

Generation, homeostasis, and regulation of memory T cells in transplantation

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Purpose of review

Sensitized individuals experience higher rates of acute rejection and decreased graft survival. Memory T cells have been implicated in these processes, and in the prevention of tolerance induction. A greater understanding of T-cell memory generation, maintenance, and regulation is needed to design new immunosuppressive strategies that prolong graft survival in the presence of alloreactive memory.

Recent findings

Memory T cells are generated against alloantigens via homologous and cross-reactive priming, and recent studies demonstrate that T-cell depletion can also paradoxically result in memory generation. While initially thought to be impervious to regulation due to their enhanced functional properties, memory T cells have shown susceptibility to certain immunomodulating therapies and immunosuppressants and, furthermore, newer targets for memory T-cell regulation show promise in controlling immunological recall.

Summary

Current immunosuppression protocols should be designed with consideration of their effects not only on naive T-cell activation, but also on memory generation, activation, and effector function. Additionally, research efforts should continue to identify and manipulate new costimulatory targets and immunosuppressants, which may be key to abrogating memory T-cell responses.

Keywords

alloreactivity, immune memory, regulation, T lymphocytes

Introduction

The immune system exhibits memory to previously encountered antigens, manifested by a recall response that is enhanced in magnitude and kinetics relative to a primary response. Memory immune responses are mediated by memory T and B lymphocytes, with memory T cells playing instrumental roles in coordinating long-lived protective immunity against diverse pathogens. In transplantation, however, the presence of memory T cells specific for alloantigens has been associated with acute rejection and serves as an impediment to longterm graft survival and tolerance induction. In this review, we discuss the generation, homeostasis, and functional properties of memory T cells in the context of transplantation and the immunomodulatory approaches that may regulate their responses.

Generation of T-cell memory

Memory T cells are generated following an initial encounter of naive T cells with antigen, resulting in activation, proliferation and differentiation into effector T cells. These effectors mediate clearance of the priming antigen, after which most die by apoptosis while a small fraction persists as long-lived memory T cells. Although linear differentiation of memory from effector T cells is the favored model, the direct cellular precursors and pathways for memory T-cell development remain unknown [1*].

Memory T cells exhibit enhanced activation, functional and migration properties compared with naive T cells. While naive T cells are confined to lymphoid tissues, require professional antigen-presenting cells (APCs) such as dendritic cells for activation, and produce primarily IL-2 when stimulated, memory T cells are activated by a broad range of APCs in diverse tissue sites [2–5,6*] and mediate rapid production of effector molecules [7]. Memory T cells are heterogeneous and have been delineated into two subsets designated effector memory (CD62L^{lo}/CCR7⁻, T_{EM}) and central memory (CD62L^{hi}/CCR7⁺, T_{CM}) that circulate in nonlymphoid or lymphoid tissues, respectively [3,4]. T_{EM} and T_{CM} differ in functional, homing and protective properties [3,8*,9*,10], although the precise nature of these distinctions can vary in different antigen systems. For example, human T_{CM} produces predominantly IL-2 and T_{EM} effector cytokines [3,11], but in other antigen systems and in mice, both T_{CM} and T_{EM} produce effector cytokines [8*,10,12]. Mechanisms for the generation and maintenance of these memory subsets remain unknown, although

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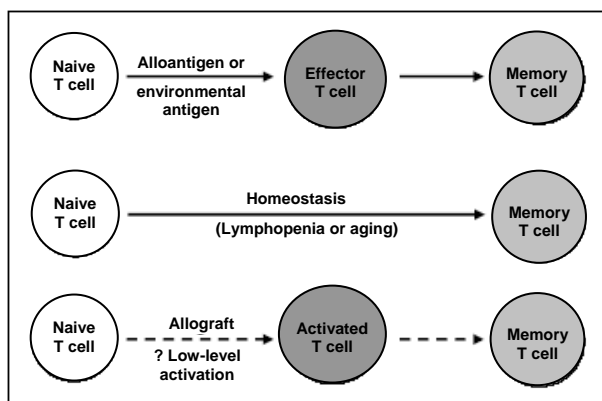
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Abbreviations

APC antigen-presenting cell
ATG antithymocyte globulin
CsA cyclosporine A
LCMV lymphocytic choriomeningitis virus
PRA panel reactive antibody

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Figure 1 Possible scenarios for generating alloreactive memory

Naive T cells may be primed against alloantigens present during blood transfusions or pregnancy, resulting in the formation of alloreactive memory T cells. Alternatively, memory T cells may also be generated after exposure to environmental antigens such as pathogens, that can crossreact and be recalled by alloantigens (top). Lymphopenia-induced homeostatic proliferation, as occurs after T-cell depletion, results in rapid division of remaining cells and an accumulation of memory T cells. In contrast, naive T cells may also undergo slow homeostatic turnover during aging and acquire a phenotypic profile and characteristics typical of memory T cells (middle). Naive T cells may undergo low-level priming by an allograft without full effector differentiation, leading to the development of graft-specific memory T cells (bottom).

recent studies suggest that they represent distinct lineages [1*,13*,14].

In transplantation, development of alloreactive memory due to a previous organ transplant has long been recognized as a risk factor for survival of a subsequent graft [15,16]; memory T cells specific for alloantigens, however, may likewise be acquired via homologous priming with other sources of alloantigens and cross-reactive (heterologous) priming (Fig. 1). For example, individuals without a prior transplant may develop alloantigen-specific memory T cells as a result of blood transfusions or pregnancy [16–18] or via cross-reactivity with pathogen-associated antigens [19,20,21**, 22,23]. The generation of alloantigen-specific responses via heterologous immunity has been demonstrated in mice previously infected with lymphocytic choriomeningitis virus (LCMV) or *Leishmania major* [22–24], and human memory CD8 T cells specific for Epstein–Barr virus or cytomegalovirus have also been found to demonstrate alloreactivity [19,20,25]. Thus, alloreactive memory is likely present even in individuals considered naive to direct alloantigen exposure. In addition, the known predisposition of transplant recipients to certain viral infections suggests that generation of alloantigen-specific memory T cells may occur even if graft-specific responses are suppressed.

The mode of alloantigen presentation and the presence of an allograft are features unique to transplantation that are

likely to impact memory T-cell generation and function. Alloactivation of naive T cells can occur via direct recognition of donor MHC on donor APCs, or indirect recognition, in which donor antigens are processed and presented by recipient APCs. It is not known whether these forms of allorecognition generate distinct types of memory responses, although we have found that direct allorecognition mediates preferential generation of the T_{EM} subset [26*]. Additionally, the allograft serves as a continuous source of antigen, and in contrast to nominal responses in which antigen is cleared, a chronic immune response to the graft might persist in the absence of clinically apparent rejection. We have shown that memory T cells can be generated from naive cells after only one day of antigen activation and in the absence of full effector differentiation [1*], suggesting that low-level immune activation may potentially contribute to memory generation and chronic rejection in the context of an allograft.

Homeostasis of memory T cells

Homeostasis of the T-cell compartment refers to the maintenance of a constant number of peripheral T cells, involving a dynamic interaction between the processes of antigen exposure, peripheral turnover and aging. In early childhood, the thymus accounts for a substantial output of naive lymphocytes, which diminishes significantly beginning at the second decade of life due to age-related thymic involution [27]. The reduction in T-cell output is compensated by a remarkable increase in memory T cells starting from birth [28,29*] due to exposure to multiple antigens [27]. Homeostatic turnover of T cells also plays an important role in the maintenance and generation of memory T cells [30**]. Peripheral lymphocytes are under increased pressure to renew and maintain the lymphocyte pool as thymic output diminishes and existing lymphocytes reach senescence. Resting memory T cells undergo periodic division at a more rapid rate than naive cells [31], further contributing to the increase in the memory T-cell pool over time.

Memory T cells can also be generated directly by the homeostatic turnover of naive T cells. This process is most strikingly manifested during lymphopenia when residual cells rapidly proliferate to replenish the peripheral T-cell compartment [32–34], but also occurs in peripheral T cells that undergo slow homeostatic turnover over time. As up to 10% of the total T-cell repertoire can exhibit alloreactivity [35], alloreactive memory T cells may potentially arise from homeostatic turnover of alloantigen-specific T cells, in the absence of overt alloantigen priming.

The generation of memory T cells via lymphopenia-induced homeostasis is of particular relevance in transplant recipients who are administered lymphocyte-depleting

agents as induction therapy. Murine studies indicate that the stimulus for this rapid homeostatic proliferation is the low-level signaling provided by commensal gut flora, self-peptide/MHC complexes [33,36*], or cytokines such as IL-7 and IL-15 [37–40], leading to a preponderance of memory-phenotype cells in the reconstituting T-cell pool [23,33,34]. Homeostatically expanded memory T lymphocytes have been found to possess functional similarities to antigen-specific memory T cells in their ability to rapidly proliferate, produce effector cytokines and prevent tolerance induction in transplantation models [41–44,45**]. Thus, memory generation may be an undesired consequence of manipulating the T-cell pool in depletion therapies.

Impact and detection of immune memory in transplantation

Prior sensitization to alloantigens is well known to unfavorably impact allograft survival, leading to the routine use of panel reactive antibody (PRA) levels to identify presensitized transplant recipients. PRA assays reflect alloantibody production and humoral sensitization that do not necessarily correlate with T-cell sensitization [46*,47*]. Recently, a greater focus has been placed on identifying alloreactive memory T cells that mark T cellsensitized patients using enzyme-linked immunospot and cytokine flow cytometric assays, two sensitive techniques for detecting donor-specific memory T cells [48–50]. In a small cohort of renal transplant patients, an increased risk for acute rejection and a decrease in posttransplant renal function have been correlated with a higher pretransplant frequency of alloreactive memory T cells [48,51]. Furthermore, donor-specific memory T cells have also been observed in patients experiencing acute rejection [50]. Identification of preformed alloreactive memory T cells may lead to more targeted immunosuppression, as memory T cells exhibit differential susceptibility to certain immunomodulating drugs [23,52**].

Regulation of memory responses

In general, pathways that serve as targets for modulation of naive T-cell activation or tolerance induction in unprimed animals are either ineffective, act differently, or have unknown effects on the memory compartment [53*]. Given the diverse functional and homing capacities of memory T cells, effective modulation of allospecific memory responses will most probably require a multilevel approach that considers their generation, activation, effector responses or trafficking (Table 1).

Immunosuppressive drugs

The majority of studies on immunosuppressive drugs has focused on naive T cells and graft survival in unprimed animals; consequently, data regarding their effects on memory T cells are limited and largely confined to invitro analyses. Corticosteroids do not inhibit memory CD4 T-cell proliferation, but can alter their cytokine profile [54]. In contrast, mycophenolate mofetil impairs memory CD8 T-cell generation and cytokine production, but not their cytolytic activity [55]. Sirolimus and FK506, in combination, inhibit in-vitro memory responses, but not its generation, whereas sirolimus and cyclosporine A (CsA) enhance memory proliferation and function [56], and earlier studies using CsA alone showed a dosedependent enhancement of memory recall [57,58]. These findings reveal that memory T cells exhibit differential susceptibility to immunosuppression and suggest that over long-term treatment, alloactivation and memory generation may still occur in transplant patients.

T-cell depletion is commonly used as induction and rescue therapy in transplant recipients. Murine studies have demonstrated that memory T cells are generated during rapid homeostatic proliferation of naive cells following T-cell depletion [34,41,59], which renders mice resistant to tolerance induction protocols [42,43]. In renal transplant patients receiving antithymocyte globulin (ATG) or alemtu-

Table 1 Effects of immunomodulating approaches on memory T cells

| Mechanism | Examples | Effects on memory T cells ^a |
|------------------------|---|---|
| Costimulation blockade | CD28/B7 (CTLA4-Ig) CD154/CD40 ICOS/ICOSL OX40/OX40L | ↓IL-2 production, in-vivo proliferation No known effect Studies contradictory; may decrease memory responses ↓Memory generation |
| T-cell depletion | Antithymocyte globulin, alemtuzumab | Depletion; promotion of T _{EM} state |
| Immunosuppressants | Corticosteroids Mycophenolate mofetil FK506 Cyclosporine | Modulates cytokine profile ↓Memory generation, cytokine production ↓Proliferation, cytokine production A Studies contradictory; may increase memory generation and responses |
| Mixed chimerism | FTY720 Nonmyeloablative conditioning and donor bone marrow transfusion | Sequesters T _{EM} in lymph nodes Elimination of alloreactive memory; maintenance of protective immunity |

^a References cited in text.

zumab, naive and TCM cells were effectively reduced, but TEM cells comprised the dominant lymphocyte population months after treatment [52**]. Interestingly, the remaining TEM cells isolated *ex vivo* exhibited susceptibility to CsA and FK506, but were resistant to sirolimus and corticosteroids [52**], findings that differ from nondepleted memory T cells (see above). Memory T cells generated after depletion and the presence of depletion-resistant memory T cells may ultimately limit the efficacy of immunomodulating drugs in these patients.

Costimulation blockade

Costimulatory pathways regulate T-cell activation and cytokine production and are, therefore, attractive targets for manipulation of unwanted responses by direct blockade. The majority of studies on costimulation blockade have focused on responses in naive animals [60], but more recent studies have begun to explore their role on memory responses [53*,61*,62]. The CD28/B7 costimulatory pathway, involving engagement of the CD28 receptor on T cells with B7 ligands expressed by activated APCs, is required for naive CD4 T-cell activation, and blockade of this pathway by CTLA4-Ig, a CTLA4-human IgG1 fusion protein that binds B7 molecules [63], results in long-term allograft survival [64]. The CD28 pathway was originally reported to be dispensable for memory T-cell recall due to their ability to be activated by B7-deficient APCs *in vitro* [5,65]; we have recently, however, demonstrated that antigen-driven IL-2 production was substantially impaired by CTLA4-Ig *in vitro* and that proliferation and propagation of the TEM subset was inhibited following in-vivo CTLA4-Ig treatment [66**]. These results suggest that CD28/B7 inhibition may prove effective in curtailing alloantigen-specific memory CD4 T-cell responses, particularly those driven by pathogenic TEM cells. Along these lines, LEA29Y, a modified form of human CTLA4-Ig with greater binding avidity for B7, is efficacious in prolonging allograft survival in primates and humans [67*,68], and may also prove to limit recall responses.

The costimulatory molecules CD154, ICOS, and OX40 are expressed following T-cell activation and also serve as effective targets for blocking primary immune responses and inducing tolerance, with variable effects on memory T cells. CD154/CD40 blockade prolongs graft survival in naive, but not alloantigen-primed mice [69–71]. ICOS/ICOSL blockade inhibited chronic rejection of cardiac allografts when administered during the effector response [72], suggesting a role for ICOS/ICOSL costimulation in the activation of effector/memory T cells, while ICOS/ICOSL and CD28/CD154 blockade did not prevent rejection of skin grafts in sensitized mice [73]. Of the inducible costimulators, OX40/OX40L appears to be the most promising target for abrogating memory responses [61*]. OX40/OX40L costimulation favors memory generation [74,75], and coordinated

blockade of the OX40, CD28 and CD154 pathways prolongs graft survival in primed mice [73].

In general, costimulation blockade reveals variable effects on the multifaceted recall response, but in combination with other immunosuppressive approaches, may prove efficacious at preventing the propagation or generation of alloantigen-specific memory responses.

Mixed chimerism

Nonmyeloablative conditioning of the host and donor bone marrow infusion results in a state of 'mixed chimerism' in which the host develops tolerance to the donor and possesses donor and host-derived hematopoietic cells [76]. Protocols inducing mixed chimerism have established tolerance to allografts and xenografts in experimental models. In these models, elimination of peripheral alloreactive memory is essential to allow donor engraftment [76], although the generation and maintenance of protective immunity must be maintained. Mixed chimerism induced donor-specific transplantation tolerance in donor-primed, lethally irradiated mice, and importantly, abrogated alloreactive memory as manifested by the permanent cessation of antidonor antibody production [77]. Another study [78] showed preexisting protective immunity to acute LCMV infection was maintained but that against chronic LCMV infection was deficient following the induction of mixed chimerism. Mixed chimerism holds potential for achieving allograft tolerance while maintaining protective immunity, although the maintenance of stable donor chimerism remains a significant hurdle.

Targeted approaches

The distinct phenotype, function, or migratory properties of memory T cells can be applied to the design of therapies that specifically target memory T cells. For example, an anti-CD2 antibody (alefacept) preferentially inhibits T_{EM} and is currently approved for use in psoriasis patients [79,80]. In addition, memory T cells are susceptible to FTY720, a sphingosine-1-phosphate agonist that prevents the departure of lymphocytes from lymphoid tissues [81,82]. In murine models, FTY720 prolonged graft survival by sequestering alloantigen-specific memory CD4 T cells in lymph nodes [83*,84*]. Finally, molecules associated with memory T-cell function or differentiation, such as the Kv1.3 potassium channel expressed by human T_{EM} cells [85] and CD30, which contributes to CD8 T_{CM} differentiation [62], may serve as new targets for inhibition.

Conclusion

The presence of memory T cells specific for alloantigens can affect long-term allograft survival and the effectiveness of immunomodulating strategies. Regulation of these memory responses will probably require simultaneous tar-

getting of memory T-cell generation, activation, function, or trafficking. In addition, consideration of preexisting and potential generation of alloreactive memory responses may allow immunosuppression tailored to the immune status of transplant recipients.

References and recommended reading

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