JEM Journal of Experimental Medicine

REVIEW

Cancer Focus

Age- and diet-instructed metabolic rewiring of the tumor–immune microenvironment

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The tumor–immune microenvironment (TIME) plays a critical role in tumor development and metastasis, as it influences the evolution of tumor cells and fosters an immunosuppressive state by intervening the metabolic reprogramming of infiltrating immune cells. Aging and diet significantly impact the metabolic reprogramming of the TIME, contributing to cancer progression and immune evasion. With aging, immune cell function declines, leading to a proinflammatory state and metabolic alterations such as increased oxidative stress and mitochondrial dysfunction, which compromise antitumor immunity. Similarly, dietary factors, particularly high-fat and high-sugar diets, promote metabolic shifts, creating a permissive TIME by fostering tumor-supportive immune cell phenotypes while impairing the tumoricidal activity of immune cells. In contrast, dietary restrictions have been shown to restore immune function by modulating metabolism and enhancing antitumor immune responses. Here, we discuss the intricate interplay between aging, diet, and metabolic reprogramming in shaping the TIME, with a particular focus on T cells, and highlight therapeutic strategies targeting these pathways to empower antitumor immunity.

Introduction

The tumor microenvironment (TME) comprises a diverse range of immune cells that are known to shape antitumor immunity and drive the evolution of tumor cells via immunoediting (Yu and Ho, 2019). Unraveling the dual role of the immune system in cancer progression has sparked interest in characterizing the tumor–immune microenvironment (TIME) with the goal of targeting and tailoring functions of immune subsets using immunotherapies (Chuang et al., 2024; de Visser and Joyce, 2023). Interestingly, immune cells are known to present unique metabolic traits linked to their immune functions, highlighting the importance of metabolic reprogramming in orchestrating their behavior (Arner and Rathmell, 2023; Biswas, 2015; Buck et al., 2017). On the other hand, tumor cells alter their metabolism to meet their metabolic needs, simultaneously shaping the metabolic milieu in the TIME due to deprivation of nutrients and accumulation of waste products (Kao et al., 2022; Li et al., 2019a). In addition, the neovasculature within the tumors contributes to hypoxia in the microenvironment. These metabolic challenges disturb the metabolic programming of immune cells, leading to impaired antitumor immunity (Schaaf et al., 2018). Therefore, understanding how the metabolic state of immune cells disrupts antitumor responses, as well as the interplay between tumor and immune cells, will pave the way for new avenues in cancer immunotherapy. Given the complex nature of the immune system in the context of tumors, this review focuses on how metabolism regulates T-cell function and fate in the TME. We also provide an overview of the tumor–immune cell crosstalk at the metabolic level. Additionally, we discuss how age-related metabolic changes disrupt the metabolic dynamics of the TIME. Furthermore, we examine the impact of diet and nutrition on the TIME, particularly under specific dietary regimes with varying macronutrient compositions. Finally, we explore the potential therapeutic implications of metabolic rewiring within the TIME.

Metabolic regulation in the TIME

Metabolic programming of immune cells orchestrates antitumor immunity

Metabolism-related processes regulate the activation, cell fate, and function of immune cells. Specifically, the metabolic state of immune cells is determined by two major processes: (1) the activation process, which includes T-cell receptor (TCR), costimulation, and cytokine signaling, leading to the reprogramming of intrinsic metabolic pathways, and (2) the uptake of nutrients and metabolites from the surrounding environment (Chapman and Chi, 2024; Shyer et al., 2020). These metabolic processes support cell expansion, orchestrate activation, and

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tailor the behavior of immune cells, constituting an important pillar of regulatory circuits for ensuring antitumor immunity in the TME. Among the intracellular metabolic pathways, glucose metabolism has been appreciated as one of the major programs to orchestrate antitumor immunity (Chapman and Chi, 2024). TCR stimulation invigorates aerobic glycolysis and glutaminolysis to sustain cell proliferation, differentiation, migration, and effector function in naïve and effector CD8⁺ T cells. Interestingly, long-lived CD8⁺ T cells, including memory T cells, resident memory T cells, and progenitor exhausted T cells, depend on fatty acid oxidation (FAO) and oxidative phosphorylation, controlled by AMPK and PPARβ (Bevilacqua et al., 2022, 2024; Chapman et al., 2020). Intriguingly, perturbations in glucose metabolism, including glucose deprivation, competition with tumor cells, and impaired glycolytic machinery, are often present in tumor-infiltrating lymphocytes (TILs) (Chang et al., 2015; Gemta et al., 2019; Ho et al., 2015). Furthermore, programmed death-1 (PD-1) is up-regulated in CD8⁺ TILs, suppressing their glycolytic capacity (Bengsch et al., 2016; Patsoukis et al., 2015). Similarly, natural killer (NK) cells also increase the glycolytic rate for their activation (O'Brien and Finlay, 2019), although tumor-infiltrating NK cells have declined glycolysis accompanied by impaired tumoricidal activity and cytokine production capacity (Cong et al., 2018; Poznanski et al., 2021). In contrast, the elevated glycolytic rate of tumor cells can lead to accumulation of lactic acid, which is known to promote protumoral macrophage polarization and impair effector functions in CD8⁺ T cells and NK cells (Brand et al., 2016). Lactate metabolism has been also shown to enforce T-cell exhaustion (Peralta et al., 2024) and inhibit CD8⁺ T-cell cytotoxicity (Elia et al., 2022), while lithium carbonate, a mood stabilizer that decreases lactate, has the ability to inhibit the lactic acid–mediated immune suppression of CD8⁺ T cells (Ma et al., 2024).

Amino acid metabolism also contributes to the regulation of the antitumor activity of T cells. As mentioned above, glutaminolysis is essential during T-cell activation and important in the context of tumors (Best et al., 2022; Johnson et al., 2018). Despite glutamine being critical for T-cell activation (Carr et al., 2010; Nakaya et al., 2014; Wang et al., 2011), transient inhibition of glutaminase does not avert the antitumor function in tumor-reactive CD8⁺ T cells (Johnson et al., 2018). Moreover, glutamine can undergo isocitrate dehydrogenase 2–mediated reductive carboxylation to tailor epigenetic control for guiding CD8⁺ T-cell differentiation (Jaccard et al., 2023). Glutamine also plays a critical role in modulating type I conventional dendritic cell (DC) function, allowing the activation of cytotoxic T cells in a FLCN-TFEB–dependent manner (Guo et al., 2023). In macrophages, glutamine metabolism is also critical for fine-tuning (Colegio et al., 2014; Jha et al., 2015; Liu et al., 2017, 2023). In addition to glutamine, arginine and tryptophan also influence the antitumor functions in T cells, DCs, and tumor-associated macrophages (TAMs) (Geiger et al., 2016; Mezrich et al., 2010; Munn et al., 2005; Norian et al., 2009; Rodriguez et al., 2004; Sharma et al., 2007). Moreover, methionine, serine, and asparagine metabolism has been also reported to modulate the antitumor activity and differentiation of T cells (Bian et al., 2020; Fernández-García et al., 2022; Gnanaprakasam et al., 2023; Hung et al., 2021; Ma et al., 2019a, 2017; Pandit et al., 2023; Rowe et al., 2023; Wu et al., 2021a).

Lipid metabolism is another important metabolic orchestrator of antitumor immunity. Lipid accumulation in the TME is associated with a disruption in the antitumor activity of CD8⁺ T cells and NK cells (Manzo et al., 2020; Michelet et al., 2018; Ringel et al., 2020; Zhang et al., 2020a), and the ability for lipid synthesis in tumor cells has been suggested to play a role in facilitating their immune evasion (Tsai et al., 2023). Mechanistically, fatty acid (FA) accumulation in CD8⁺ TILs has been linked to T-cell dysfunction and ferroptosis; however, boosting FAO activity in CD8⁺ T cells has been demonstrated to strengthen their antitumor ability against melanoma (Zhang et al., 2017). Of note, in addition to taking up lipids, Ping et al. recently reported that changes in the phospholipid composition of intratumoral CD8⁺ T cells due to PD-1–driven reduction of phospholipid phosphatase 1 expression can promote ferroptosis (Ping et al., 2024). Similarly, lipid accumulation in TAMs and tumor-infiltrating DCs can drive the protumoral phenotype of macrophages (Di Conza et al., 2021; Su et al., 2020) and impair antigen presentation in DCs (Veglia et al., 2017).

Metabolic crosstalk between tumor and immune cells

The TME is generally characterized by low glucose levels, resulting from the high glucose consumption by tumor cells through enhanced glycolysis (the Warburg effect), compared with normal tissue (Heiden et al., 2009). The scarcity of glucose together with the accumulation of metabolic wastes and suppressive metabolites, such as lactate, impairs the activation, proliferation, and function of T cells (Chang et al., 2013, 2015; Ho et al., 2015; Macintyre et al., 2014). Conversely, regulatory T cells (Tregs) within the TME maintain their functionality in the TME by engaging metabolic adaptation, including reshaping mitochondrial dynamics and activity (Wang et al., 2020), promoting lipid signaling (Lim et al., 2021), and using lactate as an energy source (Angelin et al., 2017; Watson et al., 2021). Tumor cells, together with tumor-infiltrating myeloid cells, also consume amino acids, including glutamine (Guo et al., 2023; Reinfeld et al., 2021), methionine (Bian et al., 2020; Hung et al., 2021; Pandit et al., 2023), arginine (Mills et al., 1992; Norian et al., 2009; Rodriguez et al., 2004), and tryptophan (Munn et al., 2005; Sharma et al., 2007). Amino acid consumption by these subsets limits their availability for immune cells within the TME to carry out their functional and metabolic reprogramming as previously mentioned. Furthermore, the breakdown of amino acids by tumor cells produces metabolites that inhibit the function of CD8⁺ T cells. For example, arginases 1 and 2 break down arginine to produce ornithine, which leads to the suppression of T-cell effector function (Dröge et al., 1985). Similarly, the enzyme indoleamine 2,3-dioxygenase metabolizes tryptophan into kynurenine, blocking CD8⁺ T-cell activation but fostering the generation of Tregs (Mezrich et al., 2010).

Lipids are largely accumulated in the TME caused by large lipogenesis activity in tumor cells and adipocyte accumulation (Koundouros and Poulogiannis, 2020). The uptake of lipids via CD36 and Mincle transporters by immune cells triggers

oxidative stress, ferroptosis, and T-cell dysfunction (Ma et al., 2021; Xu et al., 2021). In addition, extracellular cholesterol also drives impairment of TIL function promoting metabolic alterations and exhaustion programs in CD8⁺ T cells (Ma et al., 2019b; Song et al., 2018). Tumor-infiltrating DCs can also accumulate lipids, via lipid scavenger receptor A. As a result of the oxidation of these lipids, their capacity for antigen cross-presentation to T cells results compromised (Bosteels et al., 2023; Ramakrishnan et al., 2014; Cubillos-Ruiz et al., 2015; Herber et al., 2010; Veglia et al., 2017). Furthermore, lipids from tumor cells induce endoplasmic reticulum (ER) stress in TAMs enhancing their protumorigenic activity and survival and promoting their suppressive activity (Di Conza et al., 2021; Goossens et al., 2019).

Last but not least, hypoxia is another important environmental factor by which the TME modulates immune cells. Elevated oxygen consumption by cancer cells along with the vascular abnormalities found in tumors is responsible for creating a hypoxic environment (Riera-Domingo et al., 2020). Importantly, lymphocyte-activation gene 3 (LAG-3), T-cell immunoglobulin and mucin-domain 3 (TIM-3), and cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) inhibitory receptor expression in T cells can be enhanced by hypoxia (Doedens et al., 2013), contributing to immunosuppression in the TME. Furthermore, hypoxia also promotes the accumulation of depolarized mitochondria and a decline in mitochondrial health, which is associated with T-cell exhaustion (Scharping et al., 2021; Yu et al., 2020).

Metabolic dynamics in the TIME during aging

Senescence and immune cell function

Aging is a time-dependent progressive functional decline, which is known to increase the incidence of cancer and to compromise the immune system (López-Otín et al., 2013; Saleh et al., 2024). Aging also impacts tumor-infiltrating immune cells by increasing chronic inflammation, a phenomenon known as inflammaging. The persistent inflammatory response is considered a hallmark of aging, and it has also been linked with multiple steps in tumorigenesis, including initiation, progression, and metastatic evolution (Leonardi et al., 2018). On the other hand, aging also leads to immune cell senescence, characterized by a permanent state of cell cycle arrest. Immunosenescence is associated with functional alterations that compromise host antitumor immune responses. Senescent cells remain active at the metabolic and transcriptional levels regardless of its growth arrest, and they can modulate the environment through the production of secretory proteins (Kuilman and Peeper, 2009; Rodier et al., 2009). This cellular process has been denominated “senescence-associated secretory phenotype” (SASP) and plays a pivotal role in shaping the TME of several cancer types (Xiong et al., 2023). While some SASP components, including CXCL1, are chemoattractant and favor the antitumor immune response, other secreted factors such as IL-6 and IL-8 foster tumor progression through the induction of angiogenesis and immunosuppression (Coppé et al., 2010a, 2010b; Xiong et al., 2023). Therefore, the SASP plays a central role within the immune microenvironment, promoting cancer progression and immune dysfunction, and represents a key piece for understanding the link between inflammation, immune cell senescence, and tumor development (Fane and Weeraratna, 2020; Leonardi et al., 2018). At the metabolic level, aged immune cells present distinctive features to that of healthy young immune populations that lead to insufficiency to adapt within the TME. Consequently, senescent T cells and NK cells show decreased effector functions and a reduced ability for cytokine production. Similarly, senescent DCs exhibit diminished antigen presentation capacity (Focosi et al., 2010; Sadighi Akha, 2018; Wikby et al., 2006; Xiong et al., 2023). In the following sections, we review the main metabolic alterations within the aged TIME reported by the literature.

Aging-associated impairment in glucose immunometabolism

Aging has been associated with glucose-related metabolic alterations in cytotoxic CD8⁺ T cells (Fig. 1, left). For instance, aged T cells show defects in glycolysis and reduced lactate dehydrogenase activity, which partly contribute to decreased proliferation (Han et al., 2023; O’Leary et al., 1983; van de Griend et al., 1982). Interestingly, naïve T cells from aged mice display impaired activation due to altered respiration and one-carbon (1C) metabolism, highlighting that metabolic reprogramming is dampened in aged T cells and suggesting that metabolic modulation could potentially improve immune function during aging (Ron-Harel et al., 2018). In addition, a specific CD8⁺ T-cell subset ($CD44^{low}CD62L^{low}$ or pre-effector-like T cells) has been identified in aged mice and is characterized by the high expression of genes related to 1C metabolism (Nakajima et al., 2021). This study suggests that altered metabolism and function of the pre-effector-like T-cell subset may mediate the immune checkpoint blockade (ICB) resistance related to aging. Remarkably, aged T cells present high rates of mitochondrial DNA (mtDNA) polymorphisms, which has been suggested to modulate T-cell ability to mount effective antitumor responses (Bousquet et al., 2022). Moreover, senescent T cells show molecular and cellular similarities to exhausted T cells, which are known to accumulate in aging (Zhao et al., 2020). Interestingly, senescent T cells, characterized by CD27 and CD28 downregulation and TIM-3 upregulation (Fourcade et al., 2010; Huang et al., 2010; Vallejo, 2005), can directly suppress the activity of other immune cells or produce SASP cytokines that enhance this suppression, further weakening the antitumor immunity (Zhao et al., 2020). Furthermore, a very recent investigation has identified an age-associated dysfunctional state of TILs as a consequence of extrinsic signals from the aged TME that is different at the transcriptional and epigenetic level from exhausted T cells. Intriguingly, this cell state shows a depletion in metabolism-associated genes (Chen et al., 2024).

The proper function of T lymphocytes relies not only on high rates of glycolysis, but also on the effective secretion of lactate. Of note, the levels of lactate, a glucose metabolism–linked product, are increased during aging (Ross et al., 2010). Due to the increased lactate levels in the extracellular compartment, intracellular lactate can accumulate, potentially impairing the glycolytic flux by modulating the stability of glycolytic proteins and disrupting the levels of Nicotinamide adenine dinucleotide + Hydrogen (NADH). As a consequence, T-cell activation and proliferation can be compromised as their metabolic

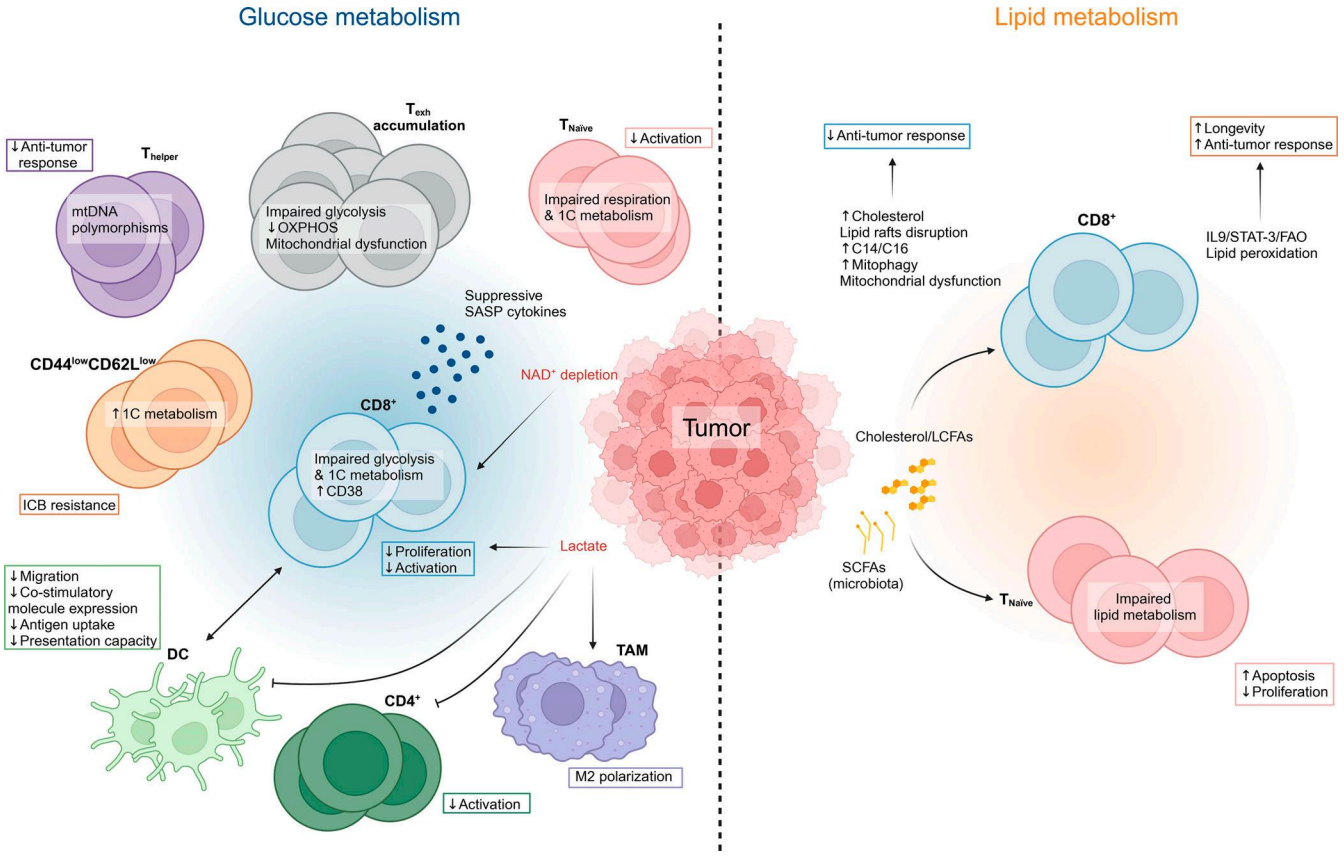

Figure 1. **Metabolic dynamics on the aged TIME.** Left: aging-associated impairment in glucose immunometabolism. Aging disrupts T-cell glucose metabolism and activation, reduces proliferation, and promotes exhaustion. Lactate depletion and NAD^+ depletion further suppress T-cell function, and disturb DCs, $CD4^+$ T cells, and TAMs. Right: age-dependent lipid remodeling in the TIME. Aging induces cholesterol buildup and lipid metabolism changes in T cells, leading to impaired mitochondrial function and reduced antitumor response, although contradictory findings have been reported. Created with http://Biorender.com.

reprogramming cannot occur (Fischer et al., 2007; Quinn et al., 2020). Additionally, lactate has been reported to suppress $CD4^+$ T cells (Comito et al., 2019), disrupt DC activation (He et al., 2019), and drive the protumor polarization of macrophages (Colegio et al., 2014; Zhang and Li, 2020). Collectively, the aged-related rise in lactate levels may represent a crucial factor to shape immune cell function during the age-related immunity decline.

Nicotinamide adenine dinucleotide (NAD^+), a crucial intermediary of energy metabolism, has been ascertained as a critical metabolic modulator in multiple immune subsets by controlling mitochondrial dynamics and NADH/NAD^+ balance (Xu et al., 2023). Interestingly, aged immune cells have been shown to increase the expression of CD38, an ectoenzyme that promotes NAD^+ degradation, which can drive aging-associated functional decline (Camacho-Pereira et al., 2016; Chini et al., 2020). Remarkably, terminally exhausted T cells also upregulate CD38 expression, and CD38 targeting has been shown to promote T-cell antitumor responses and responsiveness to PD-1 blockade (Chatterjee et al., 2018; Wu et al., 2021b). In support of this notion, NAD^+ supplement has been reported to potentiate the antitumor responses of TILs (Wang et al., 2021), as well as their mitochondrial fitness and responsiveness to ICB therapy (Yu et al., 2020). These findings highlight that aging can also impair T-cell functionality by perturbing NAD^+ metabolism, which may have a crosstalk with declined glycolytic flux, increased circulating lactate levels, and impaired mitochondrial dynamics.

Age-dependent lipid remodeling in the TIME

It is widely recognized that defective lipid metabolism significantly impacts immune responses of TILs, TAMs, DCs, and myeloid-derived suppressor cells within the TME (Wang et al., 2022). For instance, the TME frequently exhibits elevated levels of cholesterol and FAs, which can perturb the effector functions and promote exhaustion in T cells (Ma et al., 2021, 2019b; Wang et al., 2020; Xu et al., 2021). Importantly, emerging evidence shows that perturbations in lipid metabolism play a role in all hallmarks of aging, underscoring the importance of lipids in the aging process (Sharma and Diwan, 2023) (Fig. 1, right). As an example, aged T cells accumulate cholesterol and show a different distribution pattern of lipid rafts compared with young T cells (Larbi et al., 2004, 2006). Of note, ceramide accumulation driven by aging has been reported to trigger mitochondrial dysfunction in activated T cells. This aging-driven, ceramide-dependent mitophagy axis has been shown to disturb T-cell antitumor responses against melanoma (Vaena et al., 2021). In

addition, aged naïve CD8⁺ T cells exhibit impaired lipid metabolism, which results in increased apoptosis and decreased proliferation (Nicoli et al., 2022). Similarly, IL-9/STAT-3/FAO pathway has recently been shown to regulate T-cell longevity and improve antitumor responses by modulating lipid peroxidation (Xiao et al., 2022). In addition to cholesterol and long-chain fatty acids (LCFAs), the antitumor responses of immune cells within the TME can also be shaped by short-chain fatty acids (SCFAs) derived from the host microbiota (reviewed in Drapela et al. [2022]). While aging has been linked to shifts in the microbiota in favor of opportunistic microorganisms, the direct link between aged-driven alterations in the microbiome composition and the weakening of antitumor immunity has not yet been explored. The most recent findings suggest that modulating lipid metabolism and/or boosting lipid usage by stimulating mitochondrial activity may represent important approaches to tailor T-cell antitumor responses and overcome the functional decline caused by aging. Indeed, reprogrammed effector T-cell lipid metabolism has recently been shown to avoid senescence in vitro and improve their antitumor immunity in melanoma models (Liu et al., 2021). However, the decline in mitochondrial activity in T cells and TILs with aging presents a critical hurdle for rewiring lipid metabolism, as the tricarboxylic acid (TCA) cycle is essential for modulating both lipid synthesis and utilization. Moreover, glutamine-dependent production of α-ketoglutarate (α-KG) via TCA cycle plays a critical role in orchestrating metabolic and epigenetic reprogramming in immune cells (Liu et al., 2017). However, both glutamine and α-KG levels have been found to be decreased upon aging (Gomes et al., 2020; Tomás-Loba et al., 2013). Thus, we speculate that approaches aimed at simultaneously restoring mitochondrial fitness and facilitating lipid metabolism could be effective in alleviating TIL dysfunction caused by the aging TME and systemic lipid alterations in aged subjects.

Diet-driven metabolic remodeling of the TIME

Diet and immune cell function

Immune cells require a suitable nutrition to meet the energetic demands for its activation in the fight against infections and tumors (Childs et al., 2019). Specific dietary nutrients present important roles in immune modulation, and indeed, nutrient deficiencies are associated with increased susceptibility to infection, as well as inflammatory and autoimmune diseases. On the one hand, and as described above, macronutrients, including carbohydrates, FAs, and proteins, present an important role in coordinating immune responses. On the other hand, micronutrients, including vitamins and trace elements, have an impact as well in both innate and adaptive immunity (reviewed in Tourkochristou et al. [2021]). Weakened immune reactions can be originated as a result of a poor diet or malnutrition. In the following sections, we review the metabolic rewiring in the TME that has been reported to occur in relation to dietary changes, including nutrient deficiencies or supplementation.

Carbohydrates and dietary sugars

Increasing evidence points to a link between excess dietary fructose consumption and increased incidence of cancer, as dietary fructose supports cancer cell metabolism (reviewed in Ting [2024]). Nevertheless, the influence of dietary fructose on the immune TME has yet to be extensively explored. Remarkably, the antitumor immunity mediated by CD8⁺ T cells has been shown to be improved upon dietary fructose consumption through mTORC1-mediated leptin production by adipocytes. Moreover, cancer patients with elevated fructose levels in plasma present a better antitumor T-cell response, suggesting the fructose–leptin axis as a target for immunotherapy (Zhang et al., 2023b). However, the Western diet (WD), characterized for being a high source of fructose and presenting a high glycemic index (Atkinson et al., 2008), has been associated with a decreased ability of the immune system to fight tumors (Imbroisi Filho et al., 2021). These contradictory results highlight the needs to delineate the complex nature of fructose in orchestrating antitumor immunity and tumor immune evasion. On the other hand, glucose-restricted diet has been shown to inhibit lung cancer growth, in part, due to the increased effector memory CD8⁺ TILs, tissue-resident memory T cells, and NK cells (Gähler et al., 2022). Similarly, the ketogenic diet (KD), which presents low-carbohydrate and high-fat content, has been reported to modulate T-cell migration and function (Hirschberger et al., 2021; Karagiannis et al., 2022; Luda et al., 2023). Furthermore, it regulates T-cell memory development (Zhang et al., 2020b), expands γδ T cells (Goldberg et al., 2019; Ryu et al., 2021), and influences ICB efficacy (Dai et al., 2021). KD also enhances antitumor immunity through the attenuation of immune suppression and angiogenesis in the TME. Indeed, two independent groups have reported that KD modulate T-cell immune responses, restraining tumor growth (Lussier et al., 2016; Sun et al., 2022). In line with these findings, β-hydroxybutyrate (β-HB) and acetoacetate, the main ketone bodies derived from KD, are able to boost the effector function of CD8⁺ T cells and β-HB can also restore the response to ICB (Ferrere et al., 2021; Luda et al., 2023). Moreover, the gut microbiota linked to a KD lowers the abundance of pro-inflammatory T helper 17 (Th17) cells in the intestine (Ang et al., 2020). Overall, these findings suggest that KD could be used as an immune booster in combination with current immunotherapies. On the other hand, high-fiber diets, characterized by their high content in nondigestible carbohydrate polymers, have been suggested to present a profitable role in antitumor immunity (Zhang et al., 2022). Their beneficial properties come from the generation of prebiotic and immunomodulatory metabolites after the fiber degradation by the intestinal microbiota (Makki et al., 2018). For instance, the growth of melanoma tumors is inhibited by inulin fiber, as the intestinal microbiota–derived butyrate boosts T-cell infiltration in the TME (Donohoe et al., 2014; Li et al., 2020). Importantly, clinical data have shown that fiber consumption is associated with a differential response to ICB (Spencer et al., 2021). Collectively, carbohydrates and dietary sugars present a significant influence in orchestrating intratumoral immune cell function (Fig. 2, left).

Lipids and dietary fats

Obesity and the consumption of high-fat diets (HFD) are known to limit T-cell function against tumors, partly by driving T-cell

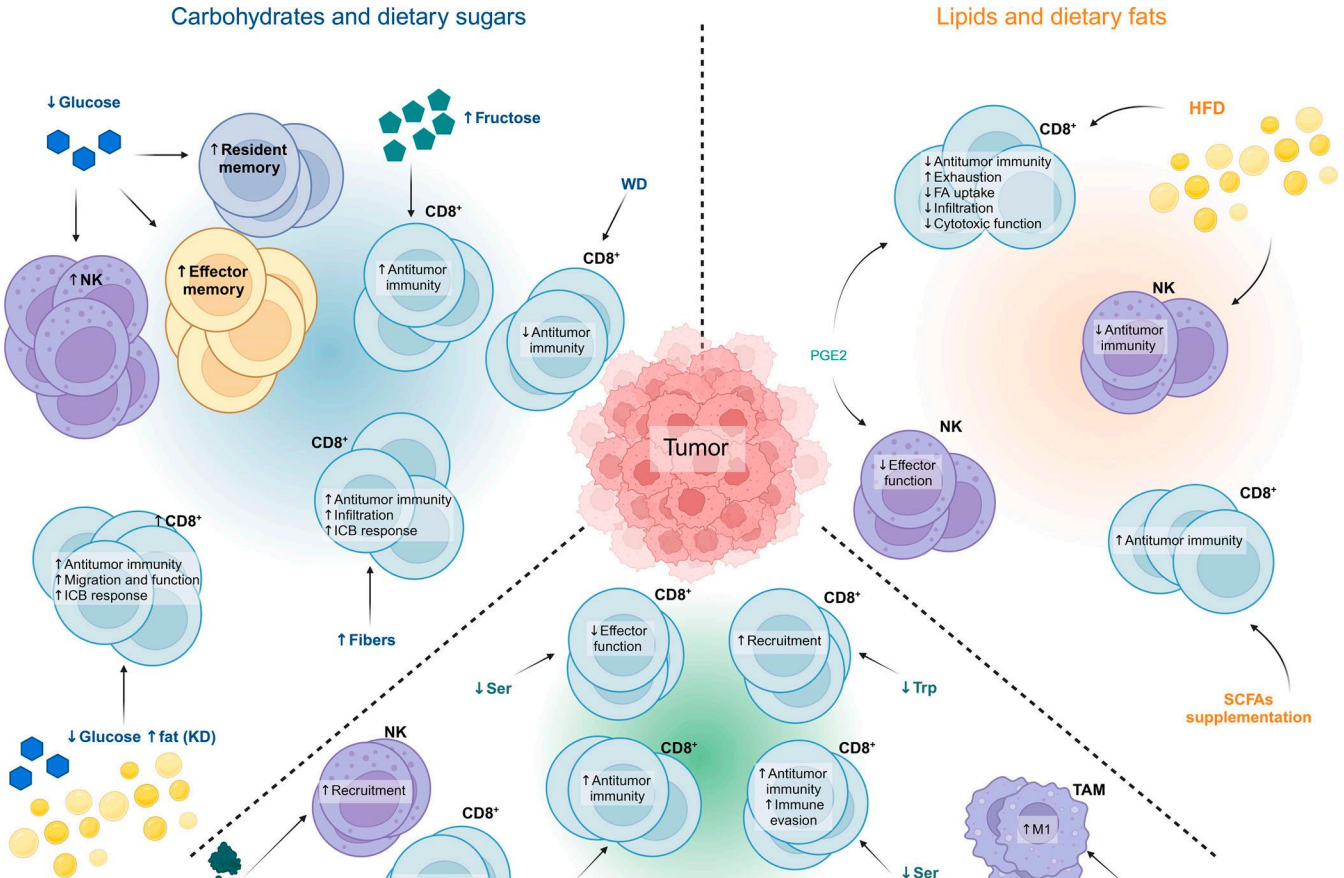

Figure 2. **Metabolic remodeling of the TIME in nutrition.** Left: carbohydrates and dietary sugars. Glucose restriction, fructose intake, and KD boost CD8⁺ T-cell function, NK cell infiltration, and antitumor immunity, while high-fiber diets enhance T-cell infiltration through microbiota metabolites. Right: lipids and dietary fats. HFD suppress T- and NK cell function, drive T-cell exhaustion, and impair CD8⁺ T-cell infiltration, fostering tumor growth. Bottom: amino acids and protein-related diets. Restricting certain amino acids (glutamine, methionine, serine, tryptophan) enhances CD8⁺ T-cell and NK cell activity and improves immune response. Created with http://Biorender.com.

exhaustion and enhancing leptin signaling (Kado et al., 2019; Wang et al., 2019; Zhang et al., 2020b; Zhao et al., 2021). Interestingly, enforced leptin expression in the TME has been shown to drive a metabolic reprogramming in CD8⁺ T cells that supports T-cell antitumor immunity (Rivadeneira et al., 2019). In addition, although HFD increases FA uptake in tumor cells, TILs exhibit reduced FA uptake, leading to altered fuel partitioning that impairs the infiltration capacity and function of CD8⁺ T cells (Ringel et al., 2020). The insulin resistance resulted from diet-induced obesity has also been suggested to promote tumor immune evasion by disrupting metabolism and cytotoxic functions in T cells (Tsai et al., 2018; Zhao et al., 2021). Intriguingly, the HFD-imposed impairment in the immune function does not affect exclusively T cells, as the antitumor response of NK cells results perturbed as well. Specifically, the lipid uptake from the TME by NK cells drives their metabolic reprogramming, impairing their fight against melanoma tumors (Michelet et al., 2018). Despite the generally unfavorable link between HFD and immune tumor control, a short-term treatment with an HFD surprisingly ameliorates the survival of tumor-bearing mice. This quick dietary intervention stimulates T-cell recruitment and activation reducing metastatic risk (Xiang et al., 2020).

Prostaglandins are synthesized from dietary polyunsaturated fatty acids (PUFAs) (Kirkup et al., 2010). In the context of tumors and chronic viral infection, binding of prostaglandin E2 (PGE2) to its receptors disrupts the effector functions and fosters exhaustion in tumor-specific and viral-specific T cells (Chen et al., 2015; Miao et al., 2017). The immunosuppressive capacity of PGE2 is not restricted exclusively to T cells, as it has also been shown to impair NK cell–mediated immune control (Bonavita et al., 2020; Böttcher et al., 2018). Importantly, the production of PGE2 can be decreased upon a reduction in the dietary ω-6:ω-3 FA ratio (Henderson et al., 1989; Zhao et al., 2021). Taking these findings into consideration, it is possible that the dietary fat content may impact tumor immunosurveillance by modulating lipid content and PGE2 production. As mentioned previously, dietary fiber consumption has an impact in the microbiota-derived generation of SCFAs. These SCFAs can modulate the host immune functions by instructing effector function and

differentiation in T cells and antigen-presenting ability in antigen-presenting cells (Nomura et al., 2020). For instance, SCFA butyrate supplementation boosts the antitumor activity of CD8⁺ T cells and stimulates the effectiveness of cancer therapy (He et al., 2021). Moreover, butyrate and pentanoate trigger a mTOR-mediated metabolic reprogramming that enhances T-cell antitumor activity (Luu et al., 2021). Acetate, on the other hand, can tailor the epigenetic reprogramming needed for T-cell differentiation (Kaymak et al., 2024). In contrast, LCFAs have also been widely shown to exhibit immunomodulatory effects and play a role in regulating cancer-related immune responses (Lim et al., 2021; Manzo et al., 2020; Wang et al., 2023; Wise et al., 2011; Zaidi et al., 2012). Overall, it is evident that the function of immune cells within tumors is modulated by lipids and dietary fats (Fig. 2, right). However, it remains largely unclear why and how lipid species can tailor T-cell immune responses in distinct manners. We speculate that using metabolic tracing to delineate the metabolic fate and spatial distribution of lipid species in T cells could provide deeper insights into how lipid-mediated immune regulations are orchestrated.

Amino acids and protein-related diets

High protein intake has been associated with increased tumor progression and overall mortality in aged individuals (Levine et al., 2014). In agreement, mouse models have demonstrated that low protein diet inhibits tumor growth and decreases tumor incidence and mortality (Fontana et al., 2013; Lamming et al., 2015; Rubio-Patiño et al., 2018; Yin et al., 2018; Zhang et al., 2023a). Mechanistically, dietary protein restriction leads to the activation of ER stress in tumor cells, which results in the recruitment of CD8⁺ T and NK cells within the TME (Rubio-Patiño et al., 2018). Several studies have further focused on unveiling the impacts of restricting specific amino acids, rather than global protein deprivation, on the immune function within the TME. Glutamine restriction provides tumor-specific CD8⁺ T cells an improved ability to eliminate tumors and allows longer survival of tumor-bearing mice (Nabe et al., 2018). In the case of methionine, a decrease in its dietary intake has been associated with reprogramming of TAMs, conferring them increased antitumor and inflammatory phenotypes and providing a modulation in response to immunotherapy (Orillion et al., 2018). In line with this finding, Li et al. reported that the absence of nonessential amino acids in the diet enhanced the effectiveness of anti-PD-1 immunotherapy in a mouse model of colon cancer (Li et al., 2019b). Conversely, another study shows how low dietary methionine disrupts antitumor immunity, aggravating tumor progression and altering the response to immunotherapy. The authors report that the alteration in the immune responses against the tumor is mediated, at least partially, by the microbiota (Ji et al., 2023). The discrepancy in the effects of methionine restriction on tumor growth highlights the need for future research to clarify how methionine shapes antitumor immunity. With regard to serine, its absence both in vitro and in vivo leads to impairments in T-cell responses (Ma et al., 2017). Remarkably, a newly published article shows that a serine/glycine-free diet presents a dual role by enhancing antitumor immunity while driving immune evasion via PD-L1 lactylation (Tong et al., 2024). Recently, a study conducted by Hezaveh et al. indicated that depletion of dietary tryptophan drove the recruitment of CD8⁺ T cells within the tumor and significantly decreased tumor growth (Hezaveh et al., 2022). Interestingly, a recent study shows that in vivo administration of glutarate, a byproduct of the breakdown of amino acids, fosters CD8⁺ T-cell cytotoxicity and increases the number of TILs (Minogue et al., 2023). Nevertheless, the relevance of its dietary intake has yet to be elucidated. Taken together, these studies suggest that the metabolic changes resulting from diets with varying protein compositions contribute to the modulation of antitumor immunity (Fig. 2, bottom). However, it remains to be determined whether these effects are intrinsically induced in T cells or result from the metabolic crosstalk within the TME.

Concluding remarks

As highlighted throughout this review, there is a significant and evolving connection between aging and nutrition with immune function. Indeed, obesity and aging share key similarities in how they impact the TME, such us promoting chronic inflammation, contributing to dysfunctional T-cell states, and increasing immunosuppressive myeloid cell populations within tumors, eventually compromising the antitumor immune response. This link between the immune system and age- or diet-induced metabolic alterations in the TME opens a new window of therapeutic opportunities. Targeting the metabolic crosstalk between immune and tumor cells, the metabolic vulnerabilities of tumor cells, and the metabolic adaptation of immune cells represent promising approaches for boosting antitumor immunity. Most recent findings highlight the potential for exploiting dietary-based approaches in combination with immunotherapies for cancer treatment. In addition to a diet with specific nutrient deprivation, fasting has shown to control tumor growth by modulating TAM polarization (Sun et al., 2017), improving the antitumor immunity driven by T and NK cells (Delconte et al., 2024), as well as enhancing responsiveness to immunotherapy (Cortellino et al., 2022). Moreover, a fasting-mimicking diet can also stimulate antitumor immunity via its actions on cytotoxic CD8⁺ T cells (Buono et al., 2023; Di Biase et al., 2017; Vernieri et al., 2022; Zhong et al., 2023). Similarly, recent studies indicate that intermittent fasting and calorie restriction enhance anticancer T-cell immune response and improve survival in tumor-bearing mice (Collins et al., 2019; Udumula et al., 2023), with a potential role of the microbiota in mediating these effects (Mao et al., 2023). Importantly, although these nutritional strategies are feasible for cancer patients, only a limited number of studies have evaluated how dietary interventions affect the functioning of the immune system in humans (Collins and Belkaid, 2022). Nevertheless, numerous clinical trials have been conducted to evaluate the effects of dietary interventions, either on their own or alongside treatment, on cancer patients (Goswami et al., 2023). In this regard, diet modulation could be considered as an adjuvant to be used in combination with immune checkpoint inhibitors. However, further research is needed to determine whether aging-related changes in systemic metabolism affect the effectiveness of diet-mediated immunomodulation, which

will be crucial for future studies. Based on current and upcoming research, metabolic reprogramming through dietary interventions and aging-related metabolic targeting shows substantial promise for enhancing immune responses and countering immunosuppression within the TIME. Advancements in technologies such as CAR-T cell therapy, integrated with these metabolic strategies, could result in innovative and more effective cancer treatments that enhance both antitumor response and longevity.

Acknowledgments

A.B. Plata-Gómez is supported by the European Molecular Biology Organization Postdoctoral Fellowship (EMBO ALTF 292-2024). P.-C. Ho is supported in part by the Swiss Cancer Foundation, the Cancer Research Institute (Lloyd J. Old STAR Award), and the Helmut Horten Stifung.

Author contributions: A.B. Plata-Gómez: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, validation, visualization, and writing—original draft, review, and editing. P.-C. Ho: conceptualization, funding acquisition, project administration, resources, supervision, validation, and writing—review and editing.

Disclosures: The authors declare no competing interests exist.

Submitted: 20 December 2024
Revised: 27 March 2025
Accepted: 28 March 2025

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