Proceedings of the 3rd International Conference on Modern Medicine and Global Health
DOI: 10.54254/2753-8818/69/2025.19915

Blocking PD-1 and Tim-3 Pathways to Overcome CD8+ T Cell Exhaustion and Enhance Cancer Immunotherapy Efficacy

Yuhan Zhang[1,a,*]

[1]*School of 120 senior school, Shenyang, China*
a. ZYH080723@outlook.com
**corresponding author*

Abstract: Although significant progress has been made in cancer immunotherapy in recent years, its overall efficacy remains limited in a large number of patients. The interaction between the tumor microenvironment (TME) and CD8+ T cells is one of the core topics in cancer immunotherapy research. CD8+ T cells can play an anti-tumor role by recognizing and killing virus-infected or mutated cells. However, in the TME, as the tumor compresses immune cells, the function of them is impaired, and studies have found that relying on PD-1 alone is not enough to resist tumor cells. Therefore, by blocking the PD-1 and Tim-3 pathways to interfere with CD8+ T cell exhaustion (TEX), the performance of CD8+ T cells can be maximized, their survival period extended, and the efficacy of positive cancer immunotherapy improved. For patients with cancer who have failed to respond to immune checkpoint inhibitors as monotherapy, multi-targeted combination therapy may achieve better results.

Keywords: Tumor microenvironment, $CD8^{+}$T cell exhaust, PD-1, TIM-3.

1. Introduction

The interaction between tumor microenvironment (TME) and CD8+T cells is one of the core contents of cancer immunotherapy research, and CD8+T cell depletion is one of the main reasons for immunotherapy failure [1]. TME is a complex mixture of cells, including tumor cells, immune cells, stromal cells, and blood vessels, which together affect tumor growth, survival, and response to therapy. CD8+ T cells, which are key to weakened immune mechanisms, play an anti-tumor role by recognizing and killing cells that have been infected or mutated by viruses. In a mouse infection model, its depletion was first identified with lymphocytic choriomeningitis virus (LCMV) [2]. However, its depletion not only occurs in chronic LCMV infection, but is also closely related to the occurrence and development of malignant tumors [3]. This is attributed to the fact that in TME, as the tumor presses on the immune cells, the function of CD8+ T cells is impaired, inhibiting their activity, resulting in the creation of immune escape mechanisms. A major obstacle is that it depletes the energy of tumor antigen-specific CD8+T cells to infiltrate lymphocytes (TILs), and leads to depletion of them that are unable to intervene in tumor cell invasion, leading to tumor progression. Recently, some studies have explored the role, depletion, immune escape mechanism of CD8+ T cells and the combination treatment plan, and it has been found that PD-1 alone is not enough to resist

DOI: 10.54254/2753-8818/69/2025.19915

tumor cells, so it is possible to interfere with CD8+ T cell depletion (TEX) by blocking the PD-1 and Tim-3 pathway together, which can maximize its performance. Prolonging their survival and improving the efficacy of aggressive cancer immunotherapy.

Therefore, this article discusses in depth that CD8+T cells play an important role in fighting infections and tumors, but they may also cause immune escape through multiple mechanisms. These mechanisms will be associated with combination therapy and personalized case support, which is the cornerstone of research and development of new immunotherapy countermeasures, providing new strategies and new programs for tumor treatment. This review focuses on the research on CD8+ TEX induced immune escape and the combined blocking of PD-1 and Tim-3 pathway to improve T cell activity.

2. CD8+T cells play a role in TME by forming TME between TILs and extracellular matrix

In TME, CD8+T cells can exert anti-tumor immune effects and play their role. They infiltrate into tumor tissues and can exert therapeutic effect [4]. Due to the complex components of TME, many barriers need to be overcome for immune cells to infiltrate tumor tissues. Among them, the dense fibrous interstitium generated by extracellular matrix deposition in TME envelops tumor tissue, forming a high-density and high-hardness physical barrier that hinders the infiltration of immune cells [5]. Meanwhile, in the TME, there are many fibroblasts (CAFs) that can lead to cancer. CAFs can secrete matrix metalloproteinases to rebuild the ECM and release some chemokines, growth factors, and angiogenic factors to promote tumor metastasis to other safe places [6], thus playing a protective role. Additionally, the TME has an inhibitory effect, which makes it harder for immune cells to penetrate into the TME. CD8+T cells need to overcome both the physical barriers and various chemokines and their receptors to migrate to the TME. Furthermore, CD8+T cells mediate tumor rejection by recognizing and directly killing tumor cells. These cells can recognize tumor antigens and directly kill transformed cells, but TILs are often rendered inactive due to interactions with growing tumor cells and the TME. This functional impairment leads to changes in transcription, function, and phenotype, reducing the host's ability to eliminate tumors.

Therefore, CD8+T plays a lot and important role in TME, which plays a protective role in the internal structure. Its cellular functional state shows significant inhibition in TME, and its interaction with other immune cells is crucial to its function. Studying its role in TME is of great significance for the development of more effective cancer immunotherapy strategies in the future.

3. CD8+ TEX process

3.1. Main features of CD8+TEX

In several diseases that seriously harm the body and even lead to death, CD8+T cell depletion occurs due to multiple factors, which is a complex process involving high expression of inhibitory receptors, metabolic dysregulation, epigenetic changes, and interactions between intrinsic and extrinsic factors. As shown in Figure 1, abnormal differentiation of cells in the TME is often caused by a sustained antigen load, ultimately leading to PD-1-induced CD8+T cell depletion. CD8+TEX state is a high expression of PD-1 state, which is characterized by increased expression of co-inhibitory receptors (including Tim-3, Lag-3, etc.) and reduced cytokine secretion, which is affected by changes in the expression of adhesion and migration-related genes, metabolic and biological function defects [7].Once CD8+T cells become exhausted and enter the PD-1hi state, the epigenetic changes during the exhaustion process will force the cells to differentiate back to the PD-L1lo state. Meanwhile, the anti-tumor response promoted by anti-PD-1 is derived from the expansion of the CD8+TEX subpopulation, ultimately leading to maximum cell apoptosis. Additionally, IRs can be temporarily

DOI: 10.54254/2753-8818/69/2025.19915

expressed in increased amounts during CD8+T cell activation, and PD-1 is usually co-expressed with TIM-3, LAG-3, and CTLA-4 in exhausted T cells' IRs. Furthermore, continuous antigen stimulation is sufficient to drive CD8+ T cell exhaustion. Therefore, in chronic viral infections, PD-1 or TIM-3 do not play a role in this process [8].

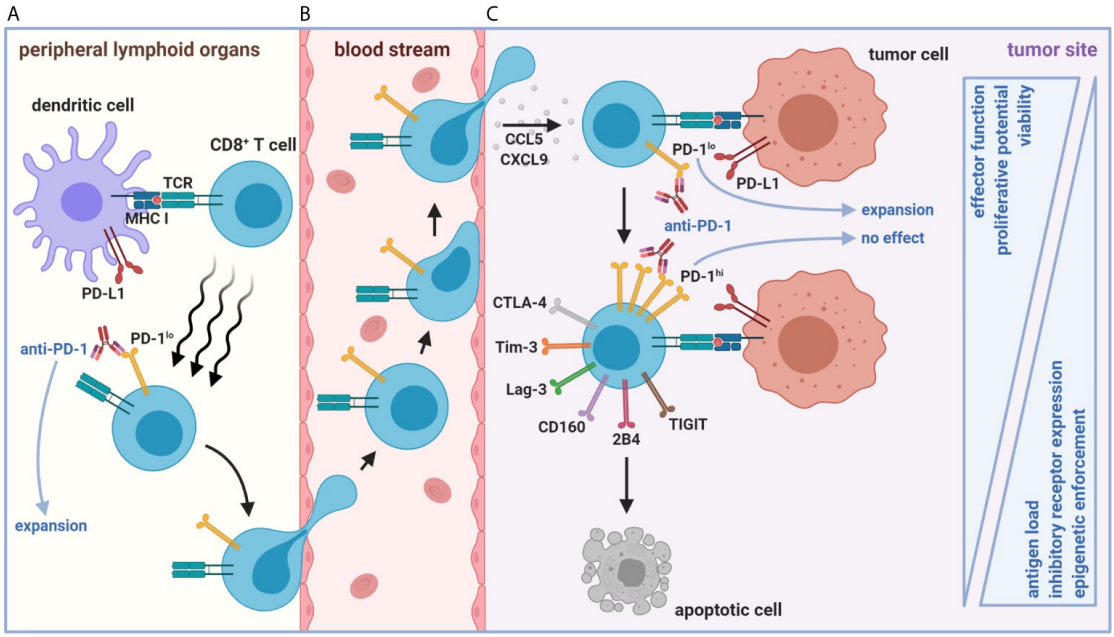

Figure 1: The CD8+TEX feature [9].

3.2. The progress of T cell exhaustion research

To date, tumor-specific CD8+T cells undergo exhaustion in the long-term presence of T cell antibody stimulation. Initially, restoration of them was effective, leading to a sudden increase in cell numbers, but IRs on them began to persistently high-express in response to persistent antigen stimulation, while cell function declined and transcription factor expression changed [9,10]. Research has shown that in a liver cancer mouse model [10], CD8+T cells were found to be in a state of exhaustion even before cell division, which suggests that long-term antigen stimulation does not fully explain CD8+TEX. This research also found that normal cells from mice with no tumors were rapidly exhausted when transplanted into mice with tumors, indicating that the negative regulatory signals from the tumor host can cover the epigenetic program of CD8+T cells, thereby promoting CD8+TEX, which is of great significance for exhaustion-based T cell therapy [10,11].

Therefore, CD8+ TEX is a complex multifactorial process involving continuous antigen exposure, metabolic reprogramming, and upregulation of inhibitory receptors, among other factors. These studies help overcome exhaustion and provide an important foundation for developing immune therapies targeting exhausted CD8+ T cells.

4. Immune evasion mechanisms and immunotherapy

4.1. Main causes of immune evasion

TME-induced CD8+T cell exhaustion is the main reason for tumor immune evasion, leading to the loss of partial function and immune evasion of T cells. These cells are regulated by T cell surface IRs, immune regulatory cell populations (such as Tregs, MDSCs, IFN-I, IL-2, and IL-7, etc.) collectively[8]. Studies have shown that, due to continuous pressure from cancer cells in the TME, T

DOI: 10.54254/2753-8818/69/2025.19915

cells are suppressed, leading to impaired killing power, thus enabling it to evade the immune system's pursuit [12]. One important pathway is through the activation of IRs. The study also found that, under normal circumstances, it can lower or prevent self-immune evasion through immune checkpoints (ICs), but in malignant tumors, these ICs can downregulate cell activity by inhibiting T cell-cancer cell interactions, thereby causing immune evasion.

4.2. Limitations of monotherapy

CD8+T cell exhaustion will result in immunotherapy being limited to short-term treatment, which is one of the important mechanisms of tumor immunotherapy [1,7]. The inability of anti-PD-1 monotherapy to fully restore exhausted T cell function is due to the involvement of other inhibitory molecules in CD8+TEX. In addition to the persistent expression of IRs, exhausted them have been shown to have impaired effector function and proliferation capacity, as well as metabolic defects such as glycolytic inhibition, lipid metabolism dysregulation, and mitochondrial dysfunction [13].These metabolic changes will further promote the depletion of CD8+T cells, and render immunotherapy ineffective. Some studies have shown that lipid peroxidation is caused by chronic inflammatory cytokine IFNI, and that this cytokine further accelerates the depletion of CD8+T cells, causing them to lose their own function and immune activity [14]. Research has shown that in mice with liver cancer treated afterward, the survival rate of WT mice treated with either anti-PD-1 or anti-IFNAR-1 monotherapy did not improve, while the survival rate of mice treated with anti-PD-1 combined with anti-IFNAR-1 therapy was significantly prolonged [15]. The above research results further demonstrate the diversity of the role of inflammatory cytokine IFN-I in promoting CD8+T cell exhaustion, but cannot fully confirm the extent to which IFN-I functions, but it does provide a new perspective for future combined treatment.

5. Combined blockade therapy

5.1. Feasibility of combining PD-1 and Tim-3 for CD8+TEX treatment

Lung cancer is a common malignant tumor, and the cure rate is very low. Immunotherapy can significantly prolong the overall survival of advanced patients, but it is not a cure-all. Many studies have shown that CD8+T cell function disorder is a key factor in the treatment of lung cancer. In lung cancer immunotherapy, some researchers have found that CD8+T cells on the surface of IRs such as PD-1, TIM-3 and LAG-3 express increased levels [12, 16]. In the TME, chronic exposure to tumor antigens leads to upregulation of LAG-3, which suppresses the function of CD8+T cells, thereby preventing immune cells from killing tumor cells [14]. This study also found that TIM-3 expression increased in tumor-infiltrating lymphocytes (TILs) after resistance to anti-PD-1 or PD-L1 therapy and that the expression of TIM-3 in CD8+T cells in pleural effusions from patients with PD-L1-negative lung adenocarcinoma who had developed resistance to anti-PD-1 or PD-L1 therapy was significantly higher than that in patients who had not received their therapy or had undergone surgery. These studies suggest that abnormal activation of TIM-3 is a feasible approach to blocking LAG-3 and TIM-3 signaling pathways, which can improve the efficacy of anti-PD-1 or PD-L1 therapy. Therefore, this strategy of enhancing the specific function of CD8+ T cells to counter immune evasion in the TME not only provides a new therapeutic target but also opens up new avenues for the development of cancer immunotherapy.

Therefore, the exhaustion of CD8+T cells in TME is associated with metabolic dysfunction and sustained high expression of IRs, but this is also the key to treating it. After anti-PD-1 therapy, although high expression was still observed, there was a marked improvement after anti-TIM-3 therapy. Therefore, this provides a reference for the treatment strategy of jointly blocking the PD-1 and Tim-3 pathways to improve the functional state of CD8+T cells. It is hoped that this can provide

DOI: 10.54254/2753-8818/69/2025.19915

a solid foundation for anti-tumor immunotherapy and increase the probability of tumor treatment success by 1%.

6. Conclusion

This study conducted a correlation analysis between CD8+TEX and immune evasion mechanisms, and the results showed that exhaustion of CD8+ T cells with anti-PD-1 could only temporarily promote cell proliferation, and over time could even lead to complete exhaustion of the cells. During this period, the expression of inhibitory receptor TIM-3 was upregulated, which indicated that a combination of anti-PD-1 and TIM-3 was the optimal solution. In summary, this study shows that CD8+ T cell exhaustion followed by anti-PD-1 negative ICs with high expression or co-expression leads to an increase in the proportion of exhausted T cells, which negatively regulates cellular immunity (TIM-3). The synergistic effects of ICs may be involved in the development of tumors, and dynamic monitoring of lymphocyte subpopulations and ICs levels in cancer patients may have important clinical value for immunotherapy. For cancer patients who have failed to respond to immune checkpoint inhibitors as monotherapy, multi-targeted combined therapy may achieve better results.

References

[1] *Mortezaee, K., & Majidpoor, J. (2023). Mechanisms of CD8+ T cell exclusion and dysfunction in cancer resistance to anti-PD-(L)1. Biomedicine & Pharmacotherapy, 163, 114824.*

[2] *Chow, A., Perica, K., Klebanoff, C. A., et al. (2022). Clinical implications of T cell exhaustion for cancer immunotherapy. Nature Reviews Clinical Oncology, 19(12), 775–790.*

[3] *Sakuishi, K., Apetoh, L., Sullivan, J. M., et al. (2010). Targeting Tim-3 and PD-1 pathways to reverse T cell exhaustion and restore anti-tumor immunity. Journal of Experimental Medicine, 207(10), 2187–2194. https://doi.org/10.1084/jem.20100643*

[4] *Verdon, D. J., Mulazzani, M., & Jenkins, M. R. (2020). Cellular and molecular mechanisms of CD8+ T cell differentiation, dysfunction, and exhaustion. International Journal of Molecular Sciences, 21(19), 7357.*

[5] *Galluzzi, L., Chan, T. A., Kroemer, G., Wolchok, J. D., & López-Soto, A. (2018). The hallmarks of successful anticancer immunotherapy. Science Translational Medicine, 10(459), eaat7807.*

[6] *Saw, P. E., Chen, J., & Song, E. (2022). Targeting CAFs to overcome anticancer therapeutic resistance. Trends in Cancer, 8(7), 527–555.*

[7] *Cheng, H. C., Ma, K. L., Zhang, L. J., et al. (2021). The tumor microenvironment shapes the molecular characteristics of exhausted CD8+ T cells. Cancer Letters, 506, 55–66.*

[8] *Kurachi, M. (2019). CD8+ T cell exhaustion. Seminars in Immunopathology, 41(3), 327–337.*

[9] *Dolina, J. S., Van Braeckel-Budimir, N., Thomas, G. D., & Salek-Ardakani, S. (2021). CD8+ T cell exhaustion in cancer. Frontiers in Immunology, 12, 715234.*

[10] *Rudloff, M. W., Zumbo, P., Favret, N. R., et al. (2023). Hallmarks of CD8+ T cell dysfunction are established within hours of tumor antigen encounter before cell division. Nature Immunology, 24(9), 1527–1539.*

[11] *Pang, B.-Y., Wang, J., & Han, Y. (2023). Research progress on the occurrence and characteristics of CD8+ T cell exhaustion and its relationship with immunotherapy resistance in cancer. Chinese Journal of Clinical Oncology, 50(23), 1217–1220.*

[12] *Alausa, A., Lawal, K. A., Babatunde, O. A., et al. (2022). Overcoming immunotherapeutic resistance in PDAC: SIRPα-CD47 blockade. Pharmacological Research, 181, 106264.*

[13] *Li, F., Liu, H. L., & Zhang, D., et al. (2022). Metabolic plasticity and regulation of T cell exhaustion. Immunology, 167(4), 482–494.*

[14] *Chen, W. X., Teo, J. M. N., Yau, S. W., et al. (2022). Chronic type I interferon signaling promotes lipid-peroxidation-driven terminal CD8+ T cell exhaustion and curtails anti-PD-1 efficacy. Cell Reports, 41(7), 111647. https://doi.org/10.1016/j.celrep.2022.111647*

[15] *Yu, R. R., Zhu, B., & Chen, D. G. (2022). Type I interferon-mediated tumor immunity and its role in immunotherapy. Cellular and Molecular Life Sciences, 79(3), 1–24.*

[16] *Qian, F. F., & Han, B. H. (2020). Mechanisms of resistance to immune checkpoint inhibitors and strategies to reverse drug resistance in lung cancer. Chinese Medical Journal, 133(20), 2444–2455.*