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REVIEW

Tumor Microenvironment and Immune Cell Interplay in Pancreatic Cancer

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SUMMARY

The unique tumor microenvironment (TME) of pancreatic cancer, one of the most deadly cancers, promotes immune evasion and immunosuppressive remodeling of the TME, contributing to tumor invasion, metastasis, and therapeutic resistance. Immune cells that play complex roles in this environment, often creating a highly immunosuppressive environment, include tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), cytotoxic T lymphocytes (CTLs), natural killer (NK) cells, dendritic cells (DCs), and B cells. The gut microbiota plays a crucial role in regulating the differentiation, activation, and function of these immune cells through metabolites such as short-chain fatty acids and signaling pathways like NF-κB and JAK-STAT. Dysbiosis, characterized by an imbalance in microbial populations, exacerbates immune suppression. It increases Tregs, MDSCs, and TAM polarization while decreasing CTL and NK cell activity. On the other hand, a balanced microbiome can enhance anti-tumor immunity, improving treatment efficacy and patient outcomes. This article provides a review of recent findings that highlight the complex relationships between immune cells and the microbiota in the pancreatic cancer TME, as well as the dual roles of these cells as both mediators of tumor progression and potential therapeutic targets. Novel approaches to treating pancreatic cancer are made possible by a promising strategy for reprogramming the immune microenvironment through modulation of the gut microbiota.

Keywords: Immune cells; microbiome; pancreatic cancer; tumor microenvironment.

INTRODUCTION

Pancreatic cancer remains one of the most lethal malignancies worldwide, still holds a dismal five-year survival rate. Its highly aggressive biological behavior, late-stage detection, and poor response to conventional therapies underscore the urgent need for enhanced understanding of the mechanisms underlying this disease. In recent years, growing attention has been directed toward the tumor microenvironment (TME), in which the processes of immune evasion, disease progression, and therapeutic resistance are central. Immune cells and gut microbiota are among the key components of the TME, whose interactions create a highly dynamic and often immunosuppressive landscape. These interactions are now believed to play a major role in pancreatic cancer development and progression, offering new perspectives for potential therapeutic interventions.[1]

The TME in pancreas cancer stands out as a dynamic and complex milieu, which largely impacts the progression of the disease, therapeutic resistance, and the general prognosis. Immune cells are the key constituents of this microenvironment, with roles ranging from either support to suppression. Importantly,

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these immune cells can be modulated by particular bacterial population of the microbiota, affecting cancer progression and the effectiveness of the therapies, either by suppressing the immune system or changing the immune environment to support anti-tumor responses.[2] This review aims to address gaps in the current literature and contribute to the identification of novel therapeutic targets by elucidating the cellular and molecular mechanisms underlying the immunosuppressive remodeling of the TME in pancreatic cancer. Furthermore, it explores how interactions between the TME and the gut microbiota influence immune regulation. In this context, the study offers innovative perspectives for reprogramming the immune environment in pancreatic cancer and provides a foundation for future immunotherapeutic strategies.

The following sections outline the major immune cell populations within the pancreatic cancer TME, their functional roles, and the modulatory effects of the microbiota on these cells:

Tumor-associated Macrophages (TAMs)

TAMs are so abundant in pancreatic cancer that they are normally polarized to an M2-like phenotype, which is closely related to tumor promotion.[3] They add up to the tumor growth by:

- Secreting cytokines and growth factors (e.g., IL-10, TGF-β, VEGF) that promote angiogenesis and tissue remodeling.[4]
- Suppressing anti-tumor immunity through the production of immunosuppressive molecules.[5]
- Enhancing cancer cell invasion and metastasis via matrix metalloproteinases (MMPs) and other proteases.[6]

The gut microbiome can modulate macrophage polarization and function by influencing the production of cytokines and the activation of signaling pathways.[7] For instance, some of the gut bacteria can produce short-chain fatty acids like butyrate and regulate the equilibrium that exists between pro-inflammatory macrophages, M1, and anti-inflammatory macrophages, M2, and drive macrophages toward M2 phenotype, which potentially inflence the progression of tumor.[8] This modulation changes through several signaling pathways, such as the NF-kB and JAK-STAT pathways, which arrange the expression of genes functioning in macrophage activation and function.[9] Also, some of the bacterial elements located in the intestines like Enterococcus faecalis or Escherichia coli have the potential to move to the pancreas which creates an immune-tolerant environment in pancreatic ductal adenocarcinoma (PDAC) by the induction of myeloid-derived suppressor cells (MDSCs) and polarization of M2 macrophages. This immune shift diminishes the action of cytotoxic CD8+ and Th1 CD4+ T cells, which allows PDAC to progress. On the other hand, when microbiota is depleted, the M1 macrophages start to play a bigger role in the activation of T cells and thus in the regression of PDAC along with programmed cell death protein 1 (PD-1) inhibition (Fig. 1).[10,11]

Myeloid-derived Suppressor Cells (MDSCs)

MDSCs are one of these immunosuppression cell populations that come together and increase in pancreatic cancer's TME.[12] They perform it in the following ways (Fig. 2):

- Inhibiting T cell activation and proliferation through the production of arginase, inducible nitric oxide synthase (iNOS), and reactive oxygen species (ROS).
- Promoting the expansion of regulatory T cells (Tregs), further dampening immune responses.[13]

The MDSCs in pancreatic cancer are really affected by the gut microbiota by impressing the infection processes, the immune system, and the metabolic pathways. Inflammation followed by dysbiosis could entail the enlargement and activation of MDSCs, and they can then accumulate in the tumor microenvironment and neutralize antitumor immunity.[14,15] Furthermore, the gut microbiota metabolism of the short-chain fatty acids related metabolites gives them advantages to switch the MDSCs between the subtype/functions and be more or less suppressive to T cells.[16] After all, the gut microbiome plays a crucial role in the immunosuppressive environment of pancreatic cancer, which has further been confirmed by MDSC behavior and treatment outcomes.[17] It was indicated by Pushalkar et al.[18] that reduction of the gut microbiota with oral antimicrobials, which resulted in a smaller tumour size and a change in the immune microenvironment of the TME in orthotopic PDAC mouse models by increasing both innate and adaptive responses to reduce MDSCs and regulate the M1-type macrophages tumour infiltration with suppression of TLR 2/5 signaling; however, the number of Th1-type CD4+ and cytotoxic CD8+ T cells was also increased.

Regulatory T Cells (Tregs)

Within the pancreatic tumor microenvironment, Tregs are key immunosuppressive cells subset of thymus-derived cells. They impact tumor growth by acting either directly on cancer cells or by suppressing of effector immune cells such as MDSCs to create a resilient net-

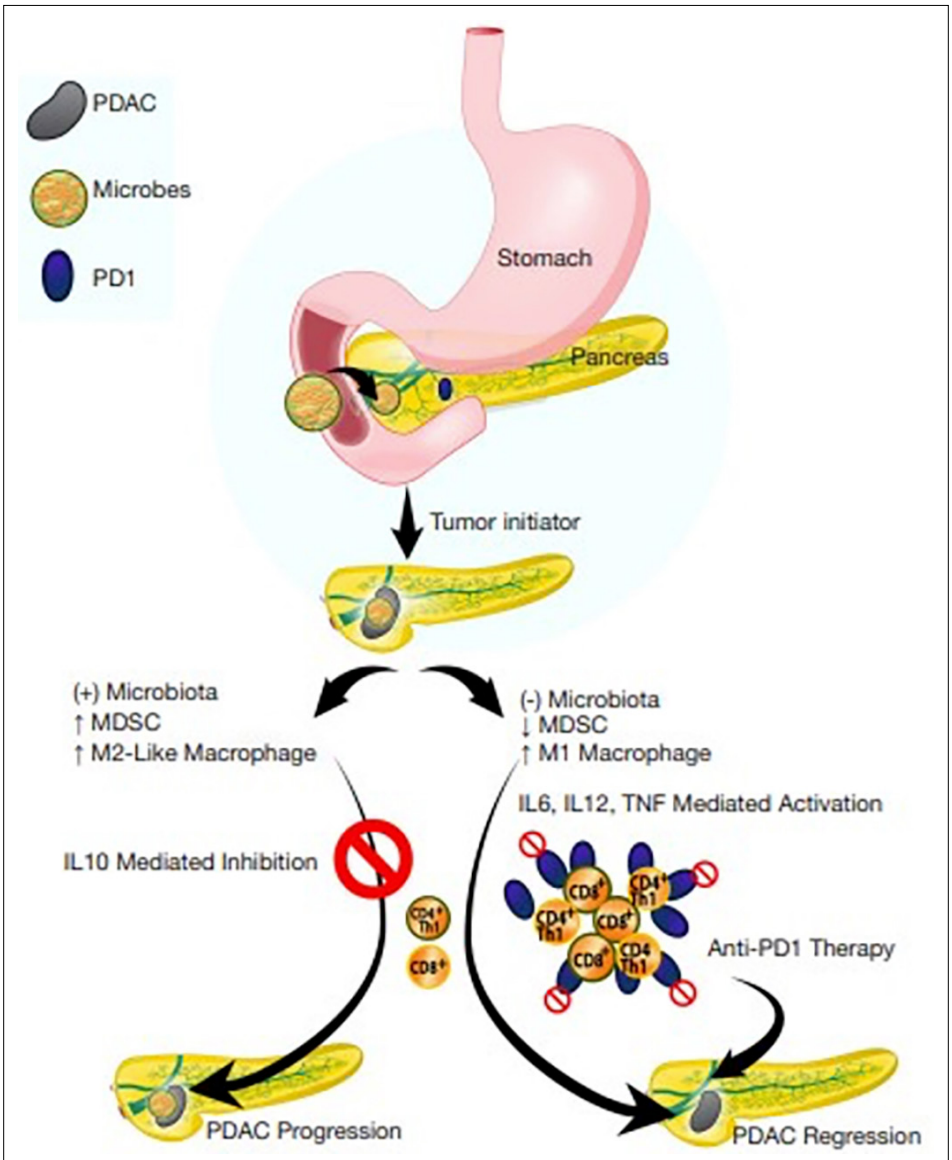

Fig. 1. The mechanism proposed for the effects of gut bacteria on the progression of pancreatic carcinogenesis. Pancreatic ductal adenocarcinoma (PDAC); programmed cell death protein 1 (PD1); and myeloid derived suppressor cell (MDSC).[11]

work that enhances tumor immunosuppression and contributes to resistance against immunotherapy.[19] Their roles are as follows:

- Suppressing effector T cell functions through the secretion of immunosuppressive cytokines like IL-10 and TGF-β.
- Promoting an immunosuppressive microenvironment, facilitating tumor growth and resistance to immune checkpoint inhibitors.[20]

The microbiota significantly affects Tregs in pancreatic cancer and thus plays an important part in the tumor's immune escape mechanism. The gut bacteria, by their metabolites such as short-chain fatty acids, are the main factors promoting Treg differentiation and expansion, which in turn results in the development of an immunosuppressive TME.[21] For instance, butyrate can enhance Treg production.[22] Treg cells are as one of the most effective antitumor immunosuppressants, which possess the potential to reduce the activity of CD4+, CD8+ and NK cells, and are linked with poor prognosis in pancreatic cancer.[7] Faecalibacterium increases the proportion of CD4+ T cells and serum CD25 production and decreases the proportion of Tregs in peripheral blood in human patients.[23] The knowledge

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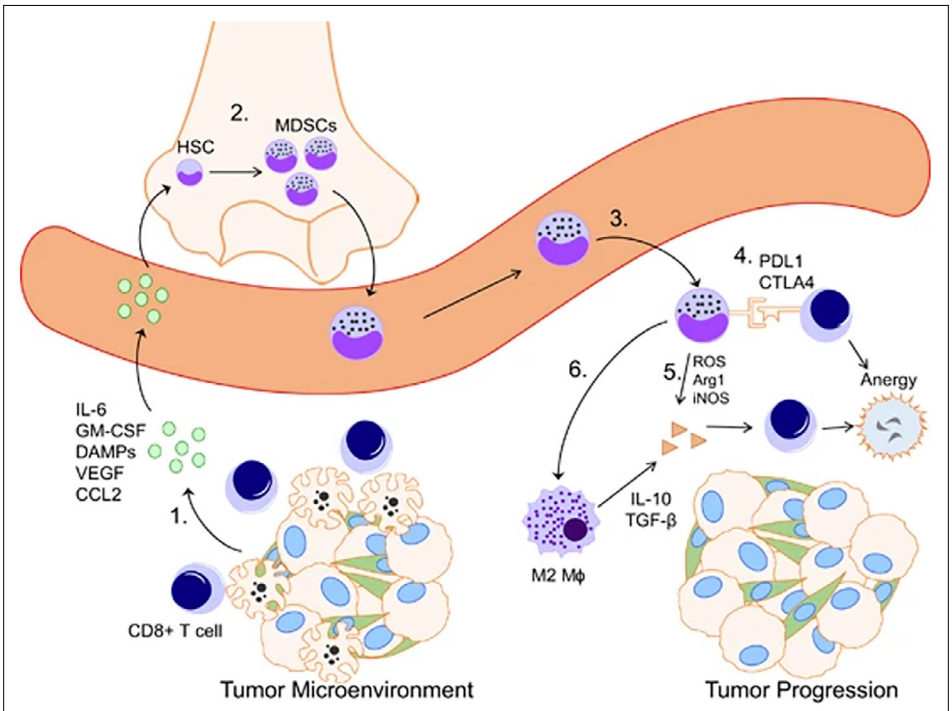

Fig. 2. Despite being the target of the host's cytotoxic response, the early pancreatic tumor microenvironment communicates with the bone marrow via DAMPs and secreted proteins. (2) Hemoietic stem cell recruitment to the tumor microenvironment and (3) proliferation to MDSCs are influenced by these signals. (4) By interacting with cytotoxic cells through PD-L1/PD-1 ligation, MDSCs can directly suppress their immune responses. (5) By releasing ROS, Arg1, and iNOS, they can also indirectly suppress the immune system. (6) MDSCs have the ability to differentiate into M2 macrophages, which release TGF-β and IL-10 and contribute to immunosuppression. Hemopoietic stem cells (HSC); programmed cell death protein 1 (PD1); cytotoxic T-lymphocyte associated protein 4 (CTLA4); damage-associated molecular patterns (DAMPs); myeloid-derived suppressor cells (MDSCs); reactive oxygen species (ROS); macrophage (Mφ); and inducible nitric oxide synthase (iNOS).[13]

of the interactions between these factors can give rise to the therapeutic strategies, such as the modulation of microbiota through the use of probiotics, diet, or fecal microbiota transplantation, all of which can lessen the immunosuppression mediated by Tregs. Introducing these to the conventional pharmacological therapies would make treatments more effective and improve pancreatic cancer patients help them to achieve remission.[24]

Cytotoxic T Lymphocytes (CTLs)

CTLs, also known as CD8+ T cells, are key players in anti-tumor immunity, but their activity is often impaired in pancreatic cancer due to the immunosuppressive TME.[25] Their role and challenges in pancreatic cancer are:

- Exhaustion and dysfunction induced by chronic antigen exposure and upregulation of inhibitory receptors like PD-1.[26]
- Physical barriers created by dense stromal components and extracellular matrix, limiting their infiltration into the tumor.[27]

The microbiota has a very powerful effect on CTLs in pancreatic cancer, determining the immunogenicity and the progression of the tumor.[25] Through the generation of metabolites and the activation of pattern recognition receptors (PRRs), gut microbiota can influence CTL metabolism which further defines the immune environment of the TME. PRRs perform a distinguished function in recognizing microbial-derived ligands that are part of the gut microbiota using the so-called pathogen-associated molecular pattern (PAMPs). For example, when they get turned, TLRs (Toll-like receptors) and NLRs (Nod-like receptors) give a green light for the immune system through the production of pro-inflammatory cytokines and type I

interferons.[28] Consequently, the release of signaling molecules like PD-L1 and other inducible ligand molecules is the main topic of DC teaching and effector cells acting at the benefit of better interaction of MHC molecules and tumor antigens with CTLs.[29] The toll-like receptor 4 (TLR4) is triggered, for instance, when it spots lipopolysaccharides on the surface of bacteria and it activates nuclear factor-kappa B, NF-κB, to manufacture cytokines such as interleukin-12 (IL-12) along with tumor necrosis factor-alpha (TNF-α) as well. These cytokines result in the facilitation of CTL activation and function of them.[30]

Nod-like receptors of the NLR family, represented by NOD2, recognize bacterial peptidoglycan components and activate innate immunity through the action of cytokines and chemokines. The process of inflammasome NLRP3 through its activation leads to the expulsion of interleukin-1β (IL-1β), which fosters CTL responses by means of inflammation and the attraction of CTLs into the TME. Apart from that, the PRRs that get activated also set balance by influencing the immunosuppressive TME's components such as Tregs and MDSCs, thus amplifying the whole immune system.[31] This is achieved by the activation of the PRRs using the microbial products and the immune cells follow the example of the autoactivation of the immune system. In such a way, PRRs are at the core of the coordination of the cellular and humoral immune systems, thus, their importance in the modulation of CTL activity, and the shaping of the immune microenvironment in pancreatic tumor.[32]

Natural Killer (NK) Cells

NK cells are one of the innate immune system's key players, which can directly rid of tumor cells. Unlike CTL, NK cells can recognize and kill the malignant cells by directly binding to surface antigens. However, in pancreatic cancer, their function is often impaired.[33] This happens due to factors such as:

- Reduced cytotoxic activity due to the presence of immunosuppressive cytokines in the TME.
- Impaired NK cell recruitment and infiltration into the tumor site.[34]

Microbiotas in the gut have the ability to effect NK cell activity by modulating the short-chain fatty acids (SCFA) and the activation of PRRs. These interactions can improve the performance of NK cells by influencing the pathways of NK cell proliferation, maturation, and cytotoxic function. For example, fermentable fiber, like butyrate, a SCFA made in the gut, elicited the production of cytokines such as IL-12 and IFN-γ, that are necessary for the activation and function of NK cells. The gut microbiota through these pathways can secure a higher level of NK cells which can be able to kill pancreatic cancer cells successfully.[35]

Not only can dysbiosis be held accountable for the lack of NK cell activity but it can likewise play a role in the formation of a more immunosuppressive TME in pancreatic cancer. This can be due to the presence of harmful bacteria or a decrease in the number of bacterial populations that produce metabolites and media with immunosuppressive factors that inhibit NK cell activity. For example, the overpopulation of certain bacterial species often triggers ongoing inflammation or induces the synthesis of metabolites that inhibit NK cell function, thus the necessary process is being undermined. This depression, in turn, is conducive to NK cell infiltration into the TME and reduced recognition and subsequent killing of cancer cells, thence facilitates tumor progression and metastasis. The modulation of gut microbiota by NK cell activity may bring about the treatment of a higher level of tumors and thereby better patient outcomes in pancreatic cancer.[36]

Dendritic Cells (DCs)

DCs are considered as the most potent professional antigen-presenting cells (APCs), bridging the innate and adaptive immune responses, play a crucial role in the tumor microenvironment.[37] The process of antigen presentation and activation of T cells plays a critical role in immune surveillance against pancreatic cancer. DCs capture and present tumor antigens to T cells, initiating an immune response crucial for combating the tumor.[38,39] However, in pancreatic cancer, there is a notable decrease in both the number and function of DCs, which hinders antigen presentation and promotes immune tolerance. In other words, ineffective antigen presentation is often occurred due to either functionally impaired or immature DCs in pancreatic cancer.[40] The tumor microenvironment (TME) is composed of immunosuppressive cytokines such as TGF-β, IL-10, inciting a thymic epithelial cells maturation failure and transiently inhibiting the function of DCs, while the factors secreted by the tumour cells result in the education of dysfunctional DCs and subsequently playing mostly immature or tolerogenic DCs.[41] These suppressive DCs provide immune tolerance rather than protective immune responses by triggering regulatory T cells and the release of anti-inflammatory cytokines.[42]

The gut microbiota profoundly affects the function of DC, and the latter in turn, affects the immune response against pancreatic cancer. The gut microbiota

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releases some metabolites like SCFAs, and triggers PRRs on the surface of DCs. These links allow DCs to improve their maturity, the secretion of cytokines, and the presentation of antigens.[23] For instance, SCFAs such as butyrate can enhance the expression of MHC molecules and co-stimulatory molecules on DCs, thus making them more powerful in their task of the activation and priming of T cells.[43] This results in a sharper immune response to the tumor and is, therefore, the key reason for the cancer to be cured.

B Cells

The role of B cells in pancreatic cancer remains unclear and somewhat multifaceted involving both anti-tumor and tumor-promoting functions.[44]

a) Anti-tumor Functions

Memory B cells and plasma cells form from B cells during the process of maturating, and from them, immunoglobulin G1 is produced after the confrontation with tumor-specific antigens which makes tumor cell destruction easier through the use of ADCC and CDC.[45,46] Besides, the complexes that are created as a result of antibody-tumor antigen reaction not only promote antigen presentation but also stimulate the activation of CTLs which has a stronger impact on tumor death.[37] B cells, too, may act as antigen-presenting cells by holding the tumor antigens MHC class II molecules for T cells to recognize, thus, co-stimulating helper T cell activation and promoting the adaptive immune reaction.[47]

b) Pro-tumor Functions

Regulatory B cells (Bregs) release the cytokines that are immunosuppressive like IL-10 and TGF-β, that can limit the activity of CTLs and NK cells and thus the development of Tregs. This leads to the creation of an immunosuppressive TME that supports tumor growth.[42] Some B cells can release pro-inflammatory cytokines that contribute to chronic inflammation, which is linked to tumor progression and metastasis in pancreatic cancer.[45,48]

The microbiota in the gut can affect B cells, in particular either by being a pro-tumor cell or by being anti-tumor cells, with or through various mechanisms. Characterized by an imbalance in the populations of gut microbes, dysbiosis results in chronic inflammation and the production of immunosuppressive metabolites. Pathogenic bacteria can produce metabolites such as kynurenine, which inhibits B cell differentiation and function by the activation of the aryl hydrocarbon receptor (AhR). This suppression results in reduced antibody production, thus the body becomes less likely to reduce or kill pancreatic cancer cells effectively. Furthermore, dysbiosis-induced chronic inflammation can cause disturbances in B cell activation and function, hence, the immune system is further crippled at the tumor site. This warped B cell activity is a factor in the successful escape of the immune system by the tumor and its dissemination in the body.[49]

Rather than that, a matched and thus healthy microbiota in the gut is an important promoter of the optimal function of B cells and it also strengthens the anti-tumor immunity. Positive effect of gut bacteria includes the synthesis of short-chain fatty acids such as butyrate, which stimulate B cell proliferation and differentiate normal functional cells into antibody-secreting plasma cells. The presence of these metabolites is also good as it enhances the normal immune environment, exerting favorable effects on antigen presentation and B cell activation. The improved B cell function and the presence of high-affinity antibodies help to kill tumor cells and eliminate tumor antigens. This can promote the immune response, which will then be more effective.[50]

CONCLUSION

In conclusion, the immune cells in the pancreatic cancer TME play complex and often contradictory roles and is basically in an immunosuppressive state. Its main players like TAMs, MDSCs, and Tregs facilitate progression of the tumor by means of the inhibition of CTLs and NK cells, which are the main cells essencial for anti-tumor immunity. The function of the immune cells in this malignant growth is carried out through the release of immunosuppressive cytokines and other factors that repress the immune response to pathogens, in other words, make the immune system depression.

The kind of bacteria that is dominating a place has control on the character of the immune response in this area so that either it is homeostatic immune response or an inappropriate immune response is promoted. Some types of microbes can make an immunosuppressive environment supports the function of TAMs, MDSCs, and Tregs, while they decrease CTLs and NK cells. The interplay between the immune system and the microbiome leads to a serious confrontation yet it can unveil an opportunity for the therapeutic modulation by the microbiome as reshaping of the microbiota could lead to the balancing of a stronger immune response towards pancreatic cancer.

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