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Donor-Reactive T Cell Stimulation History and Precursor Frequency: *Barriers to Tolerance Induction*

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Abstract

Blockade of T cell costimulatory pathways represents a potent and highly specific method of preventing naïve anti-donor T cell responses following transplantation in mouse, monkey, and man. However, numerous studies have shown that the presence of donor-reactive memory T cells in the recipient poses a sometimes insurmountable barrier to long-term graft survival and tolerance induction. Here, we discuss the ways in which donor-reactive memory T cells may arise from environmental exposure to pathogens. Pathogen-specific memory T cells, by virtue of the inherent degeneracy of TCR recognition of peptide:MHC ligands, may exhibit cross-reactivity with allogeneic peptide:MHC complexes and thereby mediate graft rejection. From the recent explosion in knowledge of the heterogeneity of memory T cell resulting from variations in frequency and duration of antigen exposure, cytokine milieu, site of priming, and a host of other factors, it is becoming increasingly well-appreciated that different memory T cell populations may exhibit differential susceptibilities to tolerance induction. Thus, the immune history of a transplant recipient and frequencies of donor-cross-reactive memory T cells within the various compartments may dictate the likelihood of success or failure of tolerance induction.

Keywords

transplant tolerance; T cell memory; heterologous immunity; alloreactivity

One of the hallmark features of the mammalian adaptive immune response is the formation of immunological memory. The existence of pre-formed humoral and cellular immunity to an invading pathogen thus provides the host, at both the individual and population level, with a large evolutionary advantage. The cardinal features of immunologic memory, including increased antigen-specific precursor frequency, lower activation threshold, and rapid effector function, provide a clear benefit for protection against re-infection with the same pathogen. However, for precisely the same reasons that they provide host protection against pathogen threats, they pose a potential barrier to transplant tolerance induction, and threaten long-term graft survival.

Of mice and men: immune history impacts susceptibility to tolerance induction

While targeting the CD28 and CD40 costimulatory pathways to induce transplantation tolerance in laboratory mice met with wide success (1,2), the initial application of these approaches proved less successful in non-human primates. It is now widely recognized that the immune history of a transplant recipient may be a major determinant of the success or failure of tolerance induction strategies (3-10). To underscore this point, memory T cells ($CD44^{hi}$) comprise only ~5-10% of the T cell compartment of specific pathogen-free experimental mice. In contrast, while absent at birth, memory T cells compromise 40-50% of the T cell pool in socially housed non-human primates by three years of age and in adult humans

(11-13). In human transplant recipients, higher levels of donor-specific memory T cells are associated with higher rejection rates (14). Given the fact that it has been estimated that 1-10% of the peripheral T cell compartments of naïve mice are allo-reactive (15), it stands to reason that this large pool of memory T cells in adult humans would stochastically contain a high frequency of donor-reactive memory T cells. The question of whether the alloreactive precursor frequency is in fact similar between memory and naïve T cell compartments has not been fully addressed, and warrants further study. However, it is likely that the relative presence of memory T cells in a given individual is a major factor in determining the relative success of tolerance induction protocols during transplantation.

Memory T cells are refractory to tolerance induction through a variety of therapeutic modalities

Secondly, memory T cell populations seem to exhibit an increased resistance to depletional therapy, either by anti-lymphocyte serum (ALS) in mice (25), or via alemtuzumab (Campath-1H) in humans (26). In a recent study by Pearl et al., it was demonstrated that memory $CD4^+$ T cells were selectively spared from depletion with Campath-1H in human recipients of renal allografts, and these T cells persisted upon repopulation of the peripheral T cell compartment (26). Third, memory T cells are relatively resistant to the effects of regulation, as demonstrated in a recent study by Jones and colleagues (27). While $CD4^+$ $CD25^+$ $FoxP3^+$ regulatory T cells were capable of attenuating naïve T cell responses in this model, memory T cell responses were less inhibited by the activity of regulatory T cells (27). In a final and perhaps most dramatic example, memory T cells appear to be refractory to the tolerizing effects of agonistic anti-CD28 monoclonal antibody therapy. While agonistic anti-CD28 based regimens were shown to be efficacious in preventing allograft rejection in murine models of fully MHC disparate bone marrow transplantation (28,29), Phase I clinical trials ended in tragedy when agonistic anti-CD28 mAbs induced a systemic inflammatory response accompanied by lung injury, renal failure, and disseminated intravascular coagulation in six out of six recipients of the drugs (30). The reason for this dichotomous result relative to the murine studies was speculated to have been caused by the presence of a high frequency of memory T cells in the human patients, as opposed to the 2-10% observed in mice (30).

How do transplant recipients develop alloreactive memory T cells?

Donor-specific memory T cells arise from prior exposures to alloantigens via transfusion, transplantation, or pregnancy. In addition to these traditional conceptions of alloantigen exposure, in more recent years it has become increasingly apparent that several other mechanisms exist by which donor-reactive memory T cells might be generated. First, memory T cells specific for a pathogen-derived epitope may express a second T cell receptor (TCR) that could be alloreactive against donor tissue. Dual receptor T cells are the result of incomplete allelic exclusion of the TCR α locus, and have been purported to comprise up to 30% of the peripheral T cells in adult humans (31). Second, alloreactive memory T cells may be generated by homeostatic proliferation of alloreactive precursors following lymphopenia in the host (32,33). This may be clinically relevant in that following lymphopenia induced by a viral pathogen such as HIV, or by therapeutic depletion of T cells for the treatment of autoimmunity or transplantation, as residual T cells are induced to undergo rapid division and the acquisition of a memory-like phenotype. Memory cells generated in this manner have also been shown to constitute a barrier to tolerance induction (34).

In addition, studies have shown that prior infections generate memory T cells that are allo-cross-reactive in a process termed heterologous immunity (4,22,35). First thought to be exquisitely specific for a given peptide:MHC complex, T cell receptors (TCRs) are now considered to undergo degenerate recognition of their ligands, in that each TCR possess

intrinsic cross-reactivity to a wide spectrum of related peptide:MHC ligands. Early studies using variations of the antigenic peptide with amino acid substitutions at TCR contact residues demonstrated that each TCR can respond to a range of peptides that vary widely in their sequences, and that these peptides elicit a spectrum of responses in the T cell (36,37). The implications of this intrinsic cross-reactivity supports the concept of heterologous immunity, suggesting that microbial pathogens might activate antigen-specific T cells that then cross-react with allogeneic tissue and result in graft rejection. Mathematical modeling of the T cell repertoire suggests that TCR cross reactivity is required for complete coverage of pathogens; for example, it has been estimated that a single TCR may be capable of recognizing up to 10^6 related ligands (38). Recently, Allen and colleagues proposed that T cells may not only possess intrinsic cross-reactivity and degeneracy but may be capable of recognizing multiple, structurally unrelated peptide:MHC complexes (15).

Cross-reactive T cell stimulation history can impact tolerance induction

Studies in murine models of infection prior to or following transplantation have revealed that both the timing and type of infection can play a large role in determining the impact on tolerance induction. For example, concurrent infection with LCMV Armstrong or with *Listeria monocytogenes* accelerates rejection and abrogrates tolerance induction (39,40). However, infection with LCMV Armstrong after tolerance has already been established does not break tolerance (39). These data suggest that the inflammatory milieu of a viral or bacterial infection may override the effects of costimulation blockade during tolerance induction, but may not affect donor-reactive T cell responses once they are already anergized or deleted. Furthermore, while prior infection with LCMV Armstrong results in inhibition of tolerance induction in only 7% of mice, prior infection with LCMV clone 13, which persists for the life of the host, completely abrogates tolerance induction in 100% of the recipients (8). Thus, the type of infection, whether it persists in the host, and the frequency and timing of T cell stimulation with antigen are all likely to play a role in determining the impact of those T cell populations on tolerance induction.

The tropism of the virus is also likely to play a role in determining its impact on T cell tolerance induction. If the virus infects the transplanted organ, as in hepatitis C virus or BK virus, viral-specific T cells may play a greater role in inhibiting tolerance induction. For example, infection with mouse polyoma virus (a relative of human BK virus, which infects the kidney) resulted in acute rejection of allogeneic but not syngeneic transplanted kidneys (41). This was accompanied by an increase in donor-reactive T cell responses in the $CD8^+$ T cell compartment (41). Thus, these results suggest that either viral-specific T cells were cross-reactive with alloepitopes, or that the inflammatory milieu generated by the viral infection in the kidney increased the activation and differentiation of the allo-reactive T cell clones.

Heterogeneity among memory T cell subsets: implications for tolerance induction

Over the past decade, major advances have helped unravel the intricacies of T cell memory. It is now recognized that subsets of memory T cells exhibit an array of phenotypes, functional properties and recirculation patterns and may serve specialized roles in protection. Memory $CD4^+$ and $CD8^+$ T cells are often segregated into two subsets, central (T_{CM}) and effector (T_{EM}) memory. T_{CM} express lymph node homing receptors (CD62L or CCR7), whereas T_{EM} lack these markers but express other chemokine receptors (CCR5 and CCR6), which direct them to peripheral tissues (42,43). In addition, T_{CM} have high proliferative potential, express CD27, produce IL-2 upon Ag recognition, but require a longer period to re-acquire cytolytic function upon rechallenge. In contrast, T_{EM} have a lower proliferative potential reside primarily in nonlymphoid tissues, are immediately cytolytic upon Ag re-exposure, and are poor

producers of IL-2 (42,44,45-47). Current thinking holds that depending on the route of exposure, dose, replication rate, and tropism of the infectious challenge, either memory T cell subset may be retained to a greater or lesser degree and subsequently play a more or less dominant role in protective immunity (48). Furthermore, there is evidence that memory $CD8^+$ T cell differentiation into T_{CM} and T_{EM} is dictated by the cumulative history of Ag exposure with repeated exposure favoring $T_{EM}>T_{CM}$ (48.).

Given that memory subsets play distinct roles in protective immunity during recall responses and differ in expression of key costimulatory, cytokine and chemokine receptors, they are likely to vary in their susceptibilities to blockade of costimulatory pathways. For example, our studies as well as those of others suggest that $CD4^+$ memory cells may be more susceptible to the effects of CD28/CD40 costimulation blockade during recall than $CD8^+$ memory T cells (22, 49). Furthermore, we have shown in a fully allogeneic model that T_{CM} that were generated by prior exposure to BALB/c antigen through a skin graft posed a greater barrier to tolerance induction than T_{EM} in a fully allogeneic murine model of skin graft rejection (22). However, in a model of donor-reactive memory T cells generated via a latent viral infection, T_{EM} generated by a latent EBV homologue posed a robust barrier to the tolerance induction (50). A recent study by Pearl et al. implicated $CD4^+$ T_{EM} as being relatively resistant to the effects of therapeutic depletion via either anti-thymocyte globulin or Campath-H1. This study also highlights the fact that subsets reside in anatomically different locations may also impact their relative access to therapeutic agents.

Increased precursor frequency alone may contribute to the costimulation blockade resistance of memory T cells

What properties of donor-reactive memory T cell populations confer costimulation independence? We recently uncovered a role for naïve $CD4^+$ and $CD8^+$ T cell precursor frequency in determining the degree of proliferation and differentiation of responding donor-reactive T cell populations during transplantation, and in mediating costimulation blockade-resistant rejection (51,52). Naive graft-specific $CD8^+$ T cells stimulated at high frequency proliferated and accumulated even in the presence of CTLA-4 Ig and anti-CD154, resulting in more “high-quality,” multi-cytokine producing effector cells and the precipitation of graft rejection (51). In contrast, naïve graft-specific $CD8^+$ T cells stimulated at lower frequency failed to accumulate and did not differentiate into high quality effectors that were capable of rejecting a skin graft (Figure 1). Thus, even naïve T cells present at high frequency appear to obviate the need for costimulation during priming. Furthermore, previous studies have shown that a critical frequency of memory T cells is also required to generate costimulation blockade-resistant rejection. For example, adoptive transfer of 10^5 but not 10^4 alloreactive memory cells into naïve recipients resulted in graft loss despite treatment with costimulation blockade (22). Therefore, in addition to their clearly reduced activation threshold, a critical component involved in the costimulation blockade resistance of memory T cells may be their heightened precursor frequency. Taken together, these studies demonstrate that high-frequency T cell responses, present either as naïve alloreactive populations or as memory T cell populations cross-reactive for an alloantigen, may obviate the need for costimulation and play a large role in mediating costimulation blockade-resistant allograft rejection.

Natural history of a given patient may therefore influence memory T cell repertoire

It is becoming increasingly well-recognized that stimulation history may play an important role in the quantity and quality of antigen-specific T cell memory. For example, T cells that had been exposed to antigen three times (so-called tertiary memory cells) exhibited

significantly increased proliferation and effector function and decreased cell death as compared to cells that had been previously exposed only once (so-called primary memory cells) (48). Thus, the functional properties of memory T cells generated by a single brief encounter with antigen (a single vaccine), repeated brief encounters (the common cold/corona viruses and influenza), or sustained exposure (latent pathogens such as EBV and CMV) may differ in the relative composition of their memory subsets as well as the function of cells within each subset. As discussed above, the panel of pathogens to which a given patient has been exposed may dictate the relative composition and frequency of $CD4^+$ and $CD8^+$ T_{EM} and T_{CM} subsets that are cross-reactive for alloantigens. Thus, the immune history of a transplant recipient and frequencies of donor-cross-reactive memory T cells within the various compartments may dictate the likelihood of success or failure of tolerance induction or even immunosuppression. By understanding the function, costimulatory and signaling requirements for recall responses mediated by the various memory T cell subsets, we may be able to tailor tolerance induction approaches to control the predominant forms of memory for specific donor-recipient combinations.

Conclusions

The presence of pre-existing anti-donor T cells in transplant recipients is increasingly being recognized as a potentially formidable barrier to tolerance induction via a variety of therapeutic modalities, including costimulation blockade, T cell depletion, and regulatory T cells. As discussed above, however, memory T cell populations contain a high degree of heterogeneity, and may vary considerably in terms of their ability to traffic into the graft, to resistant depletion, and to mediate costimulation blockade-resistant rejection. Advances in understanding the costimulatory, cytokine, adhesion, and survival requirements of different types of donor-reactive memory T cells will allow us to better tailor immunosuppression/tolerance induction protocols for a given individual based on their memory T cell profile, and will direct the future development of novel therapeutics to better target donor-reactive memory T cell populations.

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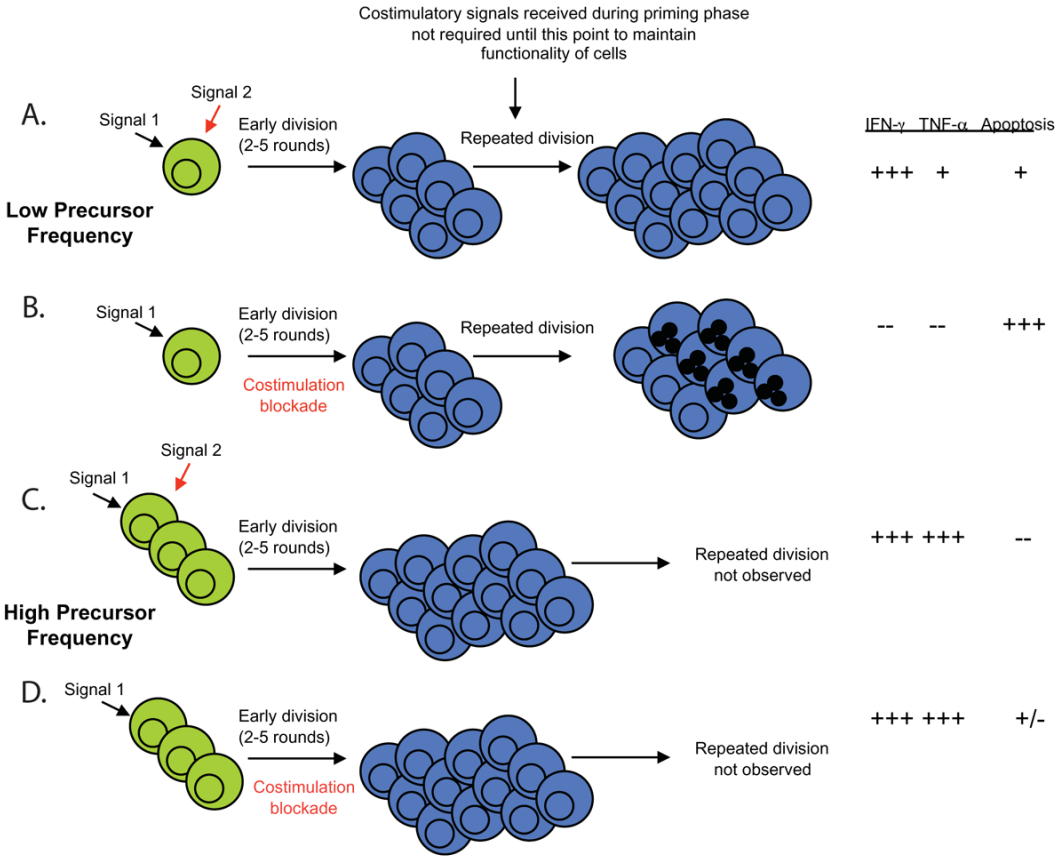

Figure 1.

Impact of antigen-specific T cell precursor frequency on susceptibility to costimulation blockade. A, Cells stimulated at low precursor frequency are required to undergo multiple rounds of division in order to generate a threshold number of effector cells needed to mediate graft rejection. B, Cells that undergo multiple rounds of division in the absence of costimulation fail to differentiate into competent effectors and undergo increased cell death at later rounds of division. C, In contrast, cells that are stimulated at high naïve T cell precursor frequency must undergo many fewer rounds of division in order to a sufficient number of effector cells to mediate graft rejection. D, Populations that had undergone fewer rounds of division in the absence of costimulation had better effector function and reduced death as compared to those that underwent more rounds of division in the absence of costimulation.