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Review Article

Exploring the role of the gut microbiome in modulating response to anti-PD-1 immunotherapy in melanoma patients

Harsh Nawal[1]*

[1]*Medical College & Hospital, Kolkata, West Bengal, India*

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ABSTRACT

The gut microbiome plays a crucial role in modulating the immune response to cancer immunotherapies, particularly anti-PD-1 inhibitors, which have revolutionized the treatment of melanoma. Despite the success of these therapies in some patients, the response remains highly variable. Recent studies suggest that the composition and diversity of the gut microbiome can influence the efficacy of anti-PD-1 therapy by shaping systemic immunity, particularly through its effects on T-cell activation and tumor microenvironment dynamics. Specific microbial species, such as Akkermansia muciniphila and Bifidobacterium, as well as microbial metabolites like short-chain fatty acids (SCFAs), have been associated with enhanced immune responses and improved treatment outcomes. Conversely, dysbiosis, or microbial imbalance, has been linked to resistance to immunotherapy. This review explores the mechanisms by which the microbiome influences immune responses and discusses strategies such as fecal microbiota transplantation (FMT), dietary interventions, and probiotics to modulate the microbiome and enhance melanoma treatment outcomes. Understanding the microbiome's role in immunotherapy could lead to more personalized, effective treatment strategies for melanoma and other cancers.

1. Introduction

The treatment landscape for melanoma has experienced a remarkable transformation with the introduction of immune checkpoint inhibitors, particularly anti-programmed cell death protein-1 (PD-1) antibodies, such as pembrolizumab and nivolumab. These therapies have significantly improved survival rates for patients with advanced melanoma, offering the potential for durable, long-lasting responses in some individuals. In certain cases, what was once considered a universally fatal diagnosis has transformed into a manageable chronic condition. The success of anti-PD-1 therapies has not only revolutionized melanoma treatment but also expanded the understanding of immune oncology.[1–4]

However, despite their success, the response to PD-1 blockade remains highly variable. While some patients experience complete or partial remissions, others either do not respond to treatment or show only transient benefits, indicating the complexity of anti-PD-1 immunotherapy. This variability is thought to be influenced by several factors, including the genetic characteristics of the tumor, the immune microenvironment, and the presence of other immune regulatory mechanisms.

In recent years, researchers have turned their attention to factors beyond the tumor itself, focusing on the gut microbiome as a potential modifier of immune response. The human microbiome, comprising trillions of microorganisms—including bacteria, viruses, fungi, and archaea—plays a crucial role in regulating host immune function. Emerging evidence suggests that the gut microbiome may significantly influence the body's response

* *Corresponding author*.
E-mail address: harshnawalarwork@gmail.com (H. Nawal).

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to immunotherapy, particularly in cancers like melanoma, where immune evasion mechanisms are pivotal.[5–8]

This review will explore the mechanisms by which the gut microbiome modulates the immune response to anti-PD-1 immunotherapy, with a particular focus on melanoma. It will discuss microbial signatures associated with treatment outcomes, potential therapeutic strategies for manipulating the microbiome, and the future implications of microbiome-based interventions for improving melanoma immunotherapy responses.[9]

1.1. Mechanisms of interaction between the gut microbiome and immune modulation

The gut microbiome plays a central role in shaping the immune system, influencing both local immune responses in the gastrointestinal tract and systemic immunity. It is in constant communication with the host immune system, and this relationship is vital for maintaining immune homeostasis and mounting effective immune responses to pathogens and tumors. The mechanisms through which the microbiome interacts with immune cells and modulates immune function are multifaceted, involving both direct microbial signaling and indirect modulation via microbial metabolites and immune cell activation.

1.2. Microbial signatures and immune cell activation

One of the primary ways in which the microbiome influences immune function is through its interaction with the gut-associated lymphoid tissue (GALT), a key component of the immune system. The GALT contains a high concentration of immune cells, such as dendritic cells, macrophages, and T-cells, and serves as a primary site for the initiation of immune responses. The gut microbiota plays a pivotal role in priming these immune cells and enhancing their ability to recognize and respond to foreign antigens, including those associated with tumors.

Commensal bacteria in the gut influence the maturation of dendritic cells, which are crucial for antigen presentation. This process helps initiate adaptive immune responses by activating T-cells, including CD4+ helper T-cells and CD8+ cytotoxic T-cells (CTLs), which are essential for mounting an effective anti-tumor immune response. Specific microbial species have been shown to promote the differentiation of CD4+ T-cells into pro-inflammatory Th1 and Th17 subsets, both of which are involved in robust anti-tumor immunity. Furthermore, certain microbial communities can regulate the balance between pro-inflammatory T-cells and immunosuppressive regulatory T-cells (Tregs), which can dampen immune responses and contribute to immune evasion in tumors.

In melanoma, where immune evasion mechanisms such as PD-1/PD-L1 signaling are a major obstacle to effective immune surveillance, the role of the microbiome in shaping T-cell responses is of particular interest. Studies have shown that the presence of specific microbiota in the gut correlates with enhanced effector T-cell activation and greater tumor infiltration by cytotoxic T-cells. This suggests that a favorable microbiome can potentially enhance the immune system's ability to recognize and attack melanoma cells, thereby increasing the effectiveness of anti-PD-1 therapies.

1.3. Microbial metabolites and immune modulation

Beyond direct interactions with immune cells, microbial metabolites are a crucial element of the microbiome's ability to modulate immune function. One of the most studied classes of microbial metabolites are short-chain fatty acids (SCFAs), which are produced during the fermentation of dietary fibers by gut bacteria. These metabolites, particularly butyrate, acetate, and propionate, have been shown to have significant immunomodulatory effects.

SCFAs influence immune function by promoting the differentiation of T-cells into subsets involved in pro-inflammatory responses, including Th1 and Th17 cells, which play important roles in anti-tumor immunity. In addition, SCFAs inhibit histone deacetylases (HDACs), enzymes that regulate gene expression. By modulating gene expression, SCFAs can increase the production of immune-related cytokines that help activate immune cells and suppress tumor growth. In the context of melanoma, SCFAs such as butyrate have been shown to enhance the effects of immune checkpoint inhibitors, including anti-PD-1 therapies, by creating a more favorable immune microenvironment.

The ability of SCFAs to modulate immune responses is thought to involve multiple mechanisms, including increased T-cell infiltration into tumors, reduction of immune suppression by Tregs and myeloid-derived suppressor cells (MDSCs), and the promotion of anti-inflammatory signaling pathways. These effects collectively enhance the body's immune response to tumors and may serve as a critical factor in determining the success of immunotherapies like anti-PD-1.

1.4. Immune checkpoints and the microbiome

Immune checkpoints are regulatory pathways that prevent the immune system from attacking the body's own cells and tissues, ensuring self-tolerance and limiting excessive inflammation.

Anti-PD-1 therapies work by blocking the interaction between PD-1 and PD-L1, thereby reinvigorating T-

cell activity and restoring anti-tumor immune responses. Interestingly, studies have shown that the composition of the gut microbiome can influence the effectiveness of PD-1 blockade by modulating immune checkpoint expression. For example, certain microbial species, such as Akkermansia muciniphila and Bifidobacterium species, have been shown to promote the activation of CD8+ T-cells and enhance the expression of PD-1 on these cells. This increases their sensitivity to immune checkpoint inhibition, potentially enhancing the effectiveness of anti-PD-1 therapies.

These findings suggest that the microbiome may not only influence the initiation of immune responses but also modulate the effectiveness of immune checkpoint inhibitors by regulating the expression of immune checkpoints themselves. This opens the possibility of using the gut microbiome as a target for enhancing the efficacy of PD-1 blockade in melanoma.

1.5. Impact on melanoma treatment outcomes

Melanoma is a highly immunogenic cancer, which makes it an ideal model for studying the role of the microbiome in modulating immune responses to immunotherapy. Several studies have investigated the relationship between the gut microbiome and the response to anti-PD-1 therapy in melanoma patients, providing valuable insights into how microbial signatures can influence treatment outcomes.

1.6. Microbial signatures associated with treatment response

Emerging research has identified specific microbial signatures that correlate with positive responses to anti-PD-1 therapy in melanoma patients. For example, Akkermansia muciniphila, a bacterium known for its role in maintaining gut barrier integrity and modulating immune responses, has been linked to improved responses to PD-1 blockade. Akkermansia is believed to enhance the anti-tumor immune response by promoting T-cell activation and increasing T-cell infiltration into tumors, which are critical for the effectiveness of immunotherapy.

Similarly, Bifidobacterium species, which produce SCFAs, have been associated with improved outcomes in melanoma patients undergoing anti-PD-1 treatment. These bacteria are thought to enhance anti-tumor immunity by promoting the differentiation of effector T-cells and creating a more favorable tumor microenvironment. Research by Gopalakrishnan et al. demonstrated that patients with more diverse gut microbiomes had better responses to anti-PD-1 therapy. Microbial diversity is believed to be a marker of immune health, as a more diverse microbiome is thought to enable the immune system to mount a broader and more effective response to pathogens and malignancies.

On the other hand, a less diverse microbiome, often referred to as dysbiosis, has been associated with poor responses to anti-PD-1 therapy. Dysbiosis, characterized by an imbalance in the composition of the gut microbiota, can impair immune responses in several ways, including promoting the expansion of Tregs, which suppress anti-tumor immunity, and reducing the infiltration of effector T-cells into tumors. These findings highlight the potential for the gut microbiome to serve as a predictive biomarker for treatment response, underscoring the need to maintain a healthy, balanced microbiome for optimal immunotherapy outcomes.

1.7. Dysbiosis and immunotherapy resistance

Dysbiosis refers to a microbial imbalance in the gut microbiome, where beneficial microbes are diminished and potentially harmful or pathogenic microbes proliferate. In the context of melanoma, dysbiosis has been implicated in resistance to immunotherapy, particularly anti-PD-1 therapy. This imbalance can alter the immune landscape in ways that reduce the effectiveness of immune checkpoint inhibitors.

Dysbiosis can lead to several immune-related issues that impair the body's ability to mount an effective anti-tumor response. One of the key mechanisms is the expansion of Tregs, a subset of T-cells that have immunosuppressive functions. Tregs are crucial for maintaining immune tolerance and preventing autoimmune diseases, but in the context of cancer, an overabundance of Tregs can suppress the activation of effector T-cells that are necessary for targeting and destroying tumor cells. In melanoma, Tregs can inhibit cytotoxic T-cells (CD8+ T-cells) and natural killer (NK) cells, both of which are essential for anti-tumor immunity. A dysbiotic microbiome may contribute to this overabundance of Tregs, thereby dampening the immune response to tumors.

Another consequence of dysbiosis is the reduction of T-cell infiltration into the tumor microenvironment. A healthy, balanced microbiome supports the migration and activation of effector T-cells, which play a key role in recognizing and killing tumor cells. However, dysbiosis has been associated with reduced immune cell trafficking into the tumor, limiting the effectiveness of immune checkpoint blockade therapies. This reduced immune cell infiltration can result in tumors evading immune surveillance and continuing to grow unchecked, even in the presence of immune checkpoint inhibitors.

Research has demonstrated that patients with a more dysbiotic microbiome are less likely to experience a durable or complete response to anti-PD-1 therapy. These findings suggest that restoring a healthy microbiome could be a potential strategy to overcome resistance to immunotherapy

and improve patient outcomes.

2. Potential Modulation Strategies to Enhance Immunotherapy Efficacy

Given the emerging evidence that the gut microbiome can influence the immune response to melanoma and impact the effectiveness of anti-PD-1 therapies, several strategies are being explored to modulate the microbiome in ways that may enhance treatment outcomes. These approaches include fecal microbiota transplantation (FMT), dietary interventions, and the use of probiotics, each of which holds promise for optimizing the immune response and improving responses to immunotherapy.[10,11]

2.1. Fecal microbiota transplantation (FMT

Fecal microbiota transplantation (FMT) is one of the most promising strategies for restoring a healthy microbiome, particularly in patients who have developed resistance to immunotherapy. FMT involves the transfer of fecal material from a healthy donor to a patient, with the goal of re-establishing a more diverse and balanced microbiome. This approach has shown considerable promise in cancer immunotherapy, particularly in melanoma, where FMT has been used to overcome resistance to anti-PD-1 treatment.

In a groundbreaking study by Davar et al. (2021),[6] FMT was shown to enhance responses to anti-PD-1 therapy in melanoma patients who had previously exhibited resistance to treatment. The transplanted microbiota from healthy donors helped restore a more favorable immune environment in the patients, promoting T-cell activation and improving tumor infiltration. This study was one of the first to provide robust evidence that manipulating the microbiome through FMT could improve the efficacy of immune checkpoint inhibitors.

FMT works by replenishing the gut with a diverse community of microbes, which can influence immune cell activation and alter the tumor microenvironment. In particular, FMT has been shown to increase the presence of specific bacteria associated with immune activation, such as Akkermansia muciniphila and Bifidobacterium species. These microbes are thought to promote the differentiation of effector T-cells, enhance immune surveillance, and reduce the activity of immunosuppressive Tregs. Furthermore, FMT may help reverse dysbiosis, which is associated with immune suppression and poor therapeutic outcomes.

Although FMT holds great promise, more research is needed to optimize the procedure, including identifying the most effective donor microbiomes, determining the best frequency and method of transplantation, and understanding the long-term safety and efficacy of the approach. Clinical trials are currently underway to further investigate the potential of FMT as a treatment adjunct to anti-PD-1 immunotherapy in melanoma and other cancers.

2.2. Dietary interventions

Diet plays a central role in shaping the gut microbiome, and dietary interventions are emerging as a viable strategy for modulating the microbiome to improve cancer treatment outcomes. Diets rich in fiber, prebiotics, and polyphenols have been shown to foster the growth of beneficial gut microbes, such as Bifidobacterium and Akkermansia muciniphila, which are associated with improved immune responses. High-fiber diets, in particular, provide the substrates needed for the production of short-chain fatty acids (SCFAs), which, as discussed earlier, play a key role in immune modulation.

Research has shown that a high-fiber diet can promote the growth of SCFA-producing bacteria, which in turn can enhance anti-tumor immunity. SCFAs such as butyrate have been linked to the activation of cytotoxic T-cells and the inhibition of Tregs, both of which are critical for improving the effectiveness of anti-PD-1 therapy. Additionally, certain polyphenols found in fruits, vegetables, and whole grains have been shown to have anti-inflammatory effects, further supporting immune function.

Dietary modifications may also help to restore microbial diversity, which is an important predictor of favorable responses to immunotherapy. A more diverse microbiome is thought to increase the immune system's ability to recognize and respond to a variety of pathogens, including cancer cells. For melanoma patients undergoing immunotherapy, dietary interventions that promote microbial diversity and SCFA production could represent a relatively simple and cost-effective strategy for enhancing the response to anti-PD-1 treatment.

While research into dietary interventions in the context of cancer immunotherapy is still in its infancy, initial studies suggest that incorporating a balanced, fiber-rich diet could serve as an adjunct to traditional therapies. Further clinical trials are needed to better understand the impact of diet on the microbiome and immune system and to determine the most effective dietary strategies for improving melanoma treatment outcomes.

2.3. Probiotics and microbiome modulation

Probiotics, which are live microorganisms that confer health benefits to the host when administered in adequate amounts, have long been considered a potential tool for modulating the microbiome. In the context of cancer immunotherapy, probiotics may be able to support immune function by promoting the growth of beneficial gut microbes and enhancing immune responses. Some studies have

suggested that probiotics could augment the effects of immune checkpoint inhibitors by fostering a microbiome that supports anti-tumor immunity.

Probiotic strains such as Lactobacillus and Bifidobacterium have been shown to promote the activation of effector T-cells and inhibit the growth of immunosuppressive Tregs. However, there are concerns about the safety and efficacy of using probiotics during cancer treatment. Some studies have suggested that the use of probiotics could disrupt the delicate balance of the microbiome, potentially leading to adverse effects such as infections or overgrowth of specific bacterial species. Therefore, the use of probiotics in combination with immunotherapy should be approached with caution.

Future research will need to identify the specific probiotic strains that are most beneficial for enhancing immune responses and determine the optimal conditions for their use in conjunction with immunotherapy. It will also be important to assess the safety of probiotic supplementation in cancer patients, particularly those undergoing treatments like chemotherapy or immunotherapy, which can alter the gut microbiome and immune system in unpredictable ways. [12–19]

3. Conclusion

The gut microbiome plays a crucial role in modulating the immune response to anti-PD-1 immunotherapy in melanoma patients. Evidence from both preclinical and clinical studies suggests that microbial diversity, specific microbial species, and microbial metabolites such as short-chain fatty acids are associated with improved treatment outcomes. By influencing immune cell activation, T-cell differentiation, and the tumor microenvironment, the microbiome has the potential to enhance the effectiveness of immune checkpoint inhibitors, providing new avenues for improving melanoma treatment responses.

Given the significant impact of the microbiome on the efficacy of anti-PD-1 therapies, strategies to modulate the gut microbiome—such as fecal microbiota transplantation, dietary interventions, and probiotics—hold considerable promise for enhancing immunotherapy outcomes. Continued research is needed to better understand the underlying mechanisms of microbiome-immune system interactions and to develop personalized treatment strategies that incorporate microbiome modulation.

In the future, we may see the integration of microbiome analysis into routine clinical practice, enabling clinicians to predict responses to immunotherapy based on microbial profiles and tailor treatment regimens accordingly. Ultimately, leveraging the power of the microbiome could represent a new frontier in cancer immunotherapy, offering more effective and personalized treatments for melanoma and other cancers. By optimizing the microbiome, clinicians may be able to improve patient outcomes, reduce resistance to treatment, and provide more durable responses to anti-PD-1 therapies.

4. Source of Funding

None.

5. Conflict of Interest

None.

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Author's biography

Harsh Nawal, Student https://orcid.org/0009-0000-1914-4037

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