Non-MHC Antigenic Targets of the Humoral Immune Response in Transplantation

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Summary of recent advances

There is a growing body of data supporting a role for non-HLA antibodies in acute and chronic rejection of solid organ transplants. While many of these non-HLA antigens remain poorly defined, the principle antigenic targets are expressed on cells of the allograft including endothelium and epithelium. These non-HLA antigens are classified as either alloantigens, such as the major histocompatibility complex class I chain-related gene A (MICA) or MICB, or tissue-specific autoantigens such as vimentin, cardiac myosin (CM), collagen V (Col V), agrin and angiotensin II receptor type I (AT1). Herein we provide an overview of the non-MHC antigenic targets that have been implicated in graft rejection and discuss the interplay between alloimmunity and autoreactivity in graft rejection.

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Introduction

Antibody-mediated rejection (AMR) remains a major limitation to solid organ transplantation. The development of more sensitive tests for detection of complement split products in the allograft and for the presence of circulating HLA antibodies have improved our ability to diagnose and treat AMR. Numerous studies have shown that the presence of donor specific HLA antibodies either before and/or after allograft transplantation is associated with acute and chronic AMR and decreased long-term graft survival. More recently, antibodies against non-HLA antigens have also been recognized to contribute to the pathogenesis of AMR as both hyperacute and acute rejection have occurred in the absence of detectable HLA antibodies [2,4-5]. The clinical importance of sensitization to non-HLA antigens is underscored by reports of hyperacute rejection of HLA-identical sibling grafts [1-3]. Pre-transplant sensitization to non-HLA antigens was strongly associated with long-term graft loss of HLA-identical sibling renal transplants suggesting that non-HLA immunity also plays a role in the pathogenesis of chronic rejection [6]. The targets of humoral responses against non-HLA antigens are primarily antigens expressed on endothelial cells and epithelial cells and categorized as non-HLA alloantigens or tissue-specific autoantigens.

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Non-MHC Alloantigens

Anti-endothelial cell antibodies

Anti-endothelial cell antibodies (AECA) have been reported to mediate endothelial cell (EC) activation, apoptosis and cell injury. AECAs represent a heterogeneous group of antibodies comprising both IgM and IgG subclasses and are directed against a variety of antigenic determinants on ECs [7]. Pretransplant AECA are associated with increased frequency of acute renal rejection and decreased long-term graft survival [8]. To investigate how AECA are involved in acute renal allograft rejection, eluates from 25 renal allografts were tested for anti-EC antibodies. Eight of 9 patients with irreversible vascular renal allograft rejection had IgM AECAs eluted from the rejected kidney, but AECA were absent in the 13 kidneys lost to other types of rejection [9]. These AECA were able to activate EC resulting in upregulation of mRNAs encoding the adhesion molecules VACM-1 and ICAM-1. In a cohort of 57 renal transplant candidates, AECA were present in 47% of patients who were sensitized to HLA and in 16% of nonsensitzed patients [10]. Although, these antibodies were mainly of the IgG isotype and did not mediate cytotoxicity, they were able to cause apoptosis of ECs *in vitro*. No significant correlation was found between the presence of AECAs and graft outcome in this cohort.

In cardiac transplantation, 17/31 patients who developed posttransplant AECA experiencedAMR compared to only 9 of 49 patients without AECAs [11]. In addition, allograft survival at 2 years was significantly better in the AECA- group compared to the AECA+ group and AECA positivity was associated with cardiac allograft vasculopathy (CAV). Pretransplant cytotoxic IgM non-HLA antibodies were as associated with a diagnosis of primary graft failure and worse survival of cardiac transplant recipients [12]. Collectively, these studies suggest that AECA may cause AMR and identify a high-risk group for CAV.

A major limitation of these studies is the lack of knowledge of the antigenic specificity of the AECA. Current lymphocyte crossmatching techniques fail to detect AECA. The XM-One assay is a novel endothelial cell flow cytometry crossmatch technique that uses Tie-2 antibody coated magnetic beads to select precursor EC directly from donor blood [13]. Results of a multicenter clinical trial evaluating the association of AECAs with renal allograft rejection showed that pretransplant donor reactive AECAs were present in significantly higher proportion of patients with rejection [13]. Additional studies are needed to confirm if this crossmatch method is useful for identifying clinically relevant AECA.

MICA

MICA is encoded by genes located within the MHC region on chromosome 6 just centromeric to HLA-B. MICA is highly polymorphic with over 68 MICA alleles. MICA is considered as a plausible target of allograft response because of its polymorphic nature and the fact that endothelial cells can express MICA on their surface under stress due to ischemia reperfusion injury and rejection [14-15]. MICA antibodies associate with acute and chronic rejection of heart, renal and pancreas transplants [14,16-20]. In a large multicenter study, pretransplant MICA antibodies were found in 217 of the 1910 patients tested and was associated with renal graft rejection and lower one-year survival [20]. The long term effect of anti-MICA antibodies was investigated in a prospective multicenter study of 1319 renal transplant recipients [19]. Patients developing posttransplant MICA antibodies had a significantly lower 4-year allograft survival (86%) compared to those without antibodies (98%). A

limitation of these studies is that they failed to discriminate between donor specific vs. third party anti-MICA antibodies. Anti-MICA antibodies have been found to mediate complement dependent cytotoxicity in vitro [21] suggesting that they may contribute to the pathogenesis of AMR through complement mediated injury. A recent study addressed the question of C4d deposition in kidney biopsy and donor specific antibodies (DSA) to HLA, MICA and GSTT1 [22]. They showed the majority of patients with C4d+ biopsies had DSA to HLA (47%), MICA (21%) or GSSTT1.

Two reports assessed the effect of MICA DSA on cardiac allograft outcome. In a study of 44 heart recipients, 60% of patients with acute rejection produced MICA DSA compared to 14% without rejection [18]. In the second study, pre- and posttransplant sera from 491 heart transplant recipients were studied for DSA to MICA. They found no effect of sensitization to MICA on episodes of rejection or CAV. The lack of concordance between these studies may be due to small sample size and/or differences in the timing of sample collection. Interestingly, both groups reported an absence of MICA expression on cardiac endothelial cells suggesting that MICA is not constitutively expressed in the transplanted heart. However, MICA genes contain a heat shock response element promoter and their expression can be induced in response to cellular stress. Ischemia reperfusion injury and cytokines such as IL-2, IL-4 and IL-15 that are produced during inflammation and rejection can also upregulate the expression of MICA in the graft [23-24]. Further studies are needed to determine the expression pattern of MIC in solid organ transplants during quiescence and rejection.

Since membrane bound MICA proteins can be upregulated during inflammation and rejection, and soluble MICA is increased in the circulation of transplant recipients [25] we posit that MICA alloreactive T cells responding via the indirect pathway are primed to donor derived soluble MICA antigens in the context of self MHC class II and induce anti-MICA antibody responses. Consistent with this possibility, several studies have shown that antibodies to MICA are produced after transplantation and their frequency is higher in regraft patients [26]. Furthermore, the immune response to mismatched HLA lead to the development of antibodies to MICA antigens expressed on the airway epithelial cells of lung transplants [27].

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Tissue Specific Antigens

Vimentin

Vimentin is a non-polymorphic intermediate filament expressed in cytosol of endothelial, vascular smooth muscle cells, activated platelets and macrophages, renal tubular cells, mesangial cells and renal stromal cells. Vimentin is strongly expressed in the intima and media of coronary arteries where vascular smooth muscle cells and fibroblasts locate. Autoimmune responses to vimentin are associated with both acute and chronic rejection of heart and renal allografts. Cardiac transplant recipients developing CAV show significantly higher titers of anti-vimentin antibodies in the first and second year posttransplant than patients who remained disease free [28]. Production of humoral immune responses to vimentin was also accompanied by the generation of vimentin-specific autoreactive CD8 positive T cells in cardiac transplant recipients [29]. Furthermore, sera containing anti-vimentin antibodies induced leukocytes, to release of platelet activating factor which in turn cased the formation of platelet-leukocyte conjugates [30]. Studies in non-human primates confirmed the findings in human heart recipients and showed that development of cellular and humoral autoimmune responses to vimentin was a prominent feature of allograft rejection and CAV [31].

Immunization of mice with vimentin resulted in development of anti-vimentin antibodies and vimentin-specific T cells and accelerated rejection of cardiac allografts, but not isografts [32]. Furthermore, anti-vimentin antibodies were necessary to cause rejection as shown by the ability of adoptively transferred serum to restore accelerated rejection in B cell deficient mice. Thus, it appears that anti-vimentin antibodies alone are insufficient to cause graft rejection and rather act in concert with the alloimmune response. An important question that emerges from these findings is how vimentin antibodies are pathogenic to the process of rejection. One theory suggests that alloreactive immune response mediate graft injury, apoptosis of endothelial cells and subsequent exposure of neoantigens such as vimentin causing an autoimmune response. Anti-vimentin antibodies bind to vimentin positive platelets, leukocytes and endothelial cells causing complement deposition and leukocyte-platelet aggregation in the microcirculation of the graft [32]. In addition, cross-reactivity between anti-streptococcal antibodies and vimentin/cardiac myosin has been described, suggesting a possible mechanism contribute to myocyte injury [33].

Cardiac Myosin

Cardiac myosin (CM) is a heart specific antigen implicated in allograft rejection [34]. Pretransplant myosin autoantibodies correlated with acute cardiac transplant rejection [35]. The expansion of alloreactive T cells was followed by an increase of cardiac myosin reactive T cells and development of anti-myosin IgG1 autoantibodies in a mouse heart transplant model mismatched for minor histocompatibility alloantigens [36]. This supports the idea that CM released during alloimmune injury of the allograft is recognized by CD4+ T helper autoreactive cells through indirect recognition pathway and triggers the generation of autoreactive CM antibodies. Notably, mature CM is not expressed in the thymus during development which may result in incomplete negative selection [37].

Collagen V

Both cellular and humoral responses to Col V act as a major risk factor in the development ofbronchiolitis obliterans syndrome (BOS) after human lung transplantation [38]. Col V is usually interstitial and not normally exposed in healthy tissue. However, Col V is unveiled during ischemia reperfusion injury or in interstitial remodeling of lung transplants and can be detected in bronchoalveolar lavage fluid. Transfer of anti-Col V antibodies to rat lung isografts induced pathology consistent with primary graft dysfunction and mediated epithelial cell cytotoxicity [39]. Col V-specific T cells appear in human and rat lung transplant recipients before the clinical onset of BOS and adoptive transfer of Col V reactive T cells induced rejection [40]. Cellular injury to Col V was mediated by IL17A which recruits monocytes and neutrophils and acts in synergy with other local inflammatory cytokines [38,41]. Th17 cells have been implicated in a number of autoimmune or inflammatory conditions and in models of allograft rejection [42]. In the absence of Th1-mediated alloimmune responses, CD4 Th17 cells mediate an aggressive proinflammatory response leading to cardiac allograft rejection and CAV [43]. Furthermore, Th17-mediated acute lung transplant rejection could be prevented by adoptive transfer of CD4+ Col V specific T regulatory cells [40].

K-$_\alpha$1 tubulin

K-$_\alpha$1 tubulin is a glycoprotein expressed in air way epithelial cells and is constitutively associated to a guanosine triphosphate (GTP). It forms microtubules in cells and plays an important role in maintaining cellular structure, microtubule-based intracellular movement. K-$_\alpha$1 tubulin is not normally expressed on cell surface, however epithelial cell damage can result in the exposure of K-$_\alpha$1

tubulin which may promote autoimmune responses. Goers et al.[44] Showed that 12/36 lung transplant recipients developed anti-K-$_\alpha$1 tubulin antibodies posttransplant in the absence of HLA sensitization and was strongly associated with BOS. The binding of K-α1 tubulin antibodies to airway epithelial cells activated a PKC-driven calcium maintenance pathway and stimulated expression of transcription factors and fibrogenic growth factors culminating in cell cycle signaling and fibroproliferation. To determine if alloimmunity induces pathogenic autoimmune responses, anti-MHC antibodies were administered intrabronchially into the native lungs of mice. Lungs of mice receiving anti-MHC class I antibodies showed increased expression of IL-17 and they developed antibodies to self-antigens K-α1 tubulin, and collagen V [45]. IL-17 neutralization resulted in reduction of autoantibody and lesions induced by anti-MHC class I antibodies. These results indicate that antibodies to donor MHC can induce pathogenic autoimmune response which may play a pivotal role in chronic rejection.

Angiotensin II receptor type I

Angiotensin type 1 receptor (AT$_1$R) is the main receptor for angiotensin II in the glomerulus and mediates arterial blood pressure and salt balance. It is also expressed in the brush border and basolateral membranes of the proximal tubules, in the vasculature, and in other components of the kidney. Anti- AT$_1$R-antibodies were found in 16/20 recipients with renal refractory vascular rejection who had no HLA antibodies [46]. Removal of AT$_1$R-antibodies by plasmapheresis in combination with intravenous immunoglobulin (IVIG) and pharmacologic AT$_1$R blockade improved renal function and graft survival in 7/16 patients as compared to the remaining 9 patients with conventional treatment. In addition, passive transfer of human AT$_1$R-antibodies into rats induced endarteritis and intravascular infiltrates within one week. The AT$_1$R-antibodies were complement-fixing IgG1 and IgG3 isotypes, however, C4d deposition was only detected in 5 out these 16 patients, suggesting the pathogenesis of AT$_1$R-antibodies may be complement independent. AT$_1$R-antibodies were shown to promote inflammatory responses and contribute to allograft rejection through the phosphorylation of ERK kinase and activation of AP-1 and nuclear factor κB(NF-κB) resulting in the production of tissue factor and reactive oxygen species. Blockade of NF- κB with decoy oligodeoxynucleotides reduced tubulointerstitial infiltration in rat renal allografts.

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Natural Antibodies and Ischemia Reperfusion Injury

Recent studies have implicated IgM natural antibodies as self-targets in the pathogenesis of ischemia reperfusion injury (IRI). Studies of different animal IRI models showed that reperfusion of ischemic tissues elicits an acute inflammatory response involving the complement system which is activated by autoreactive natural IgM [47]. Mice deficient in complement are protected against IRI. These studies suggest that hypoxia triggers the expression of neo-antigens and upon binding of the natural antibodies, initiates cellular recruitment and complement activation. Recent studies confirmed that human natural IgM could induce IRI injury in a murine intestinal model suggesting that innate autoimmunity may operate under pathogenic conditions in human [48] .However, whether similar mechanisms operate in humans is unknown. Candidate natural antibodies that have been shown to bind to ischemic endothelial cells include the nonmuscle myosin heavy chain type II A and C IgM antibodies.

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Interplay between alloimmunity and autoreactivity in graft rejection

It is increasingly recognized that alloimmune responses and tissue specific autoimmune responses act in concert to promote graft rejection (Figure 1). Alloimmune responses occur through direct and indirect recognition. The direct pathway involves presentation of allogeneic MHC class I and II antigens on donor APCs to recipient T cells and is believed to be the primary mechanism of acute rejection mediated by alloreactive cytotoxic T lymphocytes and alloantibodies resulting in graft injury. Graft injury causes the release of alloantigens and self-antigens which can in turn be presented via the indirect recognition pathway to generate pathogenic allo and autoreactive cellular and humoral immune responses [45]. The indirect pathway involves processing the donor alloantigens and/or self-antigens by recipient APCs and presentation to recipient T cells and is believed to be the major pathway for chronic rejection. Once initiated, the indirect alloimmune response can spread to additional determinants within the primary target antigen called intramolecular epitope spreading, or to epitopes on other allogeneic or self antigens called intermolecular epitope spreading [49].

Figure 1

A model for interplay between alloimmunity and autoreactivity in graft rejection. Graft damage elicited by alloreactive T and B cells primed through the direct and/or indirect allorecognition pathways results in the release of alloantigens and self-antigens. (more ...)

How alloimmunity leads to loss of tolerance to self-antigens in the transplant setting is not well understood but recent studies implicate alloreactive T cells in this process [36,45,50]. Murine skin allograft studies have shown that activation of indirectly alloantigen primed T cells can result in determinant spreading and the generation of pathogenic autoreactive T cells [50]. These findings suggest that the development of humoral responses to autoantigens could result as a consequence of alloimmune-mediated graft damage where repeated exposure of recipient CD4+ T cells to self-antigens surpasses the threshold of self-tolerance and leads to autoimmunity. Although the majority of autoreactive B cells in the periphery are functionally attenuated, [51] they can pose a danger in the development of rejection if T cell tolerance is breached permitting T cell helper activation of these autoreactive B cells. Experimental studies suggest that chronic stimulation with autoantigens can break T cell self tolerance. Tsumiyama et al [52] showed that repeated stimulation of CD4+ T cells with self-antigens led to the development of autoantibody-inducing CD4+ T cells. Thus autoimmunity resulted from over-stimulating the host's immune response by repeated immunization with antigen.

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Conclusions

Autoimmunity may be a consequence of alloreactivity induced after solid organ transplant. Continued efforts to define the non-HLA alloantigens and tissue-specific autoantigens involved in transplant rejection are critical to understanding the mechanisms and pathogenesis of non-HLA antibodies and development of treatment options.

Footnotes

Conflicts of Interest

The authors have no conflicts of interest to disclose

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