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Suppressed Factors to CD8+ Cytotoxic T Lymphocytes in Cancer Immunotherapy

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Abstract:

Cancer is a disease with a very high fatality rate. immunotherapy is a promising way to treating cancers, of which CTLs are important for the host immune system against tumor, directly killing tumor cells. However, the relative immunotherapy is limited by many factors that suppress the function and activity of CD8+ CTLs. This review aims to study the mechanisms by which CD8+ CTLs are suppressed in the tumor microenvironment. By collecting preclinical and clinical studies, this paper summarized the main factors that suppress CD8+ CTLs including the following factors: immune cells like regulatory T cell (Tregs), tumor-associated macrophage (TAM), myeloid-derived suppressor cells (MDSCs); metabolic factors like hypoxia, lactic acid accumulation, glucose competition, and immune checkpoints molecules (ICM) PD-1 and CTLA-4. The complex mechanisms of suppressing CD8+ CTLs in the tumor microenvironment are discussed in these findings, which may give clues to the relative treatment and help overcome these suppression effects on CD8+ CTLs in tumorigenesis.

Keywords: Factors; CD8+ cytotoxic T lymphocytes; Immunotherapy.

1. Introduction

Cancer immunotherapy has evolved from a vision into an integral component of cancer treatment, based on the fundamental principle of harnessing the original immune system of patient to eliminate malignant tumors within the body. Many mechanisms included developing immune checkpoint inhibitors, vaccine-induced immune response against tumors have been widely used in the treatment of tumors. Especially, the discovery of CTLs‘ key roles in the process of immune resistance makes it an effective strategy for anti-cancer therapeutic schedule. CTLs can recognize antigenic peptides presented by MHC class I molecules and then eliminate the target cells. Once they encounter antigen-presenting tumor cells, the activated cytotoxic T cells proliferate and differentiate into mature cytotoxic T cells. Activated cytotoxic T cells will release cytokines such as granzymes and perforin that induce cell death and killing of intracellular antigens in target cells. Furthermore, cytotoxic T cells have the capability to secrete cytokines, including IFN-γ and TNF-α, thereby amplifying the immune response.However, their ability to

destroy cancer cells is inhibited by the factors within the tumor environment, such as the abnormal multiplying of immune checkpoints and the fierce competition for nutrients in the tumor microenvironment [1,2].

Cancer immunotherapy has an important problem, which is resistant to treatment. One of the main reasons for resistance to immunotherapy is the existence of immunosuppressive network in the TME environment. TME contains various kinds of cells and liquids that are immune function. They can support tumor immunity through interactions and escape from antitumor effects. Various immune cells within TME, such as Tregs, TAMs, MDSCs and other immune related cytokines, etc., may have abilities to inhibit or impair cytotoxic CD8+ T cells (CTLs) immune functions. Although they are indispensable elements in normal human immune system, their capacity to restrict immune regulation functions with respect to anti-tumour immunity are the reasons responsible to result in failure of chemotherapy or antitumor treatment. Moreover, the physiological changes like hypoxia and accumulation of lactic acid and so on in terms of metabolism. Another form of resistance may involve the presence of ICM, which participate in inhibiting immune responses during antitumor processes, or their expression on certain immune cells. Therefore, it is extremely important for us to know what inhibits CTLs within TME and improve the corresponding strategies in immunotherapy, hence based upon the information form relevant literature above. To explore these points, this article aims to find those suppressed facts in regard to the CTLs function in TME. As a consequence, we are going to discuss in three aspects above, one is about immune cells, another is about the metabolic factors, last is about immune checkpoint molecules [1,3].

Finally, this paper aims to find the relative suppressed facts impacting the CTLs function in TME, which will unfold from three directions what discussed above, immune cells, Metabolic factors and immune checkpoint molecules.

2. Suppressed Factors in the Tumor Microenvironment

2.1 Immune Cell-Mediated Suppression

2.1.1 Regulatory T cells

Tregs are critically important for maintenance of immune homeostasis, yet they also contribute substantially to immunosuppression within the tumor microenvironment. These cells carry out their inhibitory functions, trough the secretion of immunosuppressive cytokines such as TGF-β and IL-10. By suppressing the expression of essential effector molecules, such as perforin and granzyme B, TGF-β acts as a strong inhibitor of the proliferation and functional activity of CTLs. Furthermore, Tregs can engage in direct cell-to-cell contact with CTLs, resulting in the induction of apoptotic pathways. A notable example is the interaction between CTLA-4 expressed on Tregs and B7 molecules present on APCs, which inhibits T cell activation and consequent impairment of CTL-mediated cytotoxicity. In addition, Tregs can alter the metabolic landscape by competing for crucial nutrients such as glucose and arginine, thereby limiting energy availability and compromising the effector functions of CTLs. Elevated frequencies of Tregs within the TME have been consistently correlated with poor clinical outcomes across multiple cancer types, underscoring their pivotal role as major suppressors of anti-tumor immunity [4].

2.1.2 Tumor-associated macrophages

TAMs are a highly diverse group of immune cells that tend to adopt an immunosuppressive phenotype in TME. TAMs are broadly categorized into two main subsets: the common activated M1 macrophages with anti-inflammation function and the alternatively activated M2 macrophages, which promote immunosuppression and facilitate tumor progression. Within the context of cancer immunotherapy, it is the M2-polarized TAMs that have been most strongly implicated in inhibiting CTL function through multiple strategies. TAMs secrete large amounts of inhibitory cytokines (e.g., TGF-β and various interleukin) that directly suppress the proliferation and cytotoxic activity of CTLs. In addition, TAMs frequently exhibit high levels of ICM, including PD-L1. When PD-L1 is engaged with PD-1‘s receptor on CTLs, there is a state of T cell exhaustion and functional impairment. Beyond these mechanisms, TAMs also modulate TME by contributing to angiogenesis and facilitating the remodeling of the extracellular matrix, processes that ultimately support immune evasion and reinforce the overall immunosuppressive nature of the TME [5].

2.1.2 Myeloid-derived suppressor cells

MDSCs are another kind of immature cells from marrow that can be further subdivided into two principal cells: monocytic MDSCs and granulocytic MDSCs, each employing distinct immunosuppressive mechanisms. MDSCs suppress CTL activity by producing reactive oxygen species (ROS) and the enzyme arginase-1. The ROS can inflict direct damage on CTLs and disrupt their functional, while arginase-1 depletes arginine, which is essential for CTLs’ multiplying and effector function. Additionally, MDSCs are capable of secreting immunosuppressive cytokines similar to Tregs and M2, which not only promote

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the survival and proliferation of MDSCs but also enhance their inhibitory capabilities. Moreover, MDSCs can also interact with other immune cells, such as dendritic cells (an APC) and natural killer cells, further modulating the anti-tumor immune response [6].

2.2 Metabolic Factors

This section will focus on two key metabolic conditions within the tumor microenvironment—hypoxia and lactic acid accumulation—both of which significantly diminish energy availability and impair the function of CTLs.

2.2.1 Hypoxia

Hypoxia is a common and consequential characteristic of the TAM that exerts profound effects on CTL function. When oxygen tension is low physiological standard, tumor cells contribute to the multiplying of expression of HIF-1α, resulting in adaptive responses that help promote tumor survival and progression. One of the most critical consequences of hypoxia is its disruptive impact on CTL metabolism. Specifically, hypoxia reduces mitochondrial oxidative phosphorylation, forcing CTLs to rely predominantly on anaerobic glycolysis—a far less efficient pathway for energy production. This metabolic shift results in diminished ATP output and a corresponding reduction in effector responses, including impaired cytokine secretion and weakened cytotoxic capacity. Hypoxia not only affects the energy supply within the TME, but also drives the upregulation of ICM, such as PD-L1, on both tumor cells and other immune cells within the microenvironment, thereby exacerbating T cell exhaustion and functional decline. Furthermore, hypoxic conditions affect the recruitment and activation of relative cells within TME, such as Tregs and MDSCs mentioned above, resulting in a immunosuppressive milieu that severely impairs CTL-mediated anti-tumor immunity [7].

2.2.2 Lactic acid accumulation and glucose competition

The accumulation of lactic acid, another hallmark of the tumor microenvironment, significantly impairs CTL function. The Warburg effect, a phenomenon where tumor cells still preferentially use glycolysis to metabolize glucose even through within sufficient oxygen, that commonly occurs in the TME, eventually causing significant production and secretion of lactic acid into the extracellular environment. Lactic acid has a direct impact on T cell metabolism by inhibiting crucial glycolytic enzymes, including pyruvate kinase M2, which is essential for glycolysis and energy generation. This results in a significant decrease in energy supply and compromised effector performance for CTLs. This metabolic side-product also promotes the expression of ICM, on the surface of CTLs, thereby accelerating the process of T cell exhaustion. Likewise, lactic acid enhances overall immunosuppression by recruiting and activating inhibitory immune cell populations. Moreover, due to the Warburg effect, tumor cells consume glucose at an exceptionally high rate, directly competing with CTLs for this vital resource. Since CTLs require glucose to sustain their energy metabolism and perform effector functions—such as cytokine production and target cell killing—this intense competition effectively starves CTLs of fuel, significantly undermining both their metabolic health and functional efficacy [8].

2.3 Immune Checkpoint Molecules

The third section will discuss two immune checkpoint molecules known to regulate CTL function.

2.3.1 PD-1/PD-L1

It represents a central immune checkpoint pathway that plays a fundamental role in suppressing CTL function within the tumor microenvironment. Absolutely all of T cells, including CTLs, express and produce the PD-1 as a trans-member receptor, while its ligand, PD-L1 is regularly expressed on the APCs, which is the significant consistence of immune regulation. Their combination triggers a series of intracellular signaling events that ultimately inhibit T cell activation and impair effector functions. More specifically, this interaction downregulates the expression of key effector molecules, such as perforin and granzyme B, and reduces the secreting of anti-inflammatory cytokines, including IFN-γ and TNF-α. This mechanism prevents the excessive activation of T lymphocytes in normal human tissues, but tumor cells also utilize the abundant ligands present on their surface to inhibit the function of CTLs. Moreover, T cell exhaustion occurs when PD-1/PD-L1 interaction, which leads to the progressive loss of T cell effector capacity, the expression of multiple inhibitory receptors, and finally failure to eliminate the tumor cells. The critical importance of PD-L1 pathway as a mechanism of immune evasion has been highlighted, whose abnormal increase is usually regarded as passive prognosis in a variety of cancers in clinic therapy. The measure of cancer immunotherapy has been revolutionized by the therapeutic targeting of this pathway through immune checkpoint inhibitors, which has demonstrated remarkable clinical efficacy in some patients, especially in the treatment of solid tumors [9].

2.3.2 CTLA-4

It is another common ICM that significantly suppresses CTL function within the tumor microenvironment. Activated T cells, such as CTLs, have CTLA-4 on the surface

and it can bind to B7 molecules on APCs, which can also bind with another membrane receptor, CD28. In contrast to the activating signals delivered by CD28, the engagement of CTLA-4 with B7 molecules transduces potent inhibitory signals that lead to the downregulation of CLTs' activation and normal physiology function. Specifically, CTLA-4 signaling inhibits the proliferation and cytokine production of CTLs and concurrently promotes the induction and expansion of Tregs, thereby further enhancing immunosuppression within the TME. Beyond its direct effects on T cells, CTLA-4 can also modulate the function of APCs by downregulating the production of co-stimulatory molecules and inducing the secretion of immunosuppressive cytokines such as IL-10. The role of CTLA-4 in suppressing anti-tumor immunity has been extensively documented, and the use of immune checkpoint inhibitors targeting CTLA-4 has yielded promising clinical outcomes across various cancer types. For example, Ipilimumab, a inhibit targeting CTLA-4 medicine, is prescribed as a single drug or in combination with nivolumab(PD-1 inhibitor monoclonal antibody) for the treatment of melanoma patient [10].

3. Limitation

This review included the most directions but also has several limitations. First, the range of analysis is restricted to three primary categories of suppressive factors—immune cells, metabolic factors, and immune checkpoint molecules—potentially overlooking other critical regulators of CD8+ CTL function in TME. The influence of cancer-associated fibroblasts (CAFs) on stromal cells, which can resist CTLs from invading tumor tissues and decrease their impact on eliminating tumor cells. Additionally, the heterogeneity of patient cohorts including variations in cancer type, stage, and prior treatment history, reduces the generalizability of conclusions regarding the relative importance of specific suppressive factors across diverse malignancies. Within the recent tumor treatment, the personalized therapeutic schedule becomes increasingly prevalent, which can efficiently reply heterogeneity of tumor tissue. Third, the interplay between the identified suppressive factors is not extensively explored. The TME is a dynamic ecosystem where immune cells, metabolic stressors, and checkpoint molecules interact synergistically. For example, hypoxia-driven PD-L1 upregulation in TAMs or MDSC-mediated arginine depletion exacerbating CTL exhaustion. During the clinic treatment, the combined treatment that therapeutic schedule regarding many-sided factors is usually. Fourth, the review focuses predominantly on well-characterized factors (e.g., PD-1/PD-L1, Tregs cell) while emerging pathways (e.g., LAG-3, TIM-3, or metabolic checkpoints like adenosine signaling) are absent. Rapid advancements in immunology continue to uncover suppressors and the likely new type therapy schedule can be benefit to patient. In summary, while this review provides a foundational overview of key CD8+ CTL suppressive mechanisms, its only focus on basic pathways, lack of clinical data, and limited analysis of interaction influence in TME [11].

4. Conclusion

The efficacy of immunotherapy is often limited by various suppressive factors present within TME. This review listed and simply analyzed the major factors contributing to CD8+ CTLs suppression, including immune cell-mediated mechanisms, metabolic alterations, and immune checkpoint molecules. At the cellular level, TAMs(M2) and MDSCs were identified as key immune cell populations that inhibit CD8+ CTLs function through diverse mechanisms such as immunosuppressive cytokine secretion and metabolic competition. Additionally, metabolic factors such as hypoxia, lactic acid accumulation, and glucose competition significantly impair the functional capacity of CD8+ CTLs by disrupting their energy metabolism. Moreover, both of above levels are associated to the final factor, ICM, which were also found to participate in directly suppressing CTLs signaling and function. While the review already need to enrich, existing content has summarize the dominating factors. A thorough understanding of the inhibitory factors to CTLs in the tumor microenvironment will be benefit to more effectively identify relevant treatment methods in future research and studies.

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