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Heterogeneity and fate choice: T cell exhaustion in cancer and chronic infections

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Abstract

CD8 T cell differentiation is a tightly regulated process generating effector and memory T cells over the course of acute infections. In cancer and chronic infection, this differentiation program is derailed, and antigen-specific CD8 T cells differentiate to a hyporesponsive state generally referred to as T cell exhaustion. Here, we review recent findings on heterogeneity of tumor-specific T cells and exhausted T cells during chronic infections, discussing distinct differentiation state dynamics, fate choices, and functional states. Delineating the regulatory mechanisms defining distinct T cell states and determining the requirements for therapeutic reprogramming of these states will provide needed insights for the design of effective immunotherapies for the treatment of cancer and chronic infections.

Introduction and terminology

Several terms are currently in use to describe hyporesponsive CD8 T cells, including tolerance, anergy, exhaustion, and dysfunction. Tolerance describes the central or peripheral inactivation of self-reactive T cells and serves to prevent autoimmunity [1]. Anergy is generally used to describe the hyporesponsive state of T cells stimulated in the absence of co-stimulatory signals [1]. In the context of chronic infections, hyporesponsive T cells are generally referred to as ‘exhausted,’ while T cells in the context of tumors have been described as ‘dysfunctional’ and/or exhausted. These different hyporesponsive states have shared and unique features. Here we will highlight (i) new insights into differentiation state dynamics and population heterogeneity of hyporesponsive T cells in chronic infections and cancer, (ii) how these states are determined by spatiotemporal factors, (iii) the underlying transcriptional and epigenetic regulation, and finally (iv) how these different states determine responses to immunotherapeutic interventions.

Conflict of interest statement

Nothing delcared.

Phenotypic and functional traits of exhausted T cells in chronic viral infection

During chronic viral infections, virus-specific CD8 T cells enter a state of 'exhaustion'—a state of functional hyporesponsiveness driven by chronic antigen stimulation [2]. Exhausted T cells lack full effector function, coinciding with the expression of numerous inhibitory receptors including PD1, LAG3, TIGIT, CD38, CD39, CD160, 2B4, TIM3, and CTLA4 [3]. These exhaustion-associated phenotypic and functional traits have distinct underlying transcriptional and epigenetic programs [2,4–9]. Virus-specific T cells initially acquire effector function during the early phase of the infection, but in the presence of persistent viral antigen and inflammation/infection, T cells become progressively exhausted, losing effector functions in a hierarchical manner (loss of proliferative capacity and IL-2 production first, followed by loss of TNFα, and ultimately loss of IFNγ production) [10]. Nevertheless, exhausted T cells are not completely unresponsive and retain some effector function, thereby allowing the host to control the pathogen without detrimental immunopathology. This is evidenced by the fact that depletion of exhausted T cells can cause fatal infection [11,12] while conversely, reinvigoration of exhausted T cells during chronic viral infection can result in fatal immunopathology [13,14]. Thus, T cell exhaustion is a state of 'effective' hyporesponsiveness, rather than a fully dysfunctional or non-responsive state, maintaining the host–pathogen stalemate [15].

Phenotypic and functional traits of hyporesponsive, tumor-reactive T cells in cancers

The study of established mouse and human tumors has demonstrated that tumor-infiltrating CD8 T cells (TIL) exhibit hallmark exhaustion features of T cells in chronic infection: TIL are impaired in the production of effector cytokines and/or cytotoxic molecules, express high levels of inhibitory receptors, and display alterations in TCR signaling pathways and transcription factor programming (including NFAT, TOX, TCF1, IRF4, BLIMP1) [16–23].

In spite of these overlapping phenotypic and functional traits, T cell differentiation during tumorigenesis is distinct from T cell differentiation in chronic infection: tumor-specific/neo-antigen-specific T cells generally do not differentiate through an early effector phase as seen with virus-specific T cells during a chronic infection; in developing tumors, tumor antigens are not presented 'acutely' in an inflammatory, stimulatory context. Instead, naïve tumor-reactive T cells are inadequately primed and/or activated in the draining lymph nodes or tumors, and enter an 'anergy'-like hyporesponsive state, which progresses into an exhaustion-like state due to progressive tumor growth and persistence of tumor antigen [18,20,24–26].

Identifying the precise differentiation state dynamics and functional states of tumor-infiltrating T cells has been difficult due to the many cell-intrinsic and extrinsic factors affecting T cell differentiation and dysfunction in tumors, including (i) antigen-specificity, (ii) TCR affinity, (iii) tumor antigen density, (iv) time present within tumor and/or exposure to tumor antigen, (v) tolerance mechanisms operating during the early, non-inflammatory

phase of tumorigenesis, or (vi) microenvironmental immunosuppressive factors present within established tumors (hypoxia, nutrient deprivation etc.). Thus, TIL represent a highly heterogeneous T cell population with a wide range of T cell specificities, activation and functional/dysfunctional states with distinct requirements for therapeutic reprogramming. The complete responses seen in some cancer patients treated with checkpoint blockade antibodies have reinvigorated the field of cancer immunotherapy; however, significant clinical responses are only observed in a subset of patients and cancer types, and it is currently unknown why only certain cancers and/or patients respond to checkpoint immunotherapy. To address these clinical challenges and design predictably effective cancer treatments, current efforts are aimed at elucidating the underlying programs that define exhaustion states of TIL and their amenability to immunotherapeutic reprogramming. Recent technological advances including single-cell analysis, TCR-seq, as well as epigenomics and transcriptomics analyses are now beginning to yield startling new insights into the heterogeneity of antigen specificity, T cell repertoires, and T cell differentiation and functional states in tumors, and how these heterogeneities might define clinical responses to immunotherapy (see below) [27–38].

Heterogeneity of the exhausted T cell population during chronic infections

Exhausted T cells during chronic infections represent a heterogeneous T cell population. Paley *et al.* first demonstrated that virus-specific exhausted T cells consist of at least two subpopulations: a $TBET^{hi}PD1^{int}$ progenitor CD8 T cell subset which proliferates and gives rise to an $EOMES^{hi}PD1^{hi}$ terminally differentiated progeny [39]. $EOMES^{hi}PD1^{hi}$ T cells do not replicate and display high expression of inhibitory receptors. The ultimate depletion of the progenitor pool and accumulation of terminally differentiated $EOMES^{hi}PD1^{hi}$ T cells is thought to result in the loss of immune control of the infection. In support of this notion, livers of patients with chronic HCV infection show depletion of $TBET^{hi}$ precursors and accumulation of the terminally differentiated exhausted progeny, in contrast to patients with controlled infections [39].

Several other subsequent studies examined T cell heterogeneity during chronic infections and identified TCF1 as a critical transcription factor. Virus-specific $TCF1^{+}$ ($PD1^{+}CXCR5^{+}TIM3^{-}$) CD8 T cells have a memory/stem cell-like phenotype, self-renew and give rise to terminally differentiated $TCF1^{low/neg}$ ($PD1^{+}CXCR5^{-}TIM3^{+}$) T cells [40–45] (Figure 1). Interestingly, these two populations are found in spatially distinct compartments: while the $TCF1^{+}$ memory/stem cell-like progenitor population is mainly found in secondary lymphoid tissues, specifically in T cell zones (white pulp), the terminally differentiated, exhausted $TCF1^{low/neg}$ T cell population is predominantly found in peripheral tissues andthered pulp of spleens—the major sites and reservoirs of infected cells and/or antigen [41]. Thus, formation and maintenance of the $TCF1^{+}$ progenitor population appear to be restricted to sites of low antigen/pathogen burden and virus replication.

Importantly, $TCF1^{+}$ (and/or $TBET^{hi}PD1^{int}$) exhausted progenitor T cells, but not terminally differentiated exhausted $TCF1^{low/neg}$ (and/or $EOMES^{hi}PD1^{hi}$) T cells, proliferate in response to PD1/PDL1 checkpoint blockade revealing that the memory/stem cell-like

progenitor population is the prime target of immunotherapeutic interventions during chronic infections [40,41] (Figure 1).

Heterogeneity of tumor-infiltrating lymphocytes (TIL)

The identification of a memory/stem cell-like progenitor T cell population in chronic infections amenable to reprogramming by checkpoint blockade antibodies has sparked the search for similar progenitor T cell populations in tumors. Previous studies demonstrated that the induction of WNT/β-catenin signaling arrests T cell differentiation and drives the generation of self-renewing, memory stem cell-like T cells [46]. More recent studies characterizing TIL populations from human tumors indeed demonstrated the presence of $TCF1^+$ TIL with stem cell-like characteristics and cytotoxic potential [29,43,47–49], and the frequency of $TCF1^+$ CD8 T cells in tumor tissue correlated with responses to immunotherapy. However, it is unclear whether these $TCF1^+$ T cells are truly tumor-reactive and/or represent a truly stable, self-renewing memory/stem cell-like progenitor T cell population as seen in chronic infections. $TCF1^+$ TIL may include non-tumor reactive, bystander, cytotoxic T cells abundant in human tumor infiltrates and phenotypically distinct, lacking hallmarks of chronic antigen stimulation [18,21,30,35] (Figure 2). Interestingly, a recent study combining single-cell RNA-seq and TCR-seq, and assessing tumor reactivity of TIL from melanoma patients, revealed that $TCF1^+$ TIL include bystander non-tumor reactive cytotoxic T cell populations, while T cell clones with tumor-reactivity had dysfunctional features including high expression of PD1, LAG3, CD39, and TOX, and low expression of TCF1 [28].

Following differentiation of a naïve tumor-specific T cell population over the course of tumorigenesis in an autochthonous tumor mouse model demonstrated that tumor-specific TIL within malignant lesions are initially $TCF1^{hi/int}$, but over the course of tumorigenesis and with continued tumor antigen encounter, gradually lose TCF1 expression, become $TCF1^{low/int}$ and ultimately $TCF1^{neg}$. This gradual loss of TCF1 coincided with the progressive upregulation of canonical inhibitory receptors and the inability to undergo functional rescue [18,20]. Thus, tumor-specific T cell dysfunction is progressive, ultimately resulting in a severe state of dysfunction/exhaustion which is highly resistant to therapeutic reprogramming. In human tumors, T cell tumor-infiltration and exposure time to tumor antigens (as well as specificity, affinity etc.; see above) is variable; thus TIL are in distinct differentiation, activation and dysfunctional states. Understanding whether and which dysfunctional T cell state(s) within tumors can be reinvigorated through immunotherapeutic interventions, or whether clinical responses require the recruitment of functional (potentially $TCF1^+$) tumor-reactive T cells from ‘outside’ (e.g. draining lymph nodes, blood etc.) is being intensely investigated and these findings will be critically important to understand and design effective immunotherapeutic strategies (Figure 2).

Epigenetic programs defining dysfunctional and exhausted T cell states and therapeutic reprogrammability

Distinct functional CD8 T cell states, such as the naïve, effector and memory states, are associated with specific epigenetic programs that regulate transcription and define functional

and phenotypic properties [50]. Recent technological advances including ATAC-seq [51] allowed the identification of chromatin states of exhausted T cells in chronic infections and tumor-specific T cells in mouse and human cancers [6–8,20,21,29]. These analyses reveal that both exhausted/dysfunctional T cells in chronic infections and tumors harbor chromatin accessibility patterns distinct from those of naïve, effector or memory T cells, with thousands of uniquely differentially accessible peaks, including in loci of genes encoding critical exhaustion-associated transcription factors and inhibitory receptors.

Studies investigating chromatin state dynamics of tumor-specific T cells over the course of tumorigenesis demonstrated that naïve tumor-specific T cells enter an epigenetically encoded program of dysfunction after encountering tumor antigen in early malignant lesions. This epigenetic landscape (chromatin state 1) was markedly distinct from that of early effector T cells during an acute infection and from early ‘exhausted’ T cells during a chronic infection [20,21]. Thus, naïve tumor-specific T cells encountering tumor antigen in early malignant lesions in a non-inflammatory context follow a distinct differentiation pathway from naïve T cells encountering antigen during an infection. With continued tumor antigen encounter and tumor progression, $PD1^{hi}$ tumor-specific T cells undergo further chromatin remodeling, entering another distinct chromatin state (state 2). These two chromatin accessibility patterns correlated temporally with the T cells’ amenability to therapeutic reprogramming [20]. Thus tumor-specific T cells initially differentiate through a plastic dysfunctional state that is functionally rescuable but ultimately enter a severe and fixed state of dysfunction that appears to be resistant to reprogramming. Interestingly, plastic and fixed dysfunctional T cells expressed similar levels of PD1 and LAG3 but could be distinguished by expression of other surface membrane proteins, including CD38, CD39, 2B4, and CD101, which were shown to be predictive biomarkers for therapeutic reprogrammability. Thus, while some inhibitory receptors such as PD1 more broadly might define TIL with tumor-reactivity, other inhibitory receptors can be utilized to determine functional states and reprogrammability of $PD1^{hi}$ TIL within mouse and human tumors [18,20,29,52]. In chronic viral infection, interestingly, it was shown that despite functional reinvigoration of exhausted virus-specific T cells by PD1 checkpoint blockade, chromatin states only changed minimally and ultimately drove T cells to reenter their previous functional and transcriptional exhausted state [6].

Together, these findings demonstrate that exhaustion of virus-specific T cells during chronic infection and tumor-specific T cells in tumors and their therapeutic reprogrammability are epigenetically encoded and suggest that effective immunotherapeutic strategies might require targeting the epigenome of T cells [50,53].

Concluding remarks

Recent technological advances have provided important insights into the heterogeneity and programming of hyporesponsive T cell populations in chronic infection and cancer. It has become increasingly clear that distinct T cell subsets with distinct transcriptional and epigenetic programs and functional states harbor distinct requirements for therapeutic reprogramming. Future studies are needed to identify (i) the precise spatiotemporal factors that determine these distinct functional states, and (ii) which T cell differentiation states and

population subsets represent the critical cellular target(s) for immunotherapy, especially in the context of cancer.

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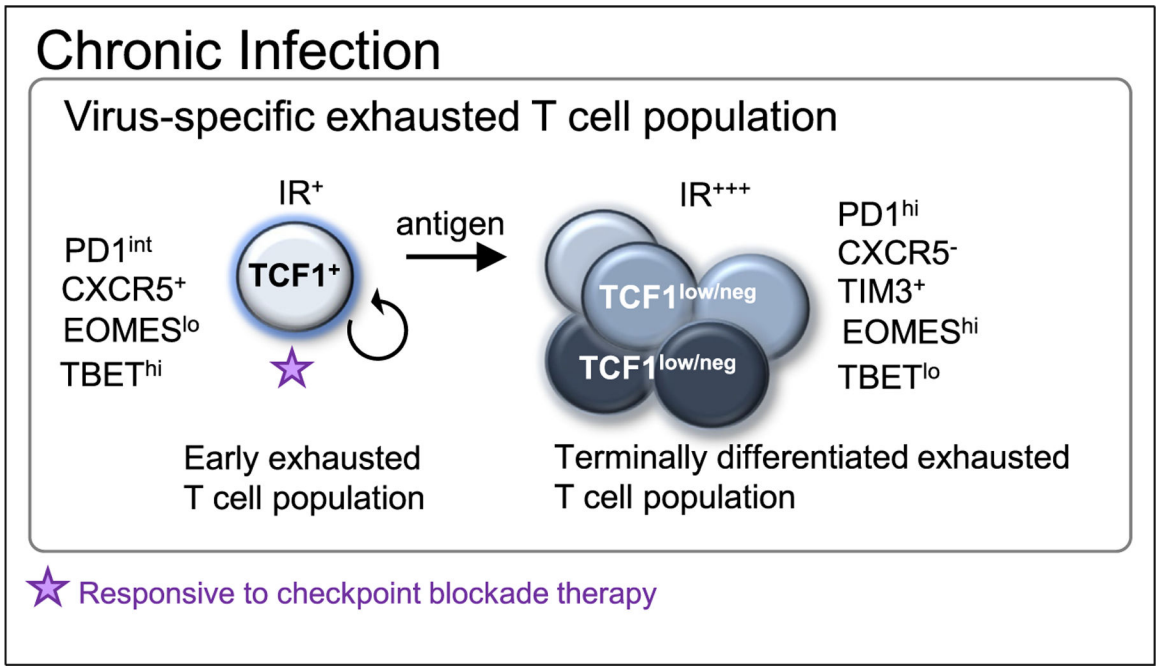

Figure 1. Heterogeneity of exhausted CD8 T cells during chronic viral infections.

Virus-specific exhausted CD8 T cells consist of an exhausted TCF1^{+} PD1^{int} T cell population with memory/stem cell-like characteristics which gives rise to a terminally differentiated, exhausted TCF1$^{low/neg}$ PD1^{hi}T cell population. PD1/PDL checkpoint blockade reinvigorates the TCF1^{+} PD1^{int} progenitor population but not the terminally differentiated TCF1 $^{low/neg}$ T cell population.

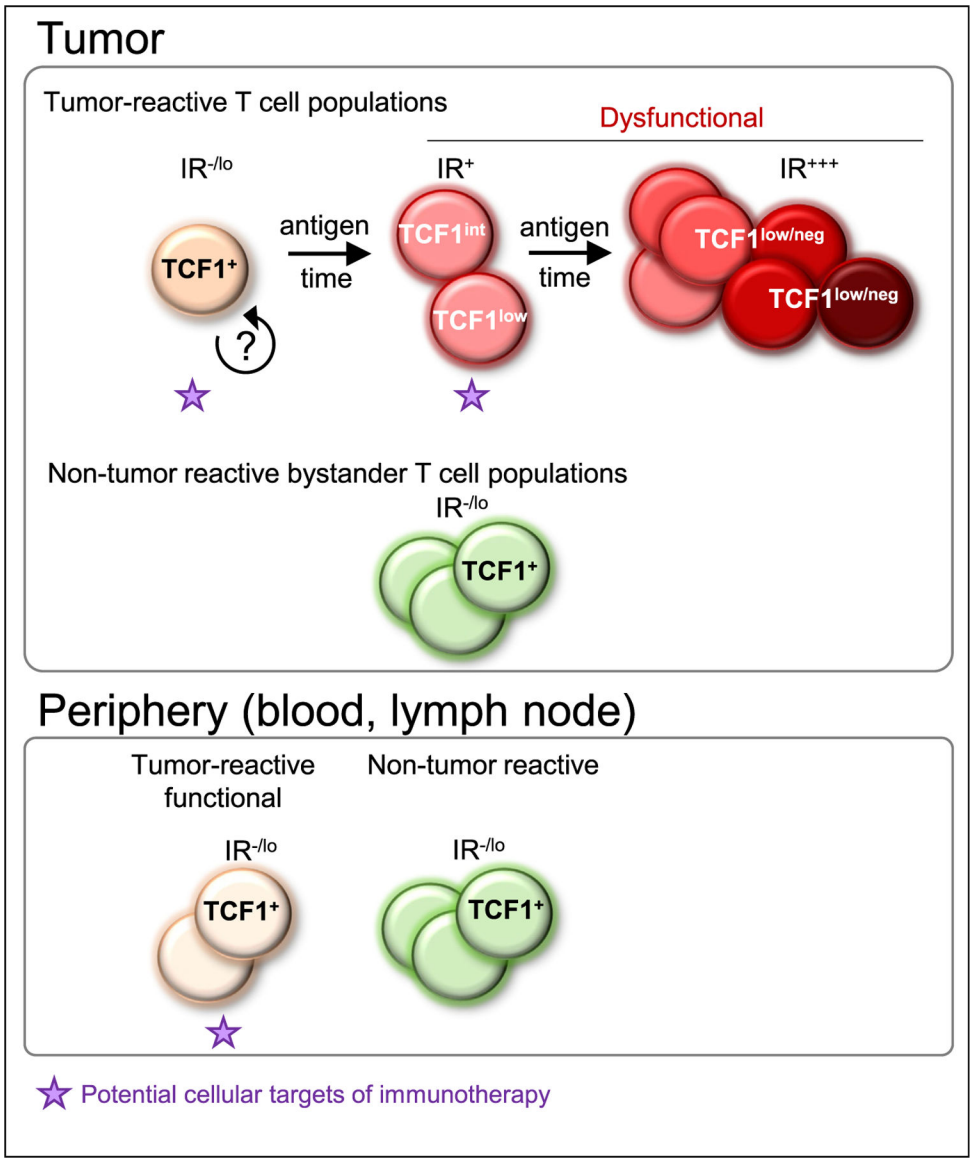

Figure 2. Heterogeneity of tumor-infiltrating lymphocyte (TIL) populations.

TIL are heterogeneous and include tumor-reactive and non-tumor reactive T cells. Non-tumor reactive, bystander T cells appear functional and cytotoxic, express high levels of TCF1 and no or low levels of inhibitory receptors (IR). Tumor-induced T cell dysfunction is progressive and various dysfunctional states exist depending on spatiotemporal factors including antigen burden and duration of tumor antigen exposure. Tumor-specific T cells are initially TCF1+ but with time lose TCF1 expression, become TCF1 $^{low/neg}$, and upregulate numerous inhibitory receptors (IR+++). It is currently not known if TCF1+ tumor-specific T cells represent a stable, self-renewing population. We hypothesize that, in human tumors, as seen in autochthonous tumor mouse models, reprogrammable and non-reprogrammable dysfunctional T cells may be present. Tumor-reactive T cells are also found in the periphery (e.g. blood and lymph nodes) and typically do not have the ‘exhausted’ phenotype, and these T cells maybe the population most amenable to immunotherapy.