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Impact of Infection on Alloreactive Immune Responses

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Introduction

Adaptive immune reaction against donor antigens is that the major barrier to successful transplantation, and alloreactive T cell responses play a central role in mediating graft rejection . Therefore, most efforts for inducing donor-specific tolerance have specifically focused on inhibiting alloreactive T cell immune responses. With an increasing knowledge of transplant-mediated adaptive immunity, a growing number of tolerance-inducing strategies have exhibited excellent long-term immunosuppression-free graft protection in preclinical models also as in clinical trials 2. However, graft protection by these promising strategies seen in quiescent hosts could also be challenged by inadvertent host infections, as a series of immune responses elicited in response to infection may alter the immune microenvironment within the body and have a big impact on both tolerance induction and maintenance in transplantation. Therefore, understanding how alloreactive T cell immune responses could also be modulated by exposure to pathogens and pro-inflammatory signals is critical for the event of therapeutic strategies which will induce and maintain potent transplantation tolerance in setting of inadvertent infections. During this section, we discuss how microbial infections may affect alloreactive T cell activation and regulation.

Effects of infection on alloreactive T cells

Full activation of alloreactive T cells requires three signals all of which may be suffering from infections. Signal 1 is that the recognition and binding of allo-antigenic peptide on antigen presenting cells (APCs) by the cognate TCR complex expressed on alloreactive T cells. The antigen binding component of the TCR complex specifically recognizes the proteolytically processed allo-antigenic peptides presented by major histocompatibility complexes (MHC) on APCs. However, it's long been known that certain pathogen-specific T cells even have the potential to acknowledge MHC molecules structurally almost like pathogen epitopes, hence the term "cross-reactive T cells" was coined. Amir et al reported that a considerable proportion of virus-specific T cells, including those with specificities to the Epstein-Barr virus (EBV), cytomegalovirus (CMV), varicella zoster virus (VZV), and influenza virus, also answer allogeneic stimulations. More recently, van den Heuvel et al demonstrated that the polyclonal immune repertoire directed against CMV alone is related to a memory response to 6 allogeneic human leukocyte antigen (HLA) molecules19. Reciprocally, one HLA-specific memory T cell clone also can answer multiple viral specificities. These data indicate a good cross-reactivity between virus-specific and alloantigen-specific T cells. Existing studies have reported that cross-reactive virus-specific T cells indeed contributed to allograft rejection. additionally, bacteria-specific T cells like those specific to Leishmania major infection also exhibit significant cross-reactivity to alloantigens and portend a negative impact on allograft survival. These findings collectively suggest that recipients with prior pathogen exposures may already harbor a repertoire of allo-reactive memory T cells forming a pre-existing barrier to tolerance induction and maintenance.

Signal 2 for T cell activation is that the engagement of costimulatory molecules expressed on APCs with their corresponding ligands expressed on T cells. This signal is critical for driving T cell clonal expansion, survival, and differentiation. There exists an outsized group of co-signaling molecules, which may either promote (costimulatory) or inhibit (coinhibitory) T cell activation. These molecules together form a posh and kinetic network during the entire phase of adaptive T cell immune responses, and it's the constellation of all the costimulatory and coinhibitory signals that determines the fate of T cells. within the absence of costimulatory signals, T cells become inactivated following an antigen encounter, but remain alive during a hypo-responsive state called "anergy" for an extended period of your time . Naturally, this critical consequence of blocking costimulatory signals during T cell activation has generated tremendous enthusiasm towards targeting costimulatory signals for transplantation tolerance induction.

However, such a hypo-responsive state of T cells are often readily subverted by infections. IL-2 may be a primary inflammatory cytokine in microbial infections 28 and is reported to reverse the hypo-responsiveness of anergic T cells. As Bendiksen et al reported, the power of anergic T cells to proliferate and produce inflammatory cytokines in response to an antigen are often fully restored by receiving intermediate stimuli from the cognate antigens plus IL-2 . The underlying mechanism of such anergy reversal was described by Myrianne et al and appears to implicate IL-2 receptor signaling through JAK3 and mTOR resulting in the inhibition of expression of anergy-inducing genes. Another key interaction in driving anti-virus T cell immune responses is between OX40-OX40L, which has also been shown to rescue self- or tumor-reactive CD8 T cells from an anergic state. These data suggest that pathogen infections may end in reactivation of anergic T cells.

Interestingly, both costimulatory and co-inhibitory signals play important roles in shaping the host T cell immune reaction to specific pathogens. as an example , during a chronic LCMV infection mouse model, Crawford et al have shown that both co-inhibitory molecules including PD-1, CTLA-4, 2B-4, LAG-3 and BTLA also as costimulatory molecules like OX40, ICOS and CD27 are increased on virus-specific T cells, though during a differential manner on CD4+versus, CD8+T cells. Therefore, attention should even be paid to inhibitory signals up-regulated on T cells during chronic infections. As an example, T cell exhaustion caused by chronic antigen stimulation is another hypo-responsive state of T cells which is characterized by decreased proliferative capacity and a loss of IL-2 production, followed by a reduced capacity to secrete tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ). These exhausted T cells are characterized by a big up-regulation of inhibitory receptor expression on their surface, among which the foremost well-characterized are PD-1 and CTLA-

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4. the present notion is that T cell exhaustion is probably going to be beneficial for transplantation tolerance. as an example , during a human liver transplant study, Bohne et al reported that operational tolerance was related to an expansion of exhausted PD1/CTLA4/2B4 positive HCV-specific circulating CD8+T cells. Their findings suggest that persistent viral infections may exert immune-regulatory effects that would contribute to allograft tolerance. Taken together, immune responses elicited by infections may regulate both stimulatory and co-inhibitory signals to make a posh co-signaling network, contributing to both transplantation rejection and tolerance.

In addition to signal 1 and signal 2, T cells also require a 3rd signal (signal 3) for the optimal generation of effector and memory populations. within the absence of signal 3, antigen recognition and Cost imulation ligation propel T cells through only weak clonal expansion and proliferation, while fail to drive them to realize strong effector functions or memory formation. Signal 3 is especially provided by inflammatory cytokines like IL-12 and type-I IFN. The critical role of IL-12 for CD8+T cell effector function has been well elucidated. During a mouse Leishmania Infection model, Novais et al have recently shown that lesion CD8+T cells fail to form effector cytokine IFN-γ due to a deficiency in IL-12, and consequently, the addition of IL-12 effectively increases their IFN-γ production within the leishmanial lesions. In another mouse melanoma model, ex vivo IL-12-conditioning of mouse CD8+T cells results in a 10–100-fold increase in their persistence and anti-tumor efficacy upon adoptive transfer to lymphodepleted mice. Importance of IL-12 during a llo reactive CD8+T cell function has also been reported: in a heart transplant model, dendritic cells conditioned to supply IL-12 are needed to supply the "third signal" for effector CD8+T cell differentiation and subversion of tolerance. almost like IL-12, type-I IFN has also been shown to be necessary for virus-specific CD8+T cell clonal expansion and memory formation. T cell s deficient in cytokine receptors for type-I IFN show reduced clonal expansion and CD8+T cell memory formation during infection. While development of memory to vaccine is supported predominantly by IL-12, both IL-12 and type-I IFN contribute to memory formation in response to Listeria. The impact of signal 3 on T cell function is further supported by gene expressions induced by signal 3. Compared with stimulation with only signal 1 and signal 2, when IL-12 or type-I IFN is additionally present, T cells are reprogrammed to reinforce the expression of the many genes involved in effector functions, proliferation, Cost imulation, survival and trafficking. In summary, the inflammatory cytokines IL-12 and type-I IFN are critical for T cell effector function and memory formation. Therefore, their production by infectious pathogens may serve to supply potent signal 3 to reinforce the effector function and memory formation of alloreactive T cells which successively impact transplantation tolerance.