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REVIEW ARTICLE

Emerging Roles of Immunometabolism and Microbiota Crosstalk in Cancer Therapy: A Comprehensive Review

Aya Osman[1,*], Shivkumar Patel[2], Alaa Osman[3]

[1]Faculty of Medicine, Napata College, Khartoum North, Sudan

[2] SBKS Medical Institute and Research Center, Vadodara, Gujarat 391760, India

[3] Faculty of medical sciences, Lebanese University, Beirut, Lebanon

***Corresponding Author:** Aya Osman
Faculty of Medicine, Napata College, Khartoum North, Sudan
Email: ayaosman0055@gmail.com

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Abstract

Recent advances in cancer immunotherapy have highlighted the critical interplay between host immunometabolism and the gut microbiota in shaping anti-tumor responses. This review provides a comprehensive examination of how metabolic reprogramming in immune cells influences their functional states within the tumor microenvironment (TME), while simultaneously exploring the emerging evidence that gut microbial communities and their metabolites systemically regulate cancer immunity. We detail the molecular mechanisms by which metabolic pathways (glycolysis, oxidative phosphorylation, fatty acid oxidation, and amino acid metabolism) dictate immune cell differentiation, activation, and exhaustion. Furthermore, we analyze how microbiota-derived signals and metabolites (short-chain fatty acids, tryptophan derivatives, bile acids) modulate host immunity through epigenetic regulation, receptor-mediated signaling, and metabolic cross-feeding. The clinical implications of targeting these pathways are thoroughly discussed, including current limitations and future directions for combining immunometabolic modulators with microbiota-based interventions to improve therapeutic outcomes. By integrating findings from preclinical models and clinical trials, this review aims to provide a roadmap for developing next-generation combination therapies in precision oncology.

1. Introduction

The remarkable success of immune checkpoint inhibitors (ICIs) and adoptive cell therapies has transformed cancer treatment paradigms (Marei et al., 2023). However, persistent challenges including variable response rates and acquired resistance underscore the need to better understand the biological networks regulating anti-tumor immunity. Two rapidly evolving fields of immunometabolism and microbiome science have recently converged to provide unprecedented insights into the extrinsic and intrinsic factors controlling immune responses against cancer (Zhou et al., 2024).

Immunometabolism investigates how intracellular metabolic pathways govern immune cell function, differentiation, and fate decisions. It is now well-established that immune cells undergo dynamic metabolic reprogramming during activation, with distinct metabolic requirements for effector functions versus regulatory roles (Kim, 2018; Stienstra et al., 2017). The nutrient-depleted, hypoxic tumor microenvironment creates intense metabolic competition between malignant and immune cells, often leading to T cell exhaustion and impaired anti-tumor activity (Augustin et al., 2020; Wegiel et al., 2018). Simultaneously, the gut microbiota has emerged as a key modulator of systemic immunity, with specific bacterial species and their metabolic byproducts capable of enhancing or suppressing responses to immunotherapy (Campbell et al., 2023).

This review synthesizes current knowledge at the intersection of these fields, focusing on three major themes: (1) the metabolic control of immune cell function in cancer; (2) mechanisms of microbiota-immune crosstalk relevant to tumor immunity; and (3) therapeutic opportunities for targeting these pathways. We critically evaluate evidence from mechanistic studies, preclinical models, and clinical trials while highlighting unanswered questions and future research directions. By providing an integrated perspective on immunometabolism-microbiota interactions, this review aims to inform the development of novel therapeutic strategies that leverage these biological networks for improved cancer treatment.

2. Metabolic Regulation of Immune Cell Function in Cancer

2.1 Fundamentals of Immunometabolism

Immune cell metabolism is dynamically regulated to meet the bioenergetic and biosynthetic demands of

activation, proliferation, and effector function (Loftus and Finlay, 2016). Quiescent immune cells primarily rely on oxidative phosphorylation (OXPHOS) for ATP generation, while activated cells undergo metabolic reprogramming to support their functional needs (Chapman et al., 2020). This metabolic plasticity is particularly evident in T cells, where naive cells maintain a catabolic metabolism dominated by OXPHOS and fatty acid oxidation (FAO) (Chiaranunt et al., 2015), but upon antigen recognition rapidly shift to aerobic glycolysis and glutaminolysis to support proliferation and effector function (Figure 1).

The tumor microenvironment presents unique metabolic challenges to immune cells, characterized by hypoxia, nutrient deprivation, and accumulation of immunosuppressive metabolites. Tumor cells exhibit high glycolytic activity (the Warburg effect), consuming glucose and releasing lactate that acidifies the extracellular space (Lebelo et al., 2019). This creates intense competition for glucose, a critical substrate for activated T cells. Additionally, amino acid depletion—particularly of tryptophan and arginine—by tumor cells and myeloid-derived suppressor cells (MDSCs) further impairs T cell function through multiple mechanisms (Yang et al., 2023).

2.2 Metabolic Control of Specific Immune Cell Populations

2.2.1 T Cells

CD8+ cytotoxic T lymphocytes (CTLs) are particularly vulnerable to metabolic constraints in the TME (Reina-Campos et al., 2021). Effective anti-tumor responses require CTLs to maintain mitochondrial fitness for persistence and memory formation, while simultaneously upregulating glycolysis for immediate effector functions. Tumor-infiltrating lymphocytes (TILs) often display metabolic defects including fragmented mitochondria, reduced OXPHOS capacity, and depleted NAD+ pools—all contributing to functional exhaustion (Janssens et al., 2022).

In contrast, regulatory T cells (Tregs) adapt well to the TME by utilizing distinct metabolic pathways. Tregs preferentially employ lipid oxidation and are more resistant to glucose restriction than effector T cells (Field et al., 2020). Their stability and suppressive function are supported by AMP-activated protein kinase (AMPK) signaling and mitochondrial metabolism. This metabolic flexibility allows Tregs to thrive in harsh tumor conditions while suppressing anti-tumor immunity.

2.2.2 Myeloid Cells

Tumor-associated macrophages (TAMs) demonstrate remarkable metabolic plasticity that correlates with their functional polarization. Classically activated M1 macrophages rely on glycolysis and pentose phosphate pathway flux, while alternatively activated M2 macrophages preferentially utilize OXPHOS and FAO (Kolliniati et al., 2022; Viola et al., 2019). In tumors, TAMs often exhibit an M2-like phenotype supported by lactate, hypoxia-inducible factors (HIFs), and peroxisome proliferator-activated receptors (PPARs). Dendritic cells (DCs) also require specific metabolic programs for proper function. Conventional DCs depend on glycolysis for activation and antigen presentation, while tolerogenic DCs utilize FAO (Sim et al., 2016). Metabolic impairment in tumor-associated DCs contributes to defective antigen presentation and T cell priming (Peng et al., 2021).

2.3 Key Metabolic Pathways as Therapeutic Targets

Glycolysis: While inhibition could theoretically impair tumor growth, systemic glycolytic inhibitors may also suppress anti-tumor immunity. More selective approaches targeting glycolytic enzymes in specific cell populations are needed.

Mitochondrial Metabolism: Enhancing mitochondrial function in T cells through NAD+ precursors or AMPK activators may improve persistence and memory formation.

Amino Acid Metabolism: IDO1 and arginase inhibitors aim to reverse amino acid depletion in the TME, though clinical results have been mixed due to pathway redundancy.

Lipid Metabolism: Modulating fatty acid synthesis and oxidation could differentially affect effector T cells versus Tregs, potentially rebalancing the immune landscape.

3. Microbiota-Immune Crosstalk in Cancer

3.1 Gut Microbiota Composition and Cancer Immunity

The gut microbiota influences systemic immunity through multiple mechanisms including molecular mimicry,

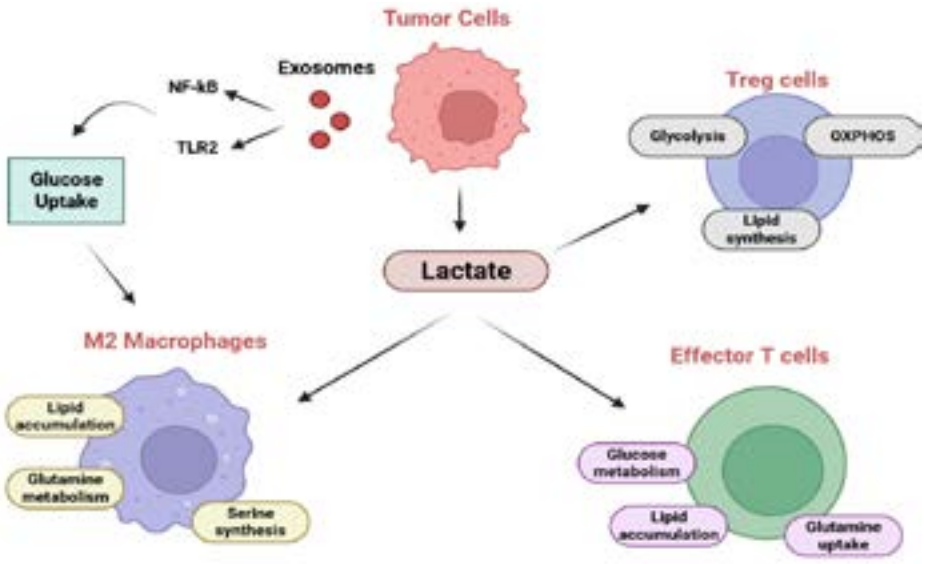

Figure 1: Metabolic regulation of immune cells in cancer. Tumor cells release lactate and exosomes via NF-κB and TLR2 signaling. Lactate alters metabolism in M2 macrophages (lipid accumulation, glutamine and serine metabolism), Treg cells (glycolysis, OXPHOS, lipid synthesis), and effector T cells (glucose metabolism, lipid accumulation, glutamine uptake), promoting an immunosuppressive tumor microenvironment.

Table 1: Key Metabolic Pathways in Tumor-Associated Immune Cells

Immune Cell Type	Dominant Metabolic Pathway	Functional Consequence	Therapeutic Target Opportunities
CD8+ T cells	Glycolysis/glutaminolysis	Effector function	HK2 inhibitors, glutamine analogs
Tregs	Fatty acid oxidation	Suppressive capacity	CPT1a inhibitors
M1 macrophages	Glycolysis/PPP	Pro-inflammatory state	PFKFB3 inhibitors
M2 macrophages	OXPHOS/FAO	Immunosuppression	AMPK activators
DCs	Glycolysis	Antigen presentation	mTOR inhibitors

Table 2: Clinically Relevant Microbiota-Immune Interactions

Bacterial Species	Metabolite/Component	Immune Effect	Cancer Type Association
Akkermansia muciniphila	Amuc_1100 (outer membrane protein)	TLR2/4 activation, IL-12 production	Melanoma (anti-PD1 response)
Bifidobacterium longum	SCFAs (butyrate)	Treg differentiation, HDAC inhibition	Colorectal cancer
Bacteroides fragilis	PSA (polysaccharide A)	Th1 polarization, IL-12 production	Prostate cancer
Fusobacterium nucleatum	FadA (adhesin)	MDSC recruitment, T cell inhibition	Colorectal cancer

antigen presentation, and metabolite production (English et al., 2023). Clinical studies have identified specific bacterial taxa associated with improved responses to immunotherapy:

Positive Correlates: Akkermansia muciniphila, Bifidobacterium spp., Faecalibacterium prausnitzii, and Eubacterium limosum have been linked to better ICI responses across multiple cancer types (Li et al., 2022; Zeriouh et al., 2023).

Negative Correlates: Bacteroides thetaiotaomicron and Ruminococcus gnavus are associated with resistance to immunotherapy (Li et al., 2022). These associations appear to be cancer-type specific, highlighting the need for personalized microbiome analysis in clinical applications.

3.2 Mechanisms of Microbiota-Mediated Immune Modulation

3.2.1 Microbial Metabolite Signaling

Short-chain fatty acids (SCFAs) particularly butyrate, propionate, and acetate are produced by bacterial fermentation of dietary fiber (Wang et al., 2019). Butyrate enhances anti-tumor immunity through:

- HDAC inhibition promoting chromatin accessibility at effector gene loci
- GPR43/GPR109A receptor signaling in immune cells
- Maintenance of intestinal barrier function reducing systemic inflammation
- Tryptophan metabolites including indole-3-aldehyde and indole-3-acetic acid activate the aryl hydrocarbon receptor (AhR), influencing IL-22 production and mucosal immunity.

3.2.2 Bacterial Antigen Cross-Reactivity

Microbial molecular patterns like lipopolysaccharide (LPS) and flagellin stimulate pattern recognition receptors (PRRs) on immune cells, promoting dendritic cell maturation and Th1 responses (Pulendran, 2004). Some bacterial antigens may cross-react with tumor antigens through molecular mimicry.

3.2.3 Bile Acid Metabolism

Gut bacteria modify primary bile acids into secondary forms that signal through nuclear receptors (FXR, PXR) and membrane receptors (TGR5) (Pulendran, 2004), influencing inflammation and immunity.

3.3 Therapeutic Modulation of the Microbiota

Fecal Microbiota Transplantation (FMT): Early clinical trials show FMT can restore ICI responsiveness in refractory melanoma patients (Jessurun et al., 2017), though standardization remains challenging.

Precision Probiotics: Engineered bacterial strains designed to deliver immunomodulatory payloads (e.g., anti-CD47 nanobodies) represent an emerging approach.

Phage Therapy: Bacteriophages could selectively eliminate immunosuppressive bacterial species while sparing beneficial taxa.

Dietary Interventions: Fiber-rich diets increase SCFA production, while tryptophan supplementation may support AhR-mediated immunity.

4. Therapeutic Integration and Clinical Translation

The translation of immunometabolic and microbiota-based interventions into clinical practice presents both opportunities and challenges. Current efforts are focused on developing pharmacological agents that target key metabolic nodes in immune cells, including inhibitors of

IDO1, arginase, and fatty acid oxidation, as well as activators of AMPK and NAD+ biosynthesis. These approaches aim to reprogram the tumor microenvironment (TME) to favor anti-tumor immunity by alleviating metabolic suppression of T cells and enhancing the function of antigen-presenting cells. However, early clinical trials with IDO1 inhibitors demonstrated limited success, likely due to compensatory mechanisms within the tryptophan-kynurenine pathway and the complexity of immune-metabolic crosstalk. This highlights the need for more sophisticated targeting strategies, such as combination therapies that simultaneously modulate multiple metabolic pathways or cell-type-specific delivery systems to minimize off-target effects.

Parallel to pharmacologic developments, microbiome-based interventions are being actively explored to enhance immunotherapy efficacy. Fecal microbiota transplantation (FMT) has shown promise in restoring responsiveness to immune checkpoint inhibitors (ICIs) in refractory melanoma patients (Borgers et al., 2022), with clinical responses correlating with the engraftment of beneficial bacterial species such as Akkermansia muciniphila and Bifidobacterium spp. However, challenges remain in standardizing FMT protocols, ensuring microbial viability, and mitigating risks such as pathogen transmission. An alternative approach involves the use of defined microbial consortia or engineered probiotics designed to deliver immunomodulatory molecules directly to the gut mucosa. For example, E. coli Nissle 1917 has been modified to secrete anti-CD47 nanobodies, demonstrating enhanced anti-tumor activity in preclinical models (Zhou and Han, 2022). Dietary interventions, including high-fiber diets and prebiotic supplementation, represent another non-invasive strategy to modulate microbial metabolite production, particularly short-chain fatty acids (SCFAs), which have been shown to enhance T cell function and reduce systemic inflammation (Liu et al., 2023).

Despite these advances, several hurdles must be addressed to optimize clinical translation. First, the pharmacokinetics of microbial metabolites—such as their short half-lives and variable absorption—complicate dosing strategies. Second, the high degree of inter-patient variability in microbiome composition necessitates personalized approaches, potentially guided by metagenomic and metabolomic profiling. Third, safety concerns, including the risk of immune-related adverse events from microbiota modulation, require careful evaluation in controlled clinical settings. Finally, the identification of robust biomarkers—such as specific microbial signatures, metabolic intermediates, or immune cell phenotypes will be critical for patient stratification and monitoring therapeutic efficacy.

5. Future Perspectives

Looking ahead, the integration of immunometabolism and microbiome research holds immense potential for advancing cancer therapy. A key priority will be the systems-level analysis of host-microbe-metabolite interactions, leveraging multi-omics technologies to map how microbial communities influence systemic immunity through metabolic rewiring. Organoid-based models and humanized mouse systems will be invaluable for dissecting these complex relationships in a controlled environment, particularly for studying non-gut microbial niches such as the oral and tumor microbiota that may also contribute to immune regulation.

Another promising direction is the rational design of microbial consortia tailored to specific cancer types or treatment regimens. Synthetic biology approaches could enable the engineering of bacterial strains that produce immunostimulatory metabolites on demand or selectively colonize tumor sites to deliver localized therapy. Additionally, the exploration of phage therapy to target pro-tumorigenic bacteria while preserving commensal species may offer a precise method for microbiome editing.

Combination strategies that simultaneously target immunometabolic pathways and the microbiome are likely to yield the most significant clinical benefits. For example, pairing SCFA-producing probiotics with inhibitors of immunosuppressive metabolites (e.g., lactate or kynurenine) could create a more favorable TME for T cell activation (Rangan and Mondino, 2022). Similarly, integrating microbiota modulation with adoptive cell therapies may enhance T cell persistence and functionality.

Ultimately, the success of these approaches will depend on interdisciplinary collaboration among immunologists, microbiologists, metabolomic experts, and clinicians. Large-scale, longitudinal clinical studies incorporating deep immune profiling, metabolomics, and microbiome analysis will be essential to validate these strategies and identify predictive biomarkers. By bridging the gap between basic science and clinical application, this emerging field has the potential to revolutionize cancer treatment, offering new hope for patients with otherwise refractory disease.

6. Conclusion

The integration of immunometabolism and microbiome science represents a paradigm shift in our understanding of cancer immunity. By elucidating how metabolic networks and microbial communities collectively shape anti-tumor responses, this interdisciplinary approach opens new avenues for therapeutic intervention. Future progress will depend on overcoming technical challenges in modulating these complex systems while developing biomarkers to guide personalized treatment strategies. Ultimately, combining metabolic and microbial interventions with existing immunotherapies may unlock more durable and widespread responses in cancer patients.

Declarations

Ethics approval statement

No ethical approval was required for the current study as it did not deal with any human or animal samples.

Consent to participate

Not applicable

Consent to publish

Not applicable

Data Availability Statement

The data are available from the corresponding author upon reasonable request

Competing Interests

The authors declare that they have no conflict of

interest

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Author contribution

Conceptualization, Data curation, Investigation: A.O, S.P, Formal analysis: A.O, Writing—review and editing: A.O, All authors have read and agreed to the published version of the manuscript

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