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Memory T Cells: How Might They Disrupt the Induction of Tolerance?

Nick D. Jones

Clinical and experimental evidences suggest that alloreactive memory T cells may be part of the normal T-cell repertoire and that such cells are detrimental to the survival of foreign organ allografts induced by the administration of conventional immunosuppression or experimental tolerance-inducing therapies. The potential mechanisms by which alloreactive memory T cell may form a barrier to the induction of tolerance will be discussed.

Keywords: Alloreactive memory T cells, Immunosuppression, Organ transplantation, Tolerance.

Current therapies to prevent the rejection of foreign organs in clinical transplantation, while relatively successful, are associated with a number of debilitating side-effects related to the long-term use of certain drugs and their non-specific mode of action. Therefore, one of the major goals in transplantation is the design of therapies to induce transplantation tolerance that can be administered in the short term with long-term effects, and which only target immune responses to the transplanted organ. Ideally the induced tolerance is self-perpetuating by inducing a regulatory network that may afford the graft protection against further immunological insults.

Certainly the induction of tolerance to allografts has been demonstrated to be readily achievable in small animal models of transplantation, but the successful application of such strategies to large animal models and clinical transplantation has proved challenging. One potential explanation that continues to gain credence is that the relative difficulty to induce tolerance may relate to the presence of alloreactive memory T cells. Indeed, Lombardi et al. (1) first demonstrated in individuals who had not been previously exposed to alloantigens that alloreactivity was contained within the memory as well as the naïve T-cell compartment. This data were confirmed and extended by Heeger et al. (2), who found that nonsensitized patients harbored significant numbers of alloreactive interferon (IFN)-γ-secreting memory T cells before transplantation and that the precursor frequency of such cells correlated with the risk of rejection episodes after renal transplantation. Such alloreactive memory T cells are likely to have been generated by cross reactivity to environmental pathogens or by homeostatic proliferation after a period of lymphopenia. Indeed, where alloreactive memory T cells have been generated in experimental models by priming with donor alloantigen (3) after viral infection (4) or after homeostatic proliferation (5) then the presence of alloreactive memory T cells has been shown to preclude the induction of tolerance.

In summary, there is now convincing evidence to suggest that alloreactive memory T cells form part of the normal peripheral T-cell pool where they may form a barrier to the induction of tolerance to allografts.

How Do Memory T Cells Disrupt the Induction of Tolerance?

Although it is clear that memory T cells may interfere with the induction of tolerance, the cause of this phenomenon remains unknown, although it is likely to be attributable.
to differential activation requirements, rapid induction of effector function, and the microenvironment in which T cells encounter alloantigen.

It is well established that memory T cells are able to respond to lower concentrations of antigen and have less of a requirement for costimulation than naïve T cells. Therefore, memory T cells may be able to respond to alloantigen despite blockade of costimulatory pathways such as the CD28-CD80/86 and the CD40-CD154 pathways (6). However, it is worth noting that although memory T cells may be reactivated in the absence of certain costimulatory molecules, this does not necessarily mean that under these conditions the memory T-cell response is unaffected, only that the response is sufficient to perturb tolerance induction. In addition, memory T cells may be able to use other costimulatory pathways such as the OX40-OX40L (7), the 4-1BB-4-1BBL (7, 8), the ICOS-ICOSL (9) and the CD27-CD70 (10) pathways, which may substitute for defective CD28 and CD40 signaling.

After antigen recognition, naïve T cells have little effector function and undergo extensive division before acquiring the ability to produce cytokines, activate other immune cells, and differentiate into effector cells and thus kill targets. In contrast, memory T cells acquire effector function rapidly on reactivation and are capable of immediate effector function that can precede cell division and clonal expansion (11, 12). Therefore, memory T cells may be able to provide “help” for naïve T cells and B cells by secreting lymphokines or providing accessory molecules that may circumvent the tolerance-inducing effect of costimulatory molecule blockade (Fig. 1). Although evidence in this regard is scant, Chen et al. (13) demonstrated that the presence of alloreactive memory CD4+ T cells prevented tolerance induction by donornpecific transfusion and anti-CD154 monoclonal antibody (mAb), which was shown to be in part because of the provision of help for both cytotoxic T lymphocytes and humoral immunity.

Finally, it is well established that regulatory T cells (Treg) are a critical component for successful tolerance induction by costimulatory molecule blockade. Just where, when, and how Treg function to induce and maintain tolerance remains an area of intense investigation. However, although it has been demonstrated that the lymphoid homing receptor CD62L is absolutely critical for regulation (14), we and others have shown that with time, the location of regulation extends to the graft itself (15, 16). Memory T cells have been shown to possess different homing properties to naïve T cells by, for example, being able to traffic through nonlymphoid and lymphoid tissues (17). Furthermore, unlike naïve T cells, memory T cells can reject allografts in the complete absence of lymphoid tissue (18). Therefore, taken together these data may imply that memory T cells circumvent regulation in the short term by trafficking to the graft and consequently bypassing conventional activation in the lymphoid tissues (Fig. 1).

We have conducted a series of experiments to compare and contrast the response of naïve and memory T cells to an allograft in vivo to attempt to dissect inherent differences between these responses, which may shed light on how memory T cells may provide a barrier to the induction of tolerance. Studies such as these are frequently hampered by the fact that as alloreactive memory T cells have received some form of prior activation (not necessarily in the form of an alloanti-

FIGURE 1. Potential mechanisms contributing to the disruption of tolerance induction by memory T cells. Memory T cells may respond to alloantigens despite blockade of certain costimulatory molecules. Memory T cells may form a barrier to tolerance induction themselves by eliciting rapid graft rejection after the activation of other immune effector cells such as polymorphonuclear cells (PMNs) (A). Furthermore, memory T-cell responses have been shown to be more resistant to suppression by regulatory T cells (Tregs; B), allowing such responses to be initiated. In addition to directly contributing to rejection, memory T cells may provide help for B cells to produce alloantibodies and naïve T cells to respond to an allograft in the absence of costimulation through the secretion of growth factors such as interleukin (IL)-2 and IL-4 (C and D). It has also been suggested that memory T cells may further activate antigen-presenting cells (APC) bearing alloantigens in a process termed “licensing,” which may result in an enhanced ability to activate naïve T cells (particularly CD8+ T cells) because of the further up-regulation of the major histocompatibility complex, alternate costimulatory molecules, and secreted lymphokines (E).

gens), they may exist at a different precursor frequency and be clonally distinct (with different specificity and affinity) from alloreactive T cells present in the naïve repertoire. Therefore, observed differences in the response of naïve and memory T cells may relate to these confounding factors rather than to a fundamental difference between naïve and memory T-cell subsets. To eradicate these problems, we have developed a model whereby the response of naïve and memory CD8+ T cells bearing a single transgenic T-Cell Receptor (TCR) (derived from BM3RAG mice, which confers reactivity to the major histocompatibility complex class I alloantigen, H2Kβ) can be visualized after transplantation of an H2Kβ+ skin allograft. We have previously shown that memory BM3 T cells that have been generated from naïve T cells after prior exposure to a skin allograft or an infusion of donor H2Kβ+ splenocytes have a memory phenotype (CD44+) and produce vast amounts of IFN-γ within 24 hr of reactivation with alloantigen in vivo (19). Importantly, the adoptive transfer of 1 × 10^5 memory BM3 T cells into syngeneic RAG−/− recipients facilitated rejection of a subsequent H2Kβ+ skin graft more rapidly than 1 × 10^5 naïve BM3 T cells (19).
Based on the literature, we proposed that rapid skin graft rejection by memory compared with naïve T cells may be the result of memory T cells (a) undergoing more rapid clonal expansion after alloantigen recognition, (b) demonstrating an increased ability to traffic to the graft, or (c) developing increased or earlier effector function.

However, when the response of naïve and memory BM3 T cells to a skin allograft was compared, we found that both subsets proliferated in an identical fashion after activation in the draining lymph nodes (as judged by loss of CarboxyFluorescein diacetate Succinimidyl Ester (CFSE); article in preparation). Furthermore, effector T cells derived from memory or naïve T cells trafficked to the graft with the same kinetics (between 5 and 10 days post-transplantation) and in the same numbers induced a similar proinflammatory gene expression profile; these studies used real-time polymerase chain reaction for the expression of a number of proinflammatory cytokines (e.g., IFN-γ), effectors (e.g., perforin, granzyme B), and chemokines (e.g., CXCL9 and 10, CCL5). However, analyses of grafts taken 10 days posttransplantation revealed that grafts transplanted to animals that had received memory but not naïve T cells harbored a significant GR-1+ (polymorphonuclear cells [PMNs]) infiltrate. Interestingly, a similar finding has been reported by Fairchild and coworkers (20).

To determine whether the recruitment of PMNs to the graft was the underlying cause of the rapid skin allograft rejection seen with memory T cells, further cohorts of RAG−/− mice received adoptive transfer of naïve or memory T cells with and without administration of a depleting anti-GR-1 mAb (kindly provided by Professor Fairchild). We found that when GR-1+ cells were depleted, naïve and memory BM3 T cells rejected allografts with an identical kinetic, thus confirming the role of PMNs in enhanced allograft rejection.

Finally, we have previously demonstrated that Tregs were unable to prevent rejection induced by CD4+ and CD8+ memory T cells while being completely effective at controlling naïve CD4+ or CD8+ T-cell-mediated rejection (21). Therefore, we asked whether Tregs were able to prevent rejection mediated by memory BM3 T cells if the rejection was attenuated by GR-1+ cell depletion. We found that in the absence of PMNs, Tregs derived from mice that had received a tolerance-inducing therapy of anti-CD4 mAb combined with a donor leukocyte infusion significantly attenuated rejection elicited by BM3 T-Cells with approximately 60% of the grafts surviving for more than 100 days (manuscript in preparation).

Taken together, these data suggest that an additional way to prevent the disruption of tolerance by memory T cells is through the transient depletion of additional effector mechanisms used by memory T cells to elicit graft rejection. Furthermore, we would suggest that the transient attenuation of memory responses may allow the establishment of regulatory mechanisms that are able to control further T-cell responses. Indeed, it has already been demonstrated that the transient depletion of PMNs can enhance the effectiveness of costimulatory molecule blockade even in the face of a memory CD8 T-cell response (22).

Unresolved Issues

Although it is clear that alloreactive memory T cells can negatively influence the induction of tolerance, a number of questions related to memory T-cell responses to allografts remain unanswered.

For example, memory T cells can be split not only into CD4+ and CD8+ T cells but also can be further divided into central and effector memory subsets (that have different trafficking and functional properties). Which of these subsets confer the greatest resistance to tolerance induction is still unknown, although there is evidence that suggests that all memory T-cell subsets may be detrimental to tolerance induction. It is also worth noting that when memory T cells are generated during the course of an infection or after immunization, these cells mount a dominant Th1, Th2, or perhaps a Th17 response according to the conditions of the primary response when the cells re-encounter the priming antigen. In contrast, alloreactive memory T cells that are present before transplantation might have originated from a number of distinct responses to a number of different infections/immunizations. Although most studies have focused on Th1 type memory T cells, it is possible that memory T cells mount multiple classes of response to an allograft. How these different memory subtypes interact, which class of response is dominant (if any), how these responses influence the subsequent alloresponse of naïve T cells, and whether the same or distinct costimulatory pathways are used by different memory T-cell subsets is unknown. The answers to these questions will be important for the future individualization of immunosuppression according to a patient’s immune history and attempts to induce tolerance by costimulatory molecule blockade in clinical transplantation.

In conclusion, clearly, our understanding of the way in which memory T cells respond to allografts, even in the presence of immunosuppression or despite the blockade of certain costimulatory molecules, remains incomplete. However, the available evidence suggests that memory T-cell responses to allografts may require distinct costimulatory molecules and that these responses are susceptible, under the right conditions, to suppression by Tregs. Therefore, these data maintain the promise of novel therapies that can induce tolerance to foreign organ transplants in the clinic, even in the face of a pool of pre-formed alloreactive memory T cells.

REFERENCES

Antagonistic Effect of Toll-Like Receptor Signaling and Bacterial Infections on Transplantation Tolerance

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The induction of donor-specific tolerance remains a major goal in the field of transplantation immunology. Therapies that target costimulatory molecules can induce tolerance to heart and pancreatic islet allografts in mouse models, but fail to do so after transplantation of skin or intestinal allografts. We have proposed that organs colonized by commensal bacteria such as skin, lung, and intestine may be resistant to such therapies as a result of bacterial translocation at the time of transplantation, which may promote antigen-presenting cell maturation and the production of proinflammatory cytokines, consequently enhancing responses of alloreactive T cells. Our results indicate that the inability to sense signaling by most toll-like receptors (TLRs), as well as by interleukin-1R and -18R, as a result of genetic ablation of myeloid differentiation factor 88 promotes the acceptance of skin allografts. Conversely, TLR signals and infections by a model bacterium, Listeria monocytogenes (LM), at the time of transplantation can prevent the induction of transplantation tolerance. The effects of the TLR9 agonist CpG are myeloid differentiation factor 88-dependent, whereas the prorejection capacity of bacteria such as skin, lung, and intestine may be resistant to such therapies as a result of bacterial translocation at the time of transplantation can result in the development of memory T cells independent of CD4+ T cells. The induction of donor-specific tolerance remains a major goal in the field of transplantation immunology. Therapies that target costimulatory molecules can induce tolerance to heart and pancreatic islet allografts in mouse models, but fail to do so after transplantation of skin or intestinal allografts. We have proposed that organs colonized by commensal bacteria such as skin, lung, and intestine may be resistant to such therapies as a result of bacterial translocation at the time of transplantation, which may promote antigen-presenting cell maturation and the production of proinflammatory cytokines, consequently enhancing responses of alloreactive T cells. Our results indicate that the inability to sense signaling by most toll-like receptors (TLRs), as well as by interleukin-1R and -18R, as a result of genetic ablation of myeloid differentiation factor 88 promotes the acceptance of skin allografts. Conversely, TLR signals and infections by a model bacterium, Listeria monocytogenes (LM), at the time of transplantation can prevent the induction of transplantation tolerance. The effects of the TLR9 agonist CpG are myeloid differentiation factor 88-dependent, whereas the prorejection capacity of LM depends on the intracellular sensing of LM and the production of type I interferon. Therefore, transiently targeting these innate, proinflammatory pathways may have therapeutic value to promote transplantation tolerance.

Keywords: Toll-like receptor, Bacterial infections, Type I IFN, Acute rejection, Tolerance.

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MICROBIAL SIGNALS AND ALLORESPONSES

Achieving cardiac allograft acceptance in the absence of chronic immunosuppression while retaining residual immune competence to nonallogeneic antigens remains a major goal in transplantation immunology. However, many hurdles hinder this goal. Microorganisms may interfere with transplantation tolerance at different levels. First, it has been shown that viral and parasitic infections before allograft transplantation can result in the development of memory T cells some of which may crossreact with alloantigens, a phenomenon sometimes referred to as heterologous immunity (1–4). Second, we have proposed that bacterial translocation after transplantation of organs colonized by commensal bacteria, such as skin, lung, and intestine, may explain the higher resistance of these organs to transplantation tolerance (5). Finally, pathogenic infections occurring at the time of surgical transplantation or later on in patients bearing stable allografts may prevent the induction of tolerance or break-established tolerance, respectively (6). Most bacterial infections in transplant recipients occur within the first month after transplantation and include wound and catheter infections, and hospital-based infections (7, 8). Infections occurring later than 6 months posttransplantation may be related to the immunosuppressive regimens administered to prevent...