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Implications of Resident Memory T Cells for Transplantation

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Abstract

Recent studies have established resident memory T cells (T_{RM}) as the dominant memory lymphocyte population surveying most non-lymphoid tissues. Unlike other memory T cell lineages, T_{RM} do not recirculate through blood and are permanently confined to their tissue of residence. T_{RM} orchestrate local immune responses and have been shown to accelerate local pathogen control in many experimental infection models. Here we briefly summarize recent advances in T_{RM} differentiation, maintenance and their protective function. While little is known, we have speculated on the potential implications of T_{RM} for transplantation biology. Areas of emphasis include the role of passenger T_{RM} in controlling latent viral recrudescence in donor organs, donor T_{RM} as a source of graft-versus-host disease (GVHD), the ability of T_{RM} to potentially induce inflammation through sensing and alarm functions and differentiation of host T cells into T_{RM} in response to local cues inside the allograft. Further investigation of T_{RM} in the context of transplantation might identify therapeutic targets to prolong graft survival.

Introduction

Memory T cells help protect against reinfections with pathogens, but may also contribute to immunopathology. They are long-lived, broadly distributed anatomically, and are rapidly activated after stimulation to express potent effector functions. However their lower threshold for activation along with faster response kinetics compared to naïve T cells make them a principal mediator of both acute and chronic allograft rejection in transplantation (1). Moreover current immunosuppressive regimens are significantly less effective against memory T cells owing to their lower reliance on costimulation (2,3). Maintaining graft tolerance without suppressing adequate protection against pathogens is an important but not fully achieved goal of transplant medicine. A better understanding of memory T cell generation, trafficking and immunosurveillance patterns could inform development of *de novo* therapies.

The paradigm of memory T cell circulation and immunosurveillance has very recently undergone a significant revision with the identification of resident memory T cells (T_{RM}). T_{RM} are non-migratory cells and comprise the most abundant memory T cell subset that

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patrols non-lymphoid tissues in both mice and humans; their total numbers rival that of recirculating subsets throughout the body (4–6). Mechanistic analyses have revealed that T_{RM} re-activation in tissues can induce potent inflammation and immune activation (7–9). It is well established that T_{RM} greatly accelerate control of many experimental reinfection events at frontline organs in mice, including local challenges with certain viruses, bacteria, and parasites (reviewed in 10–12). They have also, however, been implicated in several pathological diseases, which include autoimmunity and asthma (13,14). Owing to the functional potential of T_{RM} and sheer abundance in various transplantable organs, they could be a significant contributor to allogeneic immune responses. Accordingly T_{RM} -targeted therapies may need to be developed to ensure better allograft tolerance while preserving effective local infection control mediated by T_{RM} . Herein we summarize our current understanding of T_{RM} generation, function and behavior in response to infection and speculate on what role they might play in the setting of transplantation.

Memory T cells and their migration patterns

Naive T lymphocytes circulate between the secondary lymphoid organs, blood and lymphatics of the host in search of dendritic cells (DCs) presenting cognate antigen. Upon encountering appropriate antigen-bearing cells, naive T cells undergo an activation program and express effector functions that enable them to fight off the infection. These activated T lymphocytes are armed with selectins, chemokine receptors and integrins that allow them to migrate beyond the lymph-blood network and infiltrate non-lymphoid tissues (NLTs) to clear any pathogen localized to tissues. After clearance of infection, a fraction of activated cells further differentiate into memory lymphocytes that are present in both lymphoid and NLTs across the host. Previous studies of T cells in human peripheral blood divided memory T cells based on their expression of lymph node homing receptors CD62L and CCR7 (11,12,15). Those cells that expressed lymph node homing molecules were deemed central memory T cells (T_{CM}) because they were specialized to patrol the “the center” of the body, the lymph nodes (Figure 1). T_{CM} represent a resting population that is poised for extensive proliferation in the event that a secondary infection reaches the lymph nodes. Bloodborne memory T cells that lacked CD62L and CCR7 were proposed to embody the principal T cell population that surveyed NLTs for evidence of reinfection. These were referred to as effector memory T cells (T_{EM}), with the idea that this population not only patrolled frontline sites of infection (such as mucosal tissues, skin or solid organs) but was also specialized to execute rapid and potent effector functions rather than proliferate upon restimulation. Implicit in this model is the notion that all NLT memory T cells are recirculating, or in exchange with blood. Despite the appeal of this paradigm, the recirculation potential of bloodborne T_{EM} through NLT was not stringently tested.

For many years, several groups demonstrated that memory T cells isolated from multiple NLTs displayed unique surface markers that were absent from memory cells present in the blood (16–18). It was difficult to reconcile this compartment specific phenotypic disparity with a model of blood and tissue memory T cells being in migrational equilibrium. This prompted more stringent analyses into the trafficking dynamics of NLT memory T cell populations, and revealed that most cells in solid organs and barrier tissues were actually resident (4,5). These tissue-resident memory T cells (T_{RM}) are defined as a subset of non-

recirculating memory T cells permanently lodged in frontline barrier tissues including skin, mucosae and several non-lymphoid tissues. Research in the last few years has formally positioned this unique population as a dominant player in local immune responses.

Technical approaches to study T_{RM}

How does one determine if a population of cells is resident within a tissue? One approach is parabiosis. Here, the vasculature of two syngenic (or congenic) mice is conjoined resulting in a free exchange of blood-borne leucocyte populations. Parabiosis studies have revealed that most resting memory T cell populations in NLT fail to equilibrate (4,19). Rather, T cells seed NLT during a transient period of opportunity during the effector phase of the response (20,21). Other approaches to test residence include transplantation of tissue grafts (20,22) and selective antibody mediated depletion of circulating cells (7,23) (T cells parked within NLT are more difficult to deplete). When isolating cells from NLT, a major concern that can cloud interpretation of migration studies is the potential for bloodborne cells to significantly contaminate tissue preparations, even if the organ of interest is perfused. This can be addressed via *in vivo* antibody labeling (24). However these techniques are limited to experimental animal models, and some require a high degree of expertise. The simplest approach is to examine phenotypic markers commonly associated with residence, and this is the approach taken in human studies. Many T_{RM} are CD103+ ($\alpha_E\beta_7$) and most T_{RM} express CD69 (11). These markers however, are not absolute and major populations of T_{RM}, particularly those outside epithelia, do not express CD103. There are CD69-negative T_{RM} as well (4), although these are rarer than CD103-T_{RM}. Unfortunately, CD69 is also transiently expressed on recirculating populations in response to T cell receptor (TCR) stimulation or exposure to various cytokines, which compromises the utility of this marker, particularly in assays that require *ex vivo* stimulation to determine antigen specificity (e.g. intracellular cytokine assays). Additional markers, perhaps including the transcription factors Krüppel-like Factor 2 (KLF2) and Hobit, or T_{RM} specific signatures identified in genomic or proteomic screens, might provide more fidelitous lineage markers of T_{RM} (11,12,25).

T_{RM} generation and maintenance

CD8+ T_{RM} likely arise from common memory precursor cells that also give rise to long-lived circulating memory cells (11,12). These memory precursor cells are present among activated cells after infection and express CD127 and lack KLRG1 expression (Figure 2). Detailed investigation into skin T_{RM} development revealed that these memory precursors penetrated the epidermis soon after infection and slowly matured to T_{RM} after the resolution of infection (21). Migration of these T_{RM} precursors to the small intestine was also tightly controlled as intestinal mucosa is seeded by these cells early (4.5 days) after infection with lymphocytic choriomeningitis virus (20). Conversion of these precursor cells to T_{RM} is coupled with acquisition of a unique transcriptional signature that includes down regulation of tissue egress molecules, including KLF2, sphingosine-1-phosphate receptor-1 (S1PR1), and CCR7, and upregulation of cellular retention signals such as CD69. S1PR1 downregulation is associated with CD69 expression on T cells, putatively preventing T cells from following the S1P gradient present within afferent lymph and thereby preventing tissue egress (26). Accordingly, forced expression of S1PR1 was shown to impair T_{RM} formation

(25). Conversely, T cells lacking CD69 also fail to mature to long-lived T_{RM} in skin and lung following HSV-1 and influenza infection in mice (27,28).

A more recent study identified transcription factors Hobit and Blimp-1 to play a central role in T_{RM} maturation and their involvement was also critical for enforcing residency among other immune cell subsets (29). CD103 has also been implicated in T_{RM} maintenance. CD103 is known to interact with E-cadherin expressed on epithelial cells and this interaction is proposed to allow long-term maintenance of T_{RM} at some epithelial surfaces in many infection models (21,30,31). TGF- β signaling can induce CD103 expression and accordingly TGF- β is a key cellular factor for T_{RM} establishment in multiple tissues including small intestine, skin, lung and salivary gland (10–12). In addition to TGF- β , *in vitro* culturing of effector CD8s with IL-33, TNF α and IFN- α/β can promote T_{RM}-like phenotypes, however their requirement *in vivo* has not been established (25,30). Indeed, identification of extrinsic factors that regulate T_{RM} differentiation remains a major gap in knowledge.

Interleukin-15 (IL-15) is important for circulating memory T cell survival and homeostatic maintenance, but its precise role in T_{RM} maintenance seems to be location dependent. T_{RM} in salivary gland, kidney and skin are lost in the absence of IL-15, while those in the SLOs, female reproductive tract (FRT), small intestine and pancreas were maintained (21,32). Like IL-15, the role of antigen for T_{RM} formation is also tissue and/or context dependent. Antigen is required to trigger naïve T cell activation, which is a necessary prelude to nonlymphoid migration and T_{RM} differentiation. However, once activated T cells have arrived in NLT, antigen is dispensable for the development of intraepithelial T_{RM} cells in skin, female reproductive tract, and intestine in several infection models (30,33,34). In contrast, the presence of cognate antigen within the skin itself played a major role in potentiating T_{RM} accumulation and differentiation in a vaccinia virus infection model (35). Also, antigen persistence in brain and lung contribute to long-term T_{RM} maintenance (36,37). Interestingly, persistent antigen presentation during chronic infection was shown to be detrimental for acquisition of a CD103+ T_{RM} cell phenotype in the small intestine (11). The half-life of T_{RM} in the absence of persistent antigen has not yet been determined, although murine and primate studies suggest that they are long-lived. Taken together, a complete model describing the regulation of T_{RM} differentiation and maintenance is a work in progress.

T_{RM} function

Several studies have demonstrated that T_{RM} can significantly accelerate control after pathogen re-exposure or local viral recrudescence in nonlymphoid tissues. In mice, T_{RM} lodged in skin provided better protection against both herpes simplex virus (HSV) and vaccinia virus than circulating memory cells (19,22). A study by Watanabe et al., described the presence of two phenotypically distinct populations of T_{RM} (CD103+ and CD103-) in human skin that differed in ex vivo proliferative and cytokine expression potential (38). The presence of T_{RM} in mucosal tissues was also associated with accelerated pathogen control, notably in the context of influenza infection (37,39,40). In addition to acute infections, T_{RM} can also control latent HSV reactivation in sensory ganglia (41). Interestingly, in humans,

T_{RM} are positioned at sites of HSV recrudescence and their presence is associated with reduced disease severity during reactivation episodes (42).

The importance of T_{RM} to immunity can be partly explained by their location, or immunosurveillance, directly at sites of infected cells, which enables more immediate detection and responses. This is in contrast to T_{CM}, which become activated in secondary lymphoid organs only after peripheral antigens have drained to these sites. Once activated T_{CM} must then differentiate and localize to the site of infection. These events obviously take time, providing a window of opportunity for pathogen amplification.

In addition to rapid detection of foreign antigens in nonlymphoid tissues, T_{RM} may eliminate infected cells through prototypical cytolytic activity. While this is difficult to document *in vivo*, many T_{RM} populations constitutively express heightened levels of cytolytic granzymes compared to T_{CM}. T_{RM} also exhibit what has been described as a “sensing and alarm” function (7). This function is mediated by cytokines, including IFN γ , TNF α , and IL-2, and triggers a series of rapid immune activating events. Through secretion of IFN γ , activated T_{RM} induce chemokines and upregulation of vascular cell adhesion molecule 1 (VCAM1) on endothelial cells which recruits circulating memory B and T cells to sites of T_{RM} reactivation (7,9). Restimulated T_{RM} also trigger local natural killer cell activation, promote the maturation of DCs within the tissue, and induce antiviral gene expression in epithelia (8,9). These events can be likened to T_{RM} sounding an alarm, as first responders that alert other components of the innate and adaptive immune system to be on the lookout for a pathogenic insult. Taken together, this response can induce potent control over the offending pathogen and also establishes innate resistance against coinfections (8,9).

Besides their protective role, T_{RM} may also contribute to autoimmune, inflammatory and allergic responses. In humans, skin resident T_{RM} have been clearly implicated in many skin pathologies including psoriasis, fixed drug eruption and Mycosis fungoides (10,13). Mouse studies demonstrated CD4⁺ T_{RM} involvement in house dust mite induced allergy, which is a model of asthma (14). A major challenge for the field will be to determine to what extent resident T cell populations are major drivers of acute and chronic human diseases, and whether therapeutic interventions may be developed that target specific populations of T_{RM}.

Alloreactive Memory T Cells

Memory T cells contribute to both acute and chronic allograft rejection, and are considered a significant barrier to inducing graft tolerance (43). Indeed, pre-transplant frequencies of alloreactive memory T cells are highly correlated with graft rejection and resistance to allograft tolerance induction therapies (1,44). Alloreactive memory T cells can be generated through previous exposure to alloantigens during pregnancy, transfusions, or by previous organ transplants. In addition, memory CD4⁺ and CD8⁺ T cells generated against pathogens are shown to be frequently cross-reactive against allogeneic HLA molecules, and these memory cells can mediate robust anti-allograft responses (43). Furthermore, lymphopenia induced by the immunosuppressive regimen used during and after transplantation may also promote alloreactive memory T cell generation. Because of their reduced susceptibility to lymphocyte-depleting agents, memory T cells can preferentially survive and undergo

homeostatic proliferation to repopulate and possibly increase the size of the alloreactive memory population. These alloreactive memory cells can be potentially derived from both recirculating memory T cells and T_{RM} . Considering that T_{RM} constitute the dominant memory population in NLTs, it is highly likely that they participate in the alloimmune response. However, studies focusing on allograft responses primarily driven by T_{RM} are lacking. Below we speculate on the potential role of T_{RM} in transplantation in light of what we know of their *in situ* behavior and protective functions.

Donor-derived T_{RM}

While parameters regulating graft tolerance are multi-factorial, interestingly, those organs that contain high densities of T cells (e.g., small intestine, lung) show some of the lowest rates of graft acceptance (45). Paradoxically, this might point towards an alloreactive role played by resident lymphocytes that are being transferred to the recipient during organ transplantation. Transplanted tissues contain donor passenger resident lymphocytes. In many cases, recipient immune cells may infiltrate and kill the passenger leucocytes including donor-derived T_{RM} . While speculative, donor T_{RM} might be induced to undergo egress from the transplant upon engraftment or immunosuppression, and subsequently be eliminated by the host immune response (Figure 3). Indeed, individuals receiving intestine grafts contained donor derived T cells in their circulation 7-8 weeks post-transplantation (46). In certain cases these donor derived T cells have been shown to initiate graft-versus-host disease (GVHD), with significant frequencies reported in small intestine (5.6%) and liver (1-2%) transplant recipients (47). It is unknown if passenger T_{RM} were responsible for this effect, perhaps as a result of differentiating into effector T cells by perceiving the lymphopenic environment.

A very plausible mechanism by which donor T_{RM} might precipitate inflammation and rejection is related to their sensing and alarm function, which will be discussed below when host-derived T_{RM} are considered. 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 (48). More studies are needed to investigate if indeed passenger T_{RM} are a major determinant of graft rejection. Therapies could then be developed to specifically deplete T_{RM} from donor organs. A caveat to this approach is that donor T_{RM} may have beneficial functions by suppressing reactivation of chronic infections within donor tissues. In this case, pharmacologic suppression of T_{RM} function or rapid depletion of donor T_{RM} (including by host alloreactivity) may trigger latent pathogen reactivation events. In turn, this could promote inflammation and may contribute to graft rejection or perhaps even broadly distributed disease in the case of recipients that lack their own immunity to the reactivating pathogen. Therefore, any T_{RM} targeted therapies may have to be balanced with antivirals to ensure short-term protection against pathogen recrudescence.

Host-derived T_{RM}

Lymphocyte depleting antibodies are part of most induction therapies for patients receiving transplants, however, T_{RM} do not recirculate through blood and are less susceptible to

antibody-mediated depletion (7,23). This point was recently highlighted in studies showing that systemic treatment with anti-CD52 (Alemtuzumab) antibody removed recirculating T cells but spared T_{RM} in the skin whereas both the population were depleted when anti-CD3 antibody was used (23,38). It should be considered whether these surviving T_{RM} could penetrate adjacent grafts in response to inflammation associated with transplantation and ischemia-reperfusion injury. Encounter with cognate antigen in the graft could result in elicitation of the T_{RM} “sensing and alarm” function, further amplifying the inflammatory cascade and immune cell recruitment (7). It is important to mention here that, although the local activation of T_{RM} involves specific TCR ligation, the subsequent recruitment of leucocytes from blood to the site of reactivation is non-specific; antigen-experienced T cells of all specificities will be recruited (7). To this effect, therapies focused on attenuating migration of T cells are being developed, such as antibodies blocking the integrins lymphocyte function-associated antigen-1 and very late antigen-4. These antibodies, however, have been shown to give rise to latent viral recrudescence (49). This emphasizes the need for elimination of alloreactive T cells while maintaining beneficial pathogen-specific memory T cells to ensure continued protection.

Differentiation of host-derived T cells into T_{RM} within grafts

Studies in human lung and intestine transplant recipients showed significant host T cell repopulation of the allograft within 3-4 weeks following transplantation (46,50). Activated host T cells are thought to infiltrate the graft in response to the inflammation induced by the transplant procedure. In a cardiac transplantation animal model, donor-reactive CD8+ memory T cells infiltrate the graft as early as 24hr after transplantation (51). A recent report suggested that while chemokine receptor interaction was dispensable, cognate antigen-recognition was essential for retention of the T cells in vascularized grafts (52). Infiltrating T cells may include both donor reactive as well as pathogen specific populations, the balance of which may determine transplant outcome.

In the context of this review, we will highlight evidence that the local cytokine milieu within tissue grafts promotes differentiation of infiltrating T cells into T_{RM} . Abundant examples of this phenomenon can be inferred from studies in both humans and rodents and extend to many allografts including lung, pancreas, small intestine, and kidney (reviewed in 53). Indeed, CD103, a prototypical marker of CD8+ T_{RM} , is upregulated by a subset of infiltrating CD8+ T cells within these grafts. In mouse allograft studies, upregulation of CD103 was dependent on locally available TGF- β (53,54). Additionally, in an intestinal GVHD model, CD103 deficient T cells trafficked to the small intestine epithelium at normal levels, but failed to be maintained, indicating that CD103 is a T_{RM} retention molecule in some instances of alloreactivity (54).

In healthy individuals, T_{RM} arise from foreign antigenic stimulation. It is well known that naïve T cells proliferate in response to lymphopenic conditions and this “homeostatic proliferation” is dependent on IL-7 and self-peptide MHC recognition (55). We recently demonstrated that naive T cells undergoing homeostatic proliferation gained the ability to traffic to NLTs, which then induced their differentiation into T_{RM} (30). It is worth considering whether lymphopenia-driven T_{RM} populations might impact transplantation.

Indeed, most conditioning regimens before transplantation include lymphodepletion to prevent allograft rejection. The result may paradoxically promote proliferation and differentiation of surviving T cells into T_{RM}.

Laboratory mice: opportunities to extend the model?

Most preclinical transplantation studies utilize mice raised under specific pathogen free (SPF) conditions. Although designed to limit variations stemming from uncontrolled microbial exposure, this ultra-hygienic housing condition prevents exposure of laboratory mice to physiological infections typically experienced by free-living organisms. Indeed, most tissues in laboratory mice completely lack T_{RM} (56). This is in stark contrast to human tissues, and also to feral and pet store mice, suggesting that lack of natural pathogen exposure is to blame. Consistent with this, laboratory mice co-housed with mice from a pet store acquire infections, populate tissues with T_{RM}, and also acquire a basal level of immune gene expression that more closely aligns with that of adult humans (56). This can be partly recapitulated by infecting laboratory mice with a small number of controlled experimental infections (57). In summary, the practice of SPF husbandry, which dominates biomedical mouse research, fails to recapitulate aspects of the human immune system (including T_{RM} establishment in tissues) due to lack of infectious experience.

A critical question is whether this issue may account for some failures in translating discoveries from mice to humans, and whether extending more research to “dirty mouse” models might be of value. An elegant series of studies suggests that this may be the case. It was shown that tolerance induction therapies, such as costimulatory molecule blockade, are highly effective at maintaining allograft tolerance in naïve mice, but are less effective in mice that had previously been infected with experimental pathogens, even if that pathogen has been cleared (44). Similarly, the presence of a concurrent infection during transplantation has been shown to prevent tolerance establishment because of activation of allograft-reactive T cells, either due to infection-associated bystander activation or cross-reactive mechanisms (43). The broad reliance on “clean” SPF mice may deprive transplant investigators from incorporating these highly relevant (human-like) features into their studies. This may decrease the translation potential of therapies from laboratory to clinic. If true, dirty mouse models may provide substantial opportunities for increasing the pace of discovery.

Concluding remarks

Limiting allo-specific responses while maintaining effective anti-pathogen immunity has been an objective for transplant research. Past research has established the importance of memory T cells’ role in both of these processes. But most of those studies were focused on recirculating memory cells that were thought to include the majority of memory T cells in the human body, including those charged with the responsibility of patrolling nonlymphoid tissues. However recent studies indicate presence of an abundant non-recirculating T_{RM} subset in most transplantable solid organs. They have been shown to be important coordinators of local immune responses in multiple NLTs. Their role in suppressing latent viral reactivation suggests that may contribute to some aspects of graft tolerance. On the

other hand T_{RM} can potentially mediate anti-allograft responses through their strong immunostimulatory abilities. Future studies should be directed towards therapies that can suppress their ability to mount an allo-specific response while keeping their pathogen-specific functions intact.

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Abbreviations

T_{RM}	Resident memory T cells
T_{CM}	Central memory T cells
T_{EM}	Effector memory T cells
GVHD	Graft-versus-host disease
NLTs	Non-lymphoid tissues
KLF2	Krüppel-like Factor 2
S1PR1	Sphingosine-1-phosphate receptor-1
TGF-β	Transforming growth factor-β
SLOs	Secondary lymphoid organs
FRT	female reproductive tract
IL-15	Interleukin-15
VCAM	1 vascular cell adhesion molecule 1
NK cell	Natural Killer cell
DCs	Dendritic cells
TCR	T cell receptor
SPF	Specific pathogen free

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Fig 1. Memory T cell migration patterns

Central memory T cells (T_{CM}) circulate between blood, secondary lymphoid organs (e.g. lymph node), and efferent lymph that collect in the thoracic duct before rejoining the blood supply. Effector memory T cells (T_{EM}) migrate through blood, non-lymphoid organs, and afferent lymphatics (passing transiently through lymph nodes) before passing through the thoracic duct and rejoining the blood supply. Resident memory T cells (T_{RM}) do not recirculate and are confined to their tissue of residence.

Fig 2. T_{RM} differentiation

Upon cognate antigen encounter, naïve T cells become activated and expand in secondary lymphoid organs. Activated T cells migrate to sites of infection where they contribute to pathogen control. A fraction of these T cells, typically those lacking KLRG1 expression, differentiate into T_{RM} under the influence of local environmental signals, which may include TGF- β . This differentiation program is associated with upregulation of cell retention molecules including CD103 and/or CD69, and transcription factors Hobit and Blimp-1, as well as downregulation of the S1PR1 receptor that promotes tissue egress, transcription factor KLF2, and repressed expression of lymph node homing molecules CD62L and CCR7.

Fig 3. Possible roles of T_{RM} in transplantation outcome

T_{RM} constitutively patrol their tissue of residence to prevent latent pathogen reactivation. Left panel: T_{RM} in donor graft or host tissue, if restimulated can initiate a series of immune-activating events commonly referred to as “sensing and alarm” function. This results in production of cytokines that mediate VCAM-1 upregulation on endothelial cells and recruitment of circulating memory T cell and B cells to the site of T_{RM} activation. Restimulated T_{RM} also activate cells of the innate immune system including dendritic cells (DC) and natural killer (NK) cells. The ensuing inflammation may potentiate graft rejection. Right panel: While speculative, it is possible that donor T_{RM} may differentiate into effector cells and migrate out of grafts in the context of transplantation, subsequently giving rise to GVHD. This figure also emphasizes that T_{RM} are likely targeted by donor-reactive cells for elimination.