

The Impact of Tumour Microbiome-Derived Metabolites on Checkpoint Inhibitor Efficacy

Javier Torres*

Department of Microbiology and Immunology, University of Barcelona, Barcelona, Spain

DESCRIPTION

The success of Immune Checkpoint Inhibitors (ICIs) in oncology has revolutionized cancer treatment, offering durable responses in multiple malignancies, including melanoma, lung cancer, and urothelial carcinoma. However, response rates remain variable, with many patients exhibiting primary or acquired resistance. Emerging evidence indicates that the tumor-associated microbiome plays a pivotal role in modulating antitumor immunity and influencing ICI efficacy. Beyond microbial presence, metabolites derived from the tumor microbiome have gained attention for their capacity to shape the Tumor Microenvironment (TME), regulate immune responses, and impact therapeutic outcomes. Understanding the interplay between microbiome-derived metabolites and immune checkpoint blockade is essential to optimizing immunotherapy strategies.

The tumor microbiome, composed of bacteria, fungi, and viruses residing within or surrounding tumor tissues, contributes to local metabolic activity that can profoundly influence the TME. Metabolites such as Short-Chain Fatty Acids (SCFAs), secondary bile acids, tryptophan catabolites, and polyamines are generated through microbial metabolism and can act as signaling molecules to modulate immune cell function. SCFAs, including butyrate and propionate, are well known for their role in regulating T cell differentiation and cytokine production. In the TME, SCFAs can enhance CD8⁺ T cell cytotoxicity, promote regulatory T cell expansion, or modulate dendritic cell activity depending on concentration and local context, thereby influencing the effectiveness of ICIs.

Tryptophan metabolism is another key pathway influenced by the tumor microbiome. Microbial conversion of tryptophan into kynurenine and indole derivatives can suppress antitumor immunity by activating the Aryl hydrocarbon Receptor (AhR) on T cells and myeloid cells. Elevated kynurenine levels have been associated with increased regulatory T cell populations, decreased effector T cell activity, and poor response to PD-1

blockade. Similarly, microbial metabolites such as polyamines, produced through arginine metabolism, may promote immunosuppressive macrophage polarization and inhibit T cell proliferation. These metabolic signals highlight how the tumor microbiome can establish an immunoregulatory niche that limits checkpoint inhibitor efficacy.

Beyond modulating effector immune cells, tumor microbiome-derived metabolites can influence antigen presentation and dendritic cell maturation. For example, SCFAs can enhance histone acetylation in dendritic cells, promoting the expression of costimulatory molecules essential for effective T cell priming. Conversely, microbial indole derivatives may suppress dendritic cell function, leading to impaired T cell activation. These metabolite-mediated effects on antigen-presenting cells complement the direct modulation of T cells and collectively determine the immune tone of the TME, thereby affecting the clinical efficacy of ICIs.

Therapeutic modulation of the tumor microbiome-metabolite axis represents a promising avenue to enhance ICI efficacy. Strategies include dietary interventions, prebiotics, probiotics, and small-molecule inhibitors targeting specific microbial metabolic pathways. Combination therapies integrating ICIs with metabolite-targeted strategies are under active investigation in preclinical and early-phase clinical studies, highlighting the translational potential of this approach.

However, several challenges remain in translating microbiome-metabolite research to clinical application. Tumor microbiome composition is highly heterogeneous, influenced by tumor type, anatomical location, prior therapy, and host genetics. Metabolite concentrations are dynamic and context-dependent, making it difficult to establish universal biomarkers of ICI response. Standardization of sample collection, metabolite quantification, and data integration is essential for reproducibility across studies. Multi-institutional collaborations, high-throughput omics integration, and advanced computational modeling are critical to overcoming these challenges and enabling precision immunotherapy guided by microbiome-derived metabolites.

Correspondence to: Javier Torres, Department of Microbiology and Immunology, University of Barcelona, Barcelona, Spain, E-mail: javiertorres@ub.edu

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CONCLUSION

Tumor microbiome-derived metabolites are emerging as key regulators of immune checkpoint inhibitor efficacy. Metabolites such as SCFAs, kynurenine, indoles, and polyamines modulate T cell activity, dendritic cell function, and macrophage polarization within the TME, ultimately influencing clinical outcomes. Integrating microbiome profiling with metabolomic analyses allows identification of predictive biomarkers and offers

therapeutic opportunities to overcome resistance. Rational modulation of microbial metabolism, through dietary interventions, probiotics, or small-molecule inhibitors, holds promise to enhance ICI responses in cancer patients. As research in this field advances, understanding and manipulating the tumor microbiome-metabolite axis may become an essential component of precision immuno-oncology, improving patient stratification and treatment efficacy.