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Tumor Immune Microenvironment and Its Regulatory Mechanism

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Abstract. Gastric cancer (GC) is a highly heterogeneous tumor, and TME plays a key role in tumorigenesis and progression. TME is composed of immune cells, CAF and ECM, which regulate the growth, invasion and metastasis of GC through complex interactions. Immune escape mechanisms, such as the activation of the PD-1/PD-L1 pathway, weaken the body's anti-tumor immune response and lead to further proliferation of tumor cells. In addition, high density of immunosuppressive cells and active CAF are strongly associated with poor prognosis in patients with GC. In recent years, targeted therapeutic strategies for TME, such as immune checkpoint inhibitors (ICIs), CAF inhibitors, and ECM remodeling modulators, have shown potential therapeutic effects and become a new way to improve the survival rate of GC patients. However, due to the complexity and heterogeneity of TME, future studies still need to further explore the specific mechanism of action of TME in different stages of GC, and develop more accurate personalized treatment plans. Multidisciplinary combined treatment strategies are expected to play an important role in improving the prognosis of patients with GC.

Keywords: Tumor immune microenvironment; gastric cancer; PD-1/PD-L1.

1. Introduction

In the field of gastric cancer (GC) research, the tumor microenvironment (TME) is considered to be an important influencing factor. In recent years, key immune cells and pathways in the TME have become the focus of research. For example, studies have shown that tumor-associated macrophages (TAMs) and regulatory T cells (Tregs) play an important role in promoting immune escape and tumor progression. Targeted therapies targeting these cells are gradually becoming emerging therapeutic strategies. In addition, the role of cytokines and chemokines in the TME has been widely studied, revealing their core mechanisms in tumor progression and immune escape [1].

Novel immunotherapies, such as ICIs have achieved certain results in clinical trials. However, the effect of immunotherapy is limited by immunosuppressive cells in the TME, so the combined treatment strategy of targeting the TME and ICs has become a research hotspot. In addition, studies have also found that tumor cells communicate with other components in the TME by secreting extracellular vesicles (exosomes), promoting metastasis and treatment resistance, which provides new ideas for the development of innovative therapies in the future [2].

TAMs are one of the most abundant populations of immune cells in TME and play an important role in a variety of solid malignancies. TAMs may contribute to carcinogenesis, neovascularization, immunosuppressive TME remodeling, cancer chemotherapy resistance, recurrence and metastasis [3,4]. This review focuses on immune escape mechanism and its regulatory factors, immune cells and their functions and mechanisms, non-cellular components in microenvironment and immune microenvironment and their prognostic relationships.

2. Immune Escape Mechanism and Its Regulatory Factors

2.1. PD-1/PD-L1

In the in-depth study of the mechanism of cancer immune evasion, a core issue focuses on the specific interaction between PD-L1 molecules expressed on the surface of cancer cells and PD-1 receptors on tumor-infiltrating T lymphocytes (TILs). This PD-1/PD-L1 pathway constitutes a key link in the immunosuppressive network in the tumor microenvironment, significantly inhibiting the anti-tumor immune response of T cells. Specifically, cancer cells upregulate the expression of PD-L1 as an immune evasion strategy, binding to the PD-1 receptor on the surface of TILs, thereby triggering a series of inhibitory signal transduction, including through the regulation of SHP-2 and other phosphate The activity of the enzyme interferes with the normal pathway mediated by the T cell receptor (TCR), resulting in blocked T cell activation, limited proliferation and weakened cytotoxic function. This process effectively weakens the ability of T cells to recognize and eliminate cancer cells and promotes tumor immune evasion. For this immune checkpoint, researchers have developed PD-1/PD-L1 blocking therapy, aiming to restore the immune surveillance and anti-tumor functions of T cells by blocking this interaction. This type of therapy not only promotes the activation and proliferation of T cells, but also enhances their infiltration into tumor tissue and specific killing ability, opening up new avenues for cancer treatment [3].

It is worth noting that under normal physiological conditions, the interaction between PD-1 and PD-L1 is of great significance for maintaining immune homeostasis and preventing the occurrence of autoimmune diseases. Therefore, when developing and applying PD-1/PD-L1 blocking therapy, its potential safety and immune-related side effects must be fully considered to ensure that while enhancing anti-tumor immunity, the body's natural immune balance is not destroyed. However, in the TME, cancer cells exploit this pathway to inhibit immune surveillance, allowing tumors to grow unchecked. As shown in Figure 1, two key immune pathways involved in cancer cell immune evasion and the mechanisms targeted by ICIs. On the left, the interaction between PD-1 (on T cells) and PD-L1 (on cancer cells), which suppresses the immune response. Blocking this pathway with PD-1/PD-L1 inhibitors allows T cells to regain their activity and fight cancer cells. Additionally, CDK inhibitors influence the cell cycle to enhance T cell infiltration. On the right, the CTLA-4 pathway is shown, which also impedes T cell function by interacting with CD80/CD86. Inhibitors targeting CTLA-4 restore T cell cancer-killing activity. The use of metformin is suggested to modulate cancer cell metabolism, further promoting cancer cell death [4].

In conclusion, immune cells play a crucial role in both cancer surveillance and immune evasion. Their functions are tightly regulated by intricate pathways that can be exploited for therapeutic gain. Immunotherapy, by restoring immune cell function and overcoming tumor-induced immunosuppression, has revolutionized cancer treatment and holds great promise for improving patient outcomes. As research continues to unravel the complex mechanisms underlying immune cell function and cancer immunology, new targets and strategies for immunotherapy will emerge, further expanding our arsenal against this devastating disease.

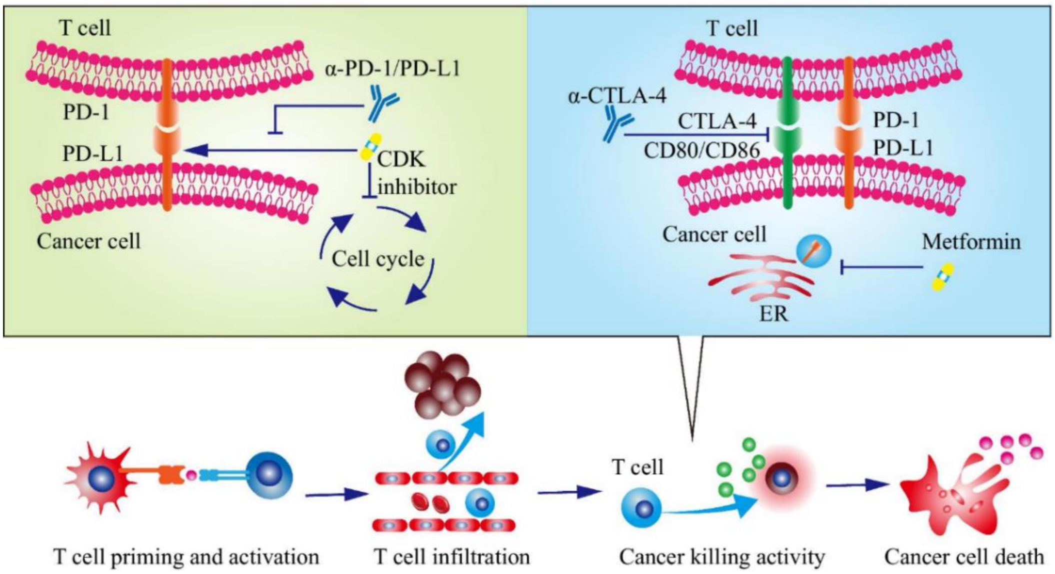

Fig. 1 ICIs and PD-L1 [5]

2.2. Inflammation-related Factors

The key role of inflammatory factors in the development of gastric precancerous lesions (PLGC) suggests that regulating the expression and pathways of these factors may be an effective strategy for the prevention and treatment of GC. For example, during the "inflammation-cancer" transition, inflammatory factors can coordinate the gastric mucosal immune microenvironment and promote PLGC development. During severe infection or injury, IL-6 secretion enhances the inflammatory response. IL-11 exacerbates PLGC by activating the STAT3 pathway. Helper T cell 17 secretes IL-17A and induces gastric epithelial cells to secrete IL-8 and other inflammatory factors. IL-32 is associated with a variety of inflammatory diseases and is produced in response to IL-1β and TNF-α stimulation. TNF-α activates pro-inflammatory or tissue regeneration pathways through its receptors, further modulating the immune response. The key role of inflammatory factors in the development of PLGC suggests that regulating the expression and pathways of these factors may be an effective strategy for the prevention and treatment of GC. [6]

In recent years, immunomodulators have played a significant role in cancer progression and treatment, especially in regulating immune escape. The persistent high expression of FOXP3 is closely associated with the poor prognosis of GCpatients, suggesting its importance in suppressing immune responses. Our study also showed that the high expression of FOXP3 in GCis associated with the ratio of naive B cells and Tregs. At the same time, the CD27/CD70 pathway is also crucial for T cell differentiation, B cell and natural killer cell function enhancement, and these immune cells play a key role in anti-tumor responses.

3. Role and Mechanisms of Immune Cells

Tumors evade immune surveillance through a variety of mechanisms, and immune cells play an important role in regulating tumor immune responses. Macrophages in the TME are divided into two categories: M1 and M2. The former helps inhibit tumor growth, while the latter promotes tumor spread by inhibiting T cell function and antigen presentation. In gastric cancer, the proportion of M2 macrophages is high, which limits the anti-tumor immune response. Therefore, future research should focus on improving treatment outcomes by regulating the balance between M1 and M2.

In addition, T cells are crucial in anti-tumor immunity, especially CD8+T cells, whose dysfunction and reduced number are associated with immune tolerance in gastric cancer. Tregs further weaken the anti-tumor response by promoting an immunosuppressive environment [4]. Therefore, restoring CD8+T cell function and reducing the proportion of Tregs may be the key to effective treatment of GC in the future.

NK cells work by directly killing tumor cells, and their activity is closely related to the prognosis of GC patients. However, the killing function of NK cells is usually limited due to the inhibition of the TME. Therefore, future studies should be aimed at improving the activity of NK cells in the TME to enhance the efficacy of immunotherapy.

In current immunotherapy research, in addition to exploring the functions of existing immune cells, attention should also be paid to how to optimize the anti-cancer effects of these cells. Further research can explore how to enhance the role of macrophages and T cells, especially by adjusting the cell microenvironment to make it more conducive to anti-tumor. The effect of immunotherapy will be improved by promoting the number of M1 macrophages and restoring the normal function of T cells and natural killer cells. In addition, reducing the inhibitory effect of Tregs is also an important way to improve the therapeutic effect. These strategies can not only enhance the efficacy of cancer treatment, but also help better control the spread of cancer cells. Future research directions should also focus on how to improve the TME so that immune cells can play a more effective role in it, thereby increasing the success rate of immunotherapy （Figure 2）.

Macrophages can either inhibit (M1) or promote (M2) tumor progression, with M2 dominance in GClimiting anti-tumor immunity. Additionally, the dysfunction of CD8+ T cells and the immunosuppressive role of Tregss further weaken the immune response. Future research aims to enhance immune cell function, restore balance, and improve the tumor microenvironment to increase the effectiveness of immunotherapies.

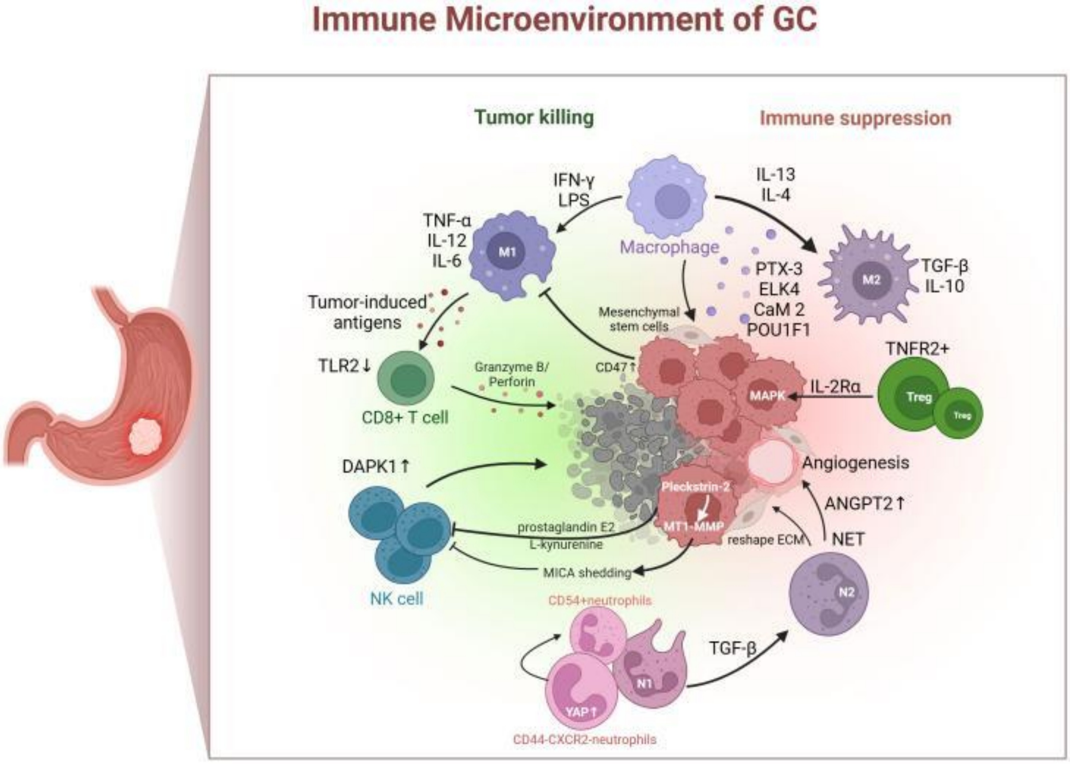

Fig. 2 The TME in GC [1].

4. Non-cellular components of the TME:

Non-cellular components of the TME play a crucial role in supporting cancer development by influencing the behavior of both tumor and immune cells. These elements include various extracellular molecules, signaling factors, and the surrounding matrix that interact with cancer cells, either promoting or suppressing tumor growth. Among these, tumor-associated neutrophils (TANs) and chemokines stand out as key contributors to the dynamic tumor landscape.

TANs, a type of white blood cell commonly involved in immune responses, are often co-opted by cancer cells to aid in tumor progression. In GC, for instance, TANs can enhance the ability of cancer cells to migrate and invade surrounding tissues. This is achieved through mechanisms like the secretion of IL-17a, which activates the JAK2/STAT3 pathway, a key player in promoting EMT — a process that allows tumor cells to become more mobile and invasive [7]. The presence of high TAN levels and their associated pathways in the TME often correlates with poor prognosis, as their activity can accelerate tumor growth and reduce the effectiveness of immune surveillance.

In addition to TANs, chemokines—small proteins responsible for guiding immune cells to sites of inflammation—are also vital non-cellular components of the TME. Two major chemokines, CCL2 and CCL5, have been shown to play important roles in shaping the immune landscape of tumors. CCL2, in particular, is involved in recruiting MDSCs, a group of immune cells known for creating an immunosuppressive environment that shields the tumor from attack by the body's immune system. By fostering such an environment, CCL2 enables tumors to grow unchecked and resist immune-based therapies. In some cancers, like gliomas, the disruption of the CCL2-CCR2 signaling axis has been found to reduce MDSC recruitment, suggesting that targeting this pathway could be a promising therapeutic strategy.

Similarly, CCL5 is another chemokine that has garnered attention for its role in tumor progression. CCL5 is linked to the suppression of anti-tumor immune responses, particularly by inhibiting the activity of cytotoxic T cells and N) cells, both of which are essential for eliminating cancer cells. In many malignancies, elevated CCL5 levels are associated with worse outcomes, as this chemokine aids in the formation of an immune-suppressive TME. By blocking the recruitment of immune cells that could otherwise attack the tumor, CCL5 indirectly supports tumor survival and metastasis.

The interactions between non-cellular components like TANs, chemokines, and immune cells are part of a broader network of signaling events that maintain the tumor's aggressive behavior. For example, the matrix that surrounds tumor cells—composed of collagen, fibronectin, and other structural proteins—can also influence how immune cells respond to the tumor. A dense, fibrous matrix can physically block immune cells from infiltrating the tumor, further enhancing the tumor's ability to evade immune detection. Additionally, molecules secreted by both tumor and immune cells, such as TGF-β, can further modulate the immune response by suppressing the activity of cytotoxic T cells and NK cells, thereby promoting tumor progression.

Overall, non-cellular components of the TME are critical players in the development and persistence of tumors. They not only provide structural support to the tumor but also actively participate in creating an environment that favors tumor growth and immune evasion. Therapeutic strategies aimed at disrupting these non-cellular elements—whether by inhibiting TANs, blocking chemokine signaling, or altering the extracellular matrix—offer promising avenues for improving cancer treatments. By targeting these components, it may be possible to weaken the tumor's defenses and restore the effectiveness of the body's natural immune response against cancer.

5. Relationship between TME and Prognosis of GC

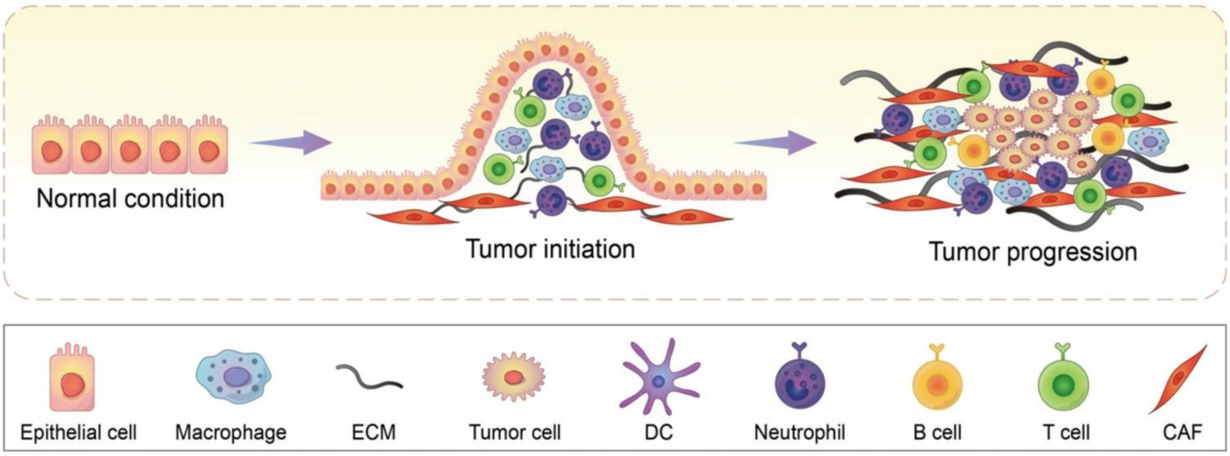

Fig. 3 Dynamic changes of TME in tumor progression [8]

Studies have shown that the type and number of immune cells infiltrated in TME, the activity of CAF, and the degree of remodeling of ECM in patients with GC may affect tumor progression and patient survival. A high density of immunosuppressive cells such as Tregs and MDSCs, are generally associated with a poorer prognosis. These cells secrete various cytokines, chemical factors and enzymes, promote the growth of tumor cells, inhibit anti-tumor immune response, and enhance the invasion and metastasis of tumor cells (Figure 3).

In addition, immune escape mechanisms in GC TME, such as activation of the PD-1/PD-L1 pathway, are also closely associated with poor prognosis. Therefore, targeted therapies targeting TME components may help to enhance the therapeutic outcome and improve the prognosis of patients with GC. This makes TME an important research direction in the treatment of GC, and provides a new idea for the development of personalized treat. The mix of cells and their activities in the tumor's surroundings greatly affects how fast cancer grows and a person's chances of survival. More cells that slow down the immune system, like Tregs and MDSCs, are linked to worse outcomes. Strategies to target these cells and their actions can improve treatment and survival chances for GCpatients.

6. Conclusion

To sum up, TME plays a key role in the occurrence and progression of tumors and the prognosis of patients. Studies have shown that there are a large number of immunosuppressive cells, such as Tregs and MDSCs, in the TME of patients with GC. These cells weaken the anti-tumor immune response by secreting immunosuppressive factors, leading to further proliferation and metastasis of tumor cells. In addition, the activity of CAF and the remodeling degree of ECM are also closely related to the malignant progression of tumors. A high density of immunosuppressive cells and active CAF are generally associated with poorer patient outcomes, further confirming the importance of TME in the course of GC.

In future research and treatment, targeted therapy of TME components may become a key strategy to improve the prognosis of GC patients. For example, inhibitors of the PD-1/PD-L1 pathway, CAF inhibitors, and ECM remodeling modulators have shown promising applications in preliminary studies. These targeted therapies are expected to delay the progression of GC and improve the survival rate of patients by improving the anti-tumor immune response and limiting the invasion ability of tumor cells. However, the complexity and heterogeneity of TME remains a major challenge, and further studies are needed to clarify the specific mechanisms of action of different TME components at different stages of GC.

Future studies should focus on uncovering the molecular mechanism between TME and GC progression, and exploring more precise and personalized targeted therapies. In addition, the multi-disciplinary combined comprehensive treatment strategy will also become an important direction of GC treatment. By integrating immunotherapy, CAF inhibition, ECM regulation and other treatment methods, it is expected to significantly improve the overall treatment effect of GC patients, and further improve their long-term survival rate and quality of life.

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