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Loss of tolerance to self after transplant

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Abstract

Organ transplantation is the widely accepted treatment for end-stage organ failure. Since the first successful kidney transplant from an identical twin donor in 1954, researchers have been studying the effects of the immune system on transplantation outcomes. Although the surgery is technically successful, the majority of grafts from genetically disparate donors are rejected due to a number of factors that stimulate recipient immune responses, ultimately resulting in graft loss despite the chronic use of immunosuppressive (IS) drugs. Unfortunately, while short-term success has greatly improved with the development of novel IS drugs, the long-term graft survival of solid organs has not improved significantly over the last few decades. The problem of late graft loss is mainly attributed to development of chronic rejection. Therefore, understanding all of the immune mechanisms involved in transplant rejection is important to prevent graft dysfunction, and eventually, graft loss. In this review, we will give an overview of allograft rejection, the progression from acute to chronic rejection, and in addition, the recent discovery of a critical role for loss of self-tolerance and development of IL-17-dependent autoimmunity in chronic rejection.

Introduction

Solid organ transplantation presents a unique immunologic environment where there is new foreign tissue, ischemic injury to that tissue, and the introduction of immunocompetent “passenger” leukocytes. The ultimate goal of transplantation is to achieve immunological tolerance [1], whereby the recipient's immune system accepts the foreign donor tissue along with its passenger components, in the absence of immunosuppressive (IS) drugs. In the case of the first successful kidney transplant, the donor and recipient were identical twins; therefore, the graft was immunogenetically “self”, and Dr. Joseph Murray and his team of surgeons could avoid the need for immunosuppression [2]. Organ transplantation involves varying amounts of surgical trauma consisting of tissue damage, ischemia, and reperfusion, all of which elicit an initial inflammatory response. This early injury is minimized in living donor transplants. The “injury response” hypothesis states that injury promotes the host immune response, which in turn enhances innate and adaptive immune responses. This problem is particularly acute in organs harvested from brain-dead donors due to cytokine release occasioned by brain injury [1, 3]. More recent studies have examined the effect of the innate response after transplantation. In a murine model of vascularized cardiac transplant, a strong innate immune response was generated 1 day after transplant, which included macrophage infiltration and upregulation of numerous cytokines and chemokines, both in the presence and absence of an adaptive immune response [4]. Another group found upregulation of matrix proteins, including the alpha chains of collagen types I and V, 2 days after transplant compared to day 50 when the allograft had healed [5]. The authors went on

to suggest that upregulation of these matrix proteins makes the graft more vulnerable to acute rejection by adoptively transferred T effector cells than a healed allograft, in which transfer of the same number of allospecific T effector cells resulted in chronic, rather than acute rejection. In lung transplantation, patients having a functional polymorphism in their toll-like receptor 4 (TLR4) loci have reduced endotoxin responsiveness, which was associated with a decreased incidence in acute rejection [6]. In line with these results, rejection of a HY-incompatible skin graft was prolonged in Myd88-deficient mice versus wild-type C57BL/6 mice (Myd88 is a key component of multiple TLR signaling pathways) [7]. However, this effect was not seen in stronger histoincompatibility models. The innate response in transplantation is important, but it is the adaptive response that ultimately drives graft rejection or acceptance.

The adaptive immune responses after transplantation from a genetically disparate donor are initially directed towards the alloantigens of the graft, including major histocompatibility (MHC) class I and class II antigens [8] as well as minor histocompatibility antigens (mHA) [9]; the latter are particularly important in transplants between HLA-identical siblings, where the immune response is limited to T and B cells that recognize non-MHC antigens. Acute cellular rejection is mainly responsible for early graft loss after transplantation. Current IS drugs are extremely successful in decreasing the incidence of acute rejection. Typically mycophenolic acid/MPA (or azathioprine/AZA) is used along with a calcineurin inhibitor, such as cyclosporine or tacrolimus, and a corticosteroid, usually prednisone. Nucleotide analogs, MPA and AZA, work by inhibiting proliferation of T and B cells responding to the graft [10, 11]. Calcineurin inhibitors prevent NFAT translocation to the nucleus and IL2 gene transcription in effector T cells, and steroids act in a complex manner by inhibiting inflammatory gene transcription while activating anti-inflammatory genes [7, 12]. Sirolimus, also known as rapamycin, is a macrolide that interferes with growth factor receptor signaling, including VEGF-R [13], downstream of the NFAT/IL-2 synthesis pathway. Unfortunately, none of these immunosuppressants have been able to stop fibro-obliteration of the airways (lung), tubules and glomeruli (kidney), and vessels of allografts that characterize the chronic rejection process. This is particularly evident in lung transplantation, which has the worst 5-year graft survival rates of major transplanted organs (<http://optn.transplant.hrsa.gov>). Obliterative bronchiolitis (OB) is the process where the bronchioles become terminally occluded by fibrosis [14–16], and current immunosuppression does little to inhibit this process.

During injury to a tissue caused by trauma, infection, or host response, cryptic self-antigens become exposed. Yet somehow, tolerance to self-antigens is maintained. We now attribute the ability to maintain self-tolerance, at least in part, to the action of Treg cells [17], which sense the inflamed environment, migrate in, and dampen potential autoimmune responses, allowing tissue repair and regeneration to proceed normally. However, after a transplant, self-tolerance is disrupted or inhibited as chronic rejection progresses. Details of this process have been emerging, and the data suggests that similar autoimmune responses are seen after transplantation similar to autoimmune disease occurring without transplant. This review outlines alloimmune response to grafts with development of autoimmunity and the current information on autoimmune diseases.

Alloimmune response

There are three pathways of antigen recognition involved in lymphocyte-mediated alloimmunity, which include the direct [18], indirect [19], and semi-direct [20]. The direct pathway involves recipient T cells directly recognizing donor MHC-peptide complex displayed on the cell surface of donor tissue. Semi-direct allorecognition is where intact donor MHC-peptide complexes and associated plasma membrane components are transferred to recipient APCs and presented to the direct pathway T cells [20]. One major

difference between semi-direct and direct pathway is strength of signal: when intact donor MHC molecules are transferred to the recipient APC, they are expressed at lower levels than on the original donor APC from which they were derived. When presented to recipient T cells, this semi-direct interaction is likely to be of lower intensity than the direct pathway, which may induce more of a regulatory response versus an effector response. Another difference is that the same recipient APC could also be stimulating an indirect pathway T cell and a direct pathway T cell [20]. In addition, there is an initially much less frequent “indirect pathway” T cell population, recognizing fragments of donor MHC proteins shed from the graft and taken up and presented as allopeptides by host APCs [19, 21, 22]. These T cells, which are similar to classical CD4 T helper cells in pathogen defense and autoimmune disease are required for allotolerance [23]. Furthermore, this indirect pathway has been shown to be the major pathway for Treg suppression of cellular immunity in tolerant transplant recipients [24]. However, humoral immunity toward donor MHC, mediated by allospecific B cells, is also dependent upon indirect pathway helper T cells [25, 26]. Most important for the purposes of understanding chronic rejection, indirect pathway may also pre-dispose to development of autoimmunity [27]. The three major pathways of allorecognition can either result in suppression of immune response, ideal for transplantation tolerance, or activation that leads to rejection.

The cellular make-up of acute rejection includes a number of cell types, but the main players are T helper (Th) 1, cytotoxic T cells, B cells, macrophages, and dendritic cells (DCs) [28, 29]. Classically, the cells involved in the acute rejection responses were thought to be either Th1 [30] or Th2 [31], but the involvement of the new effector T cell lineage, Th17, has not been entirely addressed. Th17 cells characteristically produce the pro-inflammatory cytokine IL-17A. With IL-17 receptor found on an abundant number of cells, both leukocytes and parenchymal cells, massive inflammatory responses ensue after IL-17A production and binding to its receptor [32].

The role for the proinflammatory cytokine, IL-17A, in allograft rejection has been reported even before the Th17 cell lineage was described. In a mouse cardiac transplantation model, blocking IL-17 promoted DC maturation, and inhibited alloreactive T cell proliferation in vitro, as well as prolonging the vascularized transplants [33]. During the Th1/Th2 only paradigm, studies looked at the effect of knocking out Th1 effector cytokine, IFN- γ , or transcription factor T-bet on graft rejection in mouse cardiac transplant models. Although allograft rejection is primarily driven by Th1 effectors, knocking out either IFN- γ or transcription factor, T-bet, resulted in accelerated rejection with neutrophil- rather than macrophage-dominated graft infiltrates. These effects could be attributed to CD4+ [34] Th17 cells in a class II-disparate heart allograft model or to CD8+ [35] Tc17 cells, in a fully allogeneic heart transplant model. These Th17 cells may play a role early in transplant rejection during the alloimmune response as well as later on in the development of autoimmunity and chronic rejection. Th17 or IL-17A producing T cells will be further discussed as they relate to autoimmunity.

Loss of self-tolerance to tissue-specific antigens

Much less is known about the development and progression of chronic rejection, but it is clearly distinct from acute rejection. Chronic rejection in all organs mainly manifests as fibrosis in the graft, resulting in loss of function, and eventually, graft loss. Classically, this fibro-obliteration was thought to be the result of continual immune attack mediated by alloreactive T cells [29, 36]. We have proposed that this process includes development of de novo autoreactivity to tissues as well as alloreactivity [37]. At what point after transplantation autoimmunity to tissue antigens develops is still poorly understood. It has been suggested that HLA-specific immunity precedes autoimmunity based on studies of antibody responses in lung transplant recipients [38]. A number of self-antigens have

emerged as targets of autoimmune responses after transplantation and vary depending on the transplanted organ.

Rolls et al. studied tissue-specific T cell responses in heart transplant recipients with chronic rejection, and identified cardiac myosin as a self-reactive tissue antigen [39]. Using a chronic rejection model where recipients treated with anti-CD40L mAb prevented acute rejection, results showed high IFN- γ producing cardiac myosin-specific T cells became dominant over time. They also demonstrate that these T cells had less stringent costimulation requirements [39]. These studies were limited because the authors only focused on the then current Th1/Th2 paradigm. With the number of recent studies describing the effects of Th17 cells and autoimmunity, potentially, there could also be a role for Th17 in the response to cardiac myosin. Other self-antigens targeted after heart transplant include vimentin and heat shock proteins. Vimentin is a non-polymorphic cytoskeleton protein, and vimentin-specific tetramer positive CD8⁺ T cells have been found in the peripheral blood of heart transplant patients, the first report to suggest a role for CD8⁺ T cell autoimmunity after transplantation [40]. Autoimmunity to vimentin also contributes to chronic rejection of kidney transplants [41].

Some of the most convincing data to support autoimmunity playing a contributing role in chronic rejection is seen in the lung transplant setting. Both cell-mediated and humoral immune responses have been implicated in autoreactivity to collagen type V [col(V)] in lung transplantation. Col(V) is a minor fibrillar collagen typically embedded within collagen type I fibrils [42], and therefore normally unexposed to surrounding tissues and circulating lymphocytes unless tissue damage occurs. Initial discovery of this autoreactivity occurred when antibodies were found binding the connective tissue of the bronchioles in a lung transplant patient [43]. This finding was reproduced in a mouse lung injury model and determined to be specific to col(V) [44, 45]. Evidence supporting the role for col(V)-specific CD4⁺ T cells contributing to transplant rejection was confirmed using a model of rat lung isograft transplantation. Results showed that col(V)-specific CD4⁺ T cells adoptively transferred prior to or 30 days post transplant induced pathology in the transplanted lung [46]. In human lung transplant, patients that develop col(V) reactivity post-transplant are predisposed to develop more severe bronchiolitis obliterans syndrome (BOS), the clinical correlate of chronic rejection in lung transplantation, than patients without T cell responses to col(V) [37]. This autoreactivity was driven by CD4⁺ T cells and IL-17A, IL-1 β , and TNF- α production [37, 47] suggesting this col(V)-specific response is mediated by Th17 cells as seen in many autoimmune diseases, but different from the classic Th1 driven alloimmune response seen in acute rejection. Another interesting feature of this response is the dependency on monocytes as the potential col(V)-presenting cell [47] with less requirement for DCs (M.R. Keller and W.J. Burlingham, unpublished data). Interestingly, patients with col(V) reactivity as determined by trans-vivo delayed-type hypersensitivity (tv-DTH) assay pre-transplant were at higher risk for primary graft dysfunction compared to nonreactive patients [47].

In addition to col(V)-autoimmunity development in lung transplant recipients, studies of humoral immunity during chronic rejection of the lung found antibody-mediated rejection to the epithelial tissue antigen K- α 1 tubulin. Binding of these autoantibodies resulted in the release of fibrogenic growth factors and activation of fibroproliferation, thus contributing to pathogenesis of chronic rejection [48]. Most recently, an article by Wood et al. [49] showed a higher level of anti-Hsp27 antibody in bronchoalveolar lavage samples from patients with BOS compared to controls, but not elevated levels of the classic anti-Hsp60 and anti-Hsp70 suggesting a role for local autoimmunity to Hsp27 in development of BOS [49].

As discussed, the early acute rejection stage in transplantation is primarily directed against alloantigens of the graft in a Th1-type response that immunosuppression is effective in controlling. If the T cell response driving chronic rejection post-transplant changes from an acute alloresponse to an autoimmune response, epitope spreading is occurring throughout the rejection process. Epitope spreading is the process where an immune response is induced towards an epitope that is distinct from this original disease-inducing epitope [50]. Epitope spreading can occur intramolecularly, as seen in the experimental autoimmune encephalomyelitis model (EAE) [51] and intermolecularly, as in the case of transplantation [22]. In transplantation, T cell immunity is directed initially towards alloantigens of the graft APCs by direct pathway T cells, but this soon changes to a dominant indirect pathway T cell response to donor antigen, and then to self-antigen such as col(V) [52] or cardiac myosin [27]. B cell epitope spreading has also been reported in transplantation. The major humoral response in lung transplant patients begins with antibodies directed toward donor HLA molecules and progresses to antibodies specific to self-tissue antigens, K- α 1 tubulin, and col(V) [38]. This process of activating new epitope-specific T cells could not only occur in the lymph nodes, but also within the target tissue itself, as was shown in EAE [53].

Regulatory T cells (Tregs) are responsible for inhibiting proliferation and production of inflammatory cytokines by effector cells, making them a powerful regulator of a number of immune responses that ultimately keep the host healthy and pathogen free. Classically, T cells that undergo positive and negative selection in the thymus are Foxp3⁺ CD4⁺CD25⁺, or natural Tregs [54, 55]. The other type of suppressor cell is an inducible CD25⁻ cell that can arise from the periphery and are phenotypically and functionally equivalent to natural Tregs. The association of autoimmune diseases and deficiencies of Tregs demonstrates the importance of their function [56]. It is clear that the phenotypic plasticity of T cells must also be considered. Many recent studies have shown the plasticity between Treg and Th17 cell fate. Voo et al. [57] reported that human PBMC Foxp3⁺ Treg cells produced IL-17 upon activation and could inhibit proliferation of responder T cells. This suggests the same cell has both Th17 and regulatory capabilities [57]. This plasticity between Treg and Th17 is not surprising given their requirements for differentiation. Both lineages require TGF- β , but depending on local cytokines, they may differentiate into pathogenic Th17 or tolerogenic Treg cells [58]. Typically, healthy individuals regulate responses to self-tissue antigens, such as col(V), and therefore, their Tregs suppress any autoreactive response. We recently reported a correlation between atherosclerosis and col(V)-specific T effector responses. An IL-10-regulated response was seen in Apo-E^{-/-} mice fed a regular diet at 15 weeks while mice fed a high fat diet overcame this regulation and developed a strong TH1/Th17 response as determined by the tv-DTH assay [59]. In the transplant setting, we have evidence for TGF- β -regulated anti-col(V) responses in lung transplant patients with low anti-col(V) tv-DTH after transplant (unpublished data). Both of these results suggest the immune system establishes barriers to protect from auto-reactivity, but these barriers can be overcome by repeated insults as seen in transplantation and hypercholesterolemia. In the inflammatory setting of allotransplantation, the plasticity of Tregs, coupled with the exposure of normally cryptic antigens, could explain the loss of self-tolerance to tissue-specific antigens. The presence of TGF- β coupled with IL-6 might pre-dispose to Th17 pathogenicity of the immune responses after the loss of regulation to self. This process, we believe, ultimately results in autoimmune responses that drive chronic rejection.

Conclusion

Chronic rejection ultimately results in fibro-obliteration of epithelial and vascular spaces within the transplant, a process that may be largely lacking inflammatory cell infiltrates. Lack of leukocyte components in fibro-obliteration suggests that the process is either (a) non-immunologic in nature or (b) the end result of allo- and autoimmune attacks upon the

graft that are happening prior to fibrosis. Therefore, this process needs to be well understood for potential therapeutic intervention. In summary, much work has gone into understanding the acute rejection response to alloantigens in the early post-transplantation period. Immunosuppressive regimens and advanced surgical techniques have limited graft loss in the short term, but not long term. Late loss of grafts is mainly attributed to interstitial fibrosis and tubular atrophy in kidneys and fibro-obliteration of vessels and airways within lung and heart allografts. A critical role for autoantigens and the Th17 responses to these antigens in the immunopathology of chronic rejection is now becoming more widely accepted. Understanding the immune mechanisms involved in the development of autoimmune responses both before transplant, as well as after allotransplantation, will ultimately provide targets for appropriate therapeutic intervention. For example, targeting autoimmunity at the same time as alloimmunity either before or shortly after transplantation may prevent chronic rejection in the long-term.

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Abbreviations

IS	Immunosuppressive
TLR	Toll-like receptor
HLA	Human leukocyte antigen
APC	Antigen presenting cell
col(V)	Collagen type V
mAb	Monoclonal antibody
tv-DTH	Trans-vivo delayed type hypersensitivity