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Review

Emerging insights into the impact of systemic metabolic changes on tumor-immune interactions

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SUMMARY

Tumors are inherently embedded in systemic physiology, which contributes metabolites, signaling molecules, and immune cells to the tumor microenvironment. As a result, any systemic change to host metabolism can impact tumor progression and response to therapy. In this review, we explore how factors that affect metabolic health, such as diet, obesity, and exercise, influence the interplay between cancer and immune cells that reside within tumors. We also examine how metabolic diseases influence cancer progression, metastasis, and treatment. Finally, we consider how metabolic interventions can be deployed to improve immunotherapy. The overall goal is to highlight how metabolic heterogeneity in the human population shapes the immune response to cancer.

INTRODUCTION

The idea that systemic metabolic health alters the interplay between immune cells and cancer is an emerging concept that may help explain variations in cancer progression and responsiveness to therapy. Much is known about how cancer cells remodel metabolism to support proliferation, growth, and survival, as well as how immune cells reprogram metabolism during activation and fate commitment. However, despite long-standing evidence linking metabolic health and cancer risk, the impact of the host environment on the tumor-immune interface is a relatively new area of investigation. In this review, we will consider the ways that cancer-immune interactions are remodeled by systemic metabolic changes due to factors like diet, obesity, age, and exercise.

LOCAL AND SYSTEMIC FACTORS THAT INFLUENCE THE AVAILABILITY OF NUTRIENTS IN TUMORS

The tumor niche is commonly described as a metabolically depleted microenvironment that lacks key fuels and nutrients due to avid consumption by cancer cells. However, precise quantification of metabolites within tumor interstitial fluid has revealed that this is not universally true.[1–3] Many interstitial metabolites are present at similar concentrations to circulating plasma. Other metabolites, such as complex lipids[4,5] and waste products like lactate[6–9] and ammonia,[10,11] accumulate to abnormally high levels. Overall, the levels of metabolites inside the tumor niche reflect the balance between pathways that move small molecules in and out of the tumor, as well as the net metabolic activity of all cells that comprise the tumor tissue.

Dietary metabolites that influence anti-tumor immunity

Circulating metabolites are a major source of nutrients to tumors, which is supported by the observation that concentrations of many metabolites within tumor interstitial fluid closely scale with those found in blood plasma.[1–3] As a result, any system-level change that alters the composition or quantity of nutrients in plasma has the potential to impact nutrient availability within a solid tumor. For some metabolites, studies where mice consume defined diets that lack individual nutrients have revealed direct relationships between dietary intake and availability in plasma. Methionine restriction reduces circulating levels of methionine-related metabolites[12,13] including hydrogen sulfide,[14] serine/glycine-free diets reduce the systemic availability of both serine and glycine,[15–19] dietary asparagine restriction reduces asparagine in the bloodstream,[20] and low-proline diets reduce circulating proline levels,[21] though further work needs to be done to determine if these changes are also reflected in tumor interstitial fluid.[2] Studies of this kind have raised the idea that dietary interventions targeting metabolic vulnerabilities of tumor cells may enhance the efficacy of cancer therapies. However, it is an open question whether diets can be formulated that starve tumor cells of critical nutrients while still supporting protective anti-tumor immune responses.

Diet-derived metabolites can also modulate the anti-cancer activity of immune cells, which has been most extensively studied in T cells. Elaidic acid and *trans*-vaccenic acid are both examples of dietary fatty acids that augment T cell responses against tumors.[22,23] Elaidic acid enhances major histocompatibility complex (MHC) class I expression on tumor cells, thereby improving recognition by $CD8^+$ T cells.[22] By

contrast, *trans*-vaccenic acid directly stimulates a surface receptor on CD8$^+$ T cells that enhances activation and function.[23] For other dietary fatty acids, the impact on anti-tumor immunity varies depending on how it is delivered. While pre-conditioning CD8$^+$ T cells in linoleic acid enhances anti-tumor activity upon transfer into tumor-bearing mice,[24] diets high in linoleic acid dampen anti-tumor immune responses by driving CD8$^+$ T cell apoptosis[25] and impairing mitochondrial function in CD4$^+$ T cells.[26] Acetate is another carbon source that can be derived from the diet or microbiome that influences CD8$^+$ T cell-mediated immunity. Supplementing dietary acetate enhances CD8$^+$ T cell effector function by feeding into acetyl-coenzyme A (CoA) pools that are needed for histone post-translational modifications.[27,28] These kinds of precisely controlled dietary interventions are useful for mechanistic studies and may have future utility in therapeutic applications.

Some amino acids are present in limiting concentrations within tumors, such that dietary supplementation can influence tumor progression. For example, increasing dietary glutamine enhances the ability of dendritic cells to stimulate protective anti-tumor T cell responses and slows the growth of tumors.[29] However, it is important to note that tumor cells and CD8$^+$ T cells also require glutamine for growth and survival.[30] Infusing stable isotopically labeled glutamine into mice has shown that glutamine is essential for effector T cell expansion.[31] Given that a separate study found that competition for glutamine between tumor and CD8$^+$ T cells impairs anti-tumor immunity,[30] it is not clear whether increasing glutamine in the diet can selectively enhance immune activities that promote tumor control. As a second example, avid consumption of methionine by cancer cells[32,33] limits the availability of this amino acid for anti-tumor T cells in the same niche.[34,35] Relieving the competition for methionine through dietary or therapeutic administration remodels the T cell epigenome and enhances immune-mediated tumor control by both CD4$^+$ and CD8$^+$ T cells.[34,35] Finally, microbiota can influence tumor growth by metabolizing diet-derived amino acids, offering new possibilities for metabolic interventions that target the microbiome. For example, some melanoma tumors are colonized by *Lactobacillus reuteri*, where it converts tryptophan to indole-3-aldehyde, which enhances anti-tumor CD8$^+$ T cell responses.[36] Increasing dietary tryptophan slows tumor growth and increases responsiveness to immune checkpoint blockade therapy in a manner that depends on *L. reuteri*.[36] Tryptophan is also metabolized by commensal gut bacteria belonging to the *Lactobacillus* genus into indoles, a class of compounds that serves as a ligand for the aryl hydrocarbon receptor (AhR) transcription factor.[37] As AhR activation in tumor-associated macrophages is pro-tumorigenic, interfering with the production of indoles by the gut microbiome slows the growth of pancreatic tumors and enhances CD8$^+$ T cell function.[37] Given that amino acids are necessary for the survival, proliferation, and function of all cells, it remains a challenge to develop targeted dietary interventions that selectively enhance protective anti-tumor activity.

Metabolite partitioning within the tumor niche

Another factor that controls the availability of metabolites within tumors is the metabolic state of cells inside the tumor niche, which shares local pools of nutrients as a common resource. Heightened metabolic activity is an established hallmark of cancer cells,[38,39] which has led to a common perception that cancer cell metabolism plays a dominant role in shaping nutrient availability inside tumors. However, studies comparing the uptake of individual metabolites by positron emission tomography (PET) have challenged this idea by revealing that immune cells also take up large quantities of nutrients in the tumor microenvironment.[40] While glutamine is most avidly consumed by cancer cells within solid tumors, myeloid cells and T cells both take up more glucose than tumor cells across multiple cancer types.[40] As a result, dietary interventions that reprogram the metabolism of tumor-resident cells, or alter the proportional representation of cell types, can influence tumor progression by changing how the uptake of critical fuels and nutrients partitions between cells in the tumor niche. For example, feeding mice a high-fat diet impairs CD8$^+$ T cell-mediated anti-tumor immunity and leads to faster tumor outgrowth.[41,42] Tumor cells respond to a high-fat diet by decreasing the expression of prolyl hydroxylase 3 (PHD3), which increases fat uptake by tumor cells and starves T cells in the same environment for fatty acids.[42] This is an example where diet-induced obesity leads to metabolic reprogramming in the tumor that shifts how nutrients partition between cancer and immune cells, thereby altering cancer progression.

Mechanisms by which dietary metabolites and metabolic partitioning influence anti-tumor immunity are summarized in Figure 1.

METABOLIC HORMONES REGULATE ANTI-TUMOR IMMUNITY

Many immune cells express surface receptors that sense metabolic hormones, which encompass signaling molecules and cytokines that possess metabolic regulatory functions. The production of metabolic hormones is closely linked to metabolic health. As a result, levels of metabolic hormones in circulation change acutely with nutrient availability and stress, while chronic metabolic diseases like obesity and diabetes lead to sustained dysregulation. This section will review what is known about metabolic hormones that are sensed by immune cells and how this modulates anti-tumor immune activity.

Adipokines are cytokines and signaling mediators secreted by adipose tissue that coordinate energy balance and regulate hunger and satiety.[43] The expansion of adipose tissue with overnutrition and obesity alters circulating adipokine levels. Many immune cells express adipokine receptors, meaning that these hormones can directly influence anti-tumor immune responses. As a first example, leptin is a peptide hormone secreted by adipose tissue that regulates whole-body energy balance. CD8$^+$ T cells express the leptin receptor, where chronic exposure to elevated leptin during obesity causes T cell exhaustion and promotes tumor outgrowth.[44] By contrast, acute exposure to leptin has beneficial anti-tumor effects. Loading leptin into oncolytic viruses improves anti-tumor CD8$^+$ T cell functionality in otherwise healthy mice,[45] and systemic leptin administration to lean mice also delays the growth of colorectal allografts by repolarizing tumor-associated macrophages to inflammatory anti-tumor cell states.[46] Dendritic cell vaccines pre-treated with leptin also

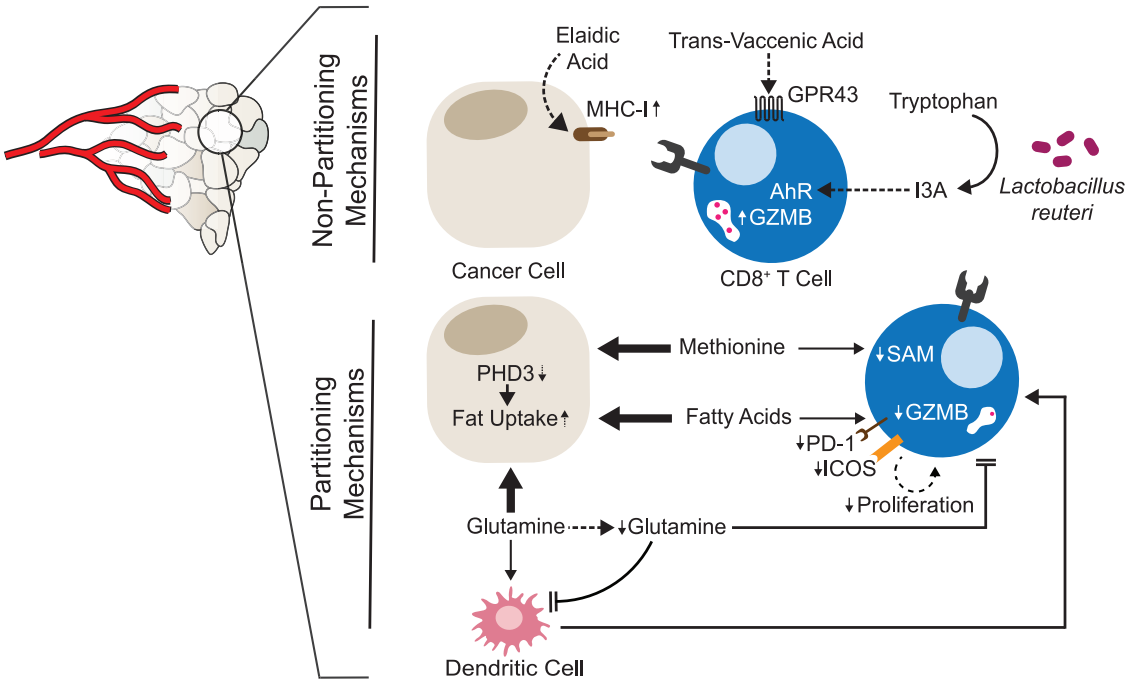

Figure 1. Metabolic processes within tumors that influence anti-tumor immunity

This figure illustrates examples of non-cell-autonomous metabolic processes within tumors that influence anti-tumor immunity. Elaidic acid promotes immune surveillance by increasing MHC class I expression on cancer cells. *Trans*-vaccenic acid inactivates the GPR43 surface receptor on $CD8^+$ T cells, leading to increased cytokine production, proliferation, ICOS expression, and GZMB expression. Tumor microbiome strains such as *L. reuteri* can promote T cell activation and GZMB production via AhR signaling with tryptophan-derived I3A. Local methionine depletion due to avid consumption by tumor cells limits T cell function by reducing SAM levels needed for histone methylation. Tumors increase fat uptake in response to a high-fat diet, sequestering fatty acids from T cells, leading to lower ICOS, proliferation, and PD-1 expression. Glutamine uptake by cancer cells limits dendritic cell function and impairs T cell priming. I3A, indole-3-aldehyde; DC, dendritic cell; ICOS, inducible T cell costimulator; PD-1, programmed cell death protein 1; AhR, aryl hydrocarbon receptor; GZMB, granzyme B; SAM, S-adenosyl methionine.

lead to better control of breast cancer tumors.[47] This illustrates how chronic dysregulation of an adipokine can lead to distinct immunological outcomes compared to acute exposure and that dosing also matters. As a second example, adiponectin is an insulin-sensitizing hormone secreted by adipose tissue. Whether the reduction in circulating adiponectin levels during obesity changes anti-tumor immune responses is still an open question. However, mice that genetically lack adiponectin exhibit potent $CD8^+$ T cell responses[48] and higher infiltration of inflammatory macrophages within tumors,[49] which suppress rhabdomyosarcoma tumor growth to a greater extent than animals with normal adiponectin expression. There is a pressing need to understand which specific cell types within tumors directly respond to hormones like adiponectin and leptin, as well as how these signaling pathways are altered during chronic dysregulation associated with obesity.

Visfatin, also known as nicotinamide phosphoribosyltransferase (NAMPT), is another adipokine with insulin-sensitizing activity[50] that becomes dysregulated with obesity.[51] Initially identified for its cytokine-like activity,[52] we now know that visfatin is a secreted enzyme that converts nicotinamide to nicotinamide mononucleotide (NMN) as part of the NAD+ salvage pathway. Therefore, visfatin is an example of a secreted signal that may control cell-extrinsic metabolite regulation. Circulating visfatin/NAMPT is largely produced by adipose tissue, but it can also be generated locally within tissues by macrophages and stromal cells.[53] There is also evidence that tumor cells make visfatin directly[54] and even raise circulating visfatin levels in the bloodstream during metastatic disease.[55] Given its enzymatic function, extracellular visfatin/NAMPT within tumors may increase local NMN levels, which can be taken up by cells through plasma membrane transporters.[56] Whether changes to visfatin alter the process of tumorigenesis and how this intersects with systemic perturbations like obesity is still incompletely understood. However, culturing $CD8^+$ T cells in nicotinamide, which is consumed by visfatin, can reverse hallmarks of dysfunction.[57] Nicotinamide treatment also attenuates the inflammatory function of macrophages.[58] By altering the availability of NAD+ precursors, changes to visfatin levels may have major impacts on NAD+-driven energy production across all cells within tumors.[59] In pancreatic cancer, which is particularly resistant to immunotherapy, delivering visfatin directly to tumors using an oncolytic virus slows tumor growth.[60] This is associated with a dramatic shift in the tumor-immune infiltrate to favor cells that control tumors, such as $CD8^+$ T cells, dendritic cells, and inflammatory macrophages, as well as a reduction in regulatory $CD4^+$ T cells. Overall, adipokines play complex and context-dependent roles in anti-tumor immunity,

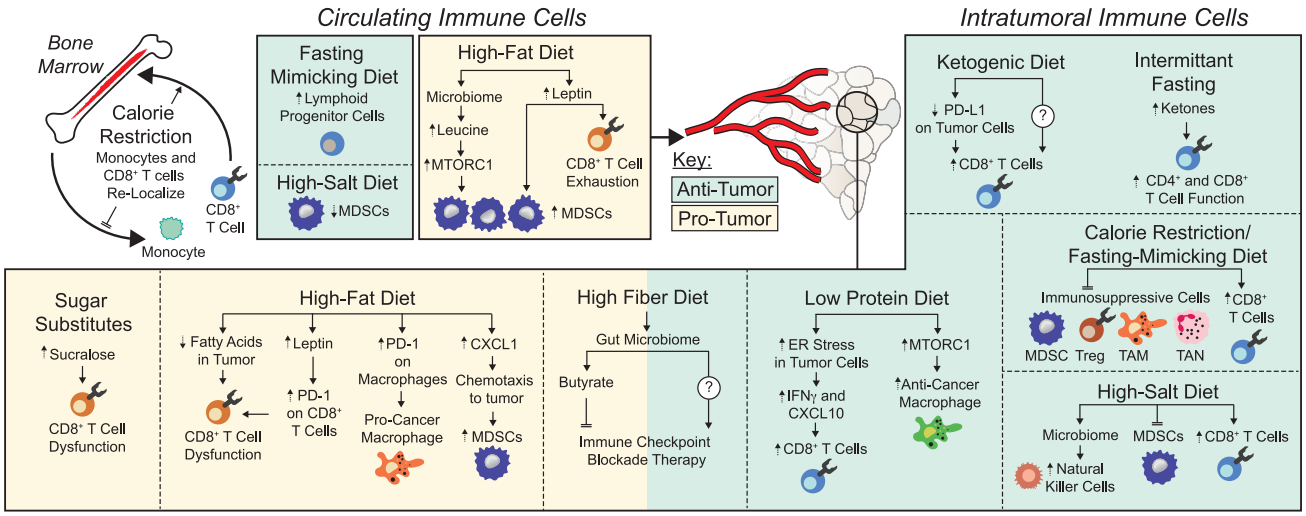

Figure 2. Systemic and intratumoral effects of diet on anti-tumor immunity

Altering the composition and quantity of dietary nutrients can change the way that immune cells function within tumors. These changes can lead to either protective anti-tumor effects or detrimental pro-tumor outcomes that promote disease progression. Some dietary interventions that influence anti-tumor immunity alter the total number, localization, or functional state of circulating immune cells. Fasting-mimicking diets increase lymphoid progenitor cells from the bone marrow that differentiate into anti-tumor T cells, a protective mechanism that slows tumor growth. High-salt diets also reduce the production of MDSC progenitors, which migrate into tumors and suppress anti-tumor immunity. Conversely, diets high in fat stimulate systemic expansion of MDSCs and drive systemic $CD8^+$ T cell exhaustion, which collectively promote tumorigenesis. Dietary interventions can also change the infiltration and functionality of immune cells within tumors. These also lead to anti-tumor or pro-tumor outcomes, as well as influence responsiveness to immune checkpoint blockade therapies. High levels of sugar substitutes and fat in the diet lead to cellular and molecular changes in tumor-infiltrating immune cells that promote tumor outgrowth. On the other hand, ketogenic diets, high-salt diets, and diets with low protein or various kinds of dietary restrictions are protective against tumor outgrowth. There are also examples of dietary interventions, such as increasing dietary fiber, that can have pro-tumor or anti-tumor effects depending on context. MDSC, myeloid-derived suppressor cell; Treg, regulatory $CD4^+$ T cell; TAM, tumor-associated macrophage; TAN, tumor-associated neutrophil; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1.

and administering adipokines has emerged as a potential strategy to improve immunotherapy.

Steroid hormones are a kind of signaling molecule derived from cholesterols, which are also dysregulated by obesity. Sex hormones include androgens, estrogens, and progestogens and can exert pro-tumor effects on cancer cells while also affecting immune responses through the activation of hormone receptors expressed ubiquitously on immune cells.[61,62] For example, estradiol in the melanoma tumor microenvironment has been shown to signal through the estrogen receptor alpha (ERα) on macrophages, polarizing them to an immune-suppressive state that hinders anti-tumor immunity.[63] Obesity may exacerbate the impact of sex hormones on anti-tumor immunity, as aromatase- and androgen-producing enzymes that make sex hormones are upregulated within fat depots across the body in this context.[64] Glucocorticoids are another kind of steroid hormone that circulate systemically but also can be produced by cancer cells and tumor-associated macrophages.[65] Local glucocorticoid production promotes infiltration by regulatory $CD4^+$ T cells into tumors[65] and directly induces dysfunction in $CD8^+$ T cells.[66,67] Additionally, glucocorticoid production by tumors such as glioblastomas can cause T cells to become sequestered within the bone marrow, thereby impairing anti-tumor responses.[68] Stress is another systemic factor that alters circulating glucocorticoid levels due to the production of cortisol. Elevating cortisol in mice, either by behavioral conditioning or glucocorticoid injection, promotes tumor growth by impairing the function of dendritic cells and effector $CD8^+$ T cells.[69] In summary, steroid hormones can be derived from circulating pools or produced locally within tumors, where they influence a variety of immune activities that regulate tumor growth.

DIET, EXERCISE, AND THE TUMOR-IMMUNE INTERFACE

Large epidemiological studies have provided compelling evidence that metabolic stress, influenced by factors such as obesity and physical activity, modulates cancer risk. Understanding the mechanisms by which food intake, diet composition, and physical activity collectively alter tumor-immune interplay has implications for cancer prevention and may offer new diet-based strategies for improving cancer therapy. The impact of diet and nutrition on anti-tumor immune responses is summarized in Figure 2.

Dietary excess and anti-tumor immunity

Obesity is the physical manifestation of chronic over-nutrition and a risk factor for 18 different cancer types.[70,71] Feeding mice a high-fat diet derived from animal lard is commonly used to model aspects of human obesity for cancer research. Across an array of cancer types, diet-induced obesity accelerates tumor growth through both tumor cell-intrinsic and immune-mediated mechanisms.[42,44,72–96] As obesity is a multi-factorial and complex condition, this section will focus on immunological changes

linked to obesity that alter anti-tumor immunity. In breast cancer, obesity increases tumor infiltration by myeloid-derived suppressor cells through multiple mechanisms, including enhancing chemotaxis to the tumor,[74] driving expansion of myeloid cells via leptin signaling,[93] and increasing MTORC1 signaling through increased leucine production by the gut microbiome.[97] Chronically elevated leptin during diet-induced obesity also drives systemic $CD8^+$ T cell exhaustion in mouse models of breast cancer, lung cancer, and melanoma, which dampens immune-mediated tumor control.[44] In pancreatic cancer, obesity remodels the tumor microenvironment to be permissive for growth and metastasis by increasing the infiltration of tumor-associated macrophages[90] and tumor-associated neutrophils.[89] Tumor-associated macrophages also express higher levels of the inhibitory programmed cell death 1 (PD-1) receptor with obesity,[76] a cell state that tends to be immunosuppressive.[98] An important question is whether any of the reported obesity-related deficits can be reversed by immunotherapy or even co-opted to enhance patient outcomes. In pre-clinical models, immune checkpoint blockade therapies targeting the PD-1 receptor tend to be effective in obese animals.[41,44,76,92,96] Weakened surveillance by the adaptive immune system can even make tumors more immunogenic, as cancer cells persist that would otherwise be eliminated by T cell-mediated killing.[92] In addition, anti-PD-1 treatment contracts immunosuppressive cell populations that pathologically expand with obesity.[96] The expression of PD-1 on tumor-associated macrophages directly enhances responsiveness to immunotherapies targeting the PD-1 receptor.[76] Distinguishing which immunological differences are due to the high-fat diet itself versus obesity is still incompletely understood. Overall, further research is warranted to explore if these differences can be leveraged to optimize immunotherapies for obese patients with cancer.

Ketogenic diet is a specific kind of high-fat diet characterized by extremely low levels of carbohydrates. In addition to raising circulating fatty acids,[99] this diet potently drives ketogenesis by the liver and increases ketones to low millimolar levels in plasma.[100] Ketone bodies are used as an alternative fuel source when glucose is limited and can function as endogenous histone deacetylase inhibitors.[101] As $CD8^+$ T cells express ketolytic machinery, ketone bodies are metabolized directly into acetyl-CoA within these cells to fuel bioenergetics and regulate histone acetylation at key effector genes upon activation.[102] Interventions that raise circulating ketones indeed sensitize immunotherapy-resistant prostate cancer,[103] as well as aggressive melanoma and renal carcinoma tumors,[104] to anti-PD-1/anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA4) treatment, suggesting that ketogenic diet may have efficacy as an adjuvant to immunotherapies that target T cells. Energetic stress caused by a ketogenic diet reduces the expression of the inhibitory programmed cell death ligand 1 (PD-L1) receptor in multiple cancer models, which is one potential mechanism for sensitizing animals to immunotherapies that target inhibitory surface receptors.[104,105] However, a better understanding of how the ketogenic diet impacts the overall tumor-immune infiltrate will be necessary if this dietary intervention is to be deployed in combination with immunotherapy. For example, macrophages also express ketogenic and ketolytic enzymes, which dynamically shift in expression in response to polarization cues.[106] While a ketogenic diet slows the growth of glioblastoma tumors in mice, it simultaneously increases local infiltration by pro-tumor macrophages.[107] As a result, combining a ketogenic diet with anti-CSF-1R treatment dramatically extends survival, underscoring the importance of considering the entire immune landscape.[107] It is important to note that a ketogenic diet has also been shown to enhance inflammatory macrophage polarization in some colorectal cancer models,[108,109] suggesting that the impact of this diet on the immune system may vary across cancer types. Finally, the extent to which the anti-cancer effects of a ketogenic diet involve the gut microbiome is still an open question. While an enrichment in *Eisenbergiella massiliensis* has been shown to correlate with circulating levels of ketone bodies in both mice and humans consuming a ketogenic diet,[104] this shift has not been causally implicated in anti-cancer immune activity. Given the pleiotropic effects that ketones have on cellular processes, future studies will uncover additional therapeutic contexts where ketone bodies can improve anti-tumor immune responses.

Other dietary additives and interventions continue to be identified that influence anti-tumor immunity. Diets high in salt lead to phenotypes associated with tumor control by many kinds of immune cells, which include stimulating anti-tumor natural killer (NK) cell activity,[110] blocking the immunosuppressive activity[111,112] and differentiation[112] of myeloid-derived suppressor cells, blunting alternative activation in macrophages,[113] dampening regulatory $CD4^+$ T cell activity,[114–116] and directly improving anti-tumor $CD4^+$ and $CD8^+$ T cell fitness and response to stimulation.[117–119] As a result, increasing dietary sodium improves responsiveness to immune checkpoint blockade therapies.[110,118,119] However, salt can also lead to pro-tumorigenic effects. Mice fed a high-salt diet exhibit increased tumor-initiating stem cells in a breast cancer model.[120] In addition, salt induces the differentiation of $CD4^+$ T helper 17 (Th17) cells in tissue culture,[121,122] which are a kind of inflammatory T cell implicated in autoimmune diseases that can promote or repress tumor progression depending on context.[123] While salt has been shown to act directly on Th17 cells,[121,122] a high-salt diet also alters the gut microbiome, where depletion of *Lactobacillus murinus* plays a role in inducing the differentiation of Th17 cells.[124] Given the phenotypic plasticity of Th17 cells, it remains to be seen whether salt-induced Th17 cells tend to promote or repress tumor growth. It is also possible that increasing the Th17-to-regulatory T cell ratio with high salt intake promotes inflammation that drives tumor initiation or co-opts tissue environments to become permissive to metastasizing tumor cells, but this requires further investigation. Fiber is another dietary component that has been linked to differences in anti-tumor immunity. In human cohorts, dietary fiber is associated with improved survival with immune checkpoint blockade therapy, which has been recapitulated by fecal microbiota transplant into germ-free mice.[125] However, feeding mice a high-fiber diet has been shown to impair responsiveness to anti-CTLA4 immunotherapy by raising serum butyrate, a fermentation product derived from the microbiome.[126] Therefore, further research is needed to fully understand the role of dietary fiber in tumorigenesis. Sucralose is another common dietary additive, comprising a non-digestible sugar substitute that enters circulation upon consumption.[127] Supplying

sucralose to tumor-bearing mice in drinking water directly impairs T cell activation and accelerates tumor growth.[128] Overall, these examples highlight how common dietary components can modulate anti-tumor immunity.

Dietary restriction and anti-tumor immunity

Calorie restriction is a dietary intervention that reduces the total intake of nutrients without causing malnutrition.[129] In addition to improving metabolic health in mice[130–132] and humans,[133,134] calorie restriction redistributes immune cells among lymphoid and non-lymphoid tissues.[135] Upon dietary restriction, inflammatory monocytes are retained in bone marrow.[136] Monocytes are the cellular precursors for some tumor-associated macrophages and monocyte-derived suppressor cells. Circulating T cells also relocate to the bone marrow during calorie restriction.[137,138] While sustained lymphopenia is generally associated with poor outcomes in patients with cancer,[139,140] the temporary residence of immune cells in the bone marrow may improve immune responses. In bacterial infections, trafficking to the bone marrow improves immunological memory.[137] Immune memory is an important feature of T cell-mediated immunity that is critical for long-lasting, relapse-free survival with immunotherapy. This raises the question of whether dietary interventions that reduce calorie intake can improve immunotherapeutic outcomes in cancer. Studies in immunocompetent mouse models of cancer have revealed that calorie restriction, as well as the related regimen of a fasting-mimicking diet, generally improves immune-mediated tumor control. A common finding is that dietary interventions mimicking calorie restriction enhance anti-tumor $CD8^+$ T cell function by depleting immunosuppressive cell populations across multiple solid tumor models.[141–143] Similarly, periodic fasting depletes anti-inflammatory M2-polarized macrophages from colorectal tumors, which relieves suppression of cytotoxic $CD8^+$ T cells and improves tumor control.[144] Calorie restriction slows tumor growth in immunocompetent mouse models of breast cancer and leads to an inflammatory immune signature with fewer immunosuppressive myeloid-derived suppressor cells, as well as increased infiltration by $CD4^+$ and $CD8^+$ T cells.[145] Building on these studies, whether immune remodeling caused by calorie restriction and fasting-mimicking diets can be harnessed to improve patient outcomes is an active and ongoing area of research. Both dietary interventions sensitize tumor-bearing mice to chemotherapy and improve survival.[142,143,146] Although the fasting-mimicking diet has also been shown to improve responsiveness to immunotherapies in both triple-negative breast cancer[147] and colorectal cancer,[148] an important point is that the underlying mechanisms differ by tumor type. In both cancers, the fasting-mimicking diet expands effector $CD8^+$ T cells inside the tumor.[147,148] However, for colorectal cancer, the mechanism requires remodeling of the gut microbiome.[148] The fasting-mimicking diet is also protective against immune-related adverse events,[147,149] even in cancer types where it does not enhance the efficacy of immunotherapy.[149] For epithelial ovarian cancer, intermittent fasting drives systemic ketogenesis, which slows tumor growth and prolongs survival by stimulating protective anti-tumor T cell responses.[150] In human patients, clinical trials have demonstrated that combining standard cancer therapies with a fasting-mimicking diet reduces circulating levels of immunosuppressive immune cells and increases signatures associated with cytotoxic anti-tumor immunity[151] while protecting T cells from damage due to chemotherapy.[152] Overall, dietary interventions that reduce calorie intake tend to slow tumor growth and stimulate anti-tumor immune activity.

While calorie restriction generally has a positive effect on immunotherapy, whether this is due to changes in nutrient availability, metabolic hormones, or both is less clear. Calorie restriction leads to a wide range of health benefits, including weight loss, altered body composition, and re-balanced whole-body energy expenditure[153,154]; reduced fasting insulin levels[154,155]; and changes to circulating metabolites.[154,156] Deciphering precisely which of these factors influences tumor growth is a challenge and likely varies based on tumor type, metabolic health, and other non-genetic sources of patient heterogeneity.

Rather than restricting total calorie intake, targeted nutritional approaches that reduce dietary protein also enhance anti-tumor immunity. Dietary protein is a major source of amino acids, which serve as buildings blocks for protein translation. Low-protein diets cause endoplasmic reticulum (ER) stress in tumor cells, which increases infiltration by $CD8^+$ T cells by inducing local chemokine expression.[157] Dietary protein restriction also reprograms tumor-associated macrophages to control tumor growth.[158,159] This is mediated by divergent signaling events in tumor cells and tumor-associated macrophages. Within macrophages, a noncanonical pathway links the low-protein diet to MTORC1 activation, whereas MTORC1 activity is suppressed within tumor cells that reside in the same niche.[159] Clinical trials are necessary to determine if combining dietary protein or individual amino acid restriction can improve patient responses to immunotherapy.

Exercise-derived metabolites that modulate immune function

Physical activity is a lifestyle habit that promotes metabolic health and is statistically associated with a reduction in cancer risk.[160–163] In addition to influencing how nutrients are mobilized and stored across the body, exercise also normalizes adipose tissue function,[164] regulates system-wide inflammation,[165] and acutely remodels the plasma metabolome.[166] The idea that exercise has potential as an adjuvant for cancer immunotherapy is a growing focus for pre-clinical and translational research.[167,168] Here, we will focus on a subset of metabolites that are released into the circulation during exercise and how they influence anti-tumor immunity.

Lactate is an abundant metabolite that changes systemically with exercise, as it is produced by contracting skeletal muscle and released into circulation.[169] In tumors, the accumulation of lactate is almost always coupled with local acidosis.[170,171] In the acidic environment of a tumor, lactic acid suppresses $CD4^+$ and $CD8^+$ T cell function[6,172–174] while promoting immunosuppressive activity by regulatory $CD4^+$ T cells[175–178] and tumor-associated macrophages.[179] The bloodstream, however, buffers lactic acid as a neutral lactate. In the absence of acidosis, neutral lactate produced by exercise training enhances anti-tumor activity by $CD8^+$ T cells.[180,181] Succinate is another metabolite derived from central carbon metabolism that is secreted by

exercising skeletal muscle into the bloodstream.[182] Within tumors, succinate can serve pro- or anti-cancer functions depending on the context. Whereas tumor-derived succinate causes macrophages to enter immunosuppressive states,[183] $CD8^+$ T cell-derived succinate enhances cytotoxicity through an autocrine signaling mechanism.[174] Whether local acidity modulates the impact of succinate or other exercise-derived metabolites[166] on anti-tumor immunity is an open question that remains to be determined. Future studies are necessary to define exercise strategies tailored to the needs of patients with cancer undergoing treatment, as well as determine whether exercise-induced changes to physiology can improve human patient outcomes.

METABOLIC CONDITIONING OF METASTASIS

Metastasis describes the process by which cancer cells spread from the primary tumor site to colonize distant tissues and is a major cause of mortality from solid tumors.[184] The process of metastasis is highly inefficient and selective,[185] as most circulating cancer cells do not ultimately seed metastatic tumors. It is now known that metastasizing cancer cells must acquire metabolic adaptations to survive dissemination through the harsh oxidative environment of the blood[186–188] and also land in a receptive tissue environment that supports outgrowth of the metastatic tumor mass.[189] In this section, we will review how dietary nutrients, systemic metabolic health, and immune function collectively influence the process of cancer metastasis.

Effect of obesity and dietary lipids on metastasis

Excess dietary lipids have been shown to enhance the intrinsic metastatic capacity of cancer cells across multiple tumor models. In prostate cancer, a high-fat diet leads to a lipogenic transcriptional signature and intracellular accumulation of lipids that drives lymph node and lung metastasis.[190] Culturing prostate cancer cells in a lipid-enriched medium is sufficient to recapitulate pro-metastatic phenotypes observed *in vivo*.[190] Mice made obese by a high-fat diet are also more susceptible to liver metastases from breast cancer and melanoma cells.[191] This effect persists with metformin treatment, suggesting it is a direct effect of dietary lipids rather than a consequence of metabolic dysfunction.[191] In oral carcinomas, palmitic acid derived from the diet programs a durable pro-metastatic cell state through epigenetic changes.[192] Dietary lipids can also create a receptive environment for metastatic tumor seeding by altering the composition and levels of local lipids. Lung interstitial fluid from mice with early-stage metastatic breast cancer fed a high-fat diet was found to contain increased levels of palmitate, which supports the metabolism of metastasizing tumor cells.[193] In this context, a high-fat diet increases palmitate in the healthy lung and predisposes to local breast cancer metastasis.[193] Finally, oleic acid in lymph fluid has been shown to provide protection against oxidative stress and ferroptosis for circulating tumor cells, increasing the propensity for metastasis at distant sites.[194] Whether high-fat diets also promote the survival of disseminating tumor cells by remodeling the fatty acid composition of lymph fluid is still an open question. Together, these studies suggest that dietary lipids directly promote cancer cell states that are amenable to metastasis.

In addition to lipids directly influencing metastatic cancer cell states, chronic inflammation and other immunological changes linked to obesity[195] can promote or suppress metastasis by remodeling local tissue environments (Figure 3). In the lung, diet-induced obesity creates a favorable environment for breast cancer metastasis by remodeling the local myeloid cell compartment. By increasing levels of interleukin (IL)-5 and granulocyte-macrophage colony-stimulating factor (GM-CSF), obesity leads to the recruitment of neutrophils into the lung, which promotes breast cancer metastasis.[196] Obesity also shifts the differentiation of circulating monocytes into cell states that promote neutrophil activation in the lung, further promoting metastatic progression of breast cancer.[197] Mechanistically, obesity-induced neutrophilia in lung tissue promotes the influx of cancer cells by impairing vascular integrity.[198] However, in other contexts, high-fat diets can instead have a protective effect against metastasis. For example, short-term exposure to a high-fat diet prevents peritoneal metastasis in colorectal carcinoma by activating adipose-resident macrophages in visceral fat, which promotes an anti-metastatic immune response.[199] Further research is needed to define how systemic obesity conditions pre-metastatic niches across diverse tissue sites and how this differs by tumor type.

Diabetic hyperglycemia and metastasis

Although many cancer cells are highly glycolytic,[39] hyperglycemia is not uniformly pro-tumorigenic. While hyperglycemia leads to varied effects on primary tumor growth,[200,201] it generally increases metastatic potential. Elevated blood glucose in a streptozotocin (STZ)-induced model of type 2 diabetes increases lung metastases from breast cancer tumors. This effect is mediated by immune signaling, as STZ treatment decreases G-CSF levels and, consequently, reduces neutrophil counts in the lung and in circulation.[201] Heterogeneous subsets of neutrophils exist, characterized by either pro- or anti-tumor functions.[202] While neutrophilia in the lung can be permissive to metastasis in some settings, reduced neutrophil counts can also decrease anti-tumor immunity and enable metastatic seeding. Treatments that normalize blood sugar levels decrease metastatic seeding of the lung in a mouse model of triple-negative breast cancer,[203] in part by reprogramming macrophages to inflammatory and anti-tumor cell states.[203] The pro-metastatic effects of hyperglycemia highlight how controlling glucose and insulin levels in patients with type 2 diabetes has implications for health beyond diabetes management and may be important for improving cancer mortality in these vulnerable patient populations.[204–208]

SYSTEMIC METABOLIC INTERVENTIONS AS CANCER TREATMENTS

The global obesity epidemic is driving an increase in the number of people who are treated for obesity-related metabolic diseases. This section will explore whether obesity-related cancer risk is reversible and examine how different weight-loss methods impact cancer outcomes. In addition to weight loss, we will also discuss how systemic metabolic therapies that are used as anti-diabetic medications and interventions targeting the commensal microbiome influence the efficacy of cancer immunotherapies.

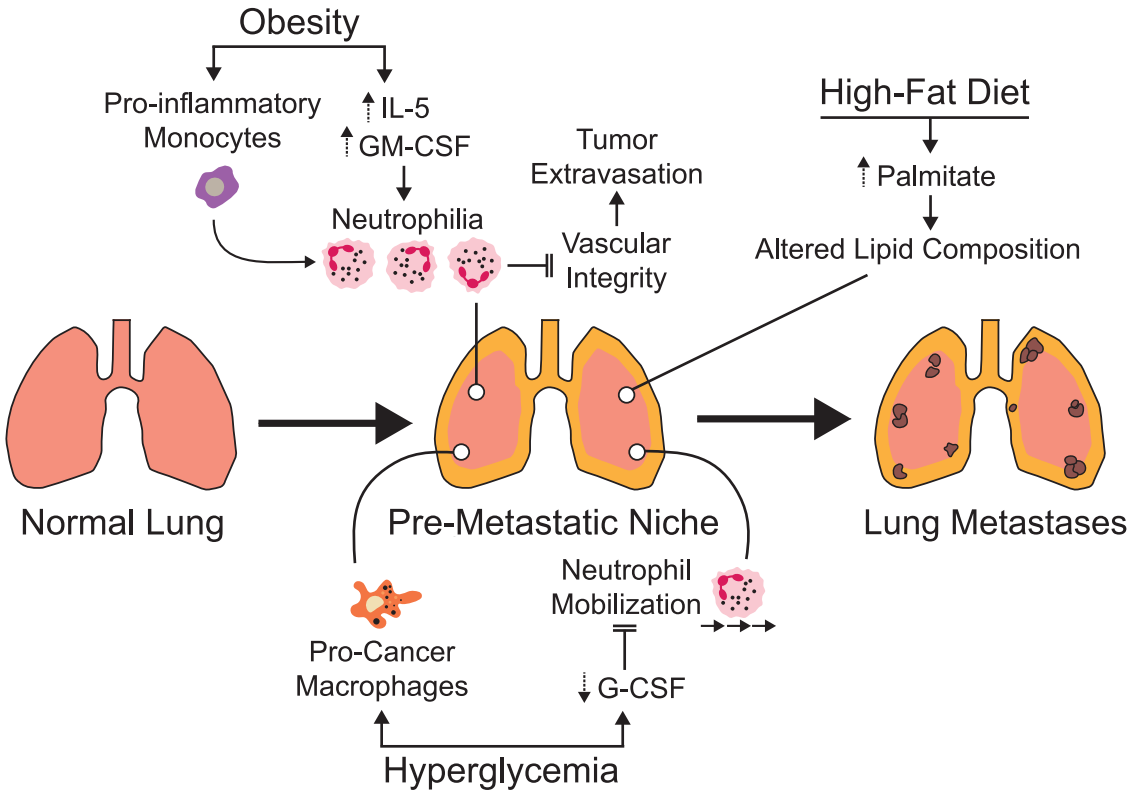

Figure 3. Metabolic conditioning of lung tissue establishes a pre-metastatic niche

Obesity, hyperglycemia, and a high-fat diet have all been shown to cause changes in lung tissue that create a permissive pre-metastatic niche and promote the establishment of metastases. Obesity polarizes monocyte identities toward a pro-inflammatory phenotype, which in turn induces neutrophil activation and neutrophilia in the lung. By remodeling the myeloid compartment, obesity additionally results in heightened levels of IL-5 and GM-CSF, which also recruits neutrophils to the lung. Neutrophilia in the lung impairs vascular integrity, thus enabling the extravasation of tumor cells from the vasculature. A high-fat diet can alter the lung pre-metastatic niche by increasing palmitate levels in the lung tissue, which supports the metabolism of metastasizing tumor cells. Finally, hyperglycemia increases the metastasis of cancer cells to the lung by impairing neutrophil mobilization and reprogramming macrophages to pro-tumor states. Neutrophil mobilization is impaired in the lung by hyperglycemia due to decreased levels of G-CSF. Although an excess of neutrophils in the lung is pro-metastatic, the impairment of a neutrophil mobilization to the lung also supports metastases formation as a healthy neutrophil count enhances anti-tumor immune responses. GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-5, interleukin 5; G-CSF, granulocyte colony-stimulating factor; MAPK, mitogen-activated protein kinase.

Reversing weight gain for cancer prevention and therapy

While obesity is a well-established risk factor for cancer, the extent to which weight loss can reverse this risk is still under investigation. Reducing excess body fat can be achieved by any combination of reducing calorie intake, increasing physical activity, surgical interventions, or medical treatments. Overall, weight loss generally improves chronic inflammation associated with obesity[209] and lowers the risk of developing many cancers.[210–213] Recent studies have uncovered, however, that the specific method of weight loss influences the extent of these benefits. For example, vertical sleeve gastrectomy and diet-induced weight loss led to similar reductions in body weight and adiposity levels in formerly obese mice.[214] However, diet-induced weight loss led to better tumor control over the surgical intervention.[214] This difference was linked to sustained deficits in anti-tumor immune responses following vertical sleeve gastrectomy, where intratumoral immune cells expressed higher levels of inhibitory checkpoint receptors and tumors were infiltrated by fewer $CD8^+$ T cells. Mice that received a vertical sleeve gastrectomy exhibited higher circulating levels of IL-6 compared to mice that lost weight by dieting alone, which may drive immune suppression in tumors. In addition to surgical weight loss, the US Food and Drug Administration (FDA) recently approved the use of glucagon-like peptide (GLP-1) analog drugs, initially prescribed as antidiabetics, as a medical intervention for the treatment of obesity.[215] Similar to what has been observed with vertical sleeve gastrectomy, obese mice that lost weight following treatment with semaglutide, a GLP-1 receptor agonist, were unable to control implanted tumors as well as mice that lost a similar amount of weight by dieting.[92] Dieting improved the effector function of tumor-infiltrating $CD8^+$ T cells, while semaglutide treatment did not. It is important to note that semaglutide-treated mice remained on a Western diet chow, while dieting mice were switched to normal chow. Thus, more work is needed to define if the difference in immune health between the two groups is a result of diet switch versus the weight-loss method. Functionally, checkpoint blockade immunotherapy

was far less effective in mice that lost weight from semaglutide treatment.[92] The poor recovery of immune function in mice treated with semaglutide is consistent with previous findings that GLP-1 analogs have anti-inflammatory effects.[216] The GLP-1 receptor is expressed on the surface of many immune cells, including macrophages and lymphocytes, and signaling through these receptors suppresses the secretion of pro-inflammatory cytokines such as IL-6, tumor necrosis factor alpha (TNF-α), interferon (IFN)-γ, and IL-17.[216–218] These findings suggest that improving metabolic health and dietary habits, not just weight loss alone, may be important for reducing cancer risk associated with obesity.

Anti-tumor potential of antidiabetic therapies

The observation that taking metformin reduces cancer risk among patients with type 2 diabetes[83] introduced the concept that antidiabetic drugs might influence the efficacy of immunotherapy[219] or be repurposed as cancer therapeutics. As a treatment for diabetes, metformin improves insulin sensitivity and blood sugar control. However, the effect of metformin on tumors is largely independent of these systemic effects. While the mechanism by which metformin improves anti-tumor immunity is still debated, pre-clinical studies have demonstrated that metformin improves immune-mediated tumor control[220] and can be used to enhance the efficacy of various kinds of immunotherapies.[221–224] Another class of antidiabetic drugs with potential as cancer therapies is sodium-glucose cotransporter 2 (SGLT2) inhibitors. These drugs reduce blood sugar levels by inhibiting the reabsorption of glucose in the kidneys. SGLT2 unexpectedly co-localizes with and stabilizes the inhibitory PD-L1 receptor on tumor cells, which dampens immune-mediated tumor control. This interaction is disrupted by the SGLT2 inhibitor canagliflozin,[225] slowing tumor growth and improving responsiveness to immune checkpoint blockade therapies.[225,226] However, canagliflozin also impairs the activation of human $CD4^+$ and $CD8^+$ T cells,[227] so there is more work to be done to define the full effect of SGLT2 inhibitors on anti-tumor immunity. In addition to the potential for repurposing antidiabetic drugs for cancer treatment in conjunction with immunotherapy, it is important to understand how these widely prescribed medications influence cancer risk and incidence.

Targeting the microbiome to improve immunotherapy

The presence or absence of specific commensal microbes within the gut, which is highly dynamic and varies between individuals,[228] is another systemic factor that has been associated with divergent outcomes in response to cancer immunotherapy. Early research in mice found that natural variation in the microbiome between commercial sources of animals influenced the growth rate of melanoma tumors and responsiveness to anti-PD-L1 immune checkpoint blockade therapy.[229] Transferring fecal microbiota was sufficient to improve $CD8^+$ T cell priming and slow tumor growth with anti-PD-L1 therapy in mice that had previously shown poor responses to this treatment.[229] This pivotal study established a causal relationship between the gut microbiome and anti-tumor immune response. Building on this finding, pre-clinical studies have established specific microbial communities,[230–233] and, in some cases, small-molecule intermediaries derived from the microbiome[234–236] that modulate anti-tumor immune cell function. In humans, microbial communities that are statistically associated with responsiveness to immune checkpoint blockade therapy have now been identified, and fecal microbiome transfers in conjunction with immune checkpoint blockade therapy have yielded promising results in clinical trials.[233,237,238] In some cases, the immune phenotypes that shift with microbiome transfer have been characterized, but the mechanisms driving these phenotypes are still largely unknown. It is important to note that studies thus far have largely focused on bacteria in the gut. There are other kinds of commensal microbes that colonize the intestinal tract,[239] and commensal microbes can be found on every surface of the body.[240] We are only beginning to understand the complex relationship between systemic metabolism and the commensal microbiome, as well as how the interplay between these factors influences anti-tumor immunity.

OTHER CANCER RISK FACTORS ASSOCIATED WITH CHANGES TO SYSTEMIC METABOLISM

Some cancer risk factors alter whole-body metabolism even though they are not directly related to diet, exercise, and nutrition. As an example, aging changes propionate metabolism in a manner that elevates methylmalonic acid in the plasma.[241] Exposure to excess methylmalonic acid makes cancer cells more aggressive[241] and promotes metastasis.[242,243] Therefore, metabolic changes associated with age work in concert with other factors, such as mutational burden, to promote tumorigenesis. More broadly, aging leads to widespread changes in circulating metabolites[244] and other kinds of systemic metabolic dysfunction like insulin resistance. Future work is needed to determine how other age-related metabolic differences mechanistically influence tumorigenesis in older patient populations and if they can be targeted to improve the efficacy of immunotherapy in the elderly. Sex-linked differences are another example of a factor that influences the whole-body metabolic state,[245,246] immune responses,[247] and cancer risk,[248–250] where the influence on the tumor microenvironment is still incompletely understood. The mechanisms by which aging, biological sex, and other, similar kinds of factors influence immune surveillance of tumors through changes in systemic metabolism require further investigation.

CONCLUSIONS

Metabolic state is a major source of population-level heterogeneity among patients with cancer. Epidemiological studies have uncovered clear associations between metabolic health and various aspects of cancer progression. However, whole-body metabolism is a complex and dynamic state. Changes to the composition and quantity of dietary nutrients lead to system-level changes in signaling, inflammation, and immune homeostasis that are all relevant to tumor development. Consequently, it is still challenging to pinpoint precise mechanisms that causally link environmental and dietary exposures to tumor progression or control. Pre-clinical models have advanced our understanding in this area, but further research is necessary to

expand and refine these findings into a comprehensive framework that integrates metabolic health into a broader understanding of cancer prevention and treatment. Ultimately, translating pre-clinical findings into clinical practice will require carefully designed trials to identify dietary interventions, exercise regimens, and metabolic therapies that are tolerated by patients with cancer and improve patient outcomes.

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AUTHOR CONTRIBUTIONS

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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