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Programmed T cell differentiation: Implications for transplantation

Rebecca L. Crepeau[a], **Mandy L. Ford**[a]

[a]Emory Transplant Center, Department of Surgery, Emory University, 101 Woodruff Circle, Suite 5208, Atlanta, GA 30322, United States

Abstract

While T cells play a critical role in protective immunity against infection, they are also responsible for graft rejection in the setting of transplantation. T cell differentiation is regulated by both intrinsic transcriptional pathways as well as extrinsic factors such as antigen encounter and the cytokine milieu. Herein, we review recent discoveries in the transcriptional regulation of T cell differentiation and their impact on the field of transplantation. Recent studies uncovering context-dependent differentiation programs that differ in the setting of infection or transplantation will also be discussed. Understanding the key transcriptional pathways that underlie T cell responses in transplantation has important clinical implications, including development of novel therapeutic agents to mitigate graft rejection.

Introduction

T cells are critical for protective immunity and for tumor surveillance, however, T cell responses against alloantigens are detrimental in the context of transplantation and are associated with graft rejection. T cell differentiation has been shown to be regulated by both cell-intrinsic transcriptional networks initiated following brief antigenic stimulation and also by cytokines in the environment. In this review we will focus on the transcriptional networks that regulate distinct programs of gene expression that control downstream effector or memory differentiation and function. Understanding these transcriptional pathways that program their development will facilitate the development of novel therapies to target these donor-reactive T cell populations.

Models of infection have shaped the majority of our understanding of programmed memory T cell differentiation, however recent reports have suggested that context-dependent programs exist, such that all of these lessons from models of microbial infection may not be applicable to the alloimmune response. This review will therefore focus on recent discoveries in the transcriptional regulation of T cell differentiation, specifically interferon regulatory factor 4 (IRF4), transcription factors associated with Th1 differentiation (Tbet

Corresponding author: Mandy Ford, Mandy.Ford@emory.edu.

and Eomesodermin) and the transcriptional regulation of tissue-resident memory cells (Trm). The impact of these results on the field of transplantation, as well as instances in which model-specific differences exist will also be discussed.

IRF4: A potent regulator of CD4+ T cell differentiation

Transplant-specific role for IRF4 in restricting T cell exhaustion

Since its essential role in lymphocyte biology was discovered 20 years ago [1], IRF4 (Interferon regulatory factor 4) has been primarily implicated in mediating the development and function of $CD4^+$ T cell subsets, including Th2 [2–4], T follicular helper (Tfh) [5], Th9 [6–8], Th17 [9–11] and T regulatory cells (Tregs) [12, 13]. However, IRF4 is also a central regulator of T helper 1 (Th1) responses. Among $CD4^+$ T cell subsets, alloreactive Th1 cells have been shown to cause allograft damage directly through Fas-Fas ligand–mediated cytotoxicity, or indirectly through the promotion of cytotoxic $CD8^+$ T cells [14]. Like $CD8^+$ T cells in chronic infection, graft-infiltrating $CD4^+$ T cells express high amounts of IRF4 [15].

It has recently been demonstrated that IRF4 deficient $CD4^+$ T cells showed impaired Th1 differentiation after *in vitro* and *in vivo* activation and that this was linked to impaired aerobic glycolysis and oxidative phosphorylation in the IRF4 deficient cells compared to controls [16, 17]. This finding was shown to be functionally relevant in a model of murine heterotopic cardiac transplantation by Wu et al. [15], where fully MHC-mismatched heart allografts survived indefinitely in mice where IRF4 was deleted conditionally in $CD4^+$ T cells and where no other immunosuppressive therapies were administered. Interestingly, only IRF4, and not BATF- or STAT3-deficient animals, permanently accepted fully allogeneic Balb/c hearts [15] which is exceptional as there are very few single gene knockouts in which the rejection of fully allogeneic transplants is completely prevented. Of note, $CD4^+$ and not $CD8^+$ T cells are necessary and sufficient for allograft rejection in this model.

Of particular interest was the mechanism by which these animals became tolerant. It was not simply a matter of fewer allo-specific $CD4^+$ T cells, nor was it Treg-mediated, as IRF4-deficient Treg cells are actually *less* suppressive than wild-type Tregs and their depletion does not result in rejection [15]. Tolerance was achieved in this setting through an IRF4-mediated *repression* of the expression of essential molecules associated with T cell dysfunction, namely PD-1 [15]. T cell dysfunction, such as exhaustion and anergy, represents a distinct T cell differentiation state following antigen encounter [18] and results in the induction of essential negative regulators that inhibit T cell function, like PD-1, amongst others [19]. This report of IRF4-mediated repression of T cell exhaustion is consistent with previous studies where IRF4-deficient T cells exhibited severe functional defects in T cell–mediated responses to microbial infection, allergy, graft-versus-host reaction, and autoimmunity [1, 6, 9, 20].

However, IRF4 has also been shown to drive the differentiation of cytotoxic effector $CD8^+$ T cells [20–24]. Like in $CD4^+$ T cells, IRF4 controls the expression of transcription factors involved in $CD8^+$ effector cell differentiation including BLIMP1, *Runx3, T-bet* and TCF-1,

as well as effector proteins such as cytokines and cytolytic proteins [23–25]. IRF4 is also involved in the metabolic changes of $CD8^+$ T cells following activation. Dynamic reprogramming of metabolism is essential for T cell effector function and memory formation and compromised metabolic fitness has been closely linked to the functional impairments of exhausted T cells. IRF4 expression levels correlate with the strength of the TCR signal, thereby linking TCR affinity with the extent of metabolic changes following $CD8^+$ T cell activation [25]. Interestingly, PD-1 signaling has also been shown to directly contribute to establishing the metabolic impairments of exhausted T cells [26], suggesting that exhaustion is underpinned by substantial rewiring of TCR signaling-mediated metabolic processes.

Interestingly, in a companion paper to Wu et al. [15], and in contrast to their findings for $CD4^+$ T cells in transplantation, Man and colleagues [27] showed that while IRF4 was required for the initial expansion and subsequent maintenance of antigen-specific $CD8^+$ T cells, high amounts of IRF4 *promoted* the establishment of T cell exhaustion in antigen-specific CD8+ T cells during chronic viral infection, including expression of the inhibitory receptors PD-1, TIM-3, and LAG-3, as well as altered cellular metabolism, and impaired cytokine secretion compared to fully functional effector and memory T cells [27].

Furthermore, they showed that IRF4, BATF, and NFAT (another TCR signaling-induced transcription factor) form a triplet that directly binds to and represses the expression of *Tcf7*, which encodes TCF1, and plays a critical role in the establishment of long-term memory T cells [28–32] thereby creating a self-reinforcing transcriptional circuit that establishes a network which promotes T cell exhaustion during chronic infection [27]. Importantly, reducing the dosage of IRF4 was sufficient to decrease expression of PD-1, increase anabolic metabolism, and partially restore secretion of IFN-γ, as well as release *Tcf7* from repression, thus allowing for the development of memory-like T cells despite persistent viremia during chronic infection [27].

What might lead to such a dramatic model-specific and/or cell-specific difference in function for IRF4? There are several potential explanations. First, analysis of publically available genome-wide binding data shows that IRF4, BATF, and NFATc2 are often recruited to adjacent binding sites and preferentially co-occupy exhaustion-specific genes in $CD8^+$ T cells, such as *Pdcd-1* (encoding PD-1) [27]. In contrast, no evidence for this association was found in wild-type $CD4^+$ T cells [15]. Rather, increased PD-1 expression correlated with the upregulation and binding of Helios (*Ikzf2*) to the *Pdcd-1* locus and forced Helios expression promoted PD-1 expression in activated wild-type $CD4^+$ T cells and since IRF4 represses Helios, PD-1 expression is not induced in activated wild-type $CD4^+$ T cells [15]. Indeed, Helios expression is a feature of exhausted $CD4^+$ but not $CD8^+$ T cells [33].

Importantly, the initial dysfunctional state described on $CD4^+$ Th1 cells by Wu et al. [15] in the setting of transplantation was shown to be reversible via blockade of the PD-1/PD-L1 signaling pathway during the initial days post-transplant, however it progressively evolved into a terminal irreversible state within 30 days post-transplant [15, 34]. Given this, as well as the recent reports describing graft rejection in stable transplant patients who were treated with PD-1 blockade for subsequent metastatic cancer [35, 36], pharmaceutical inhibition of IRF4 could be a potential novel therapeutic approach for transplantation.

Indeed, Wu et al. [15] found that the FDA approved MEK inhibitor, trametinib, effectively diminished IRF4 expression on activated $CD4^+$ T cells and transient trametinib treatment prolonged allograft survival [15] further suggesting that targeting IRF4 may be a promising new therapy in the setting of transplantation. However, given the findings of Man et al. [27], the effects of IRF4 depletion therapy on CD8-mediated protective T cell responses should be closely monitored.

IRF4 is critical for IL-10 mediated Tr1 suppressive function

Recently, an additional role for IRF4 has been discovered in a subset of $CD4^+$ regulatory T cells that are Foxp3 negative [4, 37, 38]. These cells, termed Type 1 regulatory (Tr1) cells, are driven by IL-27 and exert their immune regulation via secretion of IL-10 [39–43]. Although much is known about the development and function of traditional Treg cells, much less is known about the Tr1 subset, making the connection to the role of IRF4 in their development all the more compelling.

Interestingly, high spontaneous production of IL-10 or a polymorphism in the IL-10–592A allele has been observed to provide bone marrow transplant recipients with more favorable outcomes and fewer complications [44–47]. These observations led to a good deal of work to determine whether this alternative regulatory mechanism may play a role in promoting transplant tolerance. For instance, it has been shown that either through the adoptive transfer of IL-10 producing, Ag-specific Tr1 cells [48], or by pharmacological treatment with rapamycin plus IL-10, that active antigen-specific, long-term tolerance can be achieved in a murine model of allogeneic islet transplant via induction of Tr1 cells [49].

Tr1 cells may also play an important role in inducing transplantation tolerance in humans, as peripheral blood mononuclear cells (PBMC) isolated from patients who underwent islet transplant and became insulin independent produced significantly more IL-10 when compared with transplant subjects that continued to be insulin-dependent [47] and patients who spontaneously developed tolerance to kidney or liver grafts were shown to have an increased induction of Tr1 cells [50]. Taken together, these data indicate that IL-10-producing Tr1 cells may be naturally involved in inducing tolerance to allotransplants and targeting this population for expansion has potential to be therapeutic.

Specifically, Huang et al. [37] recently found that the Ras/MAPK pathways, downstream of T cell receptor (TCR) and IL-2 inducible T cell kinase (ITK) signaling, leads to IRF4 expression during Tr1 cell differentiation and that this expression is critical for the suppressive function of Tr1 cells [37]. These findings add to the reports of coordinated signaling of ITK and IRF4 in regulating Th9 cell differentiation [51]. Additionally, around the same time, a second group discovered that an IRF4-aryl hydrocarbon receptor (AhR)-dependent transcriptional network, induced by the cytokine Activin-A, also generates suppressive human Tr1 cells [38]. This was found to be due to IRF4 and AhR binding to IL-10 and ICOS promoter elements that controlled gene expression in human $CD4^+$ T cells [38]. Indeed, silencing IRF4 abrogated the Activin-A–driven *IL10* and *ICOS* up-regulation and thus impaired the suppressive functions of human Tr1 cells [38].

Since the ex vivo generation and expansion of Ag-specific nTreg cells remains a major challenge, the use of Tr1 cells, which are inducible Tregs and therefore able to be more easily generated *in vitro* in the presence of high levels of IL-10 and TCR stimulation [48], or by molecular manipulation [52] to be of the desired Ag specificity, the use of these cells for immunotherapy is a promising avenue for transplantation. By understanding the programmed development of Tr1 cells will facilitate the development of immunotherapies targeting this population to promote expansion and increased suppressor function *in vivo*.

T-bet and Eomesodermin: New mechanisms of old tricks

Active repression of non-Th1 CD4$^+$ subsets by T-bet

It has recently come to light that T-bet plays an active role in repressing other CD4$^+$ subsets via suppression of the Th17 master transcription factor RORγt [53]. This role for T-bet is of clinical relevance since in transplantation a role for Th17-mediated rejection has recently become appreciated. For instance, Yuan et al. [54] and Burrell et al. [55] have reported that Tbet deficient animals exhibited accelerated rejection associated with infiltration by predominantly IL-17–producing CD4 or CD8 T cells. More directly, blockade of this pathway through the use of IL-17 neutralizing antibodies or of IL-17 or RORγt deficient mice has shown prolonged renal and heart allograft survival as well as decreased severity of graft-versus-host disease (GVHD) [54, 56, 57]. Finally, Th17-producing memory cells from renal transplant recipients were shown to express high levels of the coinhibitory receptor CTLA-4 and thus are uniquely sensitive to CTLA-4-mediated inhibition [58]. This characteristic makes these cells resistant to CTLA-4 Ig-based costimulation blockade therapy, which blocks CTLA-4 as well as the intended CD28 target. Indeed, patients who experienced rejection while on belatacept exhibited increased frequencies of circulating Th17 cells relative to patients who were stable on belatacept or those that experienced rejection on tacrolimus. [58].

In addition to Th17 cell differentiation, Amarnath et al. [59] and Wang et al. [60] have recently described critical roles for T-bet in the regulation of Foxp3 expression in Tregs and for optimal T follicular helper (Tfh) cell responses, respectively. Th1, Th2, and Th17 cells have been shown to mediate acute GvHD syndromes, whereas Treg cells prevent acute GvHD and are associated with reduced clinical GvHD scores [59]. However, chronic GvHD is distinct from acute GvHD due to an autoimmune mechanism that is propagated by donor T cells that recognize host peptides presented by donor antigen-presenting cells [59]. Animal models have shown that a decrease in Treg cell numbers occurs along with an expansion of Th1 and Th17 cells leading to autoimmune-like pathology. Tbet has been shown to be vital for the development of acute GvHD [57], while its role during chronic GvHD is less clear.

Using a murine chronic GvHD model of alloreactive T-cell transfer, Amarnath and colleagues [59] found that the ability of transferred cells to secrete IFNγ did not affect the disease course, due to an equivalent ability to proliferate and traffic to target organs, even in the absence of IFNγ signaling [59]. Besancon et al. [61] have published similar findings in that T-bet, which is highly expressed in CD4$^+$ and CD8$^+$ graft-infiltrating T cells, but not IFNγ, is necessary for the development of an alloimmune response against fully mismatched pancreatic islet allografts [61]. Indeed, T-bet deficient mice permanently accepted allogeneic

islets in 100% of cases and this correlated with a dramatic reduction of T cells expressing perforin, GzmB, and FasL and with their ability to produce IFNγ and TNFα [61]. However, in the absence of IFNγ signaling *and* deletion of T-bet, they found a cumulative increase in Treg cell numbers both in the secondary lymphoid organs and in GvHD target tissues in T-bet deficient recipients, associated with the generation of peripheral Treg cells from $CD4^+$ T cells that had been primed in an alloreactive environment and this correlated with decreased pathogenesis [59].

Mechanistically, they found that T-bet directly binds to the *Foxp3* promoter, thereby identifying a novel regulatory mechanism by which T-bet modulates peripheral Treg generation [59]. These results suggest that adoptive Treg cell therapy strategies currently being pursued to treat chronic GvHD may not be fully effective until methods to control Th1 signaling can be harnessed and the T-bet pathway therefore provides a feasible target in efforts to prevent chronic GvHD.

Importantly, taken together, this work suggests that by specifically inhibiting type II IFNγ receptor signaling, one might be able to augment Treg cells during chronic GvHD while maintaining type I mediated anti-viral responses. Thus, interventions that restrict the T-bet pathway might either be used alone or in combination with adoptive Treg-cell therapy for treatment of autoimmune chronic GvHD.

T-bet has also been shown to directly control the generation and function of Tfh in a context-dependent manner [60, 62]. As a $CD4^+$ helper T cell subset specialized to aid in the germinal center (GC) reaction, Tfh cells have been reported to play important roles in many different types of immune responses [63–68]. Specifically, Wang et al. [60] found that while T-bet was dispensable for the early fate commitment of Tfh cells, it was essential for their maintenance by promoting their proliferation and inhibiting their apoptosis during acute viral infection [60]. Interestingly, T-bet deficient mice exhibited significant loss of Tfh cell responses during acute viral infection, but not in the setting of protein immunization [60], indicating a context dependent role for Tbet. These findings are of significant interest to the field of transplantation as a growing body of literature has uncovered an important role for Tfh cells in the generation of donor-specific antibody and subsequent allograft rejection [69–77]. Understanding the potential transplant-specific role for Tbet in promoting Tfh differentiation given these newly reported findings in the setting of infection and immunization may hold potential in developing Tfh-specific immunotherapies.

Complementary role for Eomesodermin in CD8+ T cell differentiation

Interestingly, it was noted early on that although $CD4^+$ T cells and natural killer (NK) cells from T-bet deficient mice were defective in their ability to express IFNγ, $CD8^+$ T cells could produce normal levels of IFNγ and had normal cytolytic function [78]. This implied a T-bet–independent pathway for effector differentiation of $CD8^+$ T cells. Indeed, eomesodermin (Eomes), another T-box factor sharing 74% homology with T-bet and formally only known for its role in development, was found to be highly expressed in activated $CD8^+$, but not $CD4^+$ T cells in the absence of T-bet [79–81]. Further studies revealed that Eomes was co-expressed with perforin and GzmB on activated T cells indicating its likely role in invoking the cytolytic effector lineage. Thus, Eomes complements the role of T-bet in regulating

cellular immunity by providing redundancy and acts cooperativity to induce T cell effector genes [79].

Since its discovery in T cells, much work has been done to further characterize the role of Eomes in $CD8^+$ T cell differentiation [22, 79, 82–86]. Specifically, Banerjee et al. [82] observed a diminished capacity of $CD8^+$ T cells lacking Eomes to compete within the Ag-specific memory population which led to defects in long-term persistence and secondary expansion post-rechallenge. These results suggest that Eomes confers competitive fitness to memory cells and supports a role for Eomes in promoting the persistence of long-lived memory ($CD127^{hi}$ KLRG-1^{lo}) rather than terminal effector ($CD127^{lo}$ KLRG-1^{hi}) cell differentiation of Ag-specific $CD8^+$ T cells [82]. Further, Paley et al. [84] discovered that during chronic viral infections, Eomes expression in virus-specific $CD8^+$ T cells was associated with markers of severe exhaustion and reduced co-production of antiviral cytokines.

While Th1 responses and T-bet expression have been linked to allograft rejection [87, 88] there is much less known about the role of Eomes in the regulation of alloimmunity. It has been shown that kidney transplant patients with primary cytomegalovirus (CMV) infection have increased expression of both T-bet and Eomes on CMV specific $CD8^+$ T-cells [89]. Relatedly, we have recently identified a context-dependent differentiation program in which antigen-specific $CD8^+$ T cells primed by a skin graft have increased recall potential and express less KLRG-1 and more CD127 compared to those primed by viral infection, which suggests that the T cell differentiation program induced in the context of transplantation is distinct from that induced in the context of exposure to a viral pathogen [90]. However, a specific role for Eomes in this dichotomy has not yet been established.

However, Ezzelarab and colleagues [85] recently observed that Eomes expression, but not T-bet expression, was upregulated on $CD8^+$ T cells from transplant patients with stable graft function at 3-months post-transplant [85]. Interestingly, this high Eomes expression was correlated with an enhanced effector phenotype in allo-stimulated $CD8^+$ T cells, independent of T-bet expression. Consistent with these findings, we have recently identified a subset of highly activated, effector $CD8^+$ T cells that express the inhibitory Fc receptor FcγRIIB which preferentially inhibits $CD44^{hi}CD62L^{lo}$ and $Eomes^{lo}$ cells [91].

Fcγ receptors play a pivotal role in immunity, controlling innate and humoral immunity by activating the effector functions of antibodies. Through both pharmacologic targeting of FcγRIIB, as well as $CD8^+$ T cell-specific genetic deletion of *Fcgr2b*, we have shown that loss of this inhibitory molecule leads to the increased accumulation of $CD8^+$ effector T cell resulting in accelerated graft rejection in mouse models. Moreover, $Fc\gamma RIIB^+$ cells have lower transcripts of CD62L and Eomes, suggesting that FcγRIIB ligation may induce a negative signal in $CD44^{hi}CD62L^{lo}$ and $Eomes^{lo}$ effector T cells that are induced to undergo apoptosis. Additionally, increased expression of FcγRIIB on $CD8^+$ T cells correlated with freedom from rejection following withdrawal from immunosuppression in a clinical trial of kidney transplant recipients [91]. Because Eomes and CD62L are canonical molecules associated with high-quality memory T cell differentiation (reviewed in [92]), these data suggest that FcγRIIB functions to inhibit highly potent effector cells.

Regulation of T-bet by mTOR and implications for transplantation

Depending on the cytokine milieu available in the environment, $CD4^+$ effector T cells differentiate into Th1, Th2, Th9, or Th17 subsets with different cytokine profiles and distinct functions. Th1 differentiation is initiated primarily through the induction of T-bet, a T-box transcription factor, leading to enhanced production of IFNγ [93]. For almost 20 years, much work has been conducted to understand the mechanisms by which T-bet regulates the expression of IFNγ, and thus drives differentiation of effector $CD4^+$ and $CD8^+$ T cells [83, 94–99].

mTOR serves as a core component of two distinct protein complexes, mTORC1 and mTORC2, which regulate different cellular processes [100, 101]. Recently, Chornoguz and colleagues [102] discovered 3 novel T-bet phosphorylation sites that were mTORC1 dependent, leading to T-bet's ability to induce IFNγ production in $CD4^+$ T cells [102]. One mechanism by which T-bet controls the expression of its target genes is by recruiting cellular machinery that delivers permissive and eliminates prohibitive epigenetic modifications. Consistent with this, simultaneous mutation of the three novel mTORC1-dependent phosphorylation sites discovered by Chornoguz et al. were found to reduce the T-bet mediated recruitment of chromatin remodeling complexes to the *Ifng* promoter [102]. These findings link mTOR-associated T cell activation with the induction of T-bet and production of IFNγ. Of note, these novel phosphorylation sites discovered in the mouse T-bet protein are also present in human T-bet [102].

Rapamycin, a macrolide antibiotic and immunosuppressive agent, has been clinically developed into two derivatives sirolimus and everolimus, which were approved by the Food and Drug Administration (FDA) for use in transplantation in 2001 and 2012, respectively [103]. Recently, intriguing data suggesting that a switch to, or the addition of, an mTOR inhibitor to the immunosuppressive regimen may aid in the successful management of posttransplant malignancies [104–106] which have historically been contraindicated for immune checkpoint inhibitor treatment, such as anti-PD-1 therapy, due to reports of upwards of 80% of patients experiencing rejection events and high overall patient mortality rates [36, 107, 108] when treated in this manner.

Specifically, Esfahani and colleagues [109], showed that pembrolizumab, an anti-PD-1 monoclonal antibody therapy, in combination with sirolimus led to the abatement of global T cell activation and proliferation, but maintained numbers of IFNγ-producing $CD4^+$ T cells and cytotoxic $CD8^+$ T cells within the circulation, thereby promoting a state of functional tolerance without a loss of immune-mediated anti-tumor activity [109]. Mechanistically, they showed that the eosinophilia-mediated allograft rejection associated with anti-PD-1 therapy [110–112] was brought under control by the addition of sirolimus [109], likely due to the effect of mTOR inhibition on T-bet-mediated recruitment of eosinophils to the graft [113–116], which can be linked to mTORc1 phosphorylation in light of Chornoguz et al.'s recent findings [102]. Interestingly, although not often discussed, eosinophilia-mediated rejection has long been noted clinically [117, 118], as has a role for Tbet expression in $CD4^+$ T cells in the recruitment of eosinophils to the airways in the setting of asthma [113, 119], infection [114] and allergens [116]. It is interesting to speculate in light of the findings of Chornoguz et al. [102] that a similar mechanism is at play in the setting of transplantation.

It has long been thought that primarily Th1 effector $CD4^+$ T cells as well as cytotoxic $CD8^+$ T cells are required to mediate acute allograft rejection; however, a growing body of evidence suggests this is not the case. For instance, studies in a murine model of fully mismatched pancreatic islets have shown that IFNγ is not absolutely required for rejection of allogeneic islets or fully mismatched cardiac allografts; as IFNγ deficient mice were shown to rapidly reject their allografts [120–124]. Several studies have shown that this is directly linked to reduced T-bet expression, as T-bet deficiency contributed to the development of aggressive $CD4^+$ and $CD8^+$ $Th17^+$ cell–mediated alloimmune responses that ultimately culminated in accelerated rejection that was costimulatory blockade resistant [54, 55, 58, 125, 126].

Moreover, mTOR has emerged as an important integrator of environmental cues which guide T cell effector and memory differentiation [86, 101, 127–130]. Interestingly, we have previously observed that blockade of the mTOR pathway, via exposure to rapamycin, paradoxically increases the quantity and quality of antigen-specific $CD8^+$ T cell responses when the antigen is presented in the context of a viral infection, but fails to do so when the antigen is presented in the context of a transplant [131], consistent with other instances of context-dependent differentiation pathways.

Tissue-resident memory cells: Important passengers with implications for tolerance or rejection

Tissue-resident memory T (Trm) cells are a subset of long-lived memory T cells that are broadly distributed anatomically and occupy non-lymphoid tissues (NLT) without recirculating [132–137]. They are transcriptionally, phenotypically, and functionally distinct from recirculating central and effector memory T cells [138]. Their restricted anatomical localization in combination with their effector memory phenotype enables Trm cells to rapidly respond to local antigens [139]. However, these characteristics also make them potential mediators of both acute and chronic allograft rejection.

Trm are most commonly identified by their constitutive expression of CD69, which is induced upon migration to their site of residence where it antagonizes S1PR1-mediated tissue egress, allowing maintenance in NLT [138, 140–144]. However, recent evidence has shown that the functional requirement for CD69 is actually highly variable, depending on the tissue examined, playing no detectable role in generation of Trm at some sites and yet critical at others [145].

CD103, the receptor for the epithelial cell-specific ligand E-cadherin, is another universal marker of Trm cells and has long been known to endow peripheral $CD8^+$ T cells with a unique capacity to access and damage the epithelial compartments of organ allografts [146–151]. More recently a direct link to a potential role for this molecule on Trm cells was made using transplant nephrectomies from immunosuppressed patients. Baan and colleagues [152] studied the presence, provenance (donor or recipient), and effector phenotype of $CD103^+$ vs. $CD103^-$ $CD69^+$ Trm cells and found that Trm cells are indeed present in the renal allograft, have strong immunostimulatory capacity, and finally, that the donor-derived cells present within the graft are mainly $CD103^+$ Trm cells which are replaced by recipient-derived T

cells within five months after transplantation [152].These data document a causal role for $CD103^+CD8^+$ T cells in promoting graft injury following allogeneic transplantation and suggest that targeting $CD103^+$ T cells is a conceivable immunosuppressive target for combatting this highly cytolytic population.

The concept of donor-derived memory T cells present in, or being transferred along with the graft contributing to alloimmunity is not a new one [153–155] and yet still commands attention. A recent study showed that the presence of passenger $CD4^+$ T cells in a donor cardiac graft enhanced cellular and humoral immune response in the recipient leading to acute graft rejection [156]. We and others have also shown that this augmentation is enhanced when donors are pre-sensitized to the recipient [156, 157]. Additionally, Zundler et al. [158] recently reported the accumulation of $CD4^+$ Trm in the gut mucosa of patients with Inflammatory Bowel Disease (IBD) which predicted disease flares. Importantly, they found that depletion of this population led to the suppression of colitis activity, indicating the therapeutic potential of targeting this population [158]. Indeed, ex vivo lung perfusion in the setting of transplantation has been shown to reduce donor leukocyte transfer into the recipient as well as decrease recipient T cell infiltration into lung allografts [159], indicating the potential to target depletion of Trm cells through perfusion. This is a promising therapeautic option, as the systemic administration of immunosuppressive agents has been shown to spare local tissue-resident T cell populations [160].

However, it is not a foregone conclusion that donor-derived memory T cells are bad and indeed several studies have shown a potentially beneficial role for this population [161–166]. Interestingly, it has recently been noted that the presence of Trm in lung and breast tumors [167–169], as well as in the livers of patients with chronic Hepatitis B Virus (HBV) infection [170], is associated with a better prognosis and better viral control, consistent with their important role in localized protective immunity. Sykes and colleagues [166, 171] have also shown T cell chimerism in the absence of graft-*versus*-host disease (GVHD) in the setting of human intestinal transplantation [166]. This chimerism led to two-way alloreactivity which dramatically impacted the rate of recipient T cell replacement in the graft mucosa, indicating the potential for donor-derived cells with graft specific TCR clones to have a positive effect by slowing down the threat of recipient-derived T cells and thus the development of rejection [171]. Thus, care and consideration must be taken in regards to depletion of this population given these data the potential exists that a rapid clearance of the donor-derived cells within the allograft may actually contribute to rejection [171].

In the setting of lung transplantation, periodic bronchoalveolar lavage (BAL) sampling of the airway enables prospective tracking of donor- and recipient-derived tissue resident T cells and the ability to potentially correlate tissue resident populations in patient BAL to clinical events [172]. Indeed, through a longitudinal single cell analysis of blood and BAL samples from more than 20 lung transplant recipients, Snyder et al. [172] was able to demonstrate through phenotypic, functional, and transcriptional analyses, that donor-derived T cells persist for more than one year post-transplantation in lung allografts as Trm T cells [172]. Rather surprisingly, they found that the long-term persistence of these donor lung Trm was associated with *reduced incidence* of clinical events that precipitate lung injury, including primary graft dysfunction, bacterial infection and acute cellular rejection [172].

This apparent discrepancy in the protective vs. pathogenic potential of Trm may be due to tissue specific Trm programing, which has recently been documented. For instance, compared to $CD8^+$ Trm cells in the skin and intestine, lung $CD8^+$ Trm cells are distinct at the transcriptional level [138], indicating specific adaptions to the local microenvironments.

Building off of their ground breaking 2013 paper in which they found a core Trm gene signature [138], Mackay et al. [173] further explored the genes encoding this signature and found the upregulation of *Zfp683* (*LOC100503878*), or "homolog of Blimp1 in T cells" (Hobit), which is a transcription factor that had previously been identified in NKT cells [174]. Additionally, Hobit was specifically up-regulated in Trm cells and worked synergistically with Blimp1 to drive the establishment of a Trm population in the skin, gut, liver and kidney of mice by silencing lymphocyte egress from the tissues and by repressing the development of circulating memory cells [141, 173, 175]. Interestingly, Behr et al. [176] found that Blimp-1, but not Hobit, is essential for the formation of lung $CD8^+$ Trm cells in the mouse. This finding highlights the unique transcriptional regulation of $CD8^+$ Trm cells in different tissues, which may have implications for immunosuppressive strategies in solid organ transplantation.

Additionally, Hobit plays a particular role in maintaining the long-term cytolytic capabilities of $CD8^+$ Trm cells within the tissue in both mice and humans [173, 177, 178] and Hobit rather than Blimp-1, is the essential transcriptional regulator in the long term maintenance of granzyme B-driven cytotoxicity of memory $CD8^+$ T cells [179]. Specifically, the transcriptional regulation of Trm cytotoxicity appears to be temporally separated in $CD8^+$ T cells with Blimp-1 *initiating* cytotoxic effector function and Hobit *maintaining* cytotoxicity in a deployment-ready state [179].

A third transcription factor, Runx3, has also been recently implicated in the differentiation and long-term maintenance of $CD8^+$ Trm cells [180]. Runx3 is a well-established regulator of $CD8^+$ T cell thymocyte development [181], and also supports cytotoxic activity of mature $CD8^+$ T cells [182]. Using a combination of computative predictive algorithms, Milner et al. [180] was able to predict Trm regulatory transcription factors and confirm their function using an *in vivo* RNA interference (RNAi) loss-of-function screen. They evaluated both barrier and non-barrier Trm cells in order to reveal transcriptional regulators independent of tissue site. Runx3 was uncovered as a novel regulator of Trm differentiation and indeed, *Runx3*-deficiency resulted in a 50–150-fold loss of $CD69^+CD103^+$ Trm cells in both barrier and non-barrier tissues [180].

Temporally depleting Runx3 through tamoxifen administration further showed a crucial role for Runx3 not only in the differentiation, but also in the maintenance of Trm cell homeostasis [180]. Of particular interest, unlike Hobit and Blimp-1 [176], Runx3 was shown to be a universal regulator of Trm cell specification and was not tissue specific [180]. Lastly, similar to many of the other T cell specific differentiation programs, Runx3 was also shown to repress genes characteristic of circulating cells and promote those of tissue residency [180, 183].

Given these exciting new findings, and owing to the functional potential of Trm and their sheer abundance in various transplantable organs, they are likely a significant contributor to allogeneic immune responses and it remains to be seen whether Trm populations may hinder or help the promotion of transplant tolerance and may in fact depend on the specific tissue being transplanted.

In summary, the last few years have illuminated many novel T cell differentiation pathways and furthered our knowledge of previously existing pathways. These discoveries arm researchers with powerful new information to facilitate the development of novel therapies for the treatment and prevention of allograft rejection. However, several studies have also shown context-dependent differentiation pathways [60, 62, 90, 131], indicating that findings regarding T cell differentiation programs induced in the context of exposure to a viral pathogen may not hold true in the context of transplantation. Thus, the model in which scientific discoveries are made should be an important consideration in the development of novel therapies.

Concluding Remarks

It is now firmly established that alloreactive T cells accelerate graft rejection and prevent transplant tolerance. Despite decades of research on developing new immunosuppressive therapies with fewer toxicities, we have made little progress toward one transplant for life. The past several years has seen significant advances in our understanding of the transcriptional networks that drive T cell-intrinsic differentiation. Here we outline a few of these exciting new discoveries and discuss their relevance to the field of transplantation. We and others are also exploring many other intriguing lines of inquiry beyond the scope of this review, especially T follicular helper (Tfh) and T follicular regulatory (Tfr) cell differentiation and the interplay between FoxP3, STAT5, BCL6 and BLIMP 1 and the potential for targeting these pathways therapeautically to prevent the development of alloantibody or to prevent GVHD [69–71, 184–188]. Harnessing this information to develop novel therapeutics to promote regulatory T cell expansion or to divert harmful differentiation pathways could be a powerful new tool to prevent allograft rejection.

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Highlights

- T cells play a critical role in protective immunity against infection, they are also responsible for graft rejection in the setting of transplantation.
- T cell differentiation is regulated by both intrinsic transcriptional pathways as well as extrinsic factors such as antigen encounter and the cytokine milieu.
- Herein, we review recent discoveries in the transcriptional regulation of T cell differentiation and their impact on the field of transplantation.
- Recent studies uncovering context-dependent differentiation programs that differ in the setting of infection or transplantation will also be discussed.
- Understanding the key transcriptional pathways that underlie T cell responses in transplantation has important clinical implications