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Anti-Human Leukocyte Antigen Antibody Induced Autoimmunity: Role In Chronic Rejection

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Abstract

Purpose of review—We provide evidence for the role of de novo development of immune responses to self-antigens in the post-transplant period and its possible induction by alloimmunity in the pathogenesis of chronic rejection following lung, heart and kidney transplantation. This review details recent findings for the two distinct yet inter-dependent immune processes in the immune-pathogenesis of chronic rejection.

Recent findings—The contribution of both humoral and cell mediated allo-immune responses against mismatched donor histocompatibility antigens (HLA) in the pathogenesis of chronic rejection is well established. Recent studies have focused on development of immune responses to self-antigens during the post-transplant period and its correlation with chronic rejection. These self-antigens include myosin and vimentin in cardiac, K-alpha-1-tubulin and collagen-V in lung and angiotensin II type 1 receptor, collagen-IV and VI in kidney transplants. During the post-transplant period, the development of immune responses to self-antigens is facilitated by induction of a distinct subset of auto-reactive T-helper cells referred to as Th17 cells.

Summary—Following organ transplantation, tissue injury and remodeling inflicted by Abs to HLA antigens is conducive to develop autoimmunity. Antibodies (Abs) to HLA and self-antigens are detectable in the serum of transplant recipients who develop chronic rejection. Anti-HLA Abs are often present transiently but precede the development of Abs to self-antigens.

Keywords

autoimmunity; alloimmunity; self-antigens

Introduction

Solid organ transplantation in the form of a vascularized allograft is the treatment of choice for patients with end-stage organ dysfunction. While significant improvement in immunosuppressive strategies has led to decreased graft loss in the early post-transplant period, there has been less progress made in addressing the effects of chronic rejection. Chronic rejection is the leading cause of long-term allograft failure in transplant recipients and it is an immunologically mediated process that causes progressive deterioration of function. Primarily,

Corresponding Author T. Mohanakumar, Ph.D. Washington University School of Medicine Department of Surgery Box 8109-3328 CSRB 660 S. Euclid Avenue St. Louis, MO 63110 Tel: 314-362-8463 Fax: 314-747-1560 kumart@wustl.edu.

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inflammation and tissue remodeling promoted by alloimmune mechanisms facilitate the induction of autoimmune responses against self-antigens. In this review, we will discuss the role of alloimmune mechanisms leading to the development of autoimmunity resulting in chronic rejection.

Immunobiology of Chronic Rejection

Chronic rejection is primarily considered to be an alloantigen-dependent event influenced by an early acute immunological injury to the graft. In other words, it is dictated by host allo-responsiveness against mismatched donor antigens [1]. Clinically, chronic rejection is characterized as a slow process resulting in the replacement of the allograft parenchyma with fibrous scar tissue. Both immune (antigen-dependent) and non-immune (antigen-independent) factors lead to fibroproliferative changes that cause occlusion of tubular structures in the allograft. This is characterized by focal cellular interstitial infiltration and glomerulosclerosis in renal allografts, coronary arteriopathy in cardiac allografts and small airway obliteration in lung allografts.

The allorecognition of mismatched donor histocompatibility antigens has been postulated as the central event that initiates chronic rejection [2-4]. Donor antigen presentation is thought to be mediated via 3 distinct but not mutually exclusive pathways of allorecognition - the direct, indirect and the semi-direct pathways [5]. Direct pathway involves recognition of intact donor MHC molecules on the surface of donor antigen presenting cells (APC) by recipient T cells. In contrast, the indirect pathway involves presentation of processed donor antigens by recipient APCs to recipient T cells. The recently described 'semi-direct' pathway, which is yet to be fully characterized in chronic rejection, likely involves recipient APCs which acquire donor MHC through cell-to-cell contact and activate a host T-cell response [6].

Chronic rejection is principally mediated through the indirect allorecognition of donor MHC-derived peptides by recipient CD4⁺ and CD8⁺ T-cells [7,8]. During rejection, the direct pathway is involved in the priming of alloreactive T cells. Allogenic APCs induce rejection-like responses via the direct pathway [9]. Furthermore, epitope spreading combined with activation of 'low affinity' autoreactive T cells which have escaped thymic deletion, can lead to indirect recognition of self-antigens during rejection [2,3].

Evidence for Alloimmunity in Chronic Rejection

Antibodies (Abs) against MHC class I antigens pose an increase risk for early allograft failure and lower survival after lung transplantation [9-11]. In a prospective analysis of sera from bronchiolitis obliterans (BOS)⁺ and BOS⁻ lung transplant patients, our laboratory has demonstrated that onset of anti-MHC class I Abs precedes the development of BOS by 20 months [12]. Airway epithelial cells (AEC) are important immunological targets in lung allograft rejection. When stimulated with anti-MHC class I Abs, AECs undergo proliferation and secretion of fibrogenic growth factors. Hence, a pathogenic role for anti-MHC class I Abs in chronic rejection exists, as increased levels of heparin-binding epidermal growth factor (HB-EGF), basic fibroblast growth factor (b-FGF), granulocyte monocyte colony-stimulating factor, insulin like growth factor-1, platelet-derived growth factor, and transforming growth factor-beta (TGF- β) were detected following stimulation of AECs by anti-MHC class I Abs. Subsequent studies have also demonstrated a correlation between development of de novo anti-MHC class II Abs and BOS [9,13].

Studies in our laboratory have confirmed the direct role of anti-MHC class I Abs in the immunopathogenesis of obstructive airway disease (OAD), a histological correlate of BOS [14]. Following heterotopic tracheal transplantation, administration of anti-MHC class I Abs into immune-deficient RAG-1-knockout mice resulted in OAD pathology. A significant

upregulation of growth factors and pro-apoptotic genes was noted in mice with anti-MHC class I Abs but not with control Ab. Thus, alloantibody induced activation of AECs can directly result in the over expression of adhesion, costimulatory, and MHC class II molecules as well as secretion of proinflammatory cytokines, chemokines, and growth factors [15].

During chronic lung allograft rejection, intact donor MHC class I and class II molecules are recognized by alloreactive CD8⁺ and CD4⁺ T cells, respectively. Studies have demonstrated that a high frequency of indirect alloreactive CD4⁺ T cells against donor MHC class I and class II molecules can be detected in a human lung allograft recipient years after transplantation and are associated with BOS [16]. Also, recipient T cells primed by the indirect allorecognition pathway are less responsive to conventional immunosuppression compared to those primed by the direct pathway. The presence of intrapulmonary lymphoid tissue has been noted to play a role in the pathogenesis of chronic rejection. Intrapulmonary lymphoid tissue contains effector memory T cells and high endothelial venules which can contribute to a local immune response in small airways leading to BOS [17].

Recently, we developed a murine model to study the role of allo-antibody induced autoimmunity following lung transplantation [18]. In this model, administration of specific anti-MHC class I Abs 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. Briefly, monoclonal Abs against strain specific MHC class I antigens were administered intrabronchially into the native lungs of 3 different strains of mice - BALB/C, C57BL/6 and HLA transgenic C57BL/6 mice on days 1, 2, 3, and 6, and then weekly thereafter. Antibodies of the same isotype (C1.18.4) and anti-keratin Abs were administered in control animals. By day 15, histopathological analysis of the anti-MHC class I Ab administered lung tissue revealed the presence of peribronchial and perivascular mononuclear infiltrates, epithelial hyperplasia and fibrosis. By day 30, there was increase in cellular infiltration around vessels and bronchioles. There was also an increase in fibrosis along with lumen occlusion of the small airways. In contrast, there was no evidence of cellular infiltration, epithelial hyperplasia or fibrosis in the isotype or anti keratin Ab treated animals. Immunohistochemical studies revealed the presence of CD4⁺ and CD11b⁺ cells around the bronchioles and vessels at both day 15 and day 30 in anti-MHC class I Ab administered mice.

Anti-MHC class I binding induces the upregulation of inflammatory chemokines, growth factors and cytokines which favors the recruitment of inflammatory cells into the organ. The ligation of MHC class I molecules expressed on the lung parenchyma with Abs significantly increased the expression of proinflammatory cytokines, chemokines and their receptors along with increased bone morphogenetic protein (BMP) and fibroblast growth factor (FGF) family of growth factors.

Similar to lung transplantation, the majority of late mortality in cardiac transplantation is due to chronic rejection. Chronic rejection of cardiac allografts is manifested by cardiac allograft vasculopathy (CAV), characterized by occlusion of coronary vessels. Despite its significant utility in improving outcomes of patients with non-transplant coronary artery disease, drug-eluting stents still seem to be of limited value in treating CAV following cardiac transplantation [19]. The 5-year incidence of CAV is 30-40% and several mechanisms have been proposed to explain the underlying process [20]. Animal studies have supported a critical role of an alloimmune response in the development of chronic rejection in cardiac allografts [21]. In clinical transplantation, the development of donor-specific HLA Abs has been correlated with chronic rejection [4]. Independent risk factors for CAV include duration and number of acute rejection episodes and donor HLA mismatching [20].

In the pathogenesis of CAV, examination of perivascular infiltrates usually reveals the presence of inflammatory cells including T cells (CD4+, CD8+), B cells, natural killer (NK) cells, macrophages and dendritic cells [22]. Experimental models reveal that depletion of recipient CD4+ but not CD8+ T cells prevent the formation of arterial lesions consistent with CAV [23-25]. Allo-Abs in conjunction with complement can have a significant role in CAV pathogenesis. The presence of circulating Abs specific to mismatched donor HLA molecules and the deposition of complement product C4d within the graft have been correlated with poor allograft outcome [23,25].

Alloreactive CD4+ Th1 and Th2 cells activated via the indirect pathway have been previously implicated in the development of CAV [1]. In a study using a T bet-/- model of CAV, Th17 cells mediated a proinflammatory response in the absence of a Th1 response leading to CAV [26]. Alloimmune responses have also been implicated in the induction of platelet derived growth factors (PDGF) A, C, D involving the TGF-beta 1 pathway and inhibition of all PDGF with the exception of PDGF-B can lead to inhibition of chronic rejection [27]. Antioxidant administration in the immediate post-transplant period can also confer protection against CAV [28].

Chronic rejection termed chronic allograft nephropathy (CAN) is the leading cause of renal function deterioration and accounts for nearly 40% of the graft loss at 10 years [29]. There is no consensus with respect to the optimal management of CAN or chronic allograft dysfunction (CAD), the latter being a non-biopsy proven entity [7]. Animal and clinical studies suggests that both the humoral and cellular limbs of alloimmunity contribute to the development of CAN [2,29,30]. Increased levels of pre-transplant anti-HLA Abs and de novo post-transplant donor specific Abs have also been associated with CAN [31]. Antibodies against MHC class I polypeptide-related sequence A (MICA) can affect renal allografts. Antibodies have also been implicated in the development of post-transplant vasculopathy, glomerulopathy and interstitial scarring [32]. CD4+ alloreactive T cells responding to donor derived peptides bound to recipient MHC class II have also been correlated with CAN [7]. As with heart transplantation, IgG as well as IgM Abs against donor HLA is associated with diminished survival of kidney allograft [33]. There are no currently available biomarkers which can detect interstitial fibrosis and tubular atrophy in the early post-transplant period. However, recent studies suggest that epithelial to mesenchymal transition in the tubular epithelial cells may predict graft fibrosis [29].

Evidence for Autoimmunity in Chronic Rejection

A proportion of the transplant recipients undergo chronic rejection despite the absence of any detectable anti- HLA Abs [3,8]. In many such cases, the role of Abs against non-HLA antigens has been proposed. Recent studies in post lung transplant patients with BOS have led to the identification of circulating Abs against self-antigens, K-alpha-1-Tubulin (KA1T), an airway epithelial surface antigen [34] and collagen V (Col-V), an extracellular matrix protein [35]. We also noted that development of Abs to HLA precedes the development of Abs against self-antigens, KA1T and Col-V (Saini D, Mohanakumar T, unpublished data).

In our study, about 50% of BOS+ patients with detectable anti-HLA Abs develop Abs against KA1T. The development of Abs against KA1T preceded the clinical diagnosis of BOS. In addition, we demonstrated that binding of anti-KA1T to AEC activates a PKC-driven calcium maintenance pathway that is regulated by heat shock proteins (HSP) 27 and 90, culminating in increased growth factor production, cellular mitosis and proliferation. Exposure of AECs to sera from BOS+ lung transplant recipients resulted in an up-regulation in transcription factors TCF5 and c-Myc and proliferation factors HB-EGF, TGF- β , and VEGF. Collectively, our experimental data strongly suggests that binding of anti-KA1T Abs to AECs results in up-

regulation of proinflammatory response genes and activation of fibroproliferation cascade. Collagen-V specific T cells were identified following lung allograft rejection in a rat model and transfer of Col-V specific CD4⁺ T cell clones can induce acute rejection-like pathology in rat lung isografts [9]. Studies from our laboratory have also shown Col-V specific T cells secreting high levels of IFN- γ and low levels of IL-10 in post-lung transplant recipients clinically diagnosed with BOS [36].

A recent longitudinal study in lung transplant patients demonstrated an association between Col-V specific IL-17 responses with onset of BOS [37]. Collagen-V-specific responses in BOS patients were found to be dependent on both CD4⁺ T cells and monocytes and required IL-17, TNF- α and IL-1 β . Further, adoptive transfer of lymph node cells expressing high levels of IL-17 and IL-23 gene transcripts from Col-V sensitized mice have been shown to induce obliterative lesions in the lung isograft. These results demonstrate that cell mediated immunity to self-antigens can lead to chronic rejection in the absence of alloantigen.

Well-established animal studies using syngenic heart transplants provided initial evidence that chronic rejection can be induced even in the absence of an alloimmune response [21,24]. T cell mediated autoreactivity against cardiac myosin develops and persists in the absence of an alloimmune response, indicating that response to myosin, a self antigen, may be associated with the pathogenesis of CAV [4,25]. Additionally, pre-transplant sensitization with cardiac myosin can result in accelerated rejection of both allo and syngenic cardiac grafts [25]. Vimentin is an intermediate cytoskeletal filament protein which is found in fibroblasts, proliferating smooth muscle cells and endothelial cells. Studies have also indicated that Abs against vimentin is an independent predictor of coronary atherosclerosis following cardiac transplantation and may contribute to the accelerated onset of transplant associated coronary vasculopathy [25,38]. Recently, the role of Abs against MICA have also been demonstrated to be associated with chronic rejection in heart allografts [39].

In kidney allografts, transplant glomerulopathy has an incidence of 20% by 5 years post-transplant [40]. A recent multi-center trial involving refractory vascular allograft rejection in the absence of detectable anti-HLA Abs demonstrated the presence of Abs directed at two epitopes of the second extracellular loop of the angiotensin II type 1 (AT1) receptor. Further, it has been suggested that detection of anti-AT1 receptor might be a useful tool to identify those at risk for refractory allograft rejection [2,40]. T cells producing proinflammatory and regulatory cytokines against HSP 60 have been demonstrated in peripheral blood and graft-infiltrating lymphocytes of renal transplant recipients [2]. Other Ab targets include perlecan and collagen types IV and VI as well as glomerular basement membrane protein agrin [2,7]. These results suggest that induction of humoral and cell mediated immune responses to various self-antigens have an important role in chronic allograft pathogenesis. Recent studies have also suggested a role for antivimentin Abs in the development of CAN [30].

Conclusion

A recent concept is establishment of a causal relationship between alloimmune responses and development of de novo autoimmunity to self-antigens in the post-transplant period. Tissue inflammation and repair mechanisms inflicted by anti-HLA Abs results in exposure of self-antigens which lead to post-transplant autoimmunity. We propose that identifying immune responses to self-antigens will provide new strategies to monitor and prevent development of late graft dysfunction. Serial monitoring for development of Abs to self-antigens can be used to predict patients at risk of developing chronic rejection. Neutralization of circulating IL-17, which promote autoimmune responses, and induction of tolerance to self-antigenic determinants are possible strategies to prevent chronic rejection.

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