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Mini Review Article

Emerging Role of the Microbiome in Cancer Immunotherapy

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Abstract

The human microbiome is a key player in regulating human physiology and disease. There is now compelling evidence from both preclinical and clinical studies suggesting that the gut microbiome plays a key role in modulating host immunity and therapeutic response in cancer. This review aims to distill some of the key findings in the field. The landscape of microbiome-based therapy will be instrumental in providing therapeutic strategies for several disease states, including cancer immunotherapy.

Key words: Microbiome; cancer; immunotherapy; preclinical; clinical

Abbreviations

Immune checkpoint inhibitors (ICIs); (TME) tumor microenvironment; PD-1, programmed death-1; (PDL-1), programmed death ligand-1; CTLA-4, cytotoxic T-lymphocyte associated protein 4, fecal microbiota transplantation (FMT).

The Human Microbiome and Cancer Immunotherapy

Tumorigenesis is a sequential and complicated process involving genetic and epigenetic modifications within the tumor cell and supportive conditions within the tumor microenvironment (TME) (Murphy, 2022). The TME comprises several cell types: immune cells, bone marrow-derived inflammatory cells, blood vessels, lymphocytes, fibroblasts, signaling molecules, and the extracellular matrix. It contains not only malignant cells but also non-malignant cells that influence the development of cancer by modulating cell proliferation Arneth, 2019). Moreover, it is now known that the TME also contains microbiota, and an increasing number of tumors harbor bacteria, modulating the complex tumor ecosystem (Nejman et al, 2020). Often called our second genome, the microbiome comprises over 1,000 species with 100 trillion microbes, including bacteria, fungi, viruses, and protozoa. (2018). It is now well-established that multiple diseases are influenced by microbiome composition (Murphy 2022). They modulate the TME not only via direct cell interaction but also via their microbial-derived metabolites. Some of the principal components include polyamine metabolites and short-chain fatty acids. Polyamines engage in several cellular processes, including proliferation, apoptosis, and signal transduction, while short-chain fatty acids (SCFAs) are essential for intestinal homeostasis and impact host physiology. Unearthing the complex interplay between microbes and the TME will yield valuable insights into potential future cancer treatments. Given the intricacy of the commensal-host interaction, microbiome diversity, and inter-individual variability, it is most likely that multiple modalities will contribute to the influence of the microbiota on immunotherapy efficacy.

Immune Checkpoint Inhibitors

Cancer immunotherapy is a novel biotherapy designed to enhance immune responses against cancer and spans a broad spectrum of immune modulation. Of all the immunotherapy drugs developed and utilized for cancer treatment, immune checkpoint inhibitors (ICIs) are the most widely used and have shown impressive efficacy in several cancer types (Zhang et al, 2023). To date, the strategy that has received most attention utilizes the suppressive monoclonal antibodies directed against immune regulatory factors, such as anti-PD-1, programmed death ligand-1 (PDL-1), and CTLA-4. Despite the promising efficacy of immunotherapy, only a limited cohort of patients benefit from it, and one of the reasons cited for this may be due to the microbiota differences within a given population. Several studies over the last few years have reported that intestinal microbiota composition has a profound impact on the therapeutic efficacy of immunotherapies and the effectiveness of conventional chemotherapy combined with immunotherapy (Zhang et al., 2020).

Cancer's ability to evade the body's immune defenses is essential for its survival and spread. It evades detection and destruction by T cells by the expression of cell surface PD-L1 and PD-L2, engaging with PD-1, and inhibiting T cell function. Monoclonal antibodies directed against these receptors is an immunotherapy that allows the T cells' attack against cancer, referred to as immune checkpoint blockade. Checkpoint blockade of PD-1 is currently used to treat 25 forms of cancer. Although these treatments have revolutionized cancer care, a subset of patients do not benefit from them. Investigating the interactions between the gut microbiota and the immune system has been the focus of intense research

over several years. Researchers have identified not just regulatory mechanisms but also specific microbial molecules and microbial enzymes that modulate the immune system (Pesheva et al., 2023).

The gut microbiome is a crucial regulator of antitumor immunity during immune checkpoint inhibitor therapy. Several preclinical murine studies have reported that several bacteria can promote an antitumor response to immune checkpoint inhibitors (Vétizou et al., 2015 and Mager et al., 2020). Moreover, the efficacy of anti-PD-1 therapy in patients with melanoma can be improved following the transplant of fecal specimens. However, this response is variable, and the mechanism regulating this phenomenon is unclear (Baruch et al., 2021 and Davar et al., 2021).

It has been reported that primary resistance to ICIs was due to abnormal gut microbiome composition, and antibiotics inhibited the clinical benefit of ICIs in patients with advanced cancer (Routy et al., 2018). In a murine model, the antitumor effects of PD-1 blockade were ameliorated following fecal microbiota transplantation (FMT) from cancer patients who responded to ICIs into germ-free or antibiotic-treated mice. In contrast, fecal microbiota transplantation (FMT) from nonresponding patients did not. The enhanced response was improved CD4 helper cell infiltration into the tumors mediated by *Akkermansia muciniphila*. Moreover, oral supplementation of *Akkermansia muciniphila* restored the efficacy of PD-1 blockade in the non-responders.

One study on metastatic melanoma patients who responded to anti-PD1 therapy possessed more diverse microbiotas than non-responders (Gopalakrishnan et al., 2018). Patients with a large abundance of *Faecalibacterium* were more than twice as likely to remain progression-free after six hundred days compared to patients with low *Faecalibacterium* abundance, and this abundance positively correlated with the frequency of myeloid-derived suppressor cells and (MDSCs) and T regulatory (Treg) cells. Matson et al. (2018) reported enhanced T-cell responses and efficacy in germ-free mice reconstituted with fecal material from responding patients to anti-PD-L1 therapy. Moreover, in a preclinical murine model study, it was reported that oral administration of *Bifidobacterium* blocked tumor growth in melanoma-bearing mice, which correlated with the accumulation of antigen-specific $CD8^+$ T cells within the tumor tumor-specific T cells in the periphery and antigen-specific $CD8^+$ T cells within the tumor (Sivan et al., 2023). Commensal *Bifidobacterium* can enhance antitumor immunity *in vivo* in an antigen-independent manner and synergistically with PD-L1 blockade.

Another study identified bacterial species that downregulate PD-L2 expression and its binding partner, repulsive guidance molecule b (RGMb), thus promoting antitumor immunity (Park et al., 2023). PD-1 binds both PD-L1 and PD-L2, but PD-L2 also binds RGMb. Here, researchers used mice whose colons were seeded with gut microbiota from patients with cancer, some of whom had responded well to immunotherapy while others had not. The response of the animals to immunotherapy mimicked the treatment response in the humans whose gut microbes were living in their intestines. One group of mice was treated with broad-spectrum antibiotics to kill gut bacteria and did not respond well to PD-1 blockade. These mice, however, had elevated levels of PD-L2. Animals that responded robustly to the same treatment had lower levels of PD-L2. Moreover, mice seeded with gut microbes from patients that responded well to cancer immunotherapy had lower levels of PD-L2. By contrast, mice seeded with gut microbes from patients with a poor response to immunotherapy had increased levels of PD-L2. This study demonstrates that specific gut bacteria, *Coprobacillus cateniformis*, can affect the activity of two immune molecules — PD-L2 and RGMb – and their interplay. It is also the first study to identify the molecule RGMb, primarily known for its role in nervous system development, as a previously unknown saboteur of the body's ability to spot and destroy tumors by regulating T-cell responses to cancer immunotherapy.

Future Considerations

As outlined above, recent studies demonstrate a potentially effective immunological approach for treating patients who do not respond to PD-1 cancer immunotherapy. This link between the clinical response and microbial composition suggests a direct mechanistic influence on immunotherapy in human cancer patients. Moreover, the mounting evidence linking the gut microbiome to immunotherapy efficacy indicates that this relationship is casual rather than correlative based on the preclinical and clinical evidence (Heimink et al., 2019). Not alone can the microbiome be used as a complementary predictive biomarker of treatment outcomes, but interventional strategies manipulating the microbiome will likely enhance the therapeutic efficacy of ICI therapy. Some of these strategies have been discussed, including dietary interventions, administration of antibiotics, probiotics, prebiotics or synbiotics, and fecal microbiota transplantation (FMT). FMT is one of the most promising methods of microbiota manipulation, and the FDA recently approved it to prevent recurrent *Clostridium difficile*-induced colitis in adults (Kempler, C. 2023). During FMT, patients receive the fecal microbiome of donors either orally or via colonoscopy or gastroscopy, and recent clinical studies show that FMT from donors showing complete response to treatments augmented the effects of ICI in a subset of melanoma patients (Baruch et al, 2021).

Although antibiotics can dramatically alter the gut microbial landscape, and their use before immunotherapy can limit their efficacy against solid tumors (Jiang et al, 2022), more studies are required to determine the relationship between antibiotic administration and ICI response. Other approaches include modulation of the dietary changes that promote the expansion of beneficial bacteria or deprive detrimental bacteria of their required nutrients, for example, polyphenols and high-fiber foods that have been shown to promote antitumor immunity (Lau et al., 2021). Microbial communities comprise a complex micro-ecosystem with significant variability among hosts and physiological states. Multiple contributory factors, including genetic parameters, influence the complexity, which leads to this profound heterogeneity (Vujkovic-Cvijin et al., 2020). Thus, the composition of non-homeostatic gut microbiota may be a person- rather than a disease-specific matter. Moreover, variations in sequencing methodologies (16S rRNA sequencing versus whole-genomic sequencing) and the selection of different reference databases have led to inconsistent results. Therefore, standardizing microbiome profiling techniques coupled with systematic study integrating gut transcriptome, proteome, and metabolome for a comprehensive understanding of the relevant microbiota is required (Li et al, 2022).

The integration of the relative contribution of the microbiome with other factors influencing immunotherapy potency, coupled with a deeper understanding of the precise mechanisms involved, will lead to the design of new treatments to overcome resistance, and improve immunotherapeutic outcomes (Zitvogel et al., 2018). Further investigation should focus on manipulating the gut microbiota to support the proliferation of beneficial microbiota while suppressing bacteria related to poor clinical outcomes.

Conclusion

Mounting evidence demonstrates the importance of the gut microbiota in oncogenesis and the response to treatment modalities. As a result, microbiota modulation for effective anticancer therapeutics has emerged as a new strategy, particularly for ICIs. A better understanding of the correlation between the tumor microenvironment and the host immune system will help mitigate the side effects of cancer immunotherapies. Future precision medicine strategies integrating companion diagnostics with therapeutic tools to identify and modulate the microbiome should facilitate enhanced therapeutic outcomes.

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