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MEMORY T CELLS IN TRANSPLANTATION—PROGRESS AND CHALLENGES

Xian C. Li, **Malgosia Kloc**, and **Rafik M. Ghobrial**
Department of Surgery, the Methodist Hospital and Transplant Immunology Program, Methodist Hospital Research Institute, Texas Medical Center, Houston, Texas

Abstract

Purpose of review—Memory T cells present a different set of challenges to transplant patients; they are needed for protection again invading pathogens, especially under conditions of immunosuppression. But their presence also threatens transplant survival, as some of them are alloreactive. Efforts to resolve this paradox will be critical in the induction of transplant tolerance.

Recent findings—There has been significant progress made in the past few years in the areas of population diversity of memory T cells, metabolic control of their induction, and mechanisms and pathways involved in memory cell exhaustion. Multiple targets on memory T cells have been identified and some of which are under vigorous testing in various transplant models.

Summary—Memory T cells are both friends and foes to transplant patients, and tolerance strategies should selectively target alloreactive memory T cells and leave other memory cells unaltered. This remains a major challenge in the clinic.

Keywords

T cells; memory; tolerance; protective immunity

Introduction

A hallmark of adaptive immunity is the generation of memory cells, which are responsible for recall responses. Generally speaking, memory cells carry with them the entire immune history of an individual residing in an open environment, so they are a vital cell type in the immune system. Thus, boosting memory T cells or memory recall responses is a major goal in protective immunity [1]. In transplant patients, however, memory T cells present a different set of challenges and resolving them is essential to survival of both patients and the transplants [2]. Memory T cells are both friends and foes to transplant patients; they are needed in fending off invading pathogens, so their absence or inhibition would expose transplant patients to great danger of infections. However, a significant proportion of memory T cells, either pre-existing or de novo generated, can directly attack transplants, which threatens transplant survival [3]. This is a significant paradox in transplant medicine,

Address correspondence to: Xian C. Li, MD, PhD., Department of Surgery, the Methodist Hospital, Methodist Hospital Research Institute, Texas Medical Center Houston, Texas 77030, xcli@tmhs.org.

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and resolving this paradox is undoubtedly important in the induction of donor specific tolerance. In the past few years, great insights have been gained in the understanding of population diversity of memory T cells, metabolic control of memory induction, and memory exhaustion. Also, new approaches have been designed and tested in modulating memory T cells in various models including transplantation. This review will highlight the latest findings in these areas and discuss potential implications in transplant tolerance.

Basic biology of memory T cells

As compared to their naïve counterparts, memory T cells possess unique features that render such cells highly efficient in triggering robust immunity [4]. Memory T cells are long-lived cells; they have survival advantages over naïve cells and can replenish themselves by constantly dividing in the periphery. For example, memory T cells readily survive depletion therapies with polyclonal anti-lymphocyte serum while naïve T cells are profoundly eliminated [5]. Importantly, memory T cells exhibit a much lower activation threshold than naïve T cells; they are also less dependent on CD28 and/or CD154 costimulation for activation [6]. So conditions that fail to activate naïve T cells may trigger robust activation of memory T cells. Also, most memory T cells are progenies of effector T cells; they are programmed (transcriptionally and epigenetically) to respond to recall antigens in a much more vigorous fashion than naïve T cells. Thus, at a per cell basis, memory T cells give rise to far more effector cells that naïve T cells do at a given time. Additionally, memory T cells are not confined to lymphoid tissue; they reside in both the lymphoid and the non-lymphoid tissues (e.g., the liver, lung, and the gut) [7]. Thus, they are readily accessible to antigens. Finally, activation of memory T cells does not require the secondary lymphoid organs, which contrasts sharply to that of naïve T cells [8]. Thus, memory T cells are well equipped and well positioned to mediate immediate responses to antigens.

There are three major mechanisms that collectively contribute to the memory pool in the immune system. Antigen sensitization remains the primary source of memory T cells, and such memory T cells exhibit well-defined antigen specificities. In transplant settings, donor antigen sensitization through blood transfusion, pregnancy (to paternal antigens) or prior transplant all lead to the induction of donor specific memory T cells [2]. Recent studies have identified other mechanisms in memory T cell induction, and such mechanisms include homeostatic proliferation and heterologous immunity [9]. Naïve T cells have remarkable potential to divide under lymphopenic conditions. This type of cell proliferation occurs in the absence of deliberate foreign antigen challenge and is often called homeostatic proliferation. Mechanistically, homeostatic proliferation is mediated primarily by the availability of cytokines, especially IL-7 and IL-15, in the lymphopenic hosts, although TCR triggering by autologous peptides may also be involved [10]. An interesting feature is that homeostatic proliferation concerts naïve T cells directly to memory phenotype, especially T effector memory phenotype [11]. This is a clinically relevant issue in transplantation as depletion therapies are commonly used in transplant patients to reduce the mass of alloreactive T cells. As can be envisioned in such therapies, residual T cells may undergo vigorous homeostatic proliferation, followed by conversion to memory T cells. This response may lead to an expanded memory pool in transplant recipients. Although such memory T cells are generated in the absence of donor antigen exposure, studies in animal

models and in humans demonstrate that they respond to allotransplants vigorously and are highly resistant to tolerization [12].

Memory T cells developed in response to one particular antigen can respond to other unrelated antigens, thereby affecting the subsequent immune responses to a wide range of different antigens. This phenomenon is called heterologous immunity [13]. A major implication of heterologous immunity is that in humans in an open environment plus a normal history of vaccinations and infections, pathogen specific memory T cells that are potentially reactive to transplant antigens are likely to be numerous. Indeed, certain studies suggest that as high as 50% of the alloreactive T cells in humans express memory phenotypes, presumably developed as a result of heterologous immunity [14]. This notion is supported by several reports demonstrating that memory T cells that are specific to pathogens such as *Leishmania Major* or LCMV can respond vigorously to transplant antigens [15]. Conversely, in large animal models and humans, a significant proportion of alloreactive memory T cells may also respond to pathogens. This has major implications in the induction of donor specific tolerance without compromising hosts' protective immunity.

The most exciting area of memory research is the discovery of metabolic pathways in the control of memory T cell generation, and such pathways are related to energy production in different phases of T cell response [16]. Transitions of naïve T cells to effector cells and then to memory T cells present distinct metabolic demand. In essence, naïve T cells are quiescent and rely on fatty acid oxidation (FAO) as an energy source. Upon activation T cells quickly switch to glucose glycolysis and glutominolysis to meet their energy demands for proliferation and differentiation to effector cells [16]. This is mediated primarily through TCR triggered activation of the PI3-Akt-mTOR axis [17]. Such activated T cells must switch back to FAO in order to become memory T cells. Otherwise they remain as effector T cells and die of apoptosis. Remarkably, transition from glycolysis to FAO becomes a critical checkpoint in memory cell generation, and pathways regulated by AMPK and TRAF6 play a significant role in this transition. This is supported by recent findings that generation of memory T cells is severely impaired in AMPK or TRAF6 deficient mice, as activated T cells fail to make the transition to FAO [18,19]. Interestingly, in certain experimental settings, inhibition of the Akt/mTOR pathway during the contraction phase of a T cell response can markedly enhance memory T cell generation by limiting glucose glycolysis [17]. These findings undoubtedly open new areas of investigation in therapeutic manipulation of memory T cells in various disease settings.

Why do memory T cells matter in transplantation?

Besides in protective immunity, memory T cells are also capable of mediating transplant rejection. It is well recognized that donor specific memory T cells mediate "second-set" rejection that is extremely difficult to inhibit [20], and all measures are used now to avoid such scenario in clinical transplantation. In animal models, memory T cells alone are sufficient to trigger rejection; they are among the first cell types infiltrating the grafts, and memory T cells don't need the secondary lymphoid tissues to gain effector functions [8]. Furthermore, T central memory and T effector memory cells appear to be equally potent in mediating the rejection response [21].

Memory T cells generated through homeostatic proliferation or heterologous immunity are also capable of mediating transplant rejection. It has been shown that memory T cells post homeostatic proliferation are potent effector cells in rejection of heart and skin allografts [6,12]. Similarly, heterologous immunity also results in the generation of memory T cells that are alloreactive in transplant settings. For example, infection of B6 mice with parasitic or viral antigens resulted in the generation of memory T cells that are directly reactive to alloantigens, and therefore, heart transplant grafted onto such pathogen challenged mice were rejected in an accelerated fashion [22]. In selected models, memory T cells are shown to be key mediators in chronic allograft rejection, suggesting a possibility that memory T cells and chronic rejection may be intimately associated. Thus, regardless of memory phenotypes or mechanisms by which they develop, memory T cells are capable of mediating rejection.

A significant concern is that memory T cells are not as amendable as their naïve counterparts in tolerance induction. In a variety of animal models, memory T cells are found to be highly resistant to tolerance induction. Thus, tolerizing therapies that produce allograft tolerance in naïve animals often fail to do so in memory-rich animals. For example, donor specific transfusion (DST) plus anti-CD154 (MR1) is very effective at inducing allograft tolerance in rodents. However, this protocol completely fails to prevent rejection in donor antigen pre-sensitized mice [23]. Similarly, transferring donor-specific memory T cells into naïve mice breaks allograft tolerance induced by DST and anti-CD154 treatment. Similarly, memory T cells developed through heterologous immunity are also barriers to tolerance induction. This is elegantly demonstrated by Adams et al that virally induced memory T cells prevented the induction of mixed bone marrow chimerism and donor specific tolerance [15]. Similar findings have also been reported in kidney transplantation in the clinic. Patients with higher frequency of memory T cells are associated with worse transplant outcomes under conventionally immunosuppression [24].

Memory T cells developed by homeostatic proliferation are also resistant to tolerization. For example, treatment of naïve B6 mice with depleting anti-CD4 and anti-CD8 mAbs induces profound depletion of peripheral T cells. However, a subset of residual T cells undergoes extensive homeostatic proliferation in the treated mice, and memory T cells post homeostatic proliferation are highly resistant to tolerization by DST plus CD154 blockade treatment [12]. Similarly, in models where memory T cells are generated in immunodeficient mice through homeostatic proliferation, CD28 and CD154 costimulatory blockade also fails to tolerize such memory cells [6]. Clearly, memory T cells are inherently resistant to tolerization.

Another significant issue is that memory T cells often evade Foxp3+ Treg-mediated suppression [25]. Thus, in transplant settings where tolerance is mediated through Tregs, memory T cells may break tolerance and trigger graft rejection. Earlier work by Yang et al showed in an adoptive transfer model that Foxp3+ Tregs effectively inhibited rejection triggered by naïve CD4+ T cells but not by memory CD4+ T cells [26]. Tregs were similarly found to be unable to suppress alloreactive memory CD8+ T cells. A study in humans showed that memory T cells are also resistant to suppression by Tregs [27]. Thus, tolerance strategies that boost Tregs as a way to achieve tolerance are unlikely to be effective against

memory T cells. What mediates resistance of memory T cells to Tregs and whether memory T cells can be rendered sensitive to Tregs are important areas of investigation.

The pursuit of memory T cell-directed therapies

Memory T cells are hurdles to tolerance induction. Ideally, therapies that target memory T cells should be selectively directed against alloreactive memory cells, while leaving non-alloreactive ones unaltered.

Current immunosuppressive drugs that are effective at inhibiting naïve T cells have minimal effects at preventing memory T cell-mediated rejection [28], confirming that the activation requirement of memory T cells is quite different from that of naïve T cells in rejection. In fact, there is a strong correlation between the presence of pre-transplant alloreactive memory T cells and acute rejection episodes that occurred despite tacrolimus- and sirolimus-based therapies. Moreover, depletion therapies (e.g., anti-thymocyte globulin or ATG) are less effective at eliminating pre-existing memory T cells [29]. In fact, following depletion therapies, memory $CD4^+$ T cells are a dominant cell type remaining and are capable of initiating rejection episodes. In some studies, the commonly used immunosuppressive drugs inhibit the ability of memory T cells to respond to alloantigens in vitro [30]. However, the poor transplant outcomes in patients with high memory T cell frequency suggest that the in vivo efficacy of conventional immunosuppression drugs in containing memory T cells is limited.

Clearly, alternative approaches are needed to targeting alloreactive memory T cells in transplant settings. Much attention is devoted to prevent activation and survival of memory T cells and ways to block their accumulation in the grafts. Memory T cells appear to use alternative costimulatory pathways for activation and effector functions [31]. For example, 4–1BB/4–1BBL interactions have been shown to be important in $CD8^+$ T-cell recall responses. Additionally, OX40/OX40L pathway is pivotal for the generation of CD4+ memory cells. In certain models, OX40 deficiency or OX40 blockade resulted in greatly impaired memory CD4+ T cells [32]. In transplant models in which rejection is dominated by memory T cells, blocking OX40/OX40L pathway facilitated survival of heart and skin allografts [6]. Thus, memory T cells require different signals to develop or function in transplant rejection, which suggests new opportunities in therapeutic intervention of memory T cells in transplant settings. However, the validity of these pathways awaits further testing in large animal models.

There have been other attempts to control memory T cells in transplant models, and progress in this area is equally exciting. For example, the NF-κB blocker 15-deoxyspergualin (DSG) prevented activation of donor specific memory CD8 T cells and synergized with costimulatory blockade to induce skin allograft survival in a mouse model [33]. Administration of the sphingosine-1 phosphate receptor agonist FTY720 resulted in sequestration of donor-specific memory CD4 T cells in the peripheral lymph nodes and delayed heart allograft rejection in mice [34]. Additionally, disruption of the integrin LAF-1 pathway showed promising effect in blocking memory T cells in non-human primate models [35].

The finding that memory T cells can be driven to exhaustion suggests that there might be other approaches to contain memory T cells [36]. In general, exhausted T cells progressively lose their effector activities [37]. This is followed by physical deletion from the T cell repertoire. Exhausted T cells express cell surface receptors that usually transduce inhibitory signals, such as PD-1, Tim-3, LAG-3, CD160, CTLA-4 and many others [38]. Some of these inhibitory receptors (e.g., PD-1) are critical to the exhausted phenotype. In addition, mechanisms that control telomere erosion in memory T cells may also be involved in regulating memory exhaustion [39].

The exact roadmap to exhaustion is unclear, but several factors favor T cell exhaustion. Antigen persistence is a key contributing factor; this can be in the form of chronic, latent infections or in the form of cancer progression. In addition, an inhibitory process, both intrinsic and extrinsic, is also required for the transition to an exhausted phenotype. The inhibitory receptors on the cell surface (mentioned above) provide an intrinsic mechanism, while the production of suppressive cytokines such as TGF-β, IL-10, IL-35 as well as the presence of regulatory T cells may constitute an extrinsic mechanisms. In certain models, lack of help from CD4+ T cells or disruption of lymphoid structures also favors T cell exhaustion [36]. All of these factors are well represented in transplant settings, and whether memory T cells could be pushed to exhaustion in favor of graft survival deserves more attention.

Progress, challenges, and concerns

In the past few years, we have gained considerable insights into population diversity of memory T cells, metabolic control of their generation, and mechanisms related to memory exhaustion. Multiple targets and pathways have been identified and some of which are under vigorous resting in various models including organ transplantation. However, there remain significant challenges in the future. Donor specific tolerance in the clinic demands selective targeting only alloreactive memory cells while leaving protective ones unaltered. Thus, the following questions need to be addressed before new strategies can be designed. 1) What are the mechanisms that control alloreactive versus non-alloreactive memory T cells? 2) Why are memory T cells resistant to Treg mediated suppression? Can they be rendered susceptible to regulation? 3) What are the events that regulate the survival advantage of memory T cells in the periphery? 4) What is the quality and quantity of heterologous memory cells that are alloreactive? What are the consequences of blocking alloreactive heterologous memory cells in transplant patients? The goal in the future is to tolerize memory T cells in an antigen-specific manner: i.e., selective deletion or suppression of alloreactive memory T cells. Otherwise, the risk of compromised protective immunity or altered T cell repertoire will be significant in transplant patients [40].

Conclusions

Memory T cells represent a great challenge in transplantation in that they are required for protection against invading pathogens, but their presence also endangers transplant survival [27]. It is imperative that tolerization of memory T cells in transplant recipients should not drastically alter patients' protective immunity. This is a significant issue in clinical

transplantation, but resolving this issue will have major impact on transplant outcomes. Knowledge gained through this inquiry will help not only the design of the greatly improved tolerance induction protocols but also stratification of donor recipient selections to reduce the risk of graft damage inflicted by alloreactive memory T cells.

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* of special interest

** of outstanding interest

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KEY POINTS

- Memory T cells are required in protective immunity, but they also mediate transplant rejection.
- Memory T cells are extremely diverse consisting of many different subsets with strikingly different functional attributes.
- Energy production and usage are key checkpoints in memory T cell generation.
- Mechanisms that controls exhaustion of other cell types may also regulate exhaustion of memory T cells.
- Memory T cells are resistant to conventional immunosuppression, and means to control alloreactive memory without compromising patients' protective immunity remains a major challenge in the clinic.