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Role of Alloimmunity and Autoimmunity in Allograft Rejection

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INTRODUCTION

Organ transplantation remains a therapeutic option for patients who suffer from many end stage organ diseases that are not responsive to other conventional therapies. However, due to limitations in the availability of donors and the increasing demand for organs, many patients will stay on organ waiting lists for long periods of time, which has caused high morbidity and mortality in these patients. Despite an increased one-year survival rate and success to prevent acute rejection in most solid organ grafts, the long-term survival remains poor due to chronic rejection leading to graft dysfunction. Regardless of the grafted organ, chronic rejection is characterized by fibrosis of vasculature and hollow structures within the graft that finally lead to graft failure, which can occur months to years after transplantation. This phenomenon is a multifactorial process, but it is thought to be initiated by a host anti-graft immune response through antigen dependent and independent pathways leading to fibroproliferative changes and subsequent dysfunction of the graft (1). The indirect pathway is considered to have a more dominant role in the development of chronic rejection (2). The role of humoral immune responses leading to antibodies (Abs) against mismatched donor human leukocyte antigen (HLA) in the immunopathogenesis has gotten much attention in recent years (3). In addition, emerging data has shown that immune responses to self-antigens (SAgs) may play an important role in the pathogenesis of chronic rejection, either alone or in conjunction with alloimmune responses to mismatched major histocompatibility complexes (MHC) (4–6). Immune responses to several tissue restricted antigens or SAgs have been implicated with development of chronic rejection. In this chapter, we will discuss recent findings regarding the role of auto- and alloimmunity in the development of chronic rejection and the pathophysiology of immune responses in posttransplant sera. Further, we will provide a summary of our recent studies attempting to confirm that immune responses to SAgs are indeed involved in the immunopathogenesis of rejection following solid organ transplantation. Since most of our current work involves the role of SAgs of the lungs and their involvement in chronic rejection following human lung transplantation, we will begin our discussion with SAgs restricted to lungs.

Evidence for a role for autoimmunity in lung allograft rejection

Chronic lung rejection, pathologically classified as obliterative bronchiolitis (OB) and clinically classified as bronchiolitis obliterans syndrome (BOS), is the limiting factor for

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long-term survival rates for lung transplantation. The histopathological correlate is chronic rejection, which is characterized by small airway epithelial disruption and progressive fibrosis, which obliterates these smaller airways. Recent studies from our laboratory and others have demonstrated that chronic rejection is an immunologically mediated process resulting in injury to the pulmonary epithelial and/or endothelial cells (7,8). Initially, chronic rejection was largely attributed to immune responses to donor HLA, alloimmunity (9). However, recent studies from our laboratory, as well as others, have demonstrated an important role for immune responses to lung associated SAgs [Collagen V (ColV) and Kα1 Tubulin (Kα1T)] in the pathogenesis of BOS following human lung transplantation (10). Our previous studies demonstrated that there are lung transplant recipients with BOS who do not have detectable donor specific anti-HLA antibodies (DSA). Using sera from such patients, we identified immune responses to tissue restricted SAg Kα1T expressed on airway epithelial cells and proposed that they may play an important role in the development of BOS. Kα1T is an epithelial gap junction associated protein and immune response to this was noted in lung transplant recipients with BOS (5). Studies from Wilkes and Burlingham demonstrated that immune response to ColV will also play a significant role in the development of BOS (11). The interstitial remodeling that occurs with transplantation has been shown to enhance exposure of ColV. Expression of ColV in the lung has been found to be increased with ischemia reperfusion injury and studies have demonstrated that matrix metalloproteases, induced by ischemia reperfusion injury, are able to cleave collagen, exposing ColV and releasing its antigen fragments following lung transplantation (12–14). Evidence from our laboratory (15,16) has shown that not only is there an association between BOS and immune responses to the above mentioned SAgs, more important is the finding that Abs to these SAgs often precede the development of BOS, suggesting a pathogenic role for immune responses to SAgs in the development of chronic rejection. De novo DSA lead to increased production of pro-inflammatory cytokines [interleukin (IL)-1β and IL-6] both in the circulation and at the local site. This can lead to increased infiltration of B-cells into the transplanted lungs that can act as antigen presenting cells resulting in augmentation of cellular immune responses to mismatched donor HLA and to lung associated SAgs, Kα1T and ColV. Vice versa, de novo developed Abs to lung-associated SAgs, Kα1T and ColV, will induce pro-inflammatory milieu leading to the development of immune responses to DSA. Taken together, the presence of Abs to non-HLA SAgs, or Abs to mismatched HLA can induce the other, suggesting cross talk between allo- and autoimmunity, both of which play a role in allograft rejection.

The link between immune responses against SAgs and alloimmune responses in the development of chronic rejection remains undefined. Our laboratory set up experiments in an animal model to determine if administration of Abs to MHC directly into the lungs of mice can lead to obliterative airway disease (OAD). In addition, we recently performed experiments where Abs to lung associated SAgs was given intraperitoneally to analyze their effect following syngenic murine lung transplantation in order to obtain direct evidence for immune responses to lung associated SAgs in the development of BOS following lung transplant.

Initial studies demonstrated that passive administration of Abs to MHC can lead to immune responses to SAgs (Kα1T and ColV), which are Th17 dependent, leading to OAD (17).

Reports from Wilkes and Burlingham, using a rat lung transplant model (4,18), have also demonstrated that immune responses to ColV play a significant role in the development of OAD. Furthermore, ColV specific T-cells collected from rejecting rat lung allografts with OAD could induce rejection of isografts when adoptively transferred into transplant recipients (19). All of these results clearly demonstrate an important role for the immune responses to these tissue restricted SAgs in the pathogenesis of chronic rejection in animal models.

Recent ongoing experiments using a murine single lung transplant model demonstrated that administration of Abs to either ColV or Kα1T following syngeneic transplantation can result in pathology similar to OAD. Further, administration of either of the Abs results in not only immune responses to that particular SAg but also to other SAgs, suggesting that there is spread of immune responses that may be involved in inducing rejection. What the mechanism is for development of such immune responses is not clear at the present time. The possibility of epitope spreading, linked immune responses as well as Ab-induced shedding of membrane along with exposed antigens are all being considered as potential mechanisms. We also demonstrated that administration of Abs to SAgs can also break the tolerance induced by co-stimulator blockade in an allogeneic lung transplant model. In this model, administration of Abs to SAgs not only results in immune responses to various SAgs but also to foreign MHC, again supporting that development of immune responses to SAgs leading to Ab production has the capability to break existing tolerance following transplantation. These findings support the published results following clinical transplantation that detection of Abs to either HLA or SAgs following transplantation poses greater risk for development of chronic rejection.

Evidence for a role for autoimmunity in cardiac allograft rejection

Cardiac myosin (CM) is an autologous contractile protein that is recognized by both T-and B-cells during the rejection phase (20). Abs to CM persist long after transplantation and it has been hypothesized that tolerance to these SAgs can be lost during the rejection process. Murine studies have shown that sensitization with CM before transplantation can lead to accelerated rejection of allogeneic and syngeneic heart grafts (20). Another tissue specific antigen that has been implicated in the development of cardiac allograft vasculopathy (CAV) is the intermediate filament protein vimentin, which is found in the cells of mesenchymal origin (21). We reported that production of anti-vimentin antibodies (AVA) in cardiac transplant recipients is associated with antibody mediated rejection (AMR) in the first year post-transplantation (22). Heart transplant recipients have also shown to have high titers of immunoglobulin-M AVA within two years post-transplant and these high titers are predictive of CAV development at five years (23). Studies have demonstrated an increase in frequency of CD4+ T-cells that secrete IL-17 in response to vimentin along with a decrease in IL-10 secreting cells in CAV recipients, indicating breakdown of tolerance to vimentin in these patients. AVA is also an independent predictor of coronary atherosclerosis after cardiac transplantation (3). Recent studies from our lab showed that increased levels of Abs to CM and vimentin are significantly associated with the development of DSA in patients with CAV after heart transplantation (22). Further, loss of IL-10 secreting CD4+ T-cells specific to cardiac SAgs may result in the breakdown of peripheral tolerance accompanied by the

development of both IL-5, IL-17, and interferon-gamma (IFN-γ) dependent CD4+ T-cell-dependent immune responses specific to the individual SAgs in post-heart transplant patients with AMR and CAV (22).

Fedoseyeva et al. have shown evidence for alloimmunity being essential to the development of autoimmunity in a murine heart transplant model (20). They found that mice that received an allograft across MHC barrier developed T-cell responses to CM, however, mice that received a syngeneic cardiac graft or those that were recipients of an allogeneic skin graft, did not demonstrate such an immune response to myosin. In this model, sensitization to myosin also led to the rejection of cardiac allografts (24). Similar results have been reported in the miniature swine model (25). Supporting data showed that pre-transplant activation of proinflammatory CM-specific T-cells accelerates rejection and also administration of CM together with incomplete Freund's adjuvant can prevent acute rejection of an allogeneic heart transplant, which is associated with CM- and allospecific T-cells secreting type 2 cytokines (IL-4, IL-5) and reduction of the frequency of proinflammatory IFN-γ-secreting (type 1) alloreactive T-cells (26). Studies have shown that AVA in conjunction with the alloimmune response has a pathogenic role in allograft rejection in mice models (27). However, it is clear that vimentin alone is not sufficient to cause graft rejection, since vimentin immunized recipients in a syngeneic model did not develop CAV and isografts continued to beat for 90 days in the presence of high titers of immunoglobulin-G AVA without the development of any pathology (27). Hence, the anti-vimentin response, unlike autoimmune response to cardiac myosin (20,26), did not result in damage to the graft. Therefore, it has been proposed that prior damage (most likely alloimmune responses) to the transplanted organ are necessary for AVA to accelerate rejection (21).

Evidence for a role for autoimmunity in renal allograft rejection

There are many reports of AMR caused by Abs to HLA class I and II following renal transplantation (28–31). There are also recent reports for Ab mediated damage resulting in poor allograft survival caused by immune response to SAgs and de novo development of Abs to SAgs such as Col-IV (32), endothelin-1 type A receptor (33), angiotensin II type 1 receptor (AT1R) (34–36), perlecan (37), and endothelial cell antigen (38,39). In a prospective study on renal transplants, it was demonstrated that development of both DSA and Abs against AT1R had the highest impact leading to significantly higher allograft rejection episodes than AMR by DSA or AT1R alone, suggesting that combinatorial effect of DSA and AT1R Abs increases the chances of allograft failure during the post-transplant period (35).

Recently, our group demonstrated that kidney transplant recipients diagnosed with transplant glomerulopathy (TG) developed de novo Abs to SAgs including Col-IV and fibronectin (FN) (40). Previous reports have clearly demonstrated that DSA are associated with TG following kidney transplantation. In this study, we determined whether kidney transplantation with TG has immune responses to SAgs, Col-IV and FN. DSA was also determined by solid phase assay, Abs against Col-IV and FN by enzyme-linked immunoassay, and CD4+ T-cells secreting IFN-γ, IL-17, or IL-10 by enzyme-linked immunosorbent spot. Development of Abs to SAgs following kidney transplant increased the

risk for TG with an odds ratio of 22 (p-value=0.001). It is of interest that pre-transplant Abs to SAgs also increased the risk of TG (22% versus 10%, $p<0.05$). Abs to SAgs were identified frequently in kidney transplantation with DSA. In addition, TG patients demonstrated increased Col-IV and FN specific CD4+ T-cells secreting IFN-γ and IL-17 with reduction in IL-10. The increased frequency of SAg specific IFN-γ and IL-17 cells with reduction in IL-10 demonstrates tolerance breakdown to Sags, which we propose play a role in the pathogenesis of TG. Taken together, our results demonstrate that development of Abs to SAgs is a risk factor and having both DSA and Abs to SAgs increases the risk for TG.

CONCLUSION

The emerging idea regarding the pathophysiology of chronic rejection is that the inflammation and subsequent tissue remodeling in the post-transplant period causes exposure of cryptic SAgs or their determinants within the graft, which along with a subsequent cytokine response, leads to loss of peripheral tolerance. These events lead to the activation of cell-mediated immunity towards development of de novo immune responses to SAgs. As we discussed above, the role for interplay between allo- and autoimmunity in the development of chronic rejection is emerging. It has been shown that endothelial and smooth muscle cells are the target for HLA class I molecules, followed by activation through Abs to HLA (41). Binding of Abs to HLA class I induces an intracellular signal through mamillian target of rapamycin (mTOR) pathway which leads to endothelial cell proliferation. Besides this, long-term pretreatment with the mTOR inhibitor rapamycin not only blocked formation of mTOR-raptor and mTOR-rictor complex but also inhibited phosphorylation of class I-induced Akt at Ser473 and Bcl-2, suggesting that exposure of the graft vasculature to Abs to HLA may promote proliferation through mTOR pathway (42). Studies from our lab showed that airway epithelial cells (AECs) that were incubated with anti-MHC class I proliferated and produced pro-fibrogenic growth factors (43). Binding of Abs leads to activation of epithelial cells resulting in the induction of several growth factors, including: epidermal growth factor (EGF), heparin-binding EGF, basic fibroblast growth factor, insulin-like growth factor-1, platelet-derived growth factor, and transforming growth factor-beta (TGF-β) (5,8,44). Studies also demonstrated that Abs against Kα1T could cause up-regulation of pro-fibrotic growth factors (5,8), suggesting that there is a direct role for Abs to SAgs in activating the pro-inflammatory cascade. Abs to Kα1T can induce lipid raft mediated activation of bronchial epithelial cells, which in turn leads to downstream activation of pro-inflammatory and pro-fibrotic cascades mediated by vascular epithelial growth factor and TGF-β (44). This activation is mediated predominantly by the activation of hypoxia inducible factor-1α, since its inhibition results in the return of fibrotic growth factor expression to basal levels. Therefore, it is likely that Abs against lung-associated SAgs may directly participate in fibrosis as seen in chronic rejection. On the other side, data from heart (45) and kidney (46) transplant recipients indicates that alloimmune response can be mediated by the activation of classical complement pathway as well (47), which is characterized by local deposition of complement split products along allograft capillaries, which is associated with downward transplant outcome.

Experimental results using murine models have clearly demonstrated that autoimmune responses to ColV and Kα1T were induced by administration of allo-Abs against class I MHC antigens (17). Further, inhibition of IL-17 did reduce the autoimmune response and development of OAD. This shows an important relationship between alloimmunity, autoimmunity to SAgs such as Kα1T, and a significant role for IL-17 pathway of immune activation. Recently, data for the role of complement activation in OB demonstrated that complement regulatory protein expression is down regulated in an IL-17 dependent manner. This can lead to complement activation and production of C3a, which was indeed found to be elevated in chronic rejection. Complement-mediated damage of AECs can lead to the expression of ColV, exposing the cryptic antigen and inducing an autoimmune response.

In summary, multiple pathways, namely alloimmune responses, apoptosis of the damaged cells, complement activation, viral infections, neutrophil infiltration, and pro-inflammatory cytokines, may cause exposure of SAgs to the immune system. Increased neutrophil infiltration in allografts was significantly associated with chronic rejection (48,49). In addition, neutrophils also express chemokines that regulate macrophage and dendritic cell infiltration (50). Besides the direct role of immune cells, apoptotic cells within the graft (epithelial, parenchymal, endothelial, and the other immune cells) have also been associated with chronic rejection (51). Antigen presenting cells (APCs) can present tissue-restricted SAgs during the process of clearing the apoptotic cells, leading to exposure of SAgs to the immune system (52). Binding of the Abs to MHC or SAgs can also result in membrane bleb formation and shedding, which are then coated by Abs, leading to more efficient opsonization by APCs (53). There is also the likelihood that Abs to MHC can alter the regulatory mechanisms leading to loss of peripheral tolerance to SAgs, resulting in immune responses to SAgs (53). Therefore, the mechanisms behind how Abs against SAgs induce chronic rejection and the interplay between allo- and autoimmunity in the development of chronic rejection still need to be determined.

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SUMMARY

Pathophysiology of chronic rejection strongly supports that inflammation and subsequent tissue remodeling during the post-transplant period cause exposure of cryptic self-antigens (SAgs) or their determinants within the graft, which, along with a subsequent cytokine response, leads to loss of peripheral tolerance. These events lead to the activation of cell-mediated immunity towards development of de novo immune responses to SAgs. There is also evidence for a role for interplay between allo- and autoimmunity in the development of chronic rejection. Experimental results using murine models of Obliterative Airway Disease (OAD) akin to chronic lung allograft rejection have clearly demonstrated that autoimmune responses to Collagen V (ColV) and K-alpha 1 Tubulin (Kα1T) were induced by administration of antibodies (Abs) against class I major histocompatibility complex antigens. Further, inhibition of interleukin (IL)-17 abrogated the autoimmune response and development of OAD. This shows an important relationship between alloimmunity, autoimmunity to SAgs such as Kα1T, and a significant role for IL-17 pathway of immune activation. Recent reports demonstrate that in addition to lung transplant recipients, kidney transplant recipients diagnosed with transplant glomerulopathy can develop de novo Abs to Sags, including Col-IV and fibronectin and heart transplant recipients can develop immune responses to cardiac myosin and vimentin. Abs to SAgs were identified frequently with donor specific anti-human leukocyte antigen antibodies, supporting the concept of crosstalk between auto- and alloimmunity. The increased frequency of SAg specific interferon-gamma and IL-17 cells with reduction in IL-10 demonstrates tolerance breakdown to SAgs which may play a significant role in the pathogenesis of chronic rejection.