



Perspective

Transient Dietary Stress and Tumor Immunity: From High-Fat Diet-Induced Ferroptotic Memory to Broader Immunometabolic Regulation

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Abstract: This perspective highlights the lasting impact of diet on tumor immunity, focusing on the long-term effects of transient high-fat diet (HFD) exposure. Short-term HFD alters CD8⁺ T-cell metabolism, causing lipid peroxidation and ferroptosis, thereby compromising antitumor immunity. The purine salvage pathway can enhance CD8⁺ T-cell antioxidant capacity, thereby partially reversing HFD-induced immune dysfunction, suggesting the metabolic reversibility of diet-induced immunosuppression. Meanwhile, other dietary components, such as high sugar, high salt, and high fiber, uniquely influence tumor immunity. Specifically, high-sugar diets promote immune evasion by upregulating PD-L1 and impairing CD8⁺ T-cell activation, high-salt intake enhances CD8⁺ T-cell effector responses under certain conditions, and high-fiber diets increase tumor-infiltrating T cells and enhance anti-PD-1 immunotherapy efficacy. These studies underscore the complexity of dietary influences on cancer immunity, suggesting that diet actively shapes immune memory and thus affects cancer progression.

Keywords: high-fat diet; dietary excess; CD8⁺ T cell; immunometabolic memory; tumor immunity

The complex relationship between dietary patterns and cancer has attracted increasing attention, highlighting the critical role of dietary components in health and disease. Dietary pattern directly determines nutrient availability within the systemic plasma and consequently shapes the metabolic microenvironment of all cells in the organism [1]. In this sense, diet is not merely a fundamental lifestyle factor, but a regulator of the metabolic environment in which cancer develops. Changes in host diet can directly alter circulating nutrient levels and their availability within the tumor microenvironment, thereby influencing the acquisition and utilization of metabolic substrates by cancer cells. These metabolic states can profoundly influence tumor cell metabolism, leading to significant shifts in proliferation rates and intrinsic metabolic requirements [2]. Furthermore, diet not only acts as a source of metabolic substrates but also regulates signal transduction via nutrient-sensitive pathways that are closely integrated with oncogenic signaling and tumor cell survival. Therefore, dietary composition may influence tumor progression via multiple interconnected mechanisms, including systemic nutrient availability, tumor metabolic plasticity, and nutrient-responsive signaling networks.

Contemporary dietary patterns are dominated by a high-fat diet (HFD), which has been recognized as an important contributor to tumor growth and progression [3]. A typical HFD is defined by a proinflammatory lipid composition, encompassing excessive saturated or trans fatty acids, an insufficient content of omega-3 polyunsaturated fatty acids, and an increased omega-6/omega-3 fatty acid ratio [4]. These HFD-related metabolic features can trigger systemic metabolic dysregulation and result in oncogenesis and tumor progression via various interdependent pathways. Two prominent mechanisms are the HFD-induced accumulation of adipose tissue and



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changes in gut microbiota composition [5]. These changes can cause systemic perturbations such as altered steroid hormone and adipokine production, chronic inflammation, and systemic metabolic disturbances. Notably, HFD-triggered gut dysbiosis may also affect therapeutic responses by altering sensitivity to chemodrugs, immune checkpoint inhibitors, and tyrosine kinase inhibitors in non-digestive cancers [6]. Moreover, excessive accumulation of adipose tissue can remodel the local immune microenvironment through immune cell infiltration and secretion of adipose-derived inflammatory mediators (such as cytokines, proteases, and adipokines), ultimately suppressing the function of immune cells [7–9]. However, most of these mechanisms emphasize the concurrent effects of HFD exposure. It remains unclear whether transient dietary stress has a durable impact on antitumor immunity after dietary normalization.

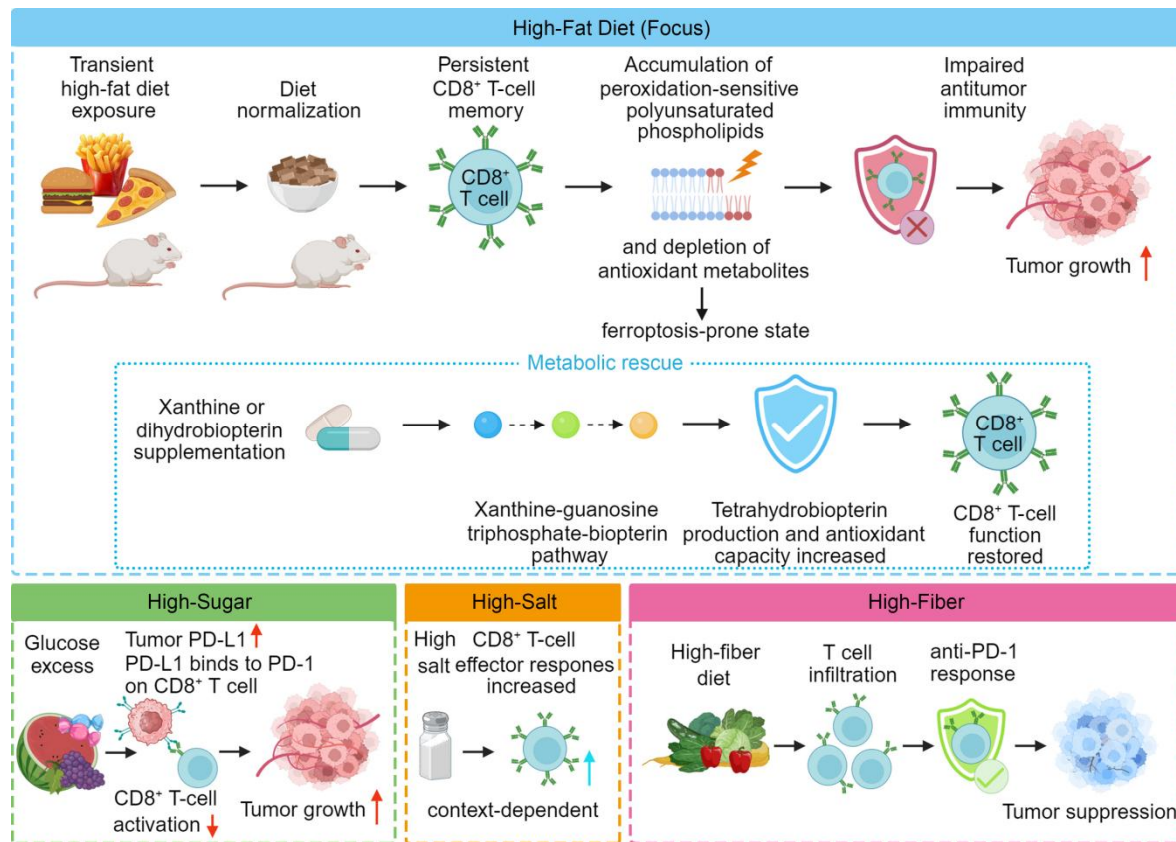
Tajima et al. addressed this gap by shifting the focus from the tumor-intrinsic lipid metabolism and systemic inflammation to the durable immunometabolic dysfunction of CD8⁺ T cells [10]. Utilizing a switched-diet model, Tajima et al. showed that transient exposure to HFD was sufficient to enhance tumor growth even after dietary normalization. This finding implied that HFD did not simply induce tumor progression by concurrent obesity-related metabolic abnormalities but could cause a long-lasting immunological defect. Mechanistically, the study further revealed that the impairment of immune function was attributable to persistent immunometabolic dysfunction of CD8⁺ T cells. Specifically, the accumulation of peroxidation-sensitive polyunsaturated phospholipids and the depletion of antioxidant metabolites both rendered these T cells intrinsically susceptible to ferroptosis. As a result, the survival and cytotoxic effector function of the CD8⁺ T cells were compromised, marking a persistent immunometabolic dysfunction. In addition to uncovering this mechanism, Tajima et al. also highlighted a compensatory xanthine—guanosine triphosphate (GTP)—biopterin pathway that served as a protective metabolic axis for CD8⁺ T cells under oxidative stress. Through purine salvage, xanthine could increase the production of GTP and tetrahydrobiopterin, thereby enhancing the antioxidant capacity of CD8⁺ T cells and reducing ferroptotic damage. The restoration of antitumor immunity by the xanthine or dihydrobiopterin supplementation further suggested that HFD-induced immune dysfunction was metabolically reversible.

This study reframed HFD-induced tumor growth as an outcome of durable immunometabolic memory rather than a transient consequence of obesity-associated inflammation. Tajima et al. demonstrated that prior exposure to HFD renders CD8⁺ T cells intrinsically vulnerable to lipid peroxidation and ferroptosis. Hence, this study extended the concept of tumor immune suppression beyond local microenvironmental constraints, highlighting diet history as a modulator of T-cell fitness. However, since the switched-diet model used an HFD-60 regimen (approximately 60% of calories derived from fat), it remained unclear whether this immunometabolic memory resulted from excessive fat intake or from the specific lipid composition of the HFD. Recent studies showed that an animal-fat-based HFD (characterized by lard, beef tallow, and butter) suppressed NK-cell and CD8⁺ T-cell function and thus accelerated tumor progression. Conversely, coconut oil-, palm oil-, or olive oil-based HFDs that caused comparable obesity levels did not compromise the same function of immune cells [11]. These results raise an intriguing possibility that if transient exposure to animal-fat-based HFDs can leave a pro-ferroptotic and immunosuppressive metabolic imprint on CD8⁺ T cells, transient exposure to plant-fat-based HFDs may conversely generate a protective immunometabolic memory. Specifically, T-cell antioxidant capacity and cytotoxic function are preserved even after dietary normalization, thereby achieving tumor suppression. Therefore, instead of reducing fat intake passively, dietary intervention can serve as a metabolic regulatory strategy that actively shapes antitumor immune memory.

Inspired by Tajima et al., we further propose that the HFD should be viewed as a representative model of dietary excess-induced immune perturbation instead of an isolated dietary pattern (Scheme 1). Among these dietary excess forms, excessive dietary sugar provides a compelling example of promoting tumor growth by suppressing antitumor immunity. High sugar intake is closely associated with chronic inflammation and metabolic dysfunction. Most research further revealed excessive sugar provided energetic substrates for rapidly proliferating tumor cells, thereby promoting cancer progression. Currently, more efforts are devoted to demonstrating the mechanism by which elevated glucose availability reshapes the tumor–host immune interface and favors immune escape. In particular, high glucose levels can increase tumor PD-L1 expression, weaken CD8⁺ T-cell infiltration and activation, thereby impairing antitumor immune surveillance [12]. This immune-suppressive effect may allow tumor cells to evade cytotoxic T cell-mediated elimination, ultimately facilitating tumor progression.

In contrast to HFD and high dietary sugar, high salt intake represents a distinct example in which dietary excess may enhance antitumor immunity under specific conditions. Although NaCl is traditionally recognized for its role in osmotic regulation and fluid balance, recent research indicated that it could also act as an immunomodulatory factor that influenced immune-cell activation, differentiation, and even effector function. High-salt diet has been reported to reduce the immunosuppressive activity of myeloid-derived suppressor cells, enhance natural killer cell activation, and strengthen CD8⁺ T-cell effector responses, thereby reshaping the immune

microenvironment and suppressing tumor growth [13]. Nevertheless, high salt could elicit the differentiation of T helper 17 cells to enhance inflammatory immune responses, thereby shaping the tumor-promoting microenvironment depending on the tissue type. Additionally, high-salt diet could alter the gut microbiome to indirectly shape immune and inflammatory conditions that may favor tumor progression.



Scheme 1. Schematic illustration of various dietary excess paradigms shaping tumor immunity.

Extending this concept to dietary fiber intake, high-fiber diets provide another example of how diet can shape antitumor immunity. Recent results from mice receiving a fiber-rich diet showed that dietary fiber modulated the gut metabolic environment, which promoted a more favorable immune state [14]. Immune analysis further showed that high-fiber intake increased T-cell infiltration within tumors, including CD4⁺ T cells and CD8⁺ T cells for robust antitumor responses. Under anti-PD-1 treatment, tumor-infiltrating lymphocytes from high-fiber-fed mice also displayed stronger immune activation than those from low-fiber-fed mice. Collectively, these findings suggested that a high-fiber diet strengthened antitumor immune surveillance to suppress tumor progression and even made tumors sensitive to immune checkpoint therapy.

In summary, this paper provides an important perspective for understanding the relationship between diet and cancer immunity. Conventionally, diet promotes cancer growth mainly through tumor-intrinsic metabolism, obesity-associated inflammation, or systemic metabolic abnormalities. Nevertheless, Tajima et al. pointed that HFD-induced metabolic stress persistently impaired CD8⁺ T cell-mediated antitumor immunity. Together with evidence from high-sugar, high-salt, and high-fiber dietary models, HFD underscores that the relationship between dietary excess and cancer is complex rather than linear. Different dietary components may either suppress or enhance antitumor immunity depending on their capacities of modulating immune-cell function, shaping inflammatory status, and remodeling the tumor immune microenvironment. Therefore, the role of dietary excess as an active regulator of cancer immunity requires further investigation to reveal its impact on cancer progression. Despite this promise, current research remains largely confined to mouse models, and translating dietary modulation into clinical applications still poses tremendous challenges. In particular, the safety and tolerability of specific dietary interventions need to be systematically evaluated. Moreover, careful attention should be paid to gastrointestinal adverse events such as diarrhea, nausea, and bloating. In addition, physiological parameters such as complete blood counts, liver and kidney function, and body mass index, should be monitored during and after dietary intervention to ensure that metabolic regulation does not damage to patient health.

Author Contributions

Q.G.: writing—original draft, conceptualization. P.H.: writing—review & editing, conceptualization. Both authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

During the preparation of this work, the authors used ChatGPT for language polishing. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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