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T-cell exhaustion in allograft rejection and tolerance

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Abstract

Purpose of review—The role of T-cell exhaustion in the failure of clearance of viral infections and tumors is well established. There are several ongoing trials to reverse T-cell exhaustion for treatment of chronic viral infections and tumors. The mechanisms leading to T-cell exhaustion and its role in transplantation, however, are only beginning to be appreciated and are the focus of the present review.

Recent findings—Exhausted T cells exhibit a distinct molecular profile reflecting combinatorial mechanisms involving the interaction of multiple transcription factors important in control of cell metabolism, acquisition of effector function and memory capacity. Change of microenvironmental cues and limiting leukocyte recruitment can modulate T-cell exhaustion. Impaired leukocyte recruitment induces T-cell exhaustion and prevents allograft rejection.

Summary—Preventing or reversing T-cell exhaustion may lead to prevention of transplant tolerance or triggering of rejection; therefore, caution should be exercised in the use of agents blocking inhibitory receptors for the treatment of chronic viral infections or tumors in transplant recipients. Further definition of the role of T-cell exhaustion in clinical transplantation and an understanding of the mechanisms of induction of T-cell exhaustion are needed to develop strategies for preventing allograft rejection and induction of tolerance.

Keywords

apoptosis; deletion; inflammation; metabolism; microenvironment; recruitment

INTRODUCTION

T-cell exhaustion is a state of T-cell dysfunction that arises during many chronic infections and cancers. It is characterized by sequential loss of interleukin (IL)-2 production,

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Conflicts of interest

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proliferative capacity, cytotoxic T-lymphocyte (CTL) activity, tumor necrosis factor (TNF)-α and interferon (IFN)-γ production and finally apoptotic death of the T cell [1]. Exhausted T cells express a variety of inhibitory receptors including programmed death 1 (PD-1), T-cell immunoglobulin and mucin domain-containing protein 3 (Tim-3), lymphocyte activation gene 3, cytotoxic T-lymphocyte–associated protein 4 (CTLA-4), B-lymphocyte and T-lymphocyte attenuator, killer cell lectin-like receptor subfamily G member 1 (KLRG1), 2B4 (CD244) and CD160, among others [2]. Blocking these inhibitory receptors reinvigorates exhausted T cells [3,4], and there are several ongoing trials testing the efficacy of targeting these molecules for the treatment of cancers and chronic viral infections [5]. Even so, the mechanisms of induction of T-cell exhaustion are not fully understood [6,7]. Currently, there is great interest, particularly among the microbe and tumor immunity researchers, in understanding the mechanisms of effective memory generation and avoidance or reversal of T-cell exhaustion for the treatment of chronic infections and cancers. However, induction of T-cell exhaustion may promote self-tolerance and transplant tolerance. Transplant tolerance is the culmination of a series of immunomodulatory events following transplantation that manifests as immunologic tolerance toward the graft in the absence of immunosuppression or generalized immunodeficiency. The series of immunomodulatory events likely involve natural regulatory T cells (Tregs), induced Tregs, clonal anergy, clonal contraction, exhaustion and deletion [8]. These mechanisms are not mutually exclusive and can occur simultaneously. Clonal deletion appears to be an important contributor to the development of durable tolerance [9,10]. Notably, T-cell exhaustion leads to attrition of polyfunctional memory T cells and thus contributes to clonal deletion [11]. It is also associated with poor memory generation [12]. Effective long-lived immunologic memory and predictable and durable tolerance are two ends of the spectrum of immune response to an antigen and are seemingly elusive goals of investigators in microbe/tumor immunity versus autoimmunity/transplantation, respectively. The bulk of the literature on T-cell exhaustion pertains to microbe and tumor immunity. The mechanisms of induction of T-cell exhaustion and its role in transplantation, however, are only beginning to be appreciated and are the focus of the present review.

T-CELL EXHAUSTION: A TERMINALLY DIFFERENTIATED STATE OR REVERSIBLE INHIBITION OF EFFECTOR FUNCTION?

Because of significant overlap in phenotypic and functional features of T cells with impaired function in chronic infections and cancers, the exhausted phenotype of T cells in these conditions, and perhaps in transplantation, has sometimes been variably referred to as anergy or senescence [13▪]. Exhausted T cells are characterized by the surface expression of a number of molecules, many of which are inhibitory receptors, including PD-1, Tim-3, CTLA-4, B-lymphocyte and T-lymphocyte attenuator, 2B4 (CD244), lymphocyte activation gene 3, KLRG1 and CD160 [2]. Blocking these inhibitory pathways either individually or in combination reverses the effector dysfunction of T cells, suggesting that T-cell exhaustion is an active process under the control of inhibitory pathways and not a terminally differentiated state. However, even though there is no single transcription factor that serves as an exhaustion determining factor, both exhausted $CD8^+$ and $CD4^+$ T cells have a distinct molecular profile from that of effector and memory T cells and share a core set of

transcription factors such as B-lymphocyte–induced maturation protein 1, basic leucine zipper transcription factor, activating transcription factor (ATF)-like and Helios [14▪▪]. Moreover, recent studies suggested that $CD8^+$ T-cell exhaustion maybe a stable and heritable state of differentiation representing functional adaptation of the T cells to protect the host from excessive immunopathology and at the same time provide some control of viral replication [15▪,16,17▪▪,18]. Regardless of what the ultimate terminology will be for this phenomenon, it is clear that under certain conditions the T cells progressively lose proliferative and effector capabilities that are up to a certain point reversible. More work is needed in better defining this phenomenon, understanding the mechanisms involved and identifying distinctive molecular and phenotypic markers of exhausted T cells.

EVIDENCE FOR T-CELL EXHAUSTION IN TRANSPLANTATION

Although T-cell exhaustion has been extensively studied in humans with cancers and chronic viral infections, until recently there were no studies describing this phenomenon in transplantation [19]. This, however, does not mean that the phenomenon of T-cell exhaustion does not occur in transplantation [20]. It is likely that it has been referred to differently, particularly as donor-specific hyporesponsiveness [21,22]. Several studies [23–28] have demonstrated that inhibitory pathways, such as CTLA-4:CD80/86, Tim-3:galectin-9 and PD-1:programmed death ligand 1/2 (PD-L1/2), that are upregulated in exhausted T cells also play a critical role in autoimmunity and transplant tolerance. CTLA-4 is expressed on exhausted T cells, more so on exhausted $CD4^+$ T cells [29], and there are data suggesting that CTLA-4 signaling is required for maintenance of transplant tolerance [27,30]. Similarly, signaling through Tim-3, which is also expressed on exhausted T cells, is required for the regulation of alloimmune responses [31–33]. Finally, the PD-1 pathway, recognized to play an important role in maintaining T-cell exhaustion, also plays a critical role in autoimmunity and transplant tolerance [23–27,34]. Together, these data can be viewed as indirect evidence supporting the notion that T-cell exhaustion may be one of the mechanisms of maintenance of transplant tolerance.

A more direct evidence of T-cell exhaustion in transplantation was provided by an elegant study [35▪▪] that demonstrated that a rapid and extensive activation and proliferation of the donor-reactive $CD8^+$ T cells in the initial period after liver transplantation was followed by $CD8^+$ T-cell exhaustion characterized by unresponsiveness and deletion of the alloreactive T-cell repertoire. The most direct evidence for T-cell exhaustion in transplantation was provided recently in a model of chronic allograft rejection [36▪] in which fucosyltransferase-VII–deficient ($Fut7^{-/-}$) recipients, with impaired selectin-dependent leukocyte recruitment, exhibited long-term graft survival with minimal vasculopathy compared with wild-type controls. Graft survival was associated with $CD4^+$ T-cell exhaustion in the periphery, characterized by impaired effector cytokine production, defective proliferation, increased expression of inhibitory receptors PD-1, Tim-3 and KLRG1, low levels of IL-7Rα on $CD4^+$ T cells and reduced polyfunctional $CD4^+$ memory T cells in the allograft. Blocking PD-1 reversed $CD4^+$ T-cell exhaustion and triggered rejection only in $Fut7^{-/-}$ recipients, whereas depleting Tregs had no effect in either $Fut7^{-/-}$ or wild-type (WT) recipients. The data summarized here taken together suggest that T-cell exhaustion plays an important role in promoting allograft survival and transplant tolerance.

FACTORS AFFECTING T-CELL EXHAUSTION

Antigen load and persistence are considered to be important factors in the development of T-cell exhaustion [37–42]. An interesting recent study [18] demonstrated that three different inocula of lymphocytic choriomeningitis virus (LCMV) result in different disease outcomes. A low dose of LCMV generated efficient $CD8^+$ T effector cells, which cleared the virus with minimal lung and liver lesions. A high dose of LCMV resulted in clonal exhaustion of T-cell responses, viral persistence and little immunopathology. An intermediate dose only partially exhausted the T-cell responses and resulted in significant mortality, and the surviving mice developed viral persistence and massive immunopathology, including necrosis of the lungs and liver. This suggests that for noncytopathic viruses such as LCMV, hepatitis C virus and hepatitis B virus, clonal exhaustion may be a protective mechanism preventing severe immunopathology and death. In the case of transplantation, the relationship between the mass of donor tissue transplanted and rejection or acceptance has previously been demonstrated in a study [43] showing that simultaneous transplantation of two kidneys and two hearts resulted in long-term graft acceptance, whereas single allogeneic heart and kidney graft were rejected acutely. Another study [35▪▪] extended these observations and demonstrated that $CD8^+$ T-cell exhaustion followed by deletion of the alloreactive T-cell repertoire was responsible for prolonged liver allograft survival compared with smaller-sized heart and kidney transplantation. Similarly, utilizing islet, skin and heart transplant models, it was demonstrated that a threshold T-cell frequency is required to mediate rejection [44], that a low ratio of T-cell frequency to donor tissue mass is a critical determinant of donor-specific hyporesponsiveness and graft survival [45] and that low-frequency donor-specific T-cell responses are regulated by the PD-1 pathway [46]. Interestingly, spontaneous tolerance induced by weakly mismatched grafts[47] and spontaneous murine liver allograft acceptance is dependent on PD-1:PD-L1 pathway, suggesting that T-cell exhaustion may be playing an important role in spontaneous transplant tolerance [48].

In situations in which donor tissue mass is relatively constant, adoptive transfer experiments in a single recipient with a heart transplant, T cells with differential ability to migrate to the allograft behaved very differently – T cells that could not migrate to the allograft exhibited features of exhaustion [36▪]. These data are consistent with a report that chemokine (C–C motif) ligand 5 (CCL5)-deficient ($CCL5^{-/-}$) recipients with impaired T-cell recruitment were unable to clear LCMV infection and $CCL5^{-/-}$ $CD8^+$ T cells exhibited features of exhaustion [49]. Together, these data strongly suggest that T cells might receive further ‘instruction’ at the site of action to become fully activated, generate effective memory and avoid exhaustion. Indeed, recent studies [50▪▪,51,52▪▪] confirm that exposure to inflammatory cytokines (type I interferon, IL-12 and IL-18 – a product of inflammasome activation) programs T cells for enhanced proliferation and effector function. Exposure to IL-12 makes the T cells less susceptible to exhaustion [53] and rescues exhausted T cells [54]. In keeping with this, inflammasome activation plays a critical role in the generation of effective innate and adaptive immune responses against infections [55,56]. Interestingly, several pathogens have evolved inherent mechanisms to avoid or inhibit inflammasome activation to evade the host immune response [57–59], perhaps by promoting pathogen-

specific T-cell exhaustion. Further, inflammasome activation seems to be critically required through adjuvants for an effective vaccine response [60]: complete Freund's adjuvant for experimental autoimmune encephalomyelitis and arthritis induction [61,62]; and alarmins for ischemia–reperfusion injury and allograft rejection [63].

A recent study indicated that von Hippel–Lindau-deficient $CD8^+$ T cells augmented glycolytic metabolism, expressed increased cytotoxic effector molecules, such as perforin, granzyme B, TNF-α and IFN-γ, and displayed enhanced control of viral infection and neoplastic growth in a hypoxia-inducible factor (HIF)-1α–dependent manner [64▪▪]. Thus, genetically activating the HIF pathway in T cells through loss of von Hippel–Lindau function bypasses exhaustion and is able to sustain the effector functions of $CD8^+$ T cells. Interestingly, in human kidney transplant recipients, expression of HIF-1α in infiltrating inflammatory cells in renal allograft biopsies correlated with the degree of rejection, chronic allograft dysfunction and poor long-term allograft survival [65]. These data suggest that hypoxia prevailing at sites of infection, tumor growth or graft microenvironment might regulate the differentiation and responses of T cells through the HIF pathway [66].

Lack of $CD4^+$ helps to exacerbate $CD8^+$ T-cell exhaustion, and restoration of $CD4^+$ help via adoptive transfer of $CD4^+$ T cells reinvigorates virus-specific responses [67]. IL-2 therapy synergizes with PD-L1 blockade in reinvigorating exhausted T cells [68]. In keeping with this, Treg cell ablation in chronically infected mice led to a striking rescue of exhausted virus-specific $CD8^+$ T cells. Interestingly, viral control was not achieved unless Treg cell depletion was combined with blockade of the PD-1 pathway. Thus, Treg cells maintain $CD8^+$ T cells in an exhausted state during persistent infections [69,70]. In another study [71], activation of CTLs by Treg-conditioned $CD80/86^{lo}$ dendritic cells within the tumor microenvironment promoted enhanced expression of both PD-1 and Tim-3 and induced a dysfunctional state in the tumor-infiltrating CTLs. Taken together, the tissue microenvironment appears to play a critical role in modulating T-cell exhaustion by presenting antigen to the T cells in a hypoxic and inflammatory milieu.

POTENTIAL STRATEGIES FOR INDUCTION OF T-CELL EXHAUSTION IN TRANSPLANTATION

Agents that inhibit migration of leukocytes are approved for clinical use in multiple sclerosis [72,73], and several others are in development for other inflammatory conditions. Even so, the fate of the autoreactive T cells that are prevented from migrating to the target organ in these inflammatory conditions remains unknown. The relatively high incidence of progressive multifocal leukoencephalopathy (a disease linked to chronic JC virus infection) with the use of these agents that block leukocyte recruitment [74] makes one wonder whether virus-specific T-cell exhaustion may have contributed, lending further support to the notion that targeting leukocyte recruitment may promote T-cell exhaustion. Further, $CCL5^{-/-}$ recipients with impaired T-cell recruitment were also unable to clear LCMV infection and $CCL5^{-/-}$ $CD8^+$ T cells exhibited features of exhaustion [49]. In the context of transplantation, the graft microenvironment is hypoxic and appears to be the predominant site of inflammasome activation following ischemia–reperfusion injury. Thus, the graft appears to provide both of the known factors (HIF stabilization and inflammatory cytokine

signaling) that prevent T-cell exhaustion. Therefore, it is tempting to speculate that if T cells are prevented from accessing the inflamed microenvironment of the graft, they might become exhausted from lack of additional signals from the target tissue. Indeed in a transplant model, *Fut7*$^{-/-}$ recipients with impaired selectin-dependent leukocyte recruitment exhibited long-term graft survival with minimal vasculopathy and features of CD4^{+} T-cell exhaustion. Adoptive transfer experiments confirmed that this CD4^{+} T-cell–exhausted phenotype is seen primarily in *Fut7*$^{-/-}$ CD4^{+} T cells. These data suggest that T-cell exhaustion contributes to prolonged allograft survival and impaired leukocyte recruitment is a novel mechanism leading to CD4^{+} T-cell exhaustion.

Targeting leukocyte recruitment may serve as a promising strategy to induce T-cell exhaustion, prevent allograft rejection and promote tolerance. Studies are needed to see whether limiting CD4^{+} help, targeting IL-2 and promoting Tregs may also promote T-cell exhaustion in transplantation.

CONCLUSION

The role of T-cell exhaustion in preventing allograft rejection and promoting transplant tolerance is being recognized. Exhausted T cells are characterized by expression of several transcription factors and inhibitory receptors contributing to their poor functional state. There are several ongoing clinical trials for the clinical development of agents targeting inhibitory pathways for reversing T-cell exhaustion and treating cancer and chronic infections [5,75,76▪▪,77]. There, however, have also been reports of adverse events related to immune activation and precipitation of autoimmunity [27,77], raising some concern regarding triggering transplant rejection. While, developing reagents that stimulate the inhibitory pathways to promote T-cell exhaustion to limit the immune response against self or transplant has proved challenging, limiting CD4^{+} help, modifying microenvironmental cues or limiting access of T cells to the microenvironmental cues, however, may prove as promising strategies to induce T-cell exhaustion to prevent allograft rejection and promote transplant tolerance.

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KEY POINTS

- T-cell exhaustion represents a poorly functional state of activated T cells that are under active control of inhibitory molecules.
- T-cell exhaustion plays an important role in shaping T-cell immunity against pathogens, tumors and allografts.
- Microenvironmental cues such as hypoxia and inflammatory cytokines modulate T-cell exhaustion. Limiting access of T cells to the hypoxic or inflamed microenvironment by targeting leukocyte recruitment may promote T-cell exhaustion.
- On the one hand, blocking inhibitory signals reverses T-cell exhaustion, reinvigorates T cells and promotes clearance of viruses and tumors, on the other hand, reversing T-cell exhaustion may precipitate allograft rejection or autoimmunity.