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Opinion

Immune Modulation Tackles the Challenges Posed by the Tumor Microenvironment in AML

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Abstract

Immune modulation has emerged as a vital strategy to tackle the challenges presented by the Tumor Microenvironment (TME) in Acute Myeloid Leukemia (AML). AML features a very complex and immunosuppressive TME that significantly affects disease progression and treatment resistance. The interaction between leukemic cells and various TME components, including immune cells and stromal elements, creates an environment that promotes immune evasion and tumor survival. Developing effective therapeutic approaches that can boost immune responses against leukemia cells is essential.

Keywords: AML; PD-1; Car T cells; ICI; CTLA-4

Opinion

Acute Myeloid Leukemia (AML) is a form of leukemia that primarily affects adults, with the majority of cases arising in this age group, while diagnoses are less common in children. For the past four decades, first-line chemotherapy has served as the cornerstone of treatment. Despite initial responses to this first-line therapy and the resolution of symptoms for many patients, only a small percentage achieve prolonged survival due to relapses resistant to chemotherapy. Improved survival rates have been noted in patients who undergo allogeneic hematopoietic stem cell transplantation; however, these individuals represent only a small fraction of AML cases, and relapse rates do not appear to decrease with graft-versus-host disease or in patients with active disease. Patients who never attain Complete Remission (CR) or who experience a relapse within six months of achieving CR have a poorer prognosis. Immune surveillance is essential for suppressing tumor growth and maturation. The immune system can identify antigens specific to tumor cells. However, the tumor microenvironment encourages immunosuppressive activities and antigen loss, ultimately resulting in immune evasion [1,2].

It is essential to recognize that Acute Myeloid Leukemia (AML) is defined by a complex and diverse Tumor Microenvironment (TME) that significantly influences the disease's pathophysiology. The microenvironment in the bone marrow of AML includes numerous cellular and molecular elements, such as hematopoietic stem cells, mesenchymal stromal cells, and immune cells like conventional and regulatory T cells, myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages. These components significantly impact the behavior of leukemic cells, along with soluble factors. The interactions among these cells and their surroundings create a supportive niche for leukemia cells, promoting their survival and proliferation [3,4].

Investigating how immunomodulatory macrophages contribute to immunosuppression in acute myeloid leukemia (AML) presents valuable opportunities for enhancing treatment strategies. Macrophages in the bone marrow produce cytokines that help maintain an immunosuppressive environment, hindering effective anti-tumor responses. The interaction between macrophages and T cells is crucial for establishing a Tumor Microenvironment (TME) that promotes the survival and proliferation of leukemic cells. Research has classified macrophages into four subsets: M2a, M2b, M2c, and M2d, each characterized by distinct stimuli and functions. M2a macrophages, primarily activated by IL-4 and IL-13, are involved in immunomodulation, tissue repair, and the phagocytosis of apoptotic cells [5]. They express high levels of mannose receptors, such as CD206, which are linked to angiogenesis and tumor recurrence, particularly in cases like lung metastasis from pancreatic ductal adenocarcinoma. In contrast, M2b macrophages are activated by immune complexes, IL-1β, and TLR agonists such as LPS, and they play a vital role in inducing TH2 cell responses essential for immunity against pathogens and parasites. It is important to note that tumor-associated macrophages exert their immunosuppressive effects by inhibiting macrophage recruitment to

the TME or repolarizing these cells from a pro-tumorigenic M2 phenotype to an anti-tumorigenic M1 phenotype [6,7].

A variety of factors, including cytokines, chemokines, and the presence of tumor cells, influence the polarization of macrophages. Naïve macrophages (M0) identify pathogens and can rapidly polarize into pro-inflammatory (M1) or anti-inflammatory (M2) phenotypes depending on the signals they receive. M1 macrophages are distinguished by their production of pro-inflammatory cytokines and play a vital role in initiating immune responses against pathogens and tumor cells. They exhibit enhanced antigen-presenting capabilities and secrete increased levels of cytokines such as IL-1 and TNF, which can further stimulate the polarization of neighboring macrophages into the M1 state. Conversely, M2 macrophages encourage tumor growth and immune suppression by releasing immunomodulatory factors like IL-10 and TGF-β, which inhibit cytotoxic immune cells such as T cells and NK cells. This dual role complicates the therapeutic targeting of macrophages in cancer treatment, as the balance between M1 and M2 polarization can shift based on the tumor microenvironment and the type of cancer [8,9].

The interaction between macrophages and regulatory T cells (Tregs) is noteworthy. Increased frequencies of TNFR2+ Tregs, which are highly inhibitory, have been observed in AML patients compared to healthy controls. The expansion of these Tregs is linked to TNF-α interaction with TNFR2, demonstrating how macrophages can create a suppressive TME by promoting Treg development and activity. Additionally, dendritic cells (DCs) in the bone marrow microenvironment can produce pro-inflammatory cytokines like IL-1, which supports the expansion of leukemic cells. These DCs often express various inhibitory receptors and ligands, such as PD-L1, further promoting an immunosuppressive environment that facilitates tumor progression [10,11].

Conclusion

Given the critical role of macrophages in regulating immune responses in AML, future research should focus on clarifying the specific signaling pathways involved in macrophage immunomodulation. Understanding these mechanisms may lead to new therapeutic options that enhance the effectiveness of treatments aimed at reversing the immunosuppressive environment typical of AML. Targeting macrophage functions and their interactions with other immune cells can improve clinical outcomes for patients with AML and boost the effectiveness of immunotherapies. Additionally, ongoing research is crucial to shed light on the mechanisms of macrophage activity and identify effective strategies for modulating their behavior within the tumor microenvironment. Considering the complexities of macrophage polarization and the immunosuppressive environment it can create further studies are necessary to explore the combination of macrophage-targeted therapies with existing treatment modalities to optimize patient outcomes in AML.

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