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Alloimmunity and autoimmunity in chronic rejection

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Abstract

Purpose of review—Recent studies demonstrate an increasing role for alloimmune responses in the disruption of self-tolerance leading to immune responses to self-antigens that play a role in the immunopathogenesis of chronic rejection following solid organ transplantation. This review summarizes recent studies and implications for the alloimmune-response-induced de-novo development of autoimmune responses following solid organ transplantations.

Recent findings—Immediately following organ transplantation, several factors lead to enduring an inflammatory milieu. Studies from our laboratory and others have demonstrated that development of antihuman leukocyte antigen antibodies precedes the development of chronic rejection. Using an in-vivo murine model, we have demonstrated that administration of anti-major histocompatibility complex (MHC) class I directly into the native lungs leads to chronic rejection pathology. Further, the in-vitro ligation of epithelial cell surface MHC class I molecules by specific anti-MHC can lead to cell activation and production of fibrinogenic growth factors.

Summary—On the basis of these findings, we hypothesized that alloimmune responses can lead to autoimmunity, thus playing an important role in chronic rejection. Characterization of both the temporal occurrence and functional significance of antibodies to self-antigens may provide insight into the pathogenesis of chronic rejection and these antibodies can serve as clinically useful biomarkers.

Keywords

alloimmunity; antibody mediated rejection; autoimmunity; chronic rejection; organ transplantation

Introduction

Chronic rejection following transplantation remains the most important problem for long-term function of the transplanted organs despite advances in understanding of donor and recipient physiology, operative technique, and immunosuppressive pharmacology. Regardless of transplanted organ, chronic rejection is characterized by fibrosis of the graft parenchyma which may develop anywhere from months to years postoperatively [1]. Chronic rejection is initiated by a host-antigraft-immune response with both antigen-

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dependent and nonimmune (antigen-independent) factors leading to fibroproliferative changes affecting graft function [2]. Inflammation and tissue remodeling promoted by alloimmune mechanisms can facilitate the induction of autoimmune responses against self-antigens [3]. In this review we discuss evidence for the role of alloimmunity and autoimmunity in chronic rejection of solid organ transplants.

Cellular and humoral immune responses in solid organ transplantation

The primary targets of the recipient immune response against the allograft are the donor major histocompatibility complex (MHC) antigens present on the allogeneic tissue. Immune recognition of mismatched donor histocompatibility antigens results in both cellular and humoral immune mechanisms which leads to allograft rejection [4,5]. Allorecognition can occur through two unique but not mutually exclusive pathways: the direct and indirect pathways of antigen presentation. The direct pathway involves recognition of intact donor MHC molecules on the cell surface, usually by antigen-presenting cells (APCs). Both $CD8^+$ and $CD4^+$ T cells can directly recognize donor MHC molecules, MHC class I and II, respectively. In contrast, the indirect pathway involves presentation of processed donor antigens by recipient APC to recipient T cells. A ‘semi-direct’ pathway has also been recently described which involves recipient APCs that acquire donor MHC through cell-to-cell contact and activate host T-cell responses which contributes to chronic rejection [6].

Whereas the direct pathway is more important for acute allograft rejection, the indirect pathway is thought to play a dominant role in chronic allograft rejection [7,8]. Experiments have demonstrated that inhibition of acute rejection by depleting passenger APC significantly delays but does not prevent development of chronic rejection [9]. It has been observed that the frequency of direct alloreactive T cells exceeds indirect alloreactive T cells in the early post-transplant period [10]. The frequency of direct alloreactive T cells declines with time following transplantation, whereas the continuous influx of the processed donor antigens by the recipient APC through the indirect pathways increases the number of indirect alloreactive T cells that are themselves more resistant to currently used immunosuppression [11,12].

Humoral alloimmune responses against mismatched donor human leukocyte antigens (HLAs) in the pathogenesis of chronic rejection are well established [13]. Studies from our group, as well as others, have shown that development of immune responses to self-antigens during the post-transplant period may also correlate with chronic rejection [14•,15,16]. Antibodies to myosin and vimentin in cardiac, K-α1 tubulin (K-α1T) and collagen V (ColV) in lung, Col-III in liver, and angiotensin II type 1 receptor, Col-IV, and VI in kidney transplants have been identified and associated with incidence of chronic rejection; however, their functional significance has not been fully characterized [14•,17–20]. It is also not clear what roles the alloimmune responses play in the development of immune responses to self-antigens. In this review, we detail recent findings for the two distinct yet interdependent immune processes in the immunopathogenesis of chronic rejection.

Cardiac transplantation

Chronic rejection of cardiac allografts is manifested by the clinical entity cardiac allograft vasculopathy (CAV), an accelerated form of occlusive coronary disease affecting both intramural and epicardial coronary arteries and veins; 5-year incidence of CAV is 30–40% [21]. Animal studies have supported a critical role of alloimmune responses in the development of chronic rejection in cardiac allografts and clinical experience has identified the number of acute rejection episodes and donor HLA mismatching as independent risk factors for CAV after heart transplant [22].

Cell-mediated immunity has been implicated in the pathogenesis of CAV as histologic examination of perivascular infiltrates often reveals a predominance of immune cells including T cells ($CD4^+$, $CD8^+$), natural killer (NK) cells, macrophages and dendritic cells. In an experimental model of CAV depletion of recipient $CD4^+$ but not $CD8^+$ T cells prevented the formation of arterial lesions [23•]. Alloreactive $CD4^+$ Th1 and Th2 cells activated via the indirect pathway have been implicated in the development of CAV as well. In a study using a T bet−/− murine model of CAV, Th17 cells mediated a proinflammatory response in the absence of a Th1 response leading to CAV [24••]. T-cell-mediated auto-reactivity against cardiac myosin has been shown to develop and persist in the absence of an alloimmune response, indicating that response to myosin, a self-antigen, is associated with the pathogenesis of CAV [25•,26••].

Humoral immunity has also been implicated in the pathogenesis of CAV. The presence of circulating antibodies specific to mismatched donor HLA molecules and the deposition of complement product C4d within the graft have been associated with poor allograft outcome. Studies utilizing syngeneic heart transplants have shown that chronic rejection can be induced even in the absence of an alloimmune response [22,27]. Studies have also indicated that antibodies against vimentin, a cytoskeleton protein, are an independent predictor of atherosclerosis following cardiac transplantation and can accelerate the course of CAV [26••, 28]. Our studies towards investigating the pathogenesis of acute antibody-mediated rejection (AMR) in the early postheart transplant period (<12months) and CAV in the late post-transplant period (>12months) demonstrated the presence of donor-specific antibody in AMR and CAV is significantly associated with development of antibodies to cardiac self-antigens myosin and vimentin. Furthermore, the induction of high $CD4^+$Th specific to cardiac self-antigens that predominantly secrete IL-5 and IL-17 suggest that alloimmune responses to donor HLA may play a significant role in the development of antibodies to self-antigens leading to AMR and CAV, respectively.

Lung transplantation

Chronic rejection after lung transplantation (LTx) is characterized by obliteration of terminal airways termed bronchiolitis obliterans syndrome (BOS). The development of BOS post-LTx is multifactorial and involves both cell-mediated and humoral immunity [29].

A high frequency of indirect alloreactive $CD4^+$ T cells against donor MHC class I and II molecules can be detected in a human lung allograft recipient years after transplantation and are associated with BOS [30]. Also, it is thought that recipient T cells primed by the indirect allorecognition pathway are less responsive to conventional immunosuppression compared to those primed by the direct pathway. Intrapulmonary lymphoid tissue has been implicated in the pathogenesis of chronic rejection as it serves as a reservoir for effector memory T cells and high endothelial venules which can contribute to a local immune response in small airways leading to BOS [31•].

Animal studies have identified ColV-reactive T cells in rat lung allografts undergoing rejection. These ColV-specific T cells derived from rat lung allografts can, in turn, mediate rejection of isografts when adoptively transferred without affecting native lung [32]. Studies from our lab have demonstrated a high frequency of ColV-reactive T cells in human lung allograft recipients and BOS was associated with expansion of IFN-γ producing ColV-specific Th-1 cells with a concurrent reduction in IL-10-secreting T cells [33]. A longitudinal study in LTx patients identified an association between ColV-specific IL-17 responses with onset of BOS [34]. ColV-specific responses in BOS patients were dependent on both $CD4^+$ T cells and monocytes and required IL-17, TNF-α, and IL-1β. Furthermore, adoptive transfer of lymph node cells expressing high levels of IL-17 and IL-23 gene

transcripts from ColV-sensitized mice have been shown to induce obliterative lesions in the lung isograft [16].

Humoral immunity has also been implicated in BOS. Several studies have demonstrated that development of anti-HLA class I antibodies is associated with the development of chronic rejection [16,26••]. On the basis of the previous studies by us [34] and others [35] the presence of 'shed' donor HLA antigens in the bronchoalveolar lavage fluids following LTx provide the substrate for antigen presentation to T helper cells and induction of alloimmunity. These T helper cells, which are engaged in indirect recognition pathways, can produce lymphokines required for the growth and maturation of allo-antibody-producing B cells. Studies have also demonstrated that anti-HLA antibodies can activate human airway epithelial cells (AECs) resulting in the production of several fibrinogenic growth factors that can play an important role in the pathogenesis of chronic rejection [14•]. Recent studies strongly suggest an important role for autoimmunity in the pathogenesis of allograft rejection. Our studies in LTx recipients have shown a strong correlation between the development of antibodies to a self-protein, K-α1T, as well as ColV and the development of BOS following human LTx [14•,36••].

Recent studies were aimed to determine whether pre-existing antibodies to self-antigens are present in patients waiting for LTx and the role of pre-existing antibodies to self-antigens in the development of primary graft dysfunction as well as chronic rejection following LTx. It is generally accepted that PGD immediately after the transplant period increases risk for development of BOS [37]. We analyzed 142 adult LTx recipients for pretransplant antibodies to self-antigens, ColV and K-α1T and those with antibodies to self-antigens had increased risk of PGD [odds ratio (OR) 3.09, 95% confidence interval (CI) 1.2–8.1, P = 0.02] compared to those without. Ab^+ patients demonstrated high levels of proinflammatory cytokines IL-1 (2.1-fold increase), IL-2 (3.0), IL-12 (2.5), IL-15 (3.0) and chemokines IP-10 (3.9) and MCP-1 (3.1, $P < 0.01$ for all). On 5-year follow-up, patients without antibodies showed greater freedom from development of HLA-antibodies compared to those with antibodies (class I: 67 vs. 38%, $P = 0.001$; class II: 71 vs. 41%, $P < 0.001$). Patients with pretransplant antibodies were found to have an independent relative risk of 2.3 (95% CI 1.7–4.5, $P = 0.009$) for developing BOS.

We and others have also previously demonstrated that development of anti-MHC class I antibodies precedes the development of BOS by 20 months [34]. As discussed above, these patients also developed antibodies to self-antigens prior to clinical onset of BOS. Therefore, to determine the mechanism by which antibodies to donor MHC may induce an immune response to self-antigen which lead to chronic rejection we developed a murine model of OAD of native lungs [36••]. In this model, administration of specific anti-MHC class I antibodies to the native lungs of mice resulted in autoimmunity leading to cellular infiltration, epithelial hyperplasia, endothelitis, fibroproliferation, collagen deposition and luminal occlusion of the small airways, the central events seen during chronic lung allograft rejection. Put together all these wide array of evidence from various laboratories point towards a cross-talk between alloimmune and autoimmune responses post LTx in the pathogenesis of chronic rejection. It is likely that a similar cross-talk between alloimmunity and autoimmunity may play an important part in the pathogenesis of chronic rejection following all solid organ transplantation.

Liver transplantation

Chronic rejection after liver transplantation is manifested as fibrous tissue replacement in the allograft, clinically mimicking cirrhosis. Fibrogenesis is a complex, dynamic process mediated by necro-inflammation and activation of hepatic stellate cells under the influence

of virally induced immunomodulation. Cell-mediated and humoral immunity are both implicated in the progression of fibrosis after liver transplant [38,39].

Studies investigating mechanisms of fibrosis in an orthotopic liver transplant (OLT) population with hepatitis C virus (HCV) have correlated progression of fibrosis with specific CD4 T-cell behavior [39]. Specifically, a lack of HCV-specific Th1-type T-cell immunity has been associated with the development of fibrosis and cirrhosis during recurrent HCV infection in the post-transplant period. Patients with higher degrees of fibrosis and cirrhosis have also been shown to have significantly higher levels of IL-17 production upon stimulation with HCV antigens (T. Mohanakumar, unpublished data). Th17 cells can lead to production of CXCL12 and activation of B cells [40••]. CXCL12 in combination with IL-17 allows germinal center formation and auto-antibody production to self-antigens including ECM Col-I, II, and V in the liver. Our studies demonstrated increased serum levels of IL-17, IL-6, IL-1β, IL-8 and MCP-1 are significantly increased in OLT who develop high-grade allograft inflammation and fibrosis secondary to HCV recurrence. This was associated with increased frequency of $CD4^+$ T cells specific to HCV that secrete IL-17 in OLT with high-grade allograft inflammation and fibrosis. This was also accompanied by a significant decline in the frequency of HCV-specific $CD4^+$ T cells that secrete IFN-γ and increased frequencies of IL-10-secreting cells in OLT with allograft inflammation and fibrosis. We also identified development of antibodies against Col-I, II, and V in chronic HCV including OLT with recurrent HCV who developed fibrosis. All these data point to a Th17-mediated autoimmune response and antibodies to self-antigens may play a part in the development of fibrosis following HCV infection of the transplanted liver.

Kidney transplantation

Chronic allograft nephropathy (CAN) is a major cause of late graft loss in renal transplant recipients. The histopathologic signs of CAN – interstitial fibrosis, tubular atrophy, glomerulopathy and vasculopathy – are nonspecific. It is thought to account for approximately 40% of graft loss at 10 years [41]. Work with both animal models and clinical studies have implicated both cell-mediated and humoral arms of alloimmunity contribute to its development [42]. $CD4^+$ alloreactive T cells responding to donor-derived peptides bound to recipient MHC class II have been correlated with CAN. Also, T cells producing proinflammatory and regulatory cytokines against HSP 60 have been demonstrated in peripheral blood and graft-infiltrating lymphocytes of renal transplant recipients with progression to CAN [43].

Increased levels of pretransplant anti-HLA antibodies and de-novo post-transplant donor-specific antibodies have also been associated with CAN. Antibodies against MHC class I polypeptide-related sequence A (MICA) can affect renal allografts. However, antibodies developed *de novo* and directed at the donor HLA are not always detectable in the circulation of patients undergoing chronic rejection, questioning the significance of antibodies to HLA in the pathogenesis of chronic rejection. Clinical experience with refractory vascular allograft rejection in the absence of detectable anti-HLA antibodies demonstrated the presence of antibodies directed at two epitopes of the second extracellular loop of the angiotensin II type 1 (AT1) receptor. Detection of anti-AT1 receptor might serve as a useful tool to identify those at risk for refractory allograft rejection Other antibody targets include perlecan and Col-IV and VI as well as glomerular basement membrane protein agrin [44,45]. Recent studies have also suggested a role for antivimentin antibodies in the development of CAN [43].

A converging model for chronic rejection

The phenomenon of chronic rejection after solid organ transplantation is likely the result of a multifactorial interplay of various effector arms of alloimmunity. Studies in the arena of heart, lung, liver, and kidney transplantation have identified putative mechanisms that contribute towards development of chronic rejection. In these instances, an emerging theme is that inflammation and subsequent tissue remodeling attendant to the post-transplant state exposes cryptic self-antigens or their determinants that, along with a favorable cytokine milieu, allows for loss of peripheral tolerance and the activation of cell-mediated immunity towards development of de-novo immune responses to self-antigens. Regulatory T cells (Tregs) are known to inhibit both autoreactive as well as alloreactive effector T cells; however, in the context of potent immunosuppression after transplant (e.g. usage of calcineurin-based immunosuppression, which inhibits regulatory T-cell proliferation) there is likely loss of peripheral tolerance to self-antigens [46] leading to immune responses to various tissue-restricted self-antigens. At present, IL-17 appears to be a strong candidate for promoting this response, and studies have showed a link to its levels and the development of fibrosis in allograft tissue, the hallmark of chronic rejection [16]. The generation of auto-antibodies in this context has been observed in multiple arenas as well; however, the clinical implications of their temporal occurrence (in relation to clinically significant and pathologically demonstrable chronic rejection) and functional significance need to be better characterized.

Conclusion

Alloimmune responses and the development of de-novo autoimmunity to self-antigens appear to be the principal player in the development of chronic rejection after solid organ transplantation. Tissue inflammation and remodeling provide the substrate for the activation of both cell-mediated and humoral effector arms. This activation of the alloimmune response is in part mediated be IL-17, which facilitates the activation of fibrinogenic pathways and the development of auto-antibodies. Future work in the field is needed to identify the mechanistic role for auto-antibodies in the development of rejection and their clinical utility as a biomarker for chronic rejection. The IL-17 represents a new pathway of focus to expand the immunosuppressive armamentarium. As most of the current results strongly suggest that alloimmune response to mismatched HLA antigen (as evidenced by the presence of circulating antibodies to donor HLA that precede the development of antibody to self-antigens), it is logical to intervene early after detection of antibodies to HLA to prevent the development of antibodies to self-antigens in an effort to prevent or delay the onset of chronic rejection. Studies in LTx recipients are currently underway to test this possibility by administering intravenous gamma globulin and rituxan as early as circulating antibodies to donor-specific HLA are identified following LTx.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 546–547).

1. Tiriveedhi V, Weber J, Seetharam A, Mohanakumar T. Cross-talk of alloimmune response and autoimmunity: role in pathogenesis of chronic rejection. Discov Med Mar;9:229–235. [PubMed: 20350490]
2. Nicod LP. Mechanisms of airway obliteration after lung transplantation. Proc Am Thorac Soc 2006;3:444–449. [PubMed: 16799090]
3. Nath DS, Basha HI, Mohanakumar T. Antihuman leukocyte antigen antibodyinduced autoimmunity: role in chronic rejection. Curr Opin Organ Transplant Feb Feb;15:16–20.
4. Game DS, Lechler RI. Pathways of allorecognition: implications for transplantation tolerance. Transpl Immunol 2002;10(2–3):101–108. [PubMed: 12216939]
5. Hernandez-Fuentes MP, Baker RJ, Lechler RI. The alloresponse. Rev Immunogenet 1999;1:282–296. [PubMed: 11256420]
6. Bharat A, Mohanakumar T. Allopeptides and the alloimmune response. Cell Immunol 2007;248:31–43. [PubMed: 18023633]
7. Shilling RA, Wilkes DS. Immunobiology of chronic lung allograft dysfunction: new insights from the bench and beyond. Am J Transplant 2009;9:1714–1718. [PubMed: 19519813]
8. Hachem RR. Lung allograft rejection: diagnosis and management. Curr Opin Organ Transplant 2009;14:477–482. [PubMed: 19617825]
9. Heeger PS. T-cell allorecognition and transplant rejection: a summary and update. Am J Transplant 2003;3:525–533. [PubMed: 12752308]
10. Benichou G, Valujskikh A, Heeger PS. Contributions of direct and indirect T cell alloreactivity during allograft rejection in mice. J Immunol 1999;162:352–358. [PubMed: 9886406]
11. Suchin EJ, Langmuir PB, Palmer E, et al. Quantifying the frequency of alloreactive T cells in vivo: new answers to an old question. J Immunol 2001;166:973–981. [PubMed: 11145675]
12. Sawyer GJ, Dalchau R, Fabre JW. Indirect T cell allorecognition: a cyclosporin A resistant pathway for T cell help for antibody production to donor MHC antigens. Transpl Immunol 1993;1:77–81. [PubMed: 8081765]
13. Stastny P, Ring S, Lu C, et al. Role of immunoglobulin (Ig)-G and IgM antibodies against donor human leukocyte antigens in organ transplant recipients. Hum Immunol 2009;70:600–604. [PubMed: 19375468]
14. Goers TA, Ramachandran S, Aloush A, et al. De novo production of K-alpha1 tubulin-specific antibodies: role in chronic lung allograft rejection. J Immunol 2008;180:4487–4494. [PubMed: 18354170] The authors discover antibodies to K-alpha1-tubulin in BOS patients.
15. Iwata T, Philipovskiy A, Fisher AJ, et al. Antitype V collagen humoral immunity in lung transplant primary graft dysfunction. J Immunol 2008;181:5738–5747. [PubMed: 18832733]
16. Burlingham WJ, Love RB, Jankowska-Gan E, et al. IL-17-dependent cellular immunity to collagen type V predisposes to obliterative bronchiolitis in human lung transplants. J Clin Invest 2007;117:3498–3506. [PubMed: 17965778]
17. Huang HJ, Yusen RD, Meyers BF, et al. Late primary graft dysfunction after lung transplantation and bronchiolitis obliterans syndrome. Am J Transplant 2008;8:2454–2462. [PubMed: 18785961]
18. Suciu-Foca N, Reed E, Marboe C, et al. The role of anti-HLA antibodies in heart transplantation. Transplantation 1991;51:716–724. [PubMed: 2006531]
19. Suciu-Foca N, Reed E, D'Agati VD, et al. Soluble HLA antigens, anti-HLA antibodies, and antiidiotypic antibodies in the circulation of renal transplant recipients. Transplantation 1991;51:593–601. [PubMed: 2006515]
20. Lee PC, Zhu L, Terasaki PI, Everly MJ. HLA-specific antibodies developed in the first year posttransplant are predictive of chronic rejection and renal graft loss. Transplantation 2009;88:568–574. [PubMed: 19696641]

21. Weis M, von Scheidt W. Cardiac allograft vasculopathy: a review. Circulation 1997;96:2069–2077. [PubMed: 9323100]
22. Jindra PT, Hsueh A, Hong L, et al. Anti-MHC class I antibody activation of proliferation and survival signaling in murine cardiac allografts. J Immunol 2008;180:2214–2224. [PubMed: 18250428]
23. Brennan TV, Hoang V, Garrod KR, et al. A new T-cell receptor transgenic model of the CD4+ direct pathway: level of priming determines acute versus chronic rejection. Transplantation 2008;85:247–255. [PubMed: 18212630] The authors note that T-cell-receptor transgenic murine models with direct CD4+ alloreactivity have been used to understand mechanisms of transplant rejection and tolerance. The study uses a murine cardiac transplant model to demonstrate that rejection of a graft by the direct CD4+ pathway is determined by susceptibility to rejection and degree of T-cell priming caused by the graft. Furthermore, transplant vasculopathy mediated by the direct CD4+ T cells can develop in grafts that are not acutely rejected.
24. Yuan X, Paez-Cortez J, Schmitt-Knosalla I, et al. A novel role of CD4 Th17 cells in mediating cardiac allograft rejection and vasculopathy. J Exp Med 2008;205:3133–3144. [PubMed: 19047438] Authors investigated the role of Tbet in the development of allograft rejection in an established MHC class II-mismatched (bm12 into B6) model of chronic allograft vasculopathy (CAV). Tbet recipients develop markedly accelerated allograft rejection accompanied by early severe vascular inflammation and vasculopathy, and infiltration by predominantly IL-17-producing CD4 T cells.
25. Kaczmarek I, Deutsch MA, Kauke T, et al. Donor-specific HLA alloantibodies: long-term impact on cardiac allograft vasculopathy and mortality after heart transplant. Exp Clin Transplant 2008;6:229–235. [PubMed: 18954302] The study investigates the impact of donor-specific humoral alloreactivity by analyzing sera from 213 heart transplant recipients.
26. Rose ML, Smith JD. Clinical relevance of complement-fixing antibodies in cardiac transplantation. Hum Immunol 2009;70:605–609. [PubMed: 19375471] A retrospective review by authors of sera from 616 cardiac transplant patients showed the presence of immunoglobulin M complement-fixing non-HLA antibodies associated with early graft failure and a diagnosis of primary graft failure.
27. Atz ME, Reed EF. Role of anti-MHC class I antibody in facilitating transplant accommodation. Crit Rev Immunol 2008;28:485–511. [PubMed: 19265506]
28. Leong HS, Mahesh BM, Day JR, et al. Vimentin autoantibodies induce platelet activation and formation of platelet-leukocyte conjugates via platelet-activating factor. J Leukoc Biol 2008;83:263–271. [PubMed: 17974709]
29. Smith CR, Jaramillo A, Duffy BF, Mohanakumar T. Airway epithelial cell damage mediated by antigen-specific T cells: implications in lung allograft rejection. Hum Immunol 2000;61:985–992. [PubMed: 11082511]
30. Bharat A, Narayanan K, Street T, et al. Early posttransplant inflammation promotes the development of alloimmunity and chronic human lung allograft rejection. Transplantation 2007;83:150–158. [PubMed: 17264811]
31. Sato M, Hirayama S, Hwang DM, et al. The role of intrapulmonary de novo lymphoid tissue in obliterative bronchiolitis after lung transplantation. J Immunol 2009;182:7307–7316. [PubMed: 19454728] The authors note that lung tissue of 13 lung transplant recipients with obliterative bronchiolitis demonstrates a large number of small, airway-associated high endothelial venules (HEVs) which are unique to lymphoid tissue. Utilizing a murine lung transplant model, they demonstrate that de-novo lymphoid tissue in the lung lacks delineated T cell and B-cell zone but have effector memory T cells and HEVs. They conclude that de-novo lymphoid tissue may have a role in chronic immune responses following lung transplantation.
32. Haque MA, Mizobuchi T, Yasufuku K, et al. Evidence for immune responses to a self-antigen in lung transplantation: role of type V collagen-specific T cells in the pathogenesis of lung allograft rejection. J Immunol 2002;169:1542–1549. [PubMed: 12133982]
33. Bharat A, Fields RC, Steward N, et al. CD4+25+ regulatory T cells limit Th1-autoimmunity by inducing IL-10 producing T cells following human lung transplantation. Am J Transplant 2006;6:1799–1808. [PubMed: 16889540]

34. Jaramillo A, Smith MA, Phelan D, et al. Development of ELISA-detected anti-HLA antibodies precedes the development of bronchiolitis obliterans syndrome and correlates with progressive decline in pulmonary function after lung transplantation. Transplantation 1999;67:1155–1161. [PubMed: 10232567]
35. Rizzo M, Sundaresan S, Lynch J, et al. Increased concentration of soluble human leukocyte antigen class I levels in the bronchoalveolar lavage of human pulmonary allografts. J Heart Lung Transplant 1997;16:1135–1140. [PubMed: 9402513]
36. Fukami N, Ramachandran S, Saini D, et al. Antibodies to MHC class I induce autoimmunity: role in the pathogenesis of chronic rejection. J Immunol 2009;182:309–318. [PubMed: 19109162] Authors develop a novel murine model for BOS, in which they directly administer anti-MHC class I antibodies directly into the native lung. There is an elevation of cytokines and autoantibodies by 30 days.
37. Daud SA, Yusen RD, Meyers BF, et al. Impact of immediate primary lung allograft dysfunction on bronchiolitis obliterans syndrome. Am J Respir Crit Care Med 2007;175:507–513. [PubMed: 17158279]
38. Schirren CA, Jung MC, Gerlach JT, et al. Liver-derived hepatitis C virus (HCV)-specific $CD4^+$ T cells recognize multiple HCV epitopes and produce interferon gamma. Hepatology 2000;32:597–603. [PubMed: 10960455]
39. Bharat A, Barros F, Narayanan K, et al. Characterization of virus-specific T-cell immunity in liver allograft recipients with HCV-induced cirrhosis. Am J Transplant 2008;8:1214–1220. [PubMed: 18522547]
40. Hsu HC, Yang P, Wang J, et al. Interleukin 17-producing T helper cells and interleukin 17 orchestrate auto-reactive germinal center development in autoimmune BXD2 mice. Nat Immunol 2008;9:166–175. [PubMed: 18157131] Authors show that blocking IL-17 signaling disrupts CD4+ T cell and B-cell interactions required for the formation of germinal centers and mice lacking the IL-17 receptor have reduced germinal B-cell development and humoral responses. Production of IL-17 correlates with up-regulated expression of the genes Rgs13 and Rgs16, which encode regulators of G-protein signaling, and results in suppression of the B-cell chemotactic response to the chemokine CXCL12.
41. Hertig A, Anglicheau D, Verine J, et al. Early epithelial phenotypic changes predict graft fibrosis. J Am Soc Nephrol 2008;19:1584–1591. [PubMed: 18434568]
42. Birnbaum LM, Lipman M, Paraskevas S, et al. Management of chronic allograft nephropathy: a systematic review. Clin J Am Soc Nephrol 2009;4:860–865. [PubMed: 19339427]
43. Li C, Yang CW. The pathogenesis and treatment of chronic allograft nephropathy. Nat Rev Nephrol 2009;5:513–519. [PubMed: 19636333]
44. Fotheringham J, Angel CA, McKane W. Transplant glomerulopathy: morphology, associations and mechanism. Nephron Clin Pract 2009;113:c1–c7. discussion c. [PubMed: 19590229]
45. Li F, Atz ME, Reed EF. Human leukocyte antigen antibodies in chronic transplant vasculopathy-mechanisms and pathways. Curr Opin Immunol 2009;21:557–562. [PubMed: 19748769]
46. Bharat A, Fields RC, Mohanakumar T. Regulatory T cell-mediated transplantation tolerance. Immunol Res 2005;33:195–212. [PubMed: 16461998]