

Gut Microbiota-Derived Metabolites in Cancer Immunotherapy: Mechanisms and Clinical Potential

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Abstract. The human gut microbiota plays a critical role in host physiology, particularly in immune regulation and cancer progression. Notably, gut microbiota-derived metabolites have emerged as crucial regulators of anti-tumor immunity and immunotherapy efficacy. This review synthesizes recent findings on how microbial metabolites, such as short-chain fatty acids (SCFAs), bile acid derivatives, and tryptophan metabolites, interact with immune cells and signaling pathways to influence cancer immunotherapy outcomes. In terms of mechanism, they coordinate innate and adaptive immune processes, reshape the tumor microenvironment, and may enhance the anti-tumor effect. In clinical practice, interventions such as fecal microbiota transplantation (FMT), probiotic supplementation and metabolite supplementation have shown the potential to improve the response rate of treatment. However, there are still many challenges. Differences between individuals, unresolved long-term safety issues, and the complexity of the interaction between the microbiota and the immune system all hinder progress in this area. A comprehensive clarification of these mechanisms is crucial to the rational design of microbial interventions aimed at improving the effectiveness of cancer immunotherapy.

1 Introduction

Cancer immunotherapy is a revolutionary advance in oncology, providing lasting clinical benefits across multiple malignancies. Immune checkpoint inhibitors (ICIs), such as antibodies targeting programmed death-1 (PD-1), its ligand PD-L1, and cytotoxic T-lymphocyte - associated protein 4 (CTLA-4), have transformed the landscape of cancer treatment by reactivating cytotoxic T-cell responses against tumour cells. Although remarkable results have been achieved, only some patients have effective responses to ICIs, and primary or acquired drug resistance still constitutes a major obstacle [1]. Therefore, analyzing the determinants of immunotherapy response has become an urgent research focus.

Accumulating evidence shows that the intestinal microbiota - trillions of microorganisms living in the gastrointestinal tract - plays a key role in regulating systemic immune response and influencing the efficacy of cancer immunotherapy [2]. In addition to their taxonomic composition, the functional products of these microorganisms (particularly microbial metabolites) have been identified as key molecular mediators of host - microbe communication [3]. These metabolites reshape the immune landscape by modulating both innate and adaptive immunity, thereby altering the tumour microenvironment and influencing therapeutic efficacy [4].

Gut microbes generate diverse metabolites such as SCFAs, bile acids, tryptophan metabolites, and

polyamines that help maintain immune balance [5]. These compounds can regulate inflammation, shape antitumor immunity, and influence responses to ICIs [6]. However, the precise mechanisms they affect immune pathways during cancer immunotherapy are still not fully understood. This review summarizes how gut microbial metabolites regulate immunity, their potential roles in cancer therapy, and prospects for clinical application.

2 Gut microbiota and host immunity

The gut microbiota helps maintain immune balance by regulating communication between microbes and the host immune system. When this interaction is disturbed, known as dysbiosis, immune function becomes impaired, leading to inflammation and tumor progression [2]. It is important to understand this balance in order to explain how microbial metabolites regulate immune function, as discussed below.

2.1 Modulation of innate immunity

The innate immune system acts as the body's first protective barrier against microbial invasion and the development of cancer. Its tone and responsiveness are largely influenced by signals from commensal bacteria, often referred to as microbe-associated molecular patterns (MAMPs). These molecular cues are sensed through pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) and NOD-like receptors

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(NLRs), which are present on intestinal epithelial cells, macrophages, and dendritic cells [7]. Through continuous but mild stimulation, commensal microbes help keep immune activity in a balanced state. They maintain the integrity of the intestinal barrier and promote small but steady amounts of cytokines like IL-10 and TGF- β . This stable immune environment limits unnecessary inflammation while keeping the host ready to respond quickly to invading pathogens.

Dysbiosis disrupts this equilibrium. The loss of beneficial microorganisms or the expansion of pathogenic bacteria will lead to excessive activation of TLR or NLR signals, causing chronic inflammation and destroying the epithelial barrier. As a result, innate immune cells are abnormally activated, the secretion of pro-inflammatory cytokines (such as IL-6 and TNF- α) increases, and the antigen presentation function is impaired. These changes can not only promote the formation of tumor microenvironment, but also weaken the anti-tumor immune response. Symbiotic metabolites (including SCFAs) play a compensatory role in the process of restoring homeostasis. SCFAs promote the expression of anti-inflammatory genes by inhibiting histone deacetylases (HDACs) and promote macrophage polarization toward the M2 phenotype to support tissue repair [4]. It is evident that microbial metabolites act as key biochemical mediators, can regulate the state of innate immune activation and prevent excessive or insufficient immune response.

2.2 Modulation of adaptive immunity

The adaptive immune system is mainly mediated by T cells and B cells, and its normal development and function also depend on microbial signals. Early intestinal bacterial colonization shapes the maturation process of lymphoid tissue and promotes tolerance to symbiotic bacteria. In adult, microbial metabolites regulate the balance between effector and regulatory immune responses. For example, SCFAs promote the differentiation of regulatory T cells (Tregs) through the epigenetic mechanism involving FOXP3 acetylation, thus maintaining immune tolerance and preventing autoimmune inflammation [3][1]. Moreover, specific SCFAs such as butyrate and propionate can enhance the cytotoxicity of CD8⁺ T cells, increasing the secretion of interferon- γ (IFN- γ) and strengthening anti-tumor activity [5].

Besides T cells, microbial signals also affect B-cell development and antibody production, helping to maintain effective humoral immunity. Gut microbes produce metabolites that affect B-cell maturation and germinal center formation, promoting IgA production and limiting harmful antibody responses [8]. These metabolites support adaptive immunity and help maintain gut immune homeostasis.

2.3 Immune homeostasis and dysregulation

Maintaining immune homeostasis requires a dynamic balance between immune activation and immune tolerance. Through continuous low-level stimulation,

the balanced microbiota not only strengthens the tolerance to symbiotic bacteria, but also maintains a strong defense against pathogens. Imbalance caused by factors such as antibiotic exposure, dietary changes, stress or disease can cause immune disorders. Bacterial flora disorder may lead to the depletion of beneficial metabolites, a decrease in the level of SCFAs, and an increase in the microbial components that induce inflammation. The imbalance between pro-inflammatory signals and regulatory signals not only creates a favorable environment for the carcinogenic process, but also weakens the response to immunotherapy.

In view of the fact that the intestinal microbiota mainly exerts immune effects through metabolic activity, microbial metabolites can be regarded as biochemical mediators for host-microbial communication. As signal molecules, they connect microbial metabolism with the host's immune pathway, and at the same time affect the local and systemic anti-tumor response. The main categories of these metabolites and their unique immunomodulation mechanisms will be discussed below.

3 Categories and functions of gut microbiota-derived metabolites

The most extensively studied microbial metabolites with immunomodulatory properties include SCFAs, secondary bile acids, and tryptophan metabolites, each exerting distinct yet complementary effects on immune regulation.

3.1 SCFAs

SCFAs, primarily acetate, propionate, and butyrate, are produced by bacterial fermentation of dietary fibres, with major contributors including species from the Firmicutes and Bacteroidetes phyla. These molecules exert immunoregulatory effects by binding to G protein-coupled receptors (GPCRs) such as GPR41 and GPR43 and by inhibiting HDACs [4]. Butyrate enhances Treg differentiation via FOXP3 acetylation, maintaining mucosal immune tolerance, while also augmenting cytotoxic T-cell responses that support anti-tumor immunity [5]. Propionate regulates macrophage polarization and promotes the anti-inflammatory M2 phenotype in certain contexts. However, the net effect of this polarization on anti-tumor immunity depends on the specific situation. SCFA also maintains the integrity of the epithelial barrier and prevents systemic inflammation by promoting mucin production and tight junction assembly [9].

3.2 Bile acid derivatives

Primary bile acids synthesized in the liver are transformed into secondary bile acids by intestinal bacteria. These metabolites modulate immune signaling through specific receptors, including the nuclear receptor farnesoid X receptor (FXR) and the G protein-coupled bile acid receptor 1 (GPBAR1, also

known as TGR5) [10]. Secondary bile acids can affect dendritic cell maturation and inhibit pro-inflammatory cytokines, indirectly affecting T cell activation. In addition, dysregulation of bile acid metabolism is associated with changes in anti-tumor immunity and reduced responsiveness to ICIs [6].

3.3 Tryptophan metabolites

Tryptophan, an essential amino acid, is metabolized by gut microbes into indole metabolites, which act through the aryl hydrocarbon receptor (AhR) pathway to modulate immune responses [11]. When AhR is activated, the mucosal barrier is strengthened, and the homeostasis of Tregs is maintained, while inflammation driven by Th17 cells is limited. Recent research also suggests that some indole metabolites can reduce tumor-promoting inflammation and boost anti-tumor immune responses.

4 Mechanisms of gut microbiota-derived metabolites in cancer immunotherapy

Gut microbial metabolites can determine the efficacy of immunotherapy through multiple interconnected mechanisms. They influence immune cell activity, remodel the tumour microenvironment (TME), and help overcome treatment resistance.

4.1 Enhancement of ICI responses

There is a significant correlation between a favourable gut microbiota composition and metabolite profile and the enhanced efficacy of ICIs. SCFAs such as butyric acid and propionic acid can promote the effector and memory functions of CD8⁺ T cells, thus enhancing the anti-PD-1-mediated tumor control effect [8]. Transplanting the FMT of ICI responders into non-responders has been proven to restore treatment responsiveness in refractory cancers [12].

Mechanistically, microbial metabolites promote effective immune activation by regulating antigen presentation and cytokine signaling pathways. SCFAs and tryptophan derivatives not only stimulate the production of IL-12 and IFN- γ , promoting Th1 differentiation and cytotoxic responses, but also support regulatory IL-10 signaling to prevent excessive inflammation [11]. By enhancing antigen presentation, maintaining the metabolic activity of T cells and finely regulating the cytokine network, microbial metabolites build an immune-promoting environment conducive to high-efficiency checkpoint blocking.

Overall, these findings highlight the role of the microbiota as a determinant of the efficacy of immunotherapy. Regulating the composition of microorganisms or supplementing beneficial metabolites may become a strategy to enhance immune activation and improve the clinical efficacy of cancer immunotherapy.

4.2 Remodeling of the tumor microenvironment

TME is an ecosystem composed of immune cells and interstitial cells. SCFAs promote the infiltration and activation of CD8⁺ T cells and natural killer (NK) cells, while suppressing the immunosuppressive activity of myeloid-derived suppressor cells (MDSCs) and Tregs [3]. In addition, bile acid metabolites influence the polarization of tumor-associated macrophages, transforming the TME into a more inflammatory and antitumor-active state [6].

4.3 Overcoming immunotherapy resistance

Resistance to ICIs is usually caused by insufficient immune activation in the TME. Microbial metabolites can counter these mechanisms by restoring T-cell receptor (TCR) signaling and metabolic adaptability [5]. For example, butyrate enhances the mitochondrial oxidative metabolism of cytotoxic T cells, improving their survival and cytolytic activity. In addition, certain metabolites can reprogram tumor metabolism and reduce lactic acid accumulation, thus alleviating the immunosuppressive acidity of the TME [13].

5 Clinical applications and future perspectives

The translational potential of intestinal microbiota-derived metabolites in cancer immunotherapy has attracted increasing clinical attention. Several therapeutic strategies aim to manipulate the microbiota-metabolite-immune axis to optimize the efficacy of immunotherapy.

5.1 Probiotics and prebiotics

Probiotics and prebiotics represent straightforward approaches to enhance beneficial microbial metabolites. Supplementation with *Clostridium butyricum*, a butyrate-producing bacterium, has been shown to improve responses to ICIs in cancer patients [9]. Similarly, prebiotics such as inulin and resistant starch can also boost SCFA production, thereby indirectly enhancing anti-tumor immunity.

5.2 Fecal microbiota transplantation (FMT)

FMT has emerged as a promising strategy to restore gut microbial diversity and rebalance key metabolites. Clinical studies in melanoma and other cancers have shown that FMT using material from patients who responded well to ICIs can markedly improve outcomes in those who did not respond to treatment [1]. Current trials are testing more standardized FMT products containing selected microbial strains and metabolites to improve the reproducibility of outcomes and ensure better safety.

5.3 Metabolite-based therapeutics

Another approach is to directly modulate or supplement microbial metabolites. Some studies are testing exogenous SCFAs or their chemical analogues to boost anti-tumor immune responses and reduce resistance to ICIs [11]. Targeting bile acid or tryptophan metabolism with specific drugs can enhance immune activation while limiting unwanted inflammation [14].

5.4 Challenges and future directions

Despite recent advances, major challenges still limit the clinical application of microbiota-based therapies. Differences in gut microbial composition result in heterogeneous treatment outcomes [15]. Future research should combine multi-omics data to define key metabolic markers for personalized therapy. Modulating the microbiota alongside ICIs or cell-based treatments may improve efficacy and reduce resistance in cancer immunotherapy.

6 Conclusion

Microbial metabolites act as messengers connecting gut microbes with the host immune system. They influence immune signaling and remodel the tumor microenvironment, enhancing the efficacy of immune checkpoint therapy. Therefore, methods such as FMT and metabolite supplementation are being explored to solve the problem of drug resistance in immunotherapy. A deeper study of these mechanisms is crucial to advancing this promising field.

However, many challenges remain. First of all, although the correlation between specific metabolites and immune efficacy has been established, the causal relationship has not been verified. In order to determine whether metabolites directly drive immune regulation or only reflect potential microbial changes, it is necessary to carry out precise mechanism research, which should include germ-free animal models and human metabolomics verification. Secondly, differences in intestinal microbial composition, genetic background, diet and drug exposure among individuals lead to significant heterogeneity of metabolic product generation and treatment effect. To solve this problem, we need to rely on the guidance of multi-omics analysis to formulate personalized microbiota intervention strategies. Third, there is insufficient understanding of the bioavailability and pharmacokinetic characteristics of microbial metabolites. Many beneficial compounds have the problem of limited systemic absorption or rapid metabolism, which hinders their conversion into therapeutic drugs.

In summary, although the clinical promise of harnessing gut microbiota-derived metabolites for cancer immunotherapy is increasingly evident, advancing this field demands integrative research to establish causality, address variability, and optimize metabolite delivery. The convergence of microbiota science, immuno-oncology, and metabolic engineering

will be essential to developing safe, precise, and effective next-generation immunotherapies.

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