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CD8+ T Cell Exhaustion and Tumor Immune Checkpoint Blockade: Mechanisms, Heterogeneity, and Combination Intervention Strategies

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Abstract

CD8+ T cells are the core effector cells in anti-tumor immunity, but under continuous tumor antigen stimulation and inhibitory microenvironment, they gradually enter a state of dysfunction, showing reduced effector secretion, decreased proliferation, persistent expression of inhibitory receptors, and abnormal metabolic adaptation, which are driven by a unified transcriptional, epigenetic, metabolic, and microenvironmental exhaustion program. T cell exhaustion is a major reason why immune checkpoint blockade (ICB) therapy has limited effectiveness and also a key target for combination treatment strategies. In recent years, single-cell sequencing, spatial transcriptomics, and functional immunology studies have shown that exhausted T cells are not a single state-they include heterogeneous subgroups such as progenitor exhausted T cells (Tpex), intermediate exhausted T cells, and terminal exhausted T cells. Blocking PD-1/PD-L1 and CTLA-4 can partly restore T cell function, but primary and secondary resistance are still common. This article reviews the unified mechanisms of CD8+ T cell exhaustion and, organized around the axis of 'mechanism–heterogeneity–ICB response–combination strategies', explores potential strategies for immune checkpoint blockade related to CD8+ T cell exhaustion, and also discusses biomarkers and future research directions.

Keywords: CD8+ T Cells; T Cell Exhaustion; Immune Checkpoint Blockade; Tumor Microenvironment; Immunotherapy

1. Introduction

Tumor immunotherapy, especially with immune checkpoint inhibitors, has changed the treatment landscape for many types of cancers (Pardoll, 2012; Topalian et al., 2015).PD-1/PD-L1 blockade, CTLA-4 blockade, and CAR-T cell therapy have shown significant clinical benefits in melanoma, non-small cell lung cancer, Hodgkin lymphoma, and blood cancers (June et al., 2018;

Sharma & Allison, 2015).However, only some patients are able to achieve a lasting response, and most solid tumors still have primary or secondary resistance. Increasing evidence suggests that $CD8^+$ T cell exhaustion is one of the key factors limiting anti-tumor immune responses and the effectiveness of ICB.Increasing evidence suggests that $CD8^+$ T cell exhaustion is one of the key factors limiting anti-tumor immune responses and the effectiveness of ICB (Chow et al., 2022; Dolina et al., 2021; Raskov et al., 2021).

T cell exhaustion was first systematically described in chronic viral infections, and was later found to also exist in tumors, autoimmune conditions, and chronic inflammatory environments (Ahmed & Gray, 1996; Wherry & Kurachi, 2015).Unlike memory T cells formed after acute infections, exhausted T cells can still recognize antigens, but their proliferation, cytokine secretion, and cytotoxic functions are significantly impaired, and they express high levels of multiple inhibitory receptors. This article aims to review the key mechanisms of $CD8^+$ T cell exhaustion and, in light of the latest advances in tumor immunotherapy, explore potential strategies to overcome exhaustion.

2. Literature Search Strategy and Scope

A comprehensive literature search was conducted in PubMed, Web of Science, and Scopus databases up to October 2026. The search terms included combinations of "$CD8^+$ T cell exhaustion," "immune checkpoint blockade," "tumor microenvironment," "Tpex," "epigenetic regulation," and "combination therapy." Articles published in English were prioritized.

Regarding the IL-17 pathway, although it plays a complex and context-dependent role in tumor immunity, it is not a canonical driver of the CD8+ T cell exhaustion program and its role in immune checkpoint blockade resistance remains controversial. Therefore, the IL-17 pathway is not included within the core scope of this review, so as to maintain focus on the established transcriptional, epigenetic, metabolic, and microenvironmental exhaustion axes. Its potential involvement in tumor microenvironment remodeling may be explored in future studies.

3. The Unified Exhaustion Program of $CD8^+$ T Cells

T cell exhaustion refers to a state where T cells progressively lose their function due to continuous antigen stimulation and inflammatory signals. Its typical features include reduced production of IFN-γ, TNF-α, and IL-2, decreased expression of granzyme B and perforin, weaker proliferation ability, and co-expression of inhibitory receptors like PD-1, TIM-3, LAG-3, and TIGIT(Wherry & Kurachi, 2015; Wherry et al., 2007).Exhaustion isn't just simple 'functional silence'; it's a stable state maintained by a combination of transcription, epigenetics, and metabolism.

In tumors and chronic infections, CD8 T cells can differentiate into precursor exhausted T cells (Tpex), intermediate exhausted T cells (Giles et al., 2022; Zheng et al., 2021), and terminal exhausted T cells. Tpex usually express TCF1, SLAMF6, and PD-1, retaining the ability to self-renew and differentiate into effector cells, making them an important source of cells that respond to ICB; whereas terminally exhausted T cells highly express TOX, CD39, TIM-3, and LAG-3, have

low effector function, and are hard to reverse with just PD-1 blockade(Hashimoto et al., 2018; McLane et al., 2019).This differentiation trajectory provides a framework for understanding ICB responses and resistance (Figure 1).

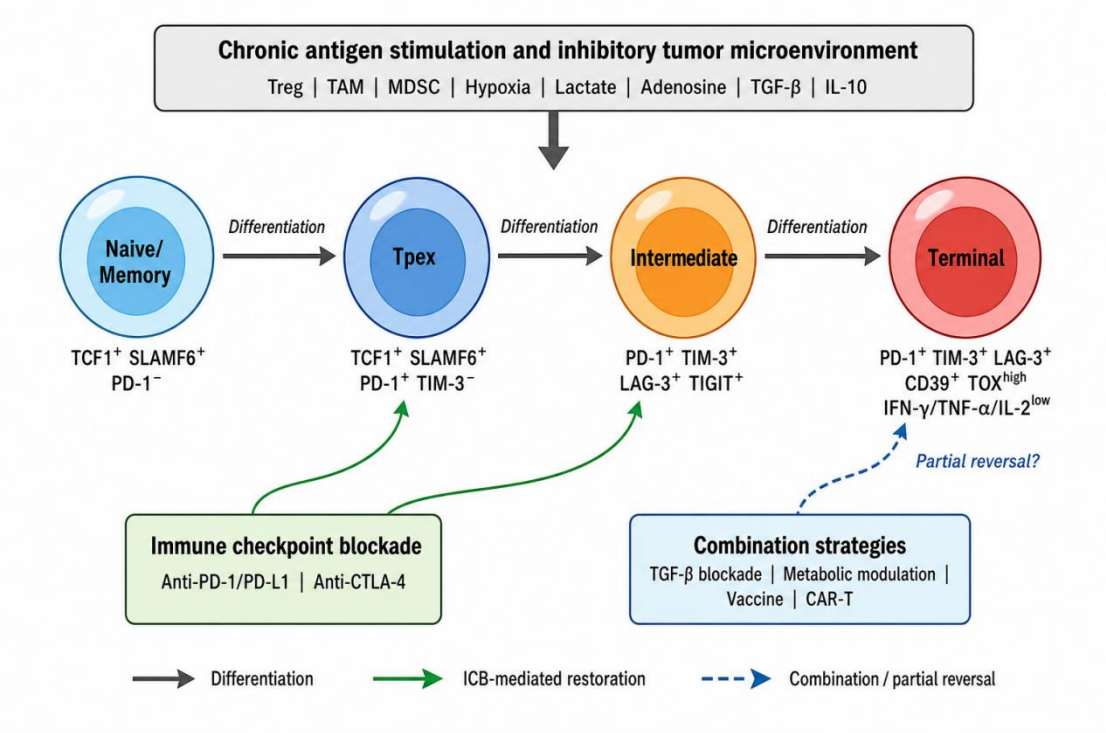


Figure 1. Schematic of the unified CD8+ T cell exhaustion program and differentiation trajectory, highlighting mechanisms, heterogeneity, and therapeutic interventions.

Chronic antigen stimulation and the inhibitory tumor microenvironment (driven by Tregs, TAMs, MDSCs, hypoxia, lactate, and adenosine) induce a unified exhaustion program via transcriptional (TOX, TCF1, NR4A, BATF), epigenetic (PDCD1, HAVCR2, LAG3 loci opening), and metabolic (mitochondrial dysfunction, ROS accumulation) rewiring. This drives the differentiation from memory-like cells to Tpex (TCF1$^+$, SLAMF6$^+$, PD-1$^+$, TIM-3$^+$), intermediate exhausted (PD-1$^+$, TIM-3$^+$, LAG-3$^+$, TIGIT$^+$), and terminal exhausted cells (PD-1high, TIM-3$^+$, LAG-3$^+$, CD39$^+$, TOX$^+$, low IFN-γ/TNF-α/IL-2). ICB (anti-PD-1/PD-L1, anti-CTLA-4) can restore Tpex proliferation and differentiation. Combination strategies (TGF-β blockade, metabolic modulators, vaccines, CAR-T) may partially reverse terminal exhaustion and CAR-T might enhance the reversal effect.Exhaustion is not merely functional silencing, but a stable state maintained by an integrated network of transcription, epigenetics, and metabolism, driven by the tumor microenvironment.These epigenetic and transcriptional changes lock the exhaustion program, which is further reinforced by metabolic and microenvironmental constraints (Abdel-Hakeem et al., 2021; Belk et al., 2022; Yates et al., 2021).TOX is considered a key regulator of the exhaustion program, helping to boost inhibitory receptor expression and keep the cells exhausted, while TCF1 is linked to maintaining Tpex cells and their memory potential (Khan et al., 2019).

The steady state of exhausted T cells depends on a series of transcription factors and epigenetic remodeling. TOX is considered a key regulator of the exhaustion program, helping to boost inhibitory receptor expression and keep the cells exhausted, while TCF1 is linked to maintaining Tpex cells and their memory potential. In addition, transcription factors like NR4A, BATF, IRF4,

and NFAT are involved in regulating the expression of genes related to exhaustion. On the epigenetic side, in exhausted T cells, gene sites like PDCD1, HAVCR2, and LAG3 show an open chromatin state, while effector gene sites like IL2 and IFNG gradually close, making it hard to completely reverse the exhausted state through short-term stimulation.These epigenetic and transcriptional changes lock the exhaustion program, which is further reinforced by metabolic and microenvironmental constraints.Tregs, tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs) can boost suppression through IL-10, TGF-β, VEGF, arginase, and tryptophan-metabolizing enzymes (Tauriello et al., 2022).

The tumor microenvironment suppresses T cell function through nutrient competition, hypoxia, lactate buildup, adenosine signaling, and abnormal lipid metabolism. Exhausted T cells have impaired mitochondrial function, an imbalance between glycolysis and oxidative phosphorylation, and accumulation of reactive oxygen species, which further weakens their ability to proliferate and kill. Tregs, tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs) can boost suppression through IL-10, TGF-β, VEGF, arginase, and tryptophan-metabolizing enzymes. So, exhaustion isn't just an internal program of T cells; it's also the result of the combined effects of the microenvironment.Therefore, exhaustion is a unified program integrating intrinsic T cell rewiring and extrinsic microenvironmental suppression.

4. Molecules Related to Exhaustion and Immune Checkpoints

4.1. Inhibitory Receptors

PD-1 is one of the most classic markers of exhausted T cells. After binding with PD-L1/PD-L2, it recruits SHP-2 and suppresses TCR signaling and co-stimulatory pathways (Pardoll, 2012; Topalian et al., 2015).CTLA-4 mainly controls early T cell activation and Treg function by competitively binding to CD80/CD86 and sending inhibitory signals.TIM-3, LAG-3, TIGIT, BTLA, and VISTA are often co-expressed with PD-1 in exhausted T cells, working together to suppress activity. The combination of different inhibitory receptors is closely linked to how exhausted the cells are, treatment responses, and resistance mechanisms(Table 1) (Korman et al., 2022; Kraehenbuehl et al., 2022).

Table 1. Main Markers and Functions of $CD8^+$ T Cell Exhaustion

Category	Marker	Main Expression/Function	Clinical & Biological Significance	Clinical Stage
Inhibitory Receptor	PD-1	Continuous expression; suppresses TCR signaling via SHP-2	Main ICB target; expression alone does not define terminal exhaustion	Approved (Multiple cancers)
Inhibitory Receptor	CTLA-4	Competes with CD80/CD86; inhibits co-stimulation	CTLA-4 blockade boosts T cell activation and depletes Tregs	Approved (Melanoma)
Inhibitory	TIM-3	Co-expressed with PD-	Correlates with severe	Phase III (Various)

Receptor		1; regulates T cell exhaustion	exhaustion; target for combination therapy	
Inhibitory Receptor	LAG-3	Binds MHC-II; suppresses T cell proliferation	Relatlimab (anti-LAG-3) combined with PD-1 blockade shows benefit	Approved (Melanoma)
Inhibitory Receptor	TIGIT	Binds CD155/CD112; suppresses NK and T cell activity	Tiragolumab combined with PD-L1 blockade under investigation	Phase III (NSCLC)

4.2. Soluble Factors and Cell Interactions

TGF-β is an important factor that promotes exhaustion and fibrosis, and it can suppress the effector function of $CD8^+$ T cells while promoting Treg differentiation. IL-10, VEGF, adenosine, and prostaglandin E2 also play a role in immune suppression (Thommen & Schumacher, 2018; Topalian et al., 2015).Tumor cells can escape immune attacks by upregulating PD-L1, downregulating MHC-I, losing antigens, and activating the Wnt/β-catenin pathway. Also, TAMs and MDSCs can suppress T cells through metabolic competition and cell contact. So, just blocking a single checkpoint usually isn’t enough to fully restore anti-tumor immunity.The molecular mechanisms of exhaustion directly shape the heterogeneous states of T cells in the TME, which in turn dictate ICB responses and inform combination strategies.

5. Heterogeneity of exhausted T cells in the tumor microenvironment

Single-cell RNA sequencing studies have shown that tumor-infiltrating $CD8^+$ T cells are highly heterogeneous Sade-Feldman and colleagues identified T cell states linked to ICB response in melanoma, finding that Tpex-like and effector-like cells are associated with good responses, while terminally exhausted cells are linked to resistance (Sade-Feldman et al., 2018).Spatial transcriptomics further shows that exhausted T cells are often found at the tumor edges or in areas rich in suppressive cells, and their spatial distance from tumor cells, TAMs, and Tregs affects their functional recovery.

Tpex cells are the key 'seed' population for ICB response. After PD-1 blockade, Tpex can proliferate and differentiate into effector-like cells, but if the Tpex pool is insufficient or the epigenetic exhaustion program is already fixed, it's hard to get a lasting response. So, treatment strategies shouldn't just focus on 'lifting inhibition,' but also on protecting or expanding Tpex and improving their differentiation environment.Sade-Feldman and colleagues identified T cell states linked to ICB response in melanoma, finding that Tpex-like and effector-like cells are associated with good responses, while terminally exhausted cells are linked to resistance (Oliveira & Wu, 2023).

6. Immune Checkpoint Blockade and Combined Interventions

Based on the mechanisms and heterogeneity described above, current ICB and combination strategies aim to target the exhaustion program at different levels.

6.1. PD-1/PD-L1 and CTLA-4

PD-1/PD-L1 blockade produces long-lasting responses in various tumors by restoring TCR signaling and effector functions. CTLA-4 blockade mainly works on the activation stage of T cells in lymph nodes and the tumor microenvironment, and it can also deplete Tregs. Combining PD-1 and CTLA-4 blockade shows a synergistic effect in melanoma, but it comes with increased toxicity. Clinical responses are linked to tumor mutation burden, PD-L1 expression, TIL infiltration, MSI-H status, and Tpex abundance (Litchfield et al., 2021).

6.2. Combination Strategy

To overcome exhaustion and drug resistance, combination therapy has become the main approach. Chemotherapy and radiotherapy can trigger immunogenic cell death and increase antigen release; anti-angiogenic treatments can improve T cell infiltration and reduce MDSCs; blocking TGF-β, inhibiting the adenosine pathway, and metabolic regulation can improve the microenvironment. LAG-3 blockade combined with PD-1 blockade has shown benefits in melanoma, and targets like TIGIT and TIM-3 are under clinical investigation (Tawbi et al., 2022). In addition, tumor vaccines, adoptive T cell therapy, and CAR-T cell therapy can supplement or reshape the T cell pool (Gumber & Wang, 2022; Lin et al., 2022; Weber et al., 2021). In addition, neoadjuvant or radical PD-1 blockade has further shown clinical benefits in long-term follow-ups for resectable NSCLC, locally advanced MMR-deficient rectal cancer, and PD-L1 high-expressing NSCLC (Cercek et al., 2022; Forde et al., 2022; Reck et al., 2021).

Table 2. Representative Immune Checkpoint Targets and Combination Strategies

Target	Representative Drugs/Strategies	Main Mechanism	Combined Direction	Clinical Stage
PD-1	Pembrolizumab, Nivolumab	Blocking PD-1/PD-L1 to restore T cell function	Chemotherapy, radiotherapy, CTLA-4, LAG-3	Approved
PD-L1	Atezolizumab, Durvalumab	Blocking PD-L1 binding to PD-1/CD80	Anti-angiogenesis, chemotherapy	Approved
CTLA-4	Ipilimumab	Boost T cell activation, deplete Tregs	PD-1 blockade	Approved
LAG-3	Relatlimab	Relieve LAG-3 mediated inhibition	PD-1 blockade	Approved (Melanoma)
TIGIT	Tiragolumab	Blocking TIGIT/CD155	PD-L1 blockade	Phase III

7. Biomarkers and Predicting Treatment Response

Currently, the commonly used clinical predictors include PD-L1 expression, tumor mutation burden, MSI-H/dMMR, TIL density, and dynamic changes in ctDNA. However, all of these markers have their limitations. Single-cell and spatial omics suggest that things like Tpex abundance, T cell states, co-expression patterns of inhibitory receptors, and the spatial structure of the microenvironment might be better at predicting ICB responses.Gut microbiota, host genetic background, and immune-related side effects might also affect treatment efficacy. For patient selection, integrating Tpex abundance, spatial immune profiles, and circulating tumor DNA (ctDNA) dynamics is crucial to identify those most likely to benefit from ICB. Biomarker-guided combination therapy, such as using LAG-3 or TIGIT expression to guide dual blockade, represents a promising avenue for personalized immunotherapy. In the future, we'll need multidimensional integrated models to achieve personalized immunotherapy.

8. Challenges and Outlook

Even though ICB has had major success, T cell exhaustion, antigen loss, MHC downregulation, immunosuppressive microenvironments, and irAEs are still the main challenges. The toxicity of combination therapies, particularly the increased risk of severe irAEs with dual checkpoint blockade (e.g: PD-1 plus CTLA-4 or LAG-3), necessitates careful patient stratification and toxicity management. Future research should focus on: understanding the plasticity and epigenetic reversibility of exhausted T cells; developing combination strategies targeting the expansion and differentiation of Tpex; using spatial multi-omics and AI to predict responses and identify new targets; optimizing the therapeutic window to balance efficacy and toxicity in biomarker-guided combination regimens; and optimizing the persistence and safety of CAR-T in solid tumors. By deeply integrating basic immunology with clinical translational research, it's possible to turn 'exhaustion' from a treatment hurdle into a target that can be intervened.

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