83,90,95]. Furthermore, toll-like receptor 9 (TLR9) expressed on prostate cancer cells activated NFκB-mediated gene transcription of the LIF cytokine [114]. Paracrine signaling of LIF was shown to attract neutrophils into prostate tumors and activated their immunosuppressive capacity by inducing STAT3-mediated expression of Arginase-1 and S100A8/A9 [114]. These examples illustrate how cancer cells can exploit inflammatory signaling molecules, such as NFκB and STAT3, to polarize neutrophils towards immunosuppression. However, targeting pathways that act in both cancer- and immune cells makes them a challenging target for anti-cancer therapies.

3.3.3. TGF-β signaling pathway

Another signaling route that impacts both cancer and immune cells is the TGF-β signaling pathway, which has a dual role in cancer initiation and is a known regulator of EMT and metastasis, while it also exerts immunomodulatory functions affecting the TME [115]. By utilizing an *in vitro* neutrophil migration assay in the context of hepatocellular carcinoma, stimulation of cancer cells with TGF-β resulted in CXCL5 expression and neutrophil migration [116]. Similarly, in a migration assay using conditioned medium from breast cancer cells, neutrophil migration was mediated by cancer cell-derived TGF-β [117]. Together, these studies illustrate that TGF-β acting on cancer cells or derived from cancer cells can both affect neutrophil dynamics. Strikingly, Fridlender et al. was the first to demonstrate that TGF-β blockade switched the phenotype of intratumoral neutrophils from pro-tumorigenic into anti-tumorigenic in cell line transplantation models of lung and mesothelioma cancer [48]. By utilizing $Ly6G^{+}$ or $CD8^{+}$ cell depleting antibodies, neutrophils were shown to suppress the adaptive immune system in the control setting, whereas the anti-tumorigenic polarization of neutrophils by TGF-β inhibition resulted in active immunity and tumor control [48]. The neutrophil phenotype switch induced by TGF-β blockade was confirmed in colorectal cancer [118]. Here, in a co-culture setting of colorectal cancer cells with neutrophils that were pre-incubated with tumor conditioned medium, blockade of TGF-β resulted in an anti-tumorigenic neutrophil phenotype indicated by enhanced cytotoxic mediators and reduced levels of immunosuppressive factors including neutrophil elastase and Arginase-1 [118]. In a recent study, the TGF-β–CXCL6 axis in hepatocellular carcinoma formed the basis of pro-tumorigenic neutrophil recruitment [119]. Interestingly, this neutrophil phenotype was supported by a multi-cellular crosstalk in the TME, as activation of cancer cell-intrinsic expression of TGF-β and CXCL6 was induced by cancer-associated fibroblast-derived CLCF1, and together provided a positive feedback loop between cancer cells, fibroblasts and neutrophils promoting cancer progression [119]. Interestingly, abrogated TGF-β signaling by conditional deletion of *Tgfbr2* in the MMTV-PyMT mammary carcinoma model enhanced CXCL5 expression and recruitment of $CD11b^{+}Gr1^{+}$ cells into the TME that supported metastasis formation [120]. Notably, mammary tumor-specific deficiency in *Tgfbr2* resulted in enhanced production of TGF-β by myeloid cells in tumor-bearing hosts [120], which could have affected the phenotype of $CD11b^{+}Gr1^{+}$ cells beyond the cancer cell-intrinsic blockade of the TGF-β signaling pathway, although this was not tested here. Together, these findings illustrate a profound role for TGF-β in cancer-induced neutrophil behavior, either by regulating the cancer cell secretome or by directly acting on neutrophils. Still, additional insights are needed to be able to utilize this pathway as a therapeutic target for immunomodulation that favors anti-tumor immunity.

These studies demonstrate how different components of intracellular signaling pathways in cancer can modulate cancer progression via the crosstalk with neutrophils. From a therapeutic perspective, it is crucial to take into account that similar intracellular signaling networks can be activated in both cancer cells and neutrophils. The total wiring of cancer cells comprises cellular regulation at the level of epigenetics, genetics and intracellular molecules that together form a cancer cell-intrinsic signaling network, which makes it complex to dissect how one feature in cancer cells alters the immune phenotype of tumors. Though, finding underlying mechanisms of how such cancer cell-intrinsic features cooperate to impact the neutrophilic landscape will aid the development of novel therapeutic strategies for cancer patients.

3.4. Cancer metabolic processes affecting neutrophil behavior

Cancer cells depend on reprogramming of cellular metabolism to survive and to sustain proliferation in the frequently harsh conditions

present in the tumor microenvironment, including deprivation from nutrients and oxygen. The metabolic wiring in cancer cells can affect tumorigenesis and cancer progression, but also the crosstalk with immune cells. Current advances on this subject have been discussed in a recent perspective [121]. Here, we will discuss examples of how cancer cell-intrinsic metabolic reprogramming and the metabolic state of tumors affect neutrophils in cancer (Fig. 1D).

3.4.1. Lipid mediators

Lipid metabolism covers multiple pathways varying from cellular uptake and processing of lipids to *de novo* synthesis of fatty acids and lipid mediators serving as energy source [122]. Altered lipid metabolism contributes to the progression of cancer by fueling cancer cell proliferation, but cancer cell-derived lipid mediators may also influence the function and metabolic state of surrounding cells in the TME. The enzyme cyclooxygenase (COX) that is involved in the formation of lipid compounds, including converting arachidonic acid into prostaglandins, is a known influencer of inflammation and can be induced by inflammatory mediators [123]. In collagen-rich mammary tumors, COX-2 enabled cancer cells to secrete cytokines resulting in neutrophil recruitment [124]. Hence, cancer cell-derived prostaglandin drove cancer progression via evasion of the adaptive immune system in multiple cancer cell line-based transplantation models [125,126]. Moreover, lung cancer cell-intrinsic prostaglandin signaling was shown to dictate the secretome of lung cancer cells involved in the recruitment of immunosuppressive neutrophils, both *in vitro* and in a mouse model for experimental lung metastasis [127]. Interestingly, uptake of arachidonic acid by cancer-induced neutrophils facilitated prostaglandin release to promote immunosuppression [128]. This is in line with recent studies showing that neutrophil-derived lipids directly act on cancer cell proliferation aiding cancer progression [129,130], although it is yet unclear whether cancer cell-intrinsic mechanisms are a fundamental part of these phenomena. One other study provides evidence for tumor-derived G-CSF and GM-CSF in inducing neutrophil-intrinsic lipid metabolism to fuel their immunosuppressive capacity [131]. Whereas cancer cells are able to use lipid metabolites to instruct immune cells, neutrophils also rely on their own metabolic state to exert inflammatory functions.

3.4.2. Glucose metabolism

Tumors employ glycolysis as main source of energy, even in the presence of oxygen and is therefore referred to as aerobic glycolysis [132]. This phenomenon – the Warburg effect, named after the German physiologist Otto Warburg – comprises enhanced glucose metabolism and lactate production by cancer cells that can benefit tumor growth, but can also affect neighboring cells in the TME. Indeed, in two breast cancer cell line-based *in vitro* and *in vivo* models, aerobic glycolysis was demonstrated to regulate immunosuppression in mammary tumors via a cascade of intracellular signaling events [133]. Mammary tumor glycolysis induced the AMPK-ULK1 autophagy pathway to activate liver-enriched transcriptional activator protein (LAP) that in turn regulated G-CSF expression in cancer cells [133]. Using cancer cell-intrinsic genetic knockdown of lactate dehydrogenase A (LDHA) to abrogate glycolysis, tumor glycolysis was shown to modulate G-CSF-mediated infiltration of immunosuppressive neutrophils into mammary tumors and to regulate cancer progression [133]. A similar immune phenotype was observed in a syngeneic mouse model for pancreatic cancer, where knockdown of LDHA in pancreatic cancer cells led to reduced numbers of intratumoral and splenic $CD11b^{+}Gr1^{+}$ cells [134]. Administration of lactate to the culture of murine bone marrow or human PBMCs cultures, exposed to medium containing GM-CSF and IL-6, increased the capability of $CD11b^{+}Gr1^{+}$ cells to suppress NK cell cytotoxicity to lymphoma cells [134]. Furthermore, radiotherapy induced the accumulation of $CD11b^{+}Gr1^{+}$ cells in the transgenic *LSL-Kras*$^{G12D/+}$*;Pdx-1-Cre* and orthotopic Panc-02 pancreatic cancer model via the activation of aerobic glycolysis in tumors [135]. Upon radiotherapy, pancreatic cancer cell-derived lactate promoted the expression of immunosuppressive genes encoding S100A8/9, iNOS and Arginase-1 in $CD11b^{+}Gr1^{+}$ cells exposed to conditioned medium from radiotherapy-treated cancer cells [135]. Interestingly, in an orthotopic transplantation-based model of hepatocellular carcinoma, treatment with VEGFR inhibitor lenvatinib resulted in glycolysis pathway enrichment in tumors, lactate production by cancer cells and the recruitment of neutrophils into the TME [136], although the link between VEGFR blockade and lactate generation was not explained here. Tumor-derived lactate activated the NFκB/COX-2 axis in neutrophils to express PD-L1, underlying the suppression of the anti-tumor immune response in lenvatinib-treated hepatocellular carcinoma-bearing mice. The efficacy of lenvatinib was improved by alleviating the neutrophil-mediated suppression of the T cell response by combination therapy of lenvatinib with COX-2 inhibitor celecoxib [136]. These studies demonstrate that cancer cell-derived lactate, as a consequence of enhanced glucose metabolism in tumors, influences neutrophil abundance and function in the TME. At the same time, changes in tumor glycolysis may have a direct effect on neutrophils, since the immune system also relies on glucose metabolism as fuel to exert their function.

3.4.3. Hypoxia

Hypoxia is a state of low oxygen availability that is due to a combination of oxygen consumption to support cell proliferation and reduced or leaky vascularization in tumors. Hypoxic conditions affect the metabolic state of cancer and immune cells present in the TME [137]. Interestingly, neutrophils gained a higher capacity to form NETs that promoted metastatic disease when these neutrophils were infiltrating hypoxic areas of tumors [138]. Cancer cells respond to low oxygen conditions by activating hypoxia-inducible transcription factors (HIFs) that in turn induce specific programs of gene expression to adapt to hypoxic conditions [137]. HIF-2α expression in colon cancer cells directly mediated CXCL1 expression via binding to hypoxia response elements of the *Cxcl1* promoter to induce transcription resulting in recruitment of neutrophils that promote tumorigenesis [139]. In contrast, the accumulated neutrophils in hypoxic areas of HIF-1α expressing uterine adenocarcinoma tend to have an anti-tumorigenic function by detaching cancer cells from the basement membrane rendering them as debris in the uterine lumen [140]. Restoring oxygen levels by creating hyperoxic conditions relieved hypoxia-induced recruitment of neutrophils, yet enhanced the amount of debris in the uterine lumen [141]. Hyperoxia rendered neutrophils that were already present in the tumor more prone to direct tumor cell killing independent of the adaptive immune system by expressing active MMP-9 and ROS, but lower levels of neutrophil elastase indicative of reduced NETosis [141]. Collectively, the hypoxic state of solid tumors shapes neutrophil dynamics in the TME and the switch between pro- and anti-tumorigenic functions of neutrophils in cancer progression, either by directly affecting neutrophils or via cancer cell-intrinsic metabolic reprogramming.

3.4.4. Senescence

Another process that is frequently observed in cancer is cellular senescence. Active secretion of cytokines and other immune mediators via the senescence-associated secretory phenotype (SASP) of cancer cells plays a key role in modulating the TME. Senescence and SASP have been reported to affect neighboring non-senescent immune cells and their inflammatory responses in cancer [142–144], and a few examples of the effect of SASP on tumor-associated neutrophils are highlighted here.

In a cell line transplantation-based mouse model for liver cancer, doxycycline-induced restoration of p53 gene expression in p53-null cancer cells resulted in senescence and altered gene expression of immune mediators including neutrophil attractant *Cxcl1* [145]. Here, neutrophil infiltration favored tumor control by mediating clearance of senescent hepatocellular carcinoma [145]. However, in two complementary studies, senescent *Pten*$^{pc-/-}$ mouse prostate tumors were infiltrated with pro-tumorigenic $CD11b^{+}Gr1^{+}$ cells [146,147]. Treatment of

prostate tumor-bearing mice with docetaxel induced senescence in prostate tumors, but was not sufficient for tumor eradication, while targeting myeloid cell recruitment in combination with docetaxel induced regression of prostate tumors [146,147]. Toso et al. demonstrated that PTEN deletion in prostates resulted in activation of the JAK2/STAT3 pathway and SASP, including neutrophil attractants CXCL1, CXCL2, G-CSF and IL-6, to mediate infiltration of immunosuppressive $CD11b^{+}Gr1^{+}$ cells into prostate tumors [146]. Blockade of the JAK2/STAT3 pathway, either by pharmacological JAK2 inhibition or by cancer cell-intrinsic ablation of STAT3 using $Pten^{pc-/-}Stat3^{pc-/-}$ mice, led to improved efficacy of docetaxel treatment in prostate cancer [146]. Likewise, Di Mitri et al. found that PTEN-null senescent prostate tumors produced CXCL1 and CXCL2 mediating $CD11b^{+}Gr1^{+}$ cell recruitment, while myeloid cell-derived IL-1RA served as protective mediator of cancer cell senescence in prostate tumors [147]. Interfering with myeloid cell recruitment using a CXCR2 antagonist enhanced the efficacy of docetaxel and reduced prostate tumor growth. Both studies demonstrate that oncogene-induced senescence in a model of mutant RAS-driven lung or prostate cancer did not lead to neutrophil infiltration, indicating a potential interplay between senescent cancer cell state and the genetic make-up of cancer cells in dictating the immune landscape, of which the latter is described in section 3.1 of this review. Together, these studies demonstrate that cancer cell senescence alters the secretome or SASP of cancer cells that impacts immune cells in the TME to exert pro- or anti-tumorigenic functions.

The findings described above only cover part of the metabolic processes occurring in cancer and highlight the role of cancer cell metabolism and cancer cell-derived metabolites in dictating neutrophil responses. Besides cancer cell-intrinsic metabolic reprogramming that affects secretome-mediated immunomodulation in the TME, cancer cell-extrinsic metabolic conditions such as stress, starvation, or hypoxia in the tumor niche can also directly influence the metabolic state of immune cells. In case of nutrient deprivation in the 4T1 breast cancer model, neutrophils are able to adapt their metabolism to ensure their immunosuppressive features against T cells are preserved [148]. Strikingly, a recent study illustrated that cell-intrinsic programs define whether nutrients are consumed by either cancer or immune cells rather than cell competition for the available nutrients in the tumor niche [149]. These findings indicate a strong intrinsic ability of immune cells to adapt to changing environments. Thus, the capacity of neutrophils to influence cancer progression is supported by metabolic programming of both cancer cells and neutrophils.

4. Exploiting cancer cell-neutrophil crosstalk for personalized immune intervention

As discussed in this review, numerous cancer cell-intrinsic programs involved in tumorigenesis guide cancer cell-neutrophil crosstalk in the TME. As such, existing targeted therapies acting on oncogenic signaling pathways to combat solid tumors will also impact neutrophil abundance and behavior. Especially the immunosuppressive nature of neutrophils towards cytotoxic lymphocytes is a key feature of primary resistance to cancer immunotherapy, indicating that there is a critical need for additional strategies to improve the success of immunomodulatory agents in cancer patients. Indeed, indirect blockade of neutrophil mobilization by pharmacological inhibition of oncogenic kinase FAK sensitized tumors to immunotherapy [104], illustrating the potential powerful combination of targeted cancer therapies and immunotherapy to modulate the cancer cell-induced immune landscape. Moreover, as cancer cell-intrinsic mechanisms shape the secretome-mediated communication with neutrophils, interfering with the secretome of cancer cells is another eligible therapeutic strategy. For instance, the accumulation of pro-metastatic neutrophils in p53-null mammary tumor-bearing mice was abrogated by therapeutically blocking the p53-induced secretion of Wnt ligands by cancer cells [70]. Such existing treatment options that have been developed as anti-cancer therapies are also promising to be exploited for the intervention with cancer-induced neutrophil responses to tackle cancer progression. Importantly, targeted cancer therapies will also directly act on neutrophil-intrinsic activity of signaling pathways affecting their phenotypical state. For example, targeting the tyrosine kinase receptor c-MET enhances the efficacy of cancer immunotherapy by relieving the immunosuppressive environment induced by a subpopulation of neutrophils that expressed c-MET [31]. However, $c\text{-}MET^{+}$ neutrophils have also been implicated to counteract tumorigenesis by direct killing of cancer cells, so targeting of c-MET gives a pro-tumoral effect in this setting [33]. In another study, stimulation of TLR-9 and simultaneous blockade of STAT3 signaling in neutrophils using oligonucleotide conjugate-based therapy abrogated cancer progression via activation of anti-tumor T cell responses [150]. These findings demonstrate the importance of oncogenic signaling in neutrophil modulation, independent of the intrinsic features of the primary tumor, and highlight the challenging part of the search for immune modulatory drugs to treat cancer.

An additional challenge of targeting cancer cell-neutrophil crosstalk lies in the extensive functions that neutrophils can exert in the context of cancer, a topic reviewed in this issue and elsewhere [151]. Here, we have provided a discussion of experimental examples demonstrating how cancer cells utilize a variety of programs to manipulate neutrophil abundance and function. Depending on cancer cell-intrinsic features and the tissue context, neutrophils can be polarized to suppress the adaptive immune system or to directly target cancer cells. For instance, neutrophil-derived molecules like ROS and NO are able to block the anti-tumor T cell response to promote tumorigenesis and metastatic spread [22,152], whereas these same factors have also been implicated in direct killing of cancer cells being beneficial for cancer prognosis [32,33,141]. Given that similar immunomodulatory mediators are involved in regulating dual functions of neutrophils in the context of cancer, it is crucial to mechanistically understand how such factors are driven by cancer cells prior to utilizing them for cancer therapy.

The majority of studies focusing on cancer-neutrophil crosstalk demonstrate the pro-tumorigenic role of neutrophils in cancer. Still, neutrophils are key players in target cell elimination and direct cancer cell killing can be achieved by granule release, phagocytosis or neutrophil antibody-dependent cellular cytotoxicity (ADCC), a topic reviewed in more detail in another contribution in this issue. Further research on how cancer cells modulate anti-tumorigenic features of neutrophils could provide additional immunomodulatory strategies to polarize neutrophils towards an anti-tumor phenotype and boost cancer cell elimination.

Although the impact of neutrophils on cancer cell state is beyond the scope of this review, it is noteworthy that cancer cell-neutrophil crosstalk is not an one-way route. Multiple studies have illustrated feedback loops between cancer cells and neutrophils illustrating how cancer cells impact neutrophils and *vice versa*. For instance, neutrophils contribute to enhancing metastatic cues by inducing EMT via juxtacrine-paracrine crosstalk with breast cancer cells [153]. In lung cancer, neutrophils induce a feedback loop comprising expression of EMT-inducer Snail, hypoxia and additional recruitment of neutrophils promoting cancer progression [154]. Interfering with such a continuum will abrogate the reinforcing effect that both cancer cells and neutrophils have on each other and is a potentially successful multi-target therapy to impact cancer progression.

Over recent years, the use of datasets of cancer patient cohorts and the application of machine learning prediction models and multi-omics techniques is being implemented to strive towards personalized immune intervention [61–64,155,156]. Importantly, single cell-sequencing analyses of cancer-associated neutrophils uncovered multiple neutrophil subsets being conserved between mice and humans indicating translational relevance of preclinical mouse studies focusing on cancer-associated neutrophils [35–37]. In addition, the introduction of somatic tumor modeling has made it easier to modify additional genetic aberrations in cancer while staying close to the original transgenic mice

in terms of tissue-specific gene expression and the time frame of cancer development [157]. Also, the inducible (in)activation of signaling, such as doxycycline- or tamoxifen-based models, enables spatiotemporal control of gene expression to assess the impact and timing of cancer cell-intrinsic mechanisms on the immune landscape [85,158]. Utilizing these sophisticated tools will encourage mechanistic unraveling of cancer cell-intrinsic programming of neutrophils and paves the way towards personalized immune intervention strategies for cancer patients.

5. Conclusion

The studies discussed in this review illustrate that cancer cell-intrinsic mechanisms shape the neutrophil compartment of the immune landscape and dictate their functional state to influence disease progression. It is important to realize that the cancer cell-neutrophil interactions described above should be considered in light of the larger intratumoral immune cell dynamics and crosstalk. Many different cancer cell-intrinsic factors are at play at the same time, which impact the great diversity of immune cell (sub)types present in tumors and thus demands development of therapeutic strategies covering multiple aspects of cancer-immune cell cascades.

Declaration of Competing Interest

K.E.d.V. reports research funding from Roche and is consultant for Macomics, outside the scope of this work. D.E.M.D. reports no competing interests.

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