Review Article

Destiny of CD8$^+$ T cells exhaustion in cancer, and rescue of it: a narrative review

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Abstract: Although immune checkpoint blockade (ICB) has shown a powerful effect in cancer treatment, a large proportion of patients can't benefit from it, including some with lymphocytic infiltration in microenvironment. The targets of ICB are immune cells that express specific antigens, especially various types of T cells, with the aim of restoring their antitumor ability after dysfunction. Increasing researches have revealed that exhausted T cells (Tex) in the tumor microenvironment are closely related to the prognosis of ICB therapy. T cell exhaustion occurs in cancers and many chronic infections, which exhibits continuous expression featured by co-inhibitory receptors and a transcriptional mode distinct from memory T cells or functional effector. Besides, in adoptive T cell therapy such as CAR T, these genetically engineered T cells injected into patients also become more suppressive receptors and lose effector function in response to continuous antigenic stimulation. Thus, there is strong interest in identifying the basis for T cell dysfunction and the mechanisms by which ICB therapy reinvigorates T cells, in order for these cells to exert anti-tumor function. In this review, we discuss the development and the molecular properties of Tex, and the therapeutic strategies targeting Tex, which may be the key to the success of immunotherapy.

Keywords: Immunotherapy; cancer; T cell; immune checkpoint blockade (ICB); chimeric antigen receptor T cell (CAR T)

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Introduction

Mature recirculating T cells without encountering their specific antigens are touted as naïve T cells. Aiming to join in an adaptive immune reaction, they meet its specific antigens within the draining lymph nodes and initiating an activation project giving rise to their clonal extension as well as differentiation into functional effector cells. In this process, CD8$^+$ T cells have received a range of particular signals basing on T-cell antigen-receptor (TCR) and other co-stimulatory molecules or cytokines encountered (1). Due to asymmetrical cell division and intraclonal competition, proliferating progeny cells subsequently receive different stimulus signals that changes relying upon the time post infection, antigen distribution as well as antigen clearance rate (2-5). The spatial and temporary stimulation signals ultimately determine the differentiation of them.

In chronic diseases, the persistence of antigens along with the environmental factors constitute the driver of variable losses of functions of CD8$^+$ T cells, including cytotoxicity as well as creation pro-inflammatory cytokines (IL-2, TNF-α and IFN-g), which is known as T cell exhaustion (6). The functional exhaustion featured by antigen-reactive CD8$^+$ T cells was primarily discovered in persistent LCMV infection, where they make the persistence with lower effector functions (7,8). Furthermore, they discoveries were spread to viral chronic infections in non-human primates and humans, such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV) (9,10). Recent years have seen the consensus that T cell exhaustion is a common trait in mouse tumor models and human cancers, of which a characteristic feature is the presentation of various inhibitory receptors (11-13). It embraces significant implications to explore the features harbored

by as well as the pathways to exhaustion for the successful checkpoint blockade and adoptive T cell transfer therapies. However, we still have incomplete comprehension on their developmental biology and potential cellular and molecular mechanisms which regulate their formations, maintenance, and reactions to immunotherapy. Amidst the backdrop, I reviewed the understanding of T cell exhaustion in the development of cancer immunology in recent years, including its differentiation fate and its functional phenotype, and discussed how can it benefit to cancer treatment therapy by targeting exhausted T cells. I present the following article in accordance with the Narrative Review reporting checklist (available at https://aob.amegroups.com/article/view/10.21037/aob-21-2/rc).

Molecular phenotype of exhausted T cells and the classification derived from it

In the duration of chronic infection and cancer in not only lymphoid but also non-lymphoid tissues, antigen-reactive $CD8^+$ T cells demonstrate persistent exposure to the high-level antigen (14-16). Continuous TCR stimulation gives rise to upregulation of co-inhibitory ICs that desensitize TCR signaling, such as PD-1, CTLA4, CD38, CD39, CD160, LAG3, Tim-3, TIGIT and 2B4 (15). In consequence, chronically stimulated T cells, in a progressive way, are deprived of their effector functions in virtue of entering a state called exhaustion. Exhaustion now receives appreciation that is a uniquely programmed differentiation state (17,18). It can prevent T cells leading to immunopathology at the existence of persistent antigen as well as out of apoptosis of antigen-specific T cells in virtue of activation-induced cell death (19,20). These receptors regulate the T cells function through different mechanisms and eventually led to the generation of T^{term}. Some of them block the activation of TCR downstream pathways such as PD-1, some make competition with ligands which paired with costimulatory receptors such as CTLA-4, others inhibit the gene transcription related to activation of T cell such as TIM-3 (21-25). In order to prevent these targets from being activated and causing the loss of T cell function, there are a great many monoclonal antibodies against a single exhausted T cell marker. but even if one is blocked, another target may increase compensatorily. Therefore, it is necessary to block mutually antagonistic targets. Take PD-L1 and CTLA-4 for example, when DC cells are in an activated state, the expression of CD80 is up-regulated. However, a large amount of CD80 binds to its own PD-L1 through cis-acting, inhibiting PD-L1 and PD-1 binding on T cells, but hard to activate CD28. Blocking PD-L1 on DCs can alleviate the cis-binding of PD-L1 and CD80, but at the same time the binding of CD80 and CD28 will be interfered by CTLA-4. Combinations of antibodies or multispecific antibodies may be good considerations, such as bispecific antibody.

In the early stages of exhaustion, the first to be generated is a small fraction of $TCF1^+$ $PD\text{-}1^{int}$ $CXCR5^+$ $Ly108^+$ progenitor exhausted cells that have self-renewal capability. According to the expression of CD69, it can be divided into progenitor 1 subset (Tex^{prog1}, $CD69^+$) and progenitor 2 subset (Tex^{prog2}, $CD69^-$) which converted from Tex^{prog1} (26-28). With the chronic antigen stimulation, Tex^{prog2} can make a greater degree of differentiation into a intermediate exhausted population (Tex^{int}) which can display effector-like functional and transcriptional features ($PD\text{-}1^+$ $TCF1^-$ $CXCR5^-$ $CD101^-$ $Tim\text{-}3^+$ $CX3CR1^+$ $CD69^-$ $Ly108^-$ granzyme B^{hi}) traced via the foundation of a great fraction of terminally exhausted cells (Tex^{term}) which lack effector function ($PD\text{-}1^+$ $TCF1^-$ $CXCR5^-$ $CD101^+$ $Tim\text{-}3^+$ $CX3CR1^-$ $CD69^+$ $Ly108^-$ granzyme B^{lo}) (29).

Tex^{prog}, which can hold on long-term anti-tumor response by the self-renew as well as production of Tex^{int}, shoulder more responsibility for the reaction to ICB therapy. The procedure was used to be called 're-invigoration' from dysfunctional states (30,31). In spite of the fact that the accurate molecular demands of the generation of Tex^{prog} shows no explicit, the expression of CXCR5 as well as the localization of them showed that secondary lymphatic organs play an important role in its growth (32). In addition, DC-mediated antigen stimulation in tumor microenvironment might be of benefit for the creation and maintenance of $TCF1^+$ Tex^{prog} along with their effector function on the prerequisite of optimal co-stimulatory signals (33). In the past, we took the exhausted T cells as a whole to formulate treatment strategies, without considering that they actually contain several types of T cells with different molecular phenotypes. It may be feasible to find the main anti-tumor cells for targeted treatment.

Upstream molecular and epigenetic factors and downstream signals of inhibitory receptor on exhausted T cells

We now know that exhausted T cells express related inhibitory receptors, but how are these inhibitory receptors produced? Let us turn our attention from the surface

Table 1 Transcription factors associated with T cell exhaustion

Transcription factor	Expression in exhausted Tex	Target genes
nuclear factor of activated T cells, NFAT	Upregulated	PD-1, CTLA-4
Thymocyte selection-associated high mobility group box protein TOX, TOX	Upregulated	PD-1
Basic leucine zipper transcriptional factor ATF-like, BATF	Upregulated	T-bet, Blimp-1, Id-2, Eomes
B lymphocyte induced maturation protein-1, Blimp-1	Upregulated	T-bet, Bcl-6, Eomes
Forkhead box protein O1, FoxO1	Downregulated	GSK3β
T-box expressed in T cells, T-bet	Downregulated	Tim-3
Pre-B-cell leukemia transcription factor 3, Pbx3	Upregulated	
Eomesodermin, Eomes	Upregulated	
Kruppel-like factor 4, Klf4	Upregulated	
Zinc finger protein Helios, Helios	Upregulated	

PD-1, programmed cell death protein 1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4.

markers of exhausted T cells to the upstream molecular activities in the cells related to them. Since there are too many surface molecules, it is impossible to list the detailed mechanisms behind them one by one. Here we only review the main ones. The current research results of those molecules that have not been reviewed are listed in *Table 1*. In the tumor microenvironment, due to the comprehensive influence of various factors, including the signals received through TCR receptors and co-inhibitor receptors or inhibitory cytokine, the appearance of some kind of metabolites (e.g., lactate) or enzymes (e.g., reactive oxygen species), acidic pH environment and the lack of nutrients, the epigenetic status of T cells has changed a lot (25,34-38). The complex regulatory network of transcription factor drives the initiation of the fatigue phenotype, including NFAT, TOX, BATF, Blimp-1, VHL, FoxO1, Bcl-6, IRF4, STAT3, cMAF, T-bet and EOMES (34,37,39-43). These factors play different roles in different stages of Tex. For example, STAT3-dependent transcriptional regulation can limit TIL recruitment and cytotoxicity by down-regulating the expression of CXCL10, CXCR3 and IFN-γ (40,43). It is worth noting that T-bet and Eomesodermin (Eomes) are expressed during the entire process of tumor development, but their ratio helps to distinguish exhausted progenitor cell subsets from terminally differentiated exhausted T cells (6,44). Nuclear factor of activated T cells (NFAT), touted for its role in T cell activation, can promote $CD8^+$ T cell dysfunction in tumor and viral infection models while boundless with activated protein (AP-1) transcription factors, which might be the most crucial cis-element for PD1 expression (45). Moreover, NFAT was proved to be up-regulation CTLA-4 transcription. Belongs to a basic leucine zipper transcription factors, BATF in the APf family can dimerize with AP-1 subunit Jun to inhibit AP-1 target gene activation, being an accelerator of T cell dysfunction in virtue of the downstream PD-1 pathway in the duration of HIV infection (46). BATF also promotes the differentiation of CD8þ T effector cells through sirt1-mediated histone acetylation, thereby up-regulating T-bet under IL-12 stimulation.

Recently, it has been published that mitochondrial dynamics regulate the production of memory $CD8^+$ T cells, and the reduction of mitochondrial biogenesis and the massive production of mitochondrial reactive oxygen species (ROS) can promote T cell dysfunction in chronic viral infections and tumors. These studies emphasize the importance of mitochondrial function in regulating the immune response of T cells. Damage to mitochondria leads to the accumulation of depolarized mitochondria in $CD8^+$ TILs. TCR and PD-1 signals contribute to this process, making it exhibit the characteristics of terminal exhaustion of T cells (47).

Activation of inhibitory receptors leads to a series of downstream reactions. The ability of Tex cells to produce immune-stimulating cytokines will be limited, as will the reduction in cytotoxicity. At the early stages of Tex, IL-2 production is lost, thus giving rise to the deprivation of cytotoxic function (48). The loss of production of TNF-α occurs at the middle stage of Tex; the production of Gzmb and IFN-γ takes place at the late stage of Tex (49,50). In

the same process, their proliferation potential gradually decreases, as they do not respond to homeostatic factors such as IL-15, IL-7 as well as IL-21 (51). But, as mentioned above, the TCF^{+}/PD-1^{int} Tex^{prog} still retains the ability to differentiate into effector-like Tex^{int}.

Attempts to reduce exhausted T cell dysfunction in cancer therapy

Despite encouraging results with PD-1 and CTLA-4 blockers, quite a number of patients remain to be of unresponsivity or incapability of producing a lasting reaction (52-54). Examining surface receptors in activation/dysfunction modules might bring about the findings of new co-inhibitory or co-stimulating receptors which might complete these therapies (55-57). The identification of unique genes which can accelerate dysfunction or activation of CD8^{+} T cells can enable the engineering of functionally resistant T cells for adoptive T cell transfer (58,59). These methods could be integrated with the expression of chimeric antigen receptors for engineering powerful anti-tumor T cells.

Kamphorst and colleagues, having explored a variety of strategies for the improvement of the effectiveness of PD-1 treatment decided the indispensable role of the CD28/B7 co-stimulatory pathway in the reversion of CD8^{+} Tex. The signal from the co-stimulatory pathway helps improve the effectiveness of PD-1 blocking therapies in carcinoma and chronic viral infections. The further suggestion is that in-depth research should be focused on exploring the application of CD28, which functions as a predictive biomarker for patients who may be sensitive to PD-1 blockade (60).

According to reports, CD8^{+} T cells showing upregulated Eomes are in relation to the generation of TEM cells. According to observation, adoptively transferred Eomes and T-bet expressing CD8^{+} T cells are able to eliminate the established tumors. Interferon regulatory factor 4 (IRF4), the transcription factor which highly expressed on mature B cells, can regulate the ratio of T-bet and Eomes expression on CD8^{+} T cells (61). The Eomes/T-bet ratio is of importance in regulate the clearance rate of chronic viral infections, for example, LCMV. High levels of IRF4 could sustain TCR signal transduction by biasing the Eomes/T-bet ratio to T-bet, which is conducive to the generation of short-term effector cells as well as antiviral function. On the contrary, the tilt of the Eomes/T-bet ratio that favors Eomes will promote the production of memory precursor CD8^{+} T cells by degrading the antiviral function. When the immune reaction is continuing, the Eomes/T-bet ratio is conducive to the creation of memory precursor cells. Accordingly, Eomes and T-bet contribute to importance transcription factors which can regulate the antiviral and antitumor functions of effector as well as memory CD8^{+} T cells (62-66). Thereby, targeting Eomes and T-bet might be a crucial part in promoting CD8^{+} T cell-mediated anti-tumor response, which can regulate the differentiation of Tex^{prog2} to Tex^{int} and preventing the generation of Tex^{term} (67-70).

The expression of B7 super family member 1 (B7S1) is made on APC and kinds of solid tumor cells. B7S1 is upgraded through IL-6 and IL-10, by binding to the receptor B7S1R on the surface of CD8^{+} T cells, thereby inhibiting the growth of CD8^{+} T cells as well as the secretion of cytokines, thereby promoting the transport and cytotoxicity of CD8^{+} T cells have negative impacts. The high expression of B7S1 marks poor prognosis within cancer patients. B7S1 can up-regulator Eomes, thus enhancing T cell exhaustion and dysfunction (71). T-bet, Eomes and B7S1 express close inter-association, therefore, attentively monitoring of B7S1 targeted therapy and the treatment of Eomes and T-bet demonstrates great significance in the field of cancer immunotherapy (72,73).

Hobit mainly marks expression on human effector CD8^{+} T cells and has been acknowledged as a critic transcription factor presented on transient effector CD8^{+} T cells, which can regulate the fate of effector CD8^{+} T cells, analogous to T-bet. Nonetheless, in-depth researches are required, in order to explicitly determine the systems and the likely and possible effects of those transcription factors upon the fate of CD8^{+} T cells. The mechanism by which Hobbit control the function of effector CD8^{+} T cells is not fully understood. More research is demanded, aiming to get an explicit identification of the systems and the likely cooperative effects of, T-bet, Eomes and Hobit on a mutual basis, along with the regulation of memory and the fate of effector CD8^{+} T cells (74,75). These studies could be applied to improving therapies oriented with T cell exhaustion, which is anticipated to be a promising task in the reversion of T cell exhaustion.

Tumor-induced chronic antigen stimulation, on a similar basis, could give rise to CAR T cell exhaustion, as is portrayed to be a condition full of hypofunctional CAR T cells (76,77). Hence, T cell persistence, might not embody more in-depth needs for the usable persistence of solid persistent tumor regression; besides, only co-

stimulation is not able to stop the long-run fatigue as a result of the inhibitory ligand expression. PD-L1 and PD-L2 made direct inhibition on CAR T cell effector function within tumor cells, in particular following chronic antigen stimulation (78-80). This effect can be seen regardless of the CAR co-stimulus domain. Both CD28 and 4-1BB CAR T cells express sensitivity to PD-L1 mediated inhibition, despite the fact that PD-1 levels expressed by 4-1BB CAR T cells are lower than CD28 and other fatigue markers, such as TIM-3 and LAG 3 after chronic antigen stimulation (78). CD19 positive recurrence after CART cell therapy was mainly due to internal immunological and genetic reasons: CART cell amplification and amplification restriction; repeated exposure to antigens led to T cell exhaustion. T cell overactivation and inhibition of receptors (such as PD-1, CTLA4, TIM3, lag-3, TIGIT, CD160, CD244), together with T cell senescence caused by over-expression. However, tumor recurrence was observed after stopping the treatment, indicating that the effectiveness of the PD-1 antibody depends on repeated administration of the antibody. PD-L1 CPB is also able to upgrade CAR T cell therapy in an effective way in virtue of handicapping PD-L1 expression on MDSC (81-83). The integrated application of CAR T cells; PD-L1 antibodies with antibodies which cause depletion MDSC (anti-GM-CSF or anti-Gr1) can bring about in-depth enhancement on the effectiveness of the therapy by highlighting the immune-suppression of PD-L1. Role L1 positive MDSC could function well in CAR T cell therapy. With the purpose of avoiding the likely toxicity linked to systemic administration of CPB, it is a good way to combine anti-HER2 CAR T cell therapy with oncolytic adenovirus expressing PD-L1 antibody, in order that PD-L1 antibody can be locally produced in the TME (84). In subcutaneous mouse models of prostate cancer, this PD-L1 oncolytic strategy is more effective compared to systemic injection of PD-L1 antibody in revitalizing CAR T cells.

The effector function of T cells had positive relevance to the distinction of $CD8^+$ T cells. Researchers made observations on the continuous survival of TCM cells in vivo, not effector $CD8^+$ T cells (85). Furthermore, the conclusion was that co-infusion of $CD4^+$ T cells with $CD8^+$ T cells in the duration of adoptive cell therapy increased the effectiveness of $CD8^+$ T cells in vivo. The effectiveness of $CD8^+$ T cells can be upgraded via $CD4^+$ T cell support. Analogously, the researchers pointed out that it is a known common sense that infusion of memory or TSCM cells can upgrade the effectiveness of CAR T cell therapy (86-88). This will address the problem of T cell exhaustion, which routinely occurs during the traditional strategy of injecting adoptive differentiation effector $CD8^+$ T cells into adoptive cells as well as CAR T cell therapy.

Conclusion

In the past few years, new technologies such as single-cell transcriptome analysis and mass cytometry has provided us with great help in understanding the heterogeneity of exhaustive T cells in chronic diseases, giving us a deeper view of the differentiation of $CD8^+$ T cells from Tex^{prog} to Tex^{term}. With transcription factors involved in the regulation of T cell exhaustion are gradually emerging, the full picture of the intricate regulatory network of that has almost revealed. The discovery of new immune checkpoints related to T cell exhaustion has sprung up in the past decade, creating more effective approaches to improve adoptive cell transfer therapy. However, there are still some unresolved problems in cancer immunotherapy. The precise molecular mechanism about how continuous antigen stimulation initiates T cell exhaustion has not been elucidated, and the interaction between Tex and other lymphocytes or tumor cells also needs to be explored. Furthermore, in different cancers, or even the same type of cancer in different people, the tumor microenvironments differ greatly, as well as the subsets of Tex. Thus, there is an urgent need for a method that can accurately determine the patient's characteristics of TME including the lymphocyte phenotype inside in a short time, so as to provide guidance for the individual's clinical medication strategy.

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Footnote

Reporting Checklist: The author has completed the Narrative Review reporting checklist. Available at https://aob.amegroups.com/article/view/10.21037/aob-21-2/rc

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at https://aob.amegroups.com/article/view/10.21037/aob-21-2/coif). The author reports that employment relationship with Guangzhou Virotech Pharmaceutical Co., Ltd. The author has no other conflicts of interest to declare.

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