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Chronic rejection: a significant role for Th17-mediated autoimmune responses to self-antigens

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Abstract

Despite progress in the field of organ transplantation for improvement in graft survival and function, long-term graft function is still limited by the development of chronic allograft rejection. Various immune-mediated and nonimmune-mediated processes have been postulated in the pathogenesis of chronic rejection. In this review, the authors discuss the important role of alloimmune responses to donor-specific antigens and autoimmune responses to tissue restricted self-antigens in the immunopathogenesis of chronic rejection following solid organ transplantation. In particular, the authors discuss the role of induction of Th17-type autoimmune responses and the crosstalk between autoimmune and alloimmune responses. These self-perpetuate each other leading to activation of profibrotic and proinflammatory cascades that ultimately result in the development of chronic rejection.

Keywords

alloimmunity; autoimmunity; chronic rejection; Th17; Tregs

The first reported organ transplantation was that of a kidney transplant carried out between identical twins in 1955 [1]. Since then, organ transplantation has become a well-accepted life saving therapeutic strategy in end stage diseases of several organs including the heart, lung, liver, kidney, pancreas, small bowel and so on. Most of this success can be attributed to significant advances in surgical technique, organ preservation, patient management and immunosuppression.

Early studies in transplantation were primarily aimed at improving outcomes and preventing acute rejection of the transplanted organ [2–6]. These strategies, including histocompatibility and blood group matching as well as newer and better immunosuppressive protocols, contributed to a significant improvement in early allograft function and survival [7–12]. This is primarily due to prevention of acute rejection resulting in improved graft survival during

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the early period following transplantation. Unfortunately, studies in the last decade have shown that despite this improvement and prevention of acute rejection, long-term survival of allografts has remained relatively unchanged, mostly due to late graft loss resulting from chronic allograft rejection [13,14]. The development of chronic rejection in allografts remains the most important limitation toward long-term organ graft survival of most of the solid organ transplants performed to date.

Chronic rejection is clinically diagnosed as cardiac allograft vasculopathy (CAV) following heart transplantation [15,16], bronchiolitis obliterans syndrome (BOS) following lung transplantation [17] and pathologically diagnosed as obliterative bronchiolitis (OB) and chronic allograft nephropathy (CAN) following kidney transplantation. The current understanding of the process of chronic allograft rejection points to it being an immune-mediated tissue inflammatory process that leads to tissue-remodeling resulting in replacement of organ parenchyma with fibrous tissue. This inflammatory process is more prominent around vascular and other tubular structures in organs (bronchioles in lung, tubules and glomeruli in kidneys), which results in their occlusion and eventual graft dysfunction.

Unlike acute rejection, which is mainly mediated by ‘alloimmune’ responses against donor MHC antigens as well as minor histocompatibility antigens, chronic rejection is hypothesized to be multifactorial in etiology.

Alloimmune responses

Studies indicate that even a single episode of acute rejection increases the risk and incidence of chronic rejection [18–21]. Acute rejection either due to cellular and/or humoral (antibody-mediated) alloimmune responses is a well-known risk factor for the development of chronic rejection. These alloimmune responses are mostly directed against human leucocyte antigens (HLA) such as, MHC class I and II antigens. The cellular responses are mediated by recipient T cells that recognize MHC antigens on the graft directly (direct allorecognition) or following presentation of processed donor antigens by the recipient’s APCs (indirect allorecognition). Alloimmune responses also lead to the development of antibodies against donor HLA. These cellular-mediated and antibody-mediated responses together can lead to cellular infiltration of the graft. Antibodies to HLA bind to endothelial cells on vessels and epithelial cells in the graft and can also lead to signaling cascades resulting in the induction and release of cytokines and chemokines that favor cellular infiltration, inflammation eventually culminating in the fibrosis within the graft. There is now convincing evidence for antibodies specific to donor mismatched HLA participating in the pathogenesis toward the development of chronic rejection [22–24].

Autoimmune responses

Immune response to cryptic self-antigens or their determinants has emerged as an important contributor in the pathogenesis of chronic rejection. These autoimmune responses to tissue restricted self-antigens are both cellular and antibody mediated in nature and studies demonstrate that they may be directed against several tissue-specific self-antigens. Current

results have shown that the immune responses to myosin and vimentin can be detected in heart transplant recipients undergoing rejection [25,26], ColV and K α 1T in lung transplant recipients with chronic rejection [27,28], and AT1R [29], Col4 [30] and MHC class I chain-related peptide A [31] in kidney transplant recipients undergoing rejection. Several studies are emerging delineating the mechanisms leading to autoimmune responses to self-antigens and their role in the immunopathogenesis of chronic rejection.

Hence, both alloimmune and autoimmune responses represent major risk factors in the development of chronic rejection. It is well accepted that both bacterial and viral infections increase the risk of chronic rejection and these may either be mediated by its ability to augment alloimmune responses mostly mediated through the by-stander pathway and/or by its ability to expose cryptic self-antigens as well as facilitate immune responses to the self-antigens by deleting or inhibiting T-regulatory cell populations [32,33]. In addition, nonspecific inflammatory processes including ischemia reperfusion injury, viral infections and environmental factors (including air pollution and so on) can enhance alloimmune and auto immune responses by altering the inflammatory milieu and thus contributing to development of chronic rejection [34,35].

One of the current hypotheses by the authors and other laboratories for the pathogenesis of chronic rejection is that alloimmune responses and the resulting inflammatory signals lead to autoimmune responses, which together lead to chronic rejection [36–38]. It has been further proposed that a crosstalk between alloimmune and autoimmune processes exist which ultimately leads to allograft dysfunction and graft loss due to chronic rejection. The authors will expand their discussion on these mechanisms with a special focus on chronic lung allograft rejection in this review (FIGURE 1).

Chronic lung allograft rejection

Chronic rejection following human lung transplantation is pathologically diagnosed as OB, and clinically diagnosed as BOS. This clinical syndrome is diagnosed as a progressive and persistent decline in post-transplant forced expiratory volume after other causes including anastomotic strictures of the airways is excluded [39]. BOS is the clinical syndrome that pathologically effects the small airways in the lungs, resulting in OB of the terminal bronchioles with an increase in cellular infiltration and development of fibrosis. The incidence of BOS within 5 years of lung transplantation is as high as around 50% by 5 years and 75% by 10 years post-transplantation making it the most important cause for long-term morbidity and mortality following lung transplantation [40].

Animal models of chronic lung rejection

Animal models have greatly contributed toward the understanding of the pathogenesis of chronic rejection [41]. The animal model correlate of human OB is known as obliterative airway disease (OAD), that pathologically resembles OB in humans. Earlier models employed heterotopic tracheal transplantation to define the pathogenesis of OAD [42]. However, OB in humans is limited to terminal bronchioles hence the tracheal transplant model has a major limitation due to the absence of smaller airways and vessels [43]. The rat

orthotopic single lung transplantation model developed by Marck and Prop more closely resembled human lung transplantation [44–46]. However, this model was technically demanding and more importantly, development of OAD in this model was highly variable. Rats also have lesser availability of knockout or transgenic strains and hence there were limitations in utilizing this model to study the immunopathogenesis of chronic lung rejection. Krupnick *et al.* standardized a murine model of lung transplantation, but this model did not develop OAD lesions in their experience [47]. However, recently, this model was further adapted and a murine lung transplantation across minor histocompatibility mismatches (C57BL/10 mice to C57BL/6 mice) reported to develop OAD lesions in 44% of the transplanted mice [48]. More recently, De Vleeschauwer *et al.* demonstrated that in a full MHC mismatch mouse lung transplantation model with immunosuppression, 25–50% of mice developed OAD by about 12 weeks [49].

Murine lung transplant models, although the most ideal due to similarity to human lung transplantation, are technically challenging and the development of OAD in this model is variable. Hence, the authors laboratory developed a murine model of OAD wherein intratracheal administration of antibodies specific to MHC class I on days 1, 2, 3 and 6 and weekly thereafter which resulted in near universal OAD lesions within 15–30 days [50]. This model although is a nontransplant model has helped not only to delineate the role of antibodies to MHC in inducing OAD but also provided new insights demonstrating that alloimmunity can induce immune responses to self-antigens (autoimmunity) and also a crosstalk between alloimmune and autoimmune responses leading to the immunopathogenesis of OAD.

Donor-specific antibodies in chronic lung rejection

Alloimmunity has an important role in the development of chronic rejection. Pretransplant antibodies to donor mismatched HLA increase the risk for primary graft dysfunction (PGD) following lung transplantation that further increases the risk of development of BOS [51]. Post-transplant *de novo* donor-specific antibodies (DSA) to mismatched donor HLA often precede the development of BOS and in the authors report, DSA was detected in one serum of lung transplant recipients several months prior to diagnosis of BOS [52]. Studies from the authors laboratory have also demonstrated that specific antibodies to HLA binding to epithelial and endothelial cells in the graft can induce the activation of several growth factors and chemokines including TGF- β resulting in an increase in pro-survival gene expression promoting both epithelial and endothelial proliferation [53,54]. Hence, both pretransplant and post-transplant antibodies to HLA, particularly to mismatched donor antigens, increase the risk of development of chronic rejection.

Autoimmunity in chronic lung rejection

The role for immune responses to self-antigens in the pathogenesis of chronic rejection is an exciting new avenue that is being explored by the authors as well as other laboratories. Clinical studies following human lung transplantation provide correlative evidence that development of immune responses to self-antigens is associated with the development of BOS [27,28,55,56]. Inflammatory changes during the perioperative period including

ischemia-reperfusion, acute rejection and so on, as well as those following bacterial and viral infection, leads to tissue inflammation and remodeling during which cryptic self-antigens can be exposed to the immune system. In this context, the role of immune responses against ColV and K α 1T have been well investigated toward the development of chronic rejection following human lung transplantation as well as animal models of OAD [24,28,48,50,55].

Although ColV is expressed ubiquitously in the lungs in the peribronchial and perivascular connective tissue in the lungs, it is incorporated within Collagen I fibrils making it immunologically protected [57]. Evidence for the exposure of ColV to the immune system following lung transplantation was obtained when ColV fibrils were detected in bronchoalveolar lavage fluid in a rat model of lung transplantation [58]. There was a demonstrable and specific T-cell response characterized by increase in IFN- γ against ColV in the lungs of the rats following transplant rejection. Furthermore, transferring these ColV-specific T cells to other transplanted rats (including isografts) resulted in development of OAD [58,59] indicating that T cells specific to this self-antigen can cause OAD following transplantation. In addition, inducing oral tolerance to ColV in rat allograft recipients have been reported to prevent the development of OAD (fibrosis and cellular infiltration around the airways) [59]. These results in animal models have further been confirmed in human lung transplantation with detection of ColV-specific immune responses in patients with chronic lung rejection [27,28,60].

The authors laboratory identified a pathogenic role for antibodies to K α 1T in the development of chronic rejection [56]. K α 1T is a component of cellular microtubules and is also expressed in the gap junction of airway epithelial and endothelial cells [61]. It is one of the six isoforms of α -tubulin and is approximately a 50-kDa protein [62,63]. Its functions include microtubule formation, GTP binding and cellular movement [64,65].

Even in the absence of DSA, antibodies to K α 1T were detectable in a third of patients following human lung transplantation and further the serum levels of antibodies to K α 1T correlated with development of chronic rejection [55,56]. Recently, the authors have also demonstrated that specific antibodies to K α 1T which bind to epithelial cells result in activation of profibrotic growth factor signaling which may play an important role in the development of chronic rejection through airway remodeling and inflammation [56].

Besides serum antibodies to self-antigens, CD4⁺ T-cell mediated responses against these antigens were seen in patients with BOS. Lung transplant patients in the early post-transplant period develop ColV- and K α 1T-specific immune response primarily inducing IL-10 response to these self-antigens that actively suppressed self-antigen specific IFN- γ responses [66,67]. However, in patients who develop BOS, there is a switch towards IFN- γ producing T cells with a marked reduction in self-antigen specific IL-10 producing cells [55]. In addition, the authors and others have obtained an emerging role of IL-17-mediated immune responses to self-antigens in the pathogenesis of chronic rejection [28,55]. IL-17 is a proinflammatory cytokine secreted by Th17 cells and have been implicated in a variety of autoimmune diseases as well as in lung fibrosis [68–70]. IL-17 has also been implicated in PGD [71] and acute lung rejection [72,73].

Induction of autoimmune responses

Following transplantation, both alloimmune and autoimmune responses may contribute toward the development of chronic rejection. Alloimmune responses in particular may facilitate the induction of autoimmune responses to self-antigens and these can then collectively lead to chronic rejection.

In a murine tracheal transplantation model in immunodeficient mice (RAG knockout), administration of antibodies to MHC class I also resulted in the development of OAD lesions in the transplanted trachea with upregulation of growth factors and cytokines [74,75]. When airway epithelial cells were stimulated with anti-MHC class I antibodies, they were found to undergo proliferation with the secretion of profibrogenic growth factors [75]. In addition, *in vitro* experiments indicated that antibodies to HLA bind to endothelial cells and result in activation of pro-fibrotic cascades [54]. Thus, the inflammation that ensues following ligation of antibodies to HLA on endothelial and epithelial cells in the graft can lead to exposure of cryptic self-antigens and their determinants to the immune system. These result in the development of immune responses to self-antigens and can allow for perpetual proliferation of T cells reacting to self-antigens by lowering the activation threshold of such T cells.

The role for induction of autoimmune responses following alloimmunity was further supported in the authors murine model of OAD wherein intrabronchial administration of antibodies to MHC class I leads to the development of immune responses to self-antigens leading to OAD lesions [50]. Intrabronchial administration of anti-MHC class I, resulted in cellular infiltration, epithelial hyperplasia and fibrosis around the vessels and bronchioles eventually resulting in OAD. This development of OAD following administration of antibodies to MHC was associated with *de novo* development of immune responses to ColV and K α 1T. There was induction of IFN- γ and IL-17 secreting cells specific to ColV and K α 1T by day 15 that increased by day 30 and also development of antibodies to both of these self-antigens.

Besides murine models, in human lung transplant recipients, it was found that *de novo* DSA develops following transplantation, which is followed by the development of antibodies to ColV and K α 1T in patients who develop BOS. It is important to note that both DSA and antibodies to self-antigens both precede the development of BOS suggesting a pathogenic role for the immune responses to these antigens in the pathogenesis of chronic rejection [55].

Both ColV and K α 1T are expressed in epithelial and endothelial cells and hence epithelial and endothelial cell injury due to any cause may be central to the pathogenesis of chronic rejection. Antibodies against HLA also bind to epithelial and endothelial cells and can further enhance inflammation [76]. These inflammatory changes may also predispose to the development of autoimmune responses.

Autoimmunity in the development of alloimmunity

From the results presented above, it is evident that inflammation due to alloimmune responses following transplantation can lead to the development of *de novo* immune

responses against self-antigens. However, due to the chronic nature of varying lung diseases that leads to failure of lung function necessitating transplantation, the authors and others postulated that a subgroup of patients waiting for lung transplantation may indeed have developed immune responses to lung-associated self-antigens [24,71]. There is some evidence that immune responses to self-antigens may exist pretransplant especially in diseases that have significant tissue inflammation and remodeling such as asthma, chronic obstructive pulmonary disease and so on [24,77]. To determine the presence of pre-existing immune responses to lung-associated self-antigens in patients waitlisted for lung transplantation and to determine its impact following lung transplantation, the authors analyzed a cohort of 142 lung transplant recipients [24]. Results demonstrated that immune response to self-antigens was present in 29% of patients pretransplant and more importantly, these recipients with pre-existing antibodies to self-antigens were at a significantly increased risk of developing PGD following transplantation [24]. PGD itself is associated with an increased risk of development of chronic rejection as well as development of immune responses to donor mismatched HLA [51,78]. Thus, pre-existing immune responses to self-antigens can augment the development of alloimmune responses to mismatched donor antigens and both can lead to the development of BOS. Hence, the results support that there is a 'crosstalk' between alloimmune and autoimmune responses that perpetuate each other leading to the pathogenesis of chronic allograft rejection.

Th17 cells in chronic allograft rejection

Cellular immune responses to self-antigens are an important mediator in the pathogenesis of chronic rejection following transplantation and until recently, attention has been to define the role of Th1 and Th2 cells in regulating immune responses to alloantigens [79,80]. However, during the past few years, emerging roles for the Th17 subpopulation of cells and the cytokine secreted primarily by these cells, IL-17, has come to great importance [81]. IL-17 favors the development of autoimmune responses leading to diseases both in animal models and humans [81]. Although, CD4 Th17 cells are a common source of IL-17, other sources for the cytokine include $\gamma\delta$ -T cells, natural killer cells as well as neutrophils [82–84] and these may also potentially play a role in the pathogenesis of chronic rejection. $\gamma\delta$ -T cells in particular have been postulated as an important innate sources of IL-17 in the lungs [83].

In the authors murine model of OAD with intrabronchial administration of anti-MHC described above, the pathogenic role for IL-17 mediated autoimmune responses in the pathogenesis of OAD was evidenced by the results that neutralization of IL-17 resulted in preventing the development of OAD along with reduction in the humoral immune responses to self-antigens [50].

The cytokines IL-1 β , IL-6, IL-23 and TGF- β are critical in the differentiation of Th17 cells [85]. These cytokines are increased in the circulation following human lung transplantation, thus facilitating the induction of IL-17 responses to self-antigens. IL-6 can also modulate Tregs to induce IL-17 in an antigen specific manner, providing an important link between the adaptive and the innate immune response to self-antigens [85].

Besides the inflammatory effects of IL-17, it may also induce the secretion of IL-8 that promotes neutrophilia [86], which is considered a hallmark of OB [87]. Neutrophils may further enhance tissue inflammation by release of matrix metalloproteinases and free radicals [88]. Hence, these may lead to further endothelial and epithelial cell injury potentiating autoimmune responses.

Azithromycin (a macrolide antibiotic) has been utilized to counteract this neutrophilia and is a suppressor of inflammation [89]. The role of azithromycin in suppressing autoimmune responses is currently not known. In addition, not all patients respond to azithromycin [90,91]. Furthermore, the prevalence of neutrophilia in BOS has been variable in various studies [92,93]. Hence Verleden and colleagues have postulated two phenotypes of BOS, a neutrophilic reversible airway dysfunction type and a fibroproliferative type [94,95]. It is currently unclear whether these phenotypes of BOS are entirely distinct and whether they represent two distinct mechanisms of chronic rejection. Furthermore, the role autoimmunity and alloimmunity play in both of these suggested phenotypes needs further study.

Chronic rejection in heart transplantation

In the heart, chronic rejection is characterized by CAV in which there is occlusion of both intramural and epicardial coronary vessels. Its incidence is 35% within 5 years following heart transplantation [96]. Similar to lung transplantation, the role of alloimmune responses in the development of CAV in heart transplantation is well established [97]. Besides alloimmune responses, humoral and T-cell mediated responses to the self-antigens myosin and vimentin have also been shown to play a role in the pathogenesis of CAV [26,98–100]. In murine heart transplantation models, it has been demonstrated that alloimmune responses are essential for the development of autoimmunity [100]. Mice that received full MHC mismatch allografts also developed T-cell responses not only to mismatched alloantigens but also to cardiac myosin [100]. However, in absence of alloimmune responses (i.e., in syngenic heart transplant), mice did not demonstrate autoimmune responses, suggesting that alloresponses are required for the development of an autoimmune response [100]. Myosin-specific T cells have also been identified in human cardiac transplant patients with chronic rejection [25].

In addition to cardiac myosin, there is also evidence for immunity to vimentin as well as MHC class I related MHC I chain-related peptide A in the pathogenesis of both acute antibody-mediated rejection as well as chronic rejection in heart transplantation recipients [26,98,101]. A serial study of heart transplant recipients revealed that DSA developed within 2.8 months of cardiac transplantation which was followed by the development of antibodies to myosin and vimentin at 4–6 months post-transplant as well as cellular immune responses to these antigens [26]. These results indicate that alloimmune and autoimmune responses often precede the development of rejection and alloimmunity may contribute to the induction of autoimmunity following human cardiac transplantation [26,98,99].

Chronic rejection in kidney transplantation

Chronic rejection in kidney allografts manifests as CAN. Studies indicate that the incidence of CAN-mediated graft loss following renal transplantation is as high as 40% within 10 years of transplantation [102]. Pretransplant DSA and post-transplant *de novo* development of donor-specific antibodies and T-cell responses increase the risk of development of CAN [103]. More recently, studies have also indicated an increased prevalence of auto-antibodies in renal transplant recipients with chronic rejection including a shared 'auto-antibodies' signature toward particular self-antigens in all patients with chronic rejection [104]. These include antibodies to AT1R, heat shock proteins, agrin and so on [104,105].

Expert commentary & five-year view

Chronic rejection remains a challenging clinical problem and our understanding of its pathogenesis continues to evolve. However, the biggest future challenge remains in the development of strategies that will improve the detection and diagnosis of chronic allograft rejection, including the development of therapeutics toward its prevention and treatment. As discussed above, DSA and immune response to self-antigens often precede the development of chronic rejection supporting their use as biomarkers for chronic rejection following transplantation. Previous dogma was that mainly alloimmune responses contribute to the pathogenesis of chronic rejection. However, more recent concepts, as discussed in this review, demonstrate that autoimmunity to tissue-restricted self-antigens may contribute to the immunopathogenesis of chronic rejection not only following human lung transplantation but also other solid organs including heart and kidney. We propose that the importance of autoimmune responses in the pathogenesis of chronic rejection should be recognized and be considered in developing new strategies for preventing and/or treating chronic rejection following transplantation. Toward preventing the development of immune responses to self-antigens following alloimmune response, our center (Washington University School of Medicine, MO, USA) initiated preliminary studies in lung transplant recipients who developed DSA but have normal lung function and were treated with antibody depleting regimens [27,106]. The results have indicated that those who cleared DSA have better BOS-free survival in comparison with those who did not clear DSA [106,107]. Further analysis demonstrated that those patients who cleared DSA as well as antibodies to self-antigens after antibody-directed treatment with rituximab and intravenous immunoglobulin are protected from the development of BOS compared with those who do not clear antibodies to self-antigens [27]. These results suggest that therapeutic interventions by monitoring for DSA and/or antibodies against self-antigens may prevent development of chronic rejection following human lung transplantation.

Azithromycin is also being explored in the treatment of chronic lung rejection due to its effects on reducing neutrophilia and inflammation as well as preventing infections. Vitamin D therapy is being investigated for treating/preventing chronic rejection due to its effects on TGF- β signaling [108]. Neutralization of IL-17 and IL-6 represents another avenue to explore as potential targets to treat chronic rejection. Secukinumab, a human IL-17A monoclonal antibody, and tocilizumab (anti-IL6) have recently been investigated in the treatment of autoimmune diseases [109,110] and their role in chronic rejection requires

further studies. However, these biologic therapies lead to an increased state of immunosuppression and may themselves predispose to increased risk of bacterial and viral infections [109].

In addition, there is evidence for the role of regulatory T cells and infections in the pathogenesis of chronic rejection [33]. Hence, immunosuppressive regimens that will spare regulatory T cells and aggressive surveillance and treatment of viral and bacterial infections in the post-transplant period may help in preventing the development of autoimmune and alloimmune responses which can lead to chronic rejection.

In summary, chronic rejection is a growing concern that significantly impacts long-term graft function and survival. Current hypotheses suggest a crosstalk between inflammatory responses by alloimmune and autoimmune mechanisms. Both these immune responses result in a constant state of tissue inflammation and remodeling with a profibrotic milieu leading to chronic rejection. There is an emerging role for the role of IL-17-type autoimmune responses in chronic rejection and its prevention may represent an important aspect of future therapeutics in preventing and treating chronic rejection following organ transplantation.

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Key issues

- Development of chronic rejection is the major determinant of long-term function and survival in solid organ transplantation.
- Donor-specific alloimmune responses both pretransplant and *de novo* development post-transplant are important risk factors for chronic rejection.
- Autoimmune responses to tissue-restricted self-antigens both humoral (antibody mediated) and cellular (predominantly of the IL-17 type) are pathogenic for chronic rejection.
- Alloimmune responses may facilitate the development of autoimmune responses and *vice versa* exhibiting a 'cross-talk' that eventually results in chronic rejection.
- Future therapies directed at preventing both alloimmune responses as well as autoimmune responses especially the IL-17-mediated responses may be important toward prevention and treatment of chronic rejection.

Figure 1.
Overview of the pathogenesis of chronic allograft rejection.