Induction of T Cell Responses to Tissue-Specific Antigens: Immune Mechanisms and Role in Transplant Rejection

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Introduction

T lymphocytes are selected to recognize and eliminate foreign components that may be encountered during life while avoiding a response to self-proteins and thus the initiation of autoimmunity. It is now firmly established that immature T cells that recognize self-antigen/major histocompatibility complexes (MHC) with sufficient affinity during development in the thymus are clonally eliminated via the process of negative selection (central tolerance).[1,2] This has been the prevailing theory for more than a decade. However, a number of autoreactive T cells escape thymic elimination. These T cells, despite their high number in the periphery, are normally harmless due to a number of ill-defined mechanisms, including immune deviation, anergy, and T cell–mediated suppression (peripheral tolerance).[3] Under certain circumstances, however, these autoreactive T cells can become activated and trigger an autoimmune process that leads to tissue injury.[4-8] Among these conditions, inflammation, infection, and tissue damage are known to provoke the release of normally sequestered autoantigens and de novo presentation by antigen-presenting cells (APCs) of a new (formerly cryptic) self-peptide.[4-8]

During the past years, our laboratory has published a series of papers that showed the activation of autoreactive peripheral T cells after transplantation of allogeneic tissues. Initially, we showed that injection of donor-irradiated splenocytes can result in the breakdown of T cell tolerance to a dominant self-MHC peptide.[9] In another study, we reported the presence of an autoreactive response to cardiac myosin, the target antigen in autoimmune myocarditis, after allogeneic heart transplantation.[10] More recently, we and others demonstrated the initiation of $CD4^+$ T cell autoimmune responses following lung and skin allotransplantation in rodents.[11-13] In the mouse lung transplant model, the target antigen of this autoimmune response is collagen type V.[11-13] Finally, we have also detected T cell autoreactivity to cardiac myosin (CM) in a large animal heart transplant model (miniature swine) and induction of de novo CM-specific B cell responses in heart-transplanted patients (unpublished observations). Taken together, these studies show that the induction of autoimmune responses to graft tissue-specific antigens represents a general feature of the immune response to transplanted organs. Here, we describe immune mechanisms that are likely to govern the initiation of transplant-associated tissue-specific autoimmune reactions and discuss how this phenomenon may influence the process of allograft rejection.

Induction of Autoimmune Response to a Dominant Self-MHC Peptide after Allotransplantation

T lymphocytes recognize foreign proteins in the form of processed peptides associated with self-MHC proteins displayed at the surface of APCs.[14,15] Seminal studies by Lorenz and Allen have provided direct evidence showing that APCs continuously process self-proteins and present self-peptides to autoreactive T cells.[16-18] Supporting this finding, chemical elution and analysis of the peptides bound to MHC molecules have revealed that self-peptides constitute the vast majority of the peptides that occupy MHC peptide-binding grooves.[19-21]

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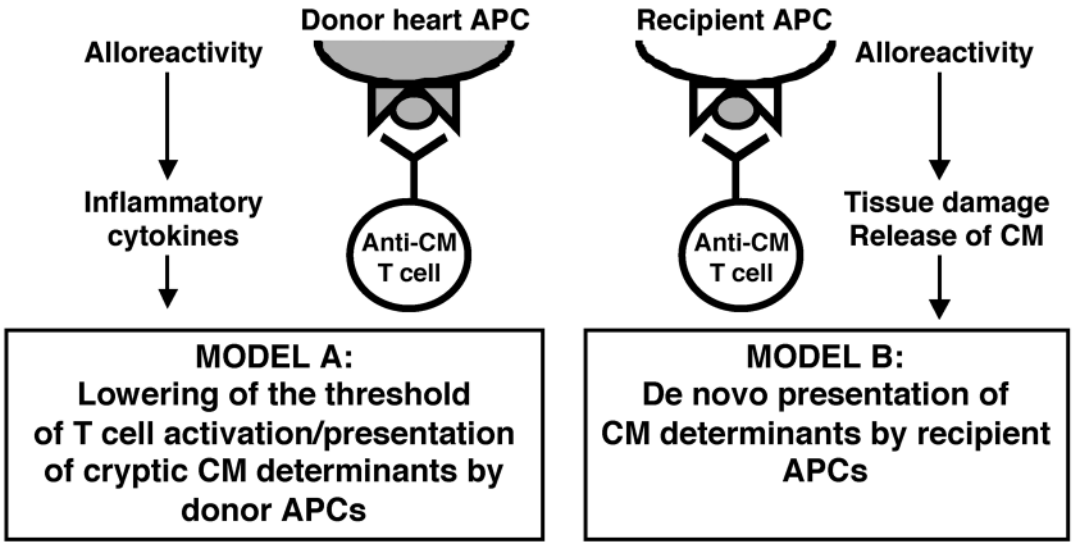

Figure 1. Possible mechanisms involved in the induction of autoimmunity to CM after heart transplantation. Model A: Local inflammation and cytokine release at the site of the graft associated with upregulation of major histocompatibility complex (MHC) class II expression and induction of costimulatory receptors on cardiac antigen-presenting cells (APCs) of donor origin may lead to efficient presentation of CM/donor MHC class II complexes to anti-CM T cells. Model B: Tissue damage at the site of the graft may induce the release of cardiac myosin and its processing and presentation in peptide form by infiltrating macrophages and dendritic cells of recipient origin. Such de novo presentation of CM determinants in recipient MHC class II context could induce the activation of anti-CM autoreactive T cells of recipient origin.

This presentation of self-peptides plays a critical role in the process of negative and positive selection of immature T cells in the developing thymus.[1,2,22-27] Likewise, in adults, it is believed that T cell recognition of self-peptides continuously displayed on APCs may regulate the immune response to foreign proteins and contribute to maintaining self-tolerance in the periphery.

It has become clear that, like other autologous proteins, self-MHC molecules are regularly processed and presented to autoreactive T cells.[28-31] This self-MHC processing gives rise to 2 types of determinants: the dominant and cryptic self-MHC peptides.[28,32-35] "Dominant" self-MHC determinants are efficiently processed and presented, and they trigger T cell elimination/inactivation of corresponding autoreactive T cells during thymic selection. Immunization with these peptides does not trigger T cell responses in adults. Conversely, the "cryptic" peptides, despite their high affinity for MHC, cannot be generated in sufficient quantity to ensure complete tolerance induction during ontogeny. Thereby, these cryptic self-peptides induce vigorous T cell responses in adult lymph nodes and spleens following subcutaneous injection.[28,32-35]

We have previously reported that allotransplantation can result in the breakdown of tolerance and the development of an autoimmune $CD4^+$ T cell response to a dominant self-peptide.[9] BALB/c ($H\text{-}2^d$) mice are normally tolerant to the self-peptide D^d 61-80, derived from the $\alpha 1$ domain of MHC class I D^d autoantigen.[28,36,37] Indeed, the D^d 61-80 peptide binds with high affinity to A^d MHC class II protein, and it is regularly processed and presented at the surface of BALB/c APCs.[28,36,37] Such efficient processing and presentation of this self-MHC peptide presumably account for its ability to tolerize corresponding T cells during development. Consequently, subcutaneous immunization of BALB/c mice with this self-peptide along with CFA does not trigger a $CD4^+$ T cell proliferative response. It is noteworthy that the D^d 61-80 peptide can be immunogenic when seen as an allopeptide because it induces potent T cell responses in CBA/J and B10.BR mice ($H\text{-}2^k$) whose anti-D^d 61-80 T cells have not been rendered tolerant.[28]

AUTOIMMUNITY:

An immune response in which one's own tissues are subject to deleterious effects of the immune system, as in autoimmune disease.

Based on our initial data, we assumed that D^d 61-80 self-peptide reactive T cells had been deleted during development. However, a subsequent study showed that this assumption was incorrect. We observed that transplantation of BALB/c mice with allogeneic B10.A ($H\text{-}2^a$) splenocytes could, in fact, induce an autoimmune T cell response toward this self-peptide.[9] These transplanted mice also mounted vigorous indirect alloresponses (response to donor MHC peptides presented by recipient APCs) to another peptide derived from the donor MHC class I molecule K^k 61-80. Given their strong sequence homology, it was possible that indirect response to K^k 61-80 had broken T cell tolerance to its counterpart peptide on self-MHC class I (i.e., D^d 61-80). Supporting this hypothesis, we found that immunization with K^k 61-80 was sufficient to elicit an autoimmune response to the D^d 61-80 peptide in BALB/c mice.[9] This demonstrated that these two MHC peptides are cross-reactive and that induction of an indirect alloresponse to the donor MHC peptide could abrogate tolerance to its cross-reactive homologous peptide on self-MHC. It is noteworthy that this response was heteroclytic, in that immunization with D^d 61-80 itself could never trigger a response to D^d 61-80 or to K^k 61-80. This suggests that the allogeneic K^k 61-80 peptide was much more immunogenic than its self-counterpart in BALB/c mice. This showed that, unlike initially assumed, tolerance to the D^d 61-80 self-peptide in BALB/c mice was not complete. We surmise that immunization with the K^k 61-80 peptide may have primed certain low-affinity D^d 61-80-reactive T cells by lowering their threshold of activation, a phenomenon also observed by us and Cesaroli et al. in other models.[38-41] Alternatively, it is possible that some low-affinity D^d 61-80-reactive T cells that escaped thymic deletion are maintained in an anergic state in the periphery, owing to continuous presentation of the self-peptide D^d 61-80 at the surface of BALB/c APCs. In this scenario, the K^k 61-80 cross-reactive peptide could act as an agonist[39,40] and provide the necessary signals required to reverse the anergic state of some anti-D^d 61-80 self-reactive T cells.[41]

In summary, our data showed that indirect alloresponse to a donor peptide can trigger a concomitant autoimmune response to a cross-reactive dominant self-peptide. Whether this response contributes to the rejection process remains open to question.

Induction of Autoimmunity to Cardiac Mysosin after Heart Transplantation

To investigate whether autoimmunity occurs after transplantation of a solid organ and to determine its influence on the rejection, we first tested the presence of autoimmune responses in A/J mice transplanted with MHC class I–mismatched hearts from A.TL donors. At the time of rejection (day 9 postgrafting), recipient lymph nodes and spleens were screened for T and B cell responses against a panel of antigens derived from heart and other tissues. While no response was found to actin, troponin, collagen, and ovalbumin, a vigorous autoreactive response was detected to cardiac myosin (CM), a major contractile protein of heart muscle expressed exclusively in the heart.[10] This response was mediated by $CD4^+$ MHC class II–restricted T cells displaying TH1 phenotype and by B cells secreting anti-CM antibodies of IgG1 subclass.[10] No response to CM was detected in nontransplanted mice and in mice engrafted with an allogeneic skin from the same donor. This clearly indicated that this autoimmune response was not only antigen specific but also specifically associated with heart transplantation.

Cardiac myosin has been identified as the target autoantigen in a T cell–mediated autoimmune disease, experimental autoimmune myocarditis (EAM).[8,42-47] Two observations suggested that anti-CM autoimmunity induced after cardiac transplantation could contribute to heart tissue damage in a fashion similar to that observed during autoimmune myocarditis:

1. Histological analysis revealed the presence of epicardial and endocardial interstitial inflammatory cell infiltrates, myocyte dropout, and necrosis in both transplanted and myocarditic hearts.
2. Similar to the response in transplanted mice, B cell response in EAM is characterized by high titers of anti-CM IgG1, a set of antibodies that have been shown to play an important role in the autoimmune pathogenesis.[48-50]

Meanwhile, other data showed that the mechanisms by which the anti-CM response caused tissue injury in heart transplantation and in EAM are not

identical. First, while region 334-352 on the CM heavy α chain has been shown to contain the dominant determinant that initiates EAM, no response to this peptide was found in heart-transplanted mice tested at the time of acute rejection (10 to 12 days posttransplantation).[10,51] This indicates that the CM response in heart-grafted mice uses another, yet unidentified, determinant on CM.[10] Second, while induction of EAM resulted in inflammatory infiltration and tissue damage of mouse heart, the native heart of cardiac-transplanted mice remained apparently intact. At first glance, it is surprising that CM autoimmunity had apparently not affected the native's mouse cardiac tissue. The absence of trauma and of local inflammation in the nontransplanted heart associated with the lack of chemokine and inflammatory cytokine production and of adhesion molecule upregulation could explain the absence of infiltration by activated lymphocytes. It is also important to note that initiation of EAM requires coinjection of CM antigen and pertussis toxin. By recruiting/activating APCs, pertussin toxin may elicit or exacerbate the presentation of CM to autoreactive T cells, thereby promoting local inflammation and cellular infiltration in the otherwise unmanipulated heart tissue.

Direct and Indirect Types of Alloreactivity and Their Relationships to CM Autoimmunity in Heart-Grafted Mice

An important insight into the mechanism underlying the induction of autoimmunity after heart transplantation was provided by the observation that allogeneic but not syngeneic grafts triggered an anti-CM response.[10] It is therefore clear that CM response is elicited as a result of antidonor alloimmune response. The alloresponse to donor MHC antigens can be mediated via 2 distinct pathways (i.e., direct and indirect allorecognition). In direct allorecognition, recipient T cells recognize intact allo-MHC molecules on grafted cells.[52-55] Alternatively, T cells recognizing alloantigens in indirect fashion interact with donor-derived peptides presented in the self-MHC context on recipient APCs.[56-63] We investigated the involvement of these pathways in the onset of CM response following heart transplantation. In the A/J-A.TL model, donor and recipient differ by a single MHC class I allele (K^s vs. K^k). In this type of combination, we have shown that $CD4^+$ T cell alloresponse is primarily mediated via an indirect pathway,[64] and a response to CM is regularly detected. This showed that in A.TL mice engrafted with an allogenic A/J heart, indirect CD4 alloresponse is sufficient to initiate autoimmunity to CM. In another set of experiments, a series of antibodies directed to self and donor MHC class I and II molecules were tested for their ability to suppress anti-CM responses of T cells isolated from A.TL mice transplanted with MHC class II–mismatched BALB/c hearts. We observed that antibodies directed to recipient MHC class II abrogated the CM response, while anti-MHC class I antibodies and antibodies recognizing donor MHC class II molecules had no effect (unpublished observations). This showed that recipient class II molecules present CM determinants to autoreactive T cells in vivo. These data further supported the idea that indirect rather than direct alloresponse is responsible for induction of CM autoimmunity after cardiac transplantation. To confirm this, BALB/c mice were transplanted with hearts derived from B6 mice devoid of the MHC class II molecule (MHC class II knockout [KO]). Evidence has been provided for the absence of $CD4^+$ T cell direct allorecognition in recipients when donors or their APCs are devoid of MHC class II expression.[59,64,65] We found that BALB/c mice transplanted with B6 class II KO hearts mounted a potent anti-CM response (unpublished observations), a result that demonstrated that indirect alloreactivity mediated by $CD4^+$ T cells is sufficient to elicit autoimmunity to CM.

How Does Alloimmunity Lead to Autoimmunity?

Autoimmunity is thought to be initiated via 2 main mechanisms:

1. Following infection, some microbial antigens can "mimic" self-antigens and activate some normally resting autoreactive T cells (antigen mimicry).
2. Tissue damage associated with infection and/or inflammation can cause the release of normally sequestered autoantigens and the subsequent activation of some undeleted self-reactive peripheral T cells.

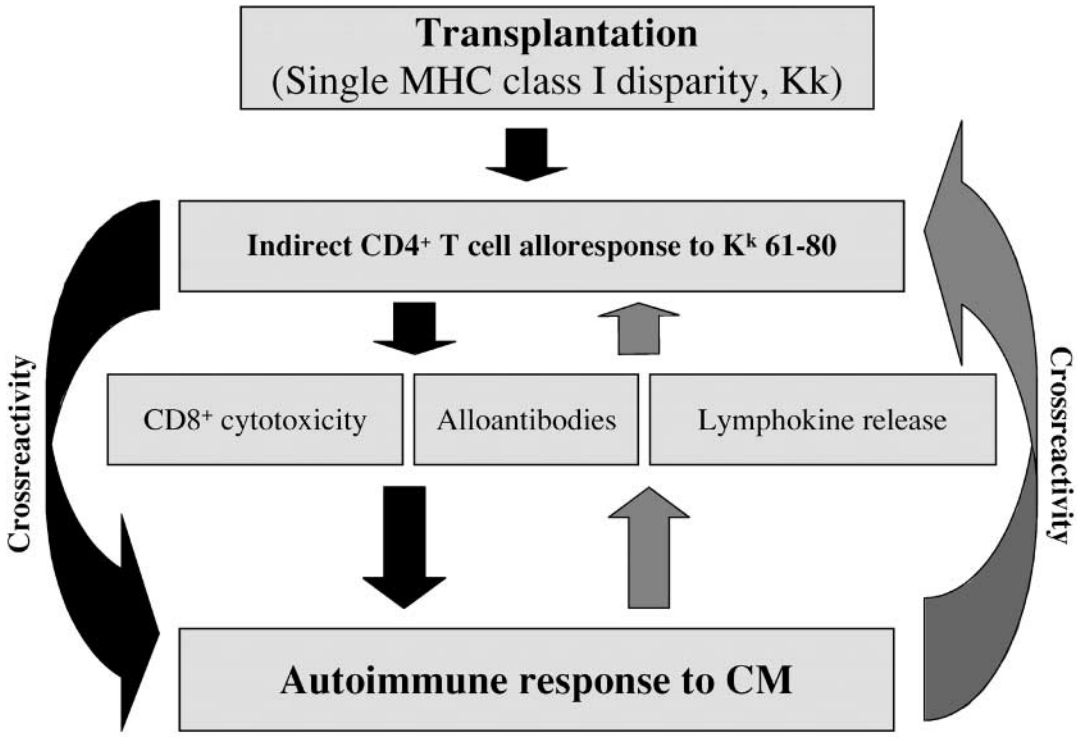

Figure 2. Possible mechanisms by which alloresponse can cause an autoimmune response to cardiac myosin (CM) in A.TL mice grafted with a single major histocompatibility complex (MHC) class I disparate (K^k) heart from A/J mice. (1) Indirect $CD4^+$ T cell alloresponse mediates heart transplant tissue damage by inducing activation of $CD8^+$ CTL and alloantibody production by B cells. Tissue damage causes the release of CM and its exogenous processing and presentation by recipient antigen-presenting cells (APCs) to CM-specific T cells. (2) Activated alloreactive T cells release inflammatory cytokines, which stimulate cardiac APCs. Up-regulation of MHC class II and/or antigen processing cause the presentation of new (formerly cryptic) determinants on CM and subsequent activation of undeleted (presumably low-affinity) anti-CM autoimmune T cells. (3) Cross-reactivity (antigen mimicry) between K^k 61-80 dominant allopeptide and a determinant on CM can result in intermolecular spreading of alloresponse to an autoimmune response. Shaded arrows suggest a positive feedback in which a sustained autoimmune response could eventually amplify/perpetuate the indirect alloresponse.

We tested whether either 1 or both of these mechanisms could also be associated with the activation and expansion of CM-specific T cells after cardiac allografting in mice.

We first investigated whether antigen mimicry could account for induction of autoimmunity after allotransplantation. In the A/J-A.TL combination, donor and recipient differ by a single MHC class I allele (K^k vs. K^s). We reasoned that if indirect $CD4^+$ T cell alloresponse to K^k were sufficient to elicit a response to CM, the K^k molecule might contain a peptide that could cross-react with a determinant on CM. Indirect alloresponse to K^k in recipient mice was directed to a dominant allopeptide corresponding to region 61-80, K^k 61-80 (EVF, unpublished observations). Interestingly, we found that immunization of A.TL mice with the K^k 61-80 allopeptide could elicit an autoimmune response to CM on its own, in the absence of transplantation. This showed that some alloreactive T cells directed to K^k 61-80 could also recognize a determinant on CM. This suggests that antigen mimicry could account for initiation of CM autoimmunity after engraftment of A.TL mice with an A/J heart. Identification of the CM determinant cross-reacting with K^k 61-80 is in progress in our laboratory.

Another possibility was that damage and myocyte death in the grafted heart tissue mediated by the alloresponse and/or the inflammation could cause the release of CM in the extracellular milieu and in the blood. In this scenario, it is likely that circulating CM would undergo exogenous processing and

MHC class II presentation by recipient "professional" APCs and subsequent T cell autoimmunity to this cardiac autoantigen. It is noteworthy that the mature form of CM is not expressed in the thymus during development.[66] This presumably accounts for the incomplete negative selection to this self-protein and the apparent survival of some high-affinity anti-CM autoreactive T cells. Since, under normal conditions, CM is never released in the periphery, corresponding autoreactive peripheral T cells should remain silent. However, these T cells may become activated after heart transplantation if CM is released from injured cardiac muscle tissue. To address this possibility, we collected and tested peripheral blood samples from heart-transplanted mice using an ELISA assay for the presence of CM. High titers of circulating CM were detected in heart-grafted mice (EVF, unpublished data), a finding that has also been reported in transplanted patients.[67] No CM was detected in the blood of non-transplanted mice and skin-grafted mice. Therefore, cardiac transplantation is associated with the release of CM in the circulation. Whether this phenomenon is actually responsible for the induction of autoimmunity to CM remains to be established.

Does Posttransplantation Autoimmunity Contribute to Allograft Rejection?

It was important to determine whether the induction of autoimmunity we observed in heart-grafted mice contributed to tissue damage and influenced the process of rejection. In a first set of experiments, A/J mice were immunized subcutaneously with purified CM protein emulsified in complete Freund's adjuvant. Twenty-one days later, these mice were engrafted with an allogeneic heart derived from MHC class I–mismatched A.TL. Pretransplantation sensitization with CM invariably resulted in accelerated rejection (no treatment: 9.4 ± 0.3; control antigen [OVA] treatment: 9.5 ± 0.6 days; CM treatment: 5.2 ± 0.6 days, $P < 0.001$).[10] The next set of experiments provided direct evidence that anti-CM T cell response induced after heart transplantation has the potential to play a critical role in the rejection process. A.TL mice were presensitized with CM in CFA and then grafted with a syngeneic heart. Strikingly, while control nontreated mice retained their heart grafts indefinitely, all CM-treated mice rejected syngeneic cardiac transplants within 40 days.[10] Histological examination of cardiac tissue revealed massive lymphocytic infiltration as well as myocyte dropout and necrosis typically observed in acutely rejected heart allotransplants. In turn, no apparent signs of cardiac allograft vasculopathy were detected, thus ruling out the presence of chronic rejection. This result demonstrated that, even in the absence of allogeneic stimulation, induction of an anti-myosin autoimmune response is sufficient to elicit acute graft rejection. It is important to note that in all CM sensitization experiments, mice were injected with murine CM in the absence of pertussis toxin, an adjuvant that is required for EAM induction. Consequently, there was no inflammatory cell infiltration in the recipient's own heart. Taken together, the results obtained in CM-sensitized mice strongly suggest that the CM response recorded in mice transplanted with an allogeneic heart is likely to contribute to the rejection of these transplants.

The most convincing evidence of the contribution of anti-CM autoimmune response to the rejection of allogeneic hearts in mice was provided by a series of experiments in which recipients were injected with CM emulsified in incomplete Freund's adjuvant (IFA). We observed that induction of a type 2 response (IL-4, IL-5) to CM can significantly prolong heart graft survival.[68] Together with the CM immunization experiments, this supports the view that T cell response to CM is an essential element of acute rejection of heart allografts.

Conclusion

Since the publication of the studies described in this paper, the presence of de novo immune responses to tissue-specific antigens expressed by the graft has been observed after transplantation of different allogeneic organs (heart, skin, lung) in various species (mice, mini-swine, humans).[10-12,69-70] In addition to our study, evidence of the role of autoimmunity in allograft rejection has been provided by D. Wilkes and his colleagues in a lung transplant model. In their study, they clearly demonstrate the induction of autoimmunity to collagen type V and provide evidence that modulation of this response can lead to increased survival of lung allografts in rodents.[11-13] Taken together with

ALLOGENEIC:

Intraspecies genetic variations.

TISSUE-SPECIFIC ANTIGEN:

A heterogenetic antigen with tissue specificity.

our results in the heart transplantation model, this suggests that induction of this type of immunity is likely to represent a general phenomenon in allotransplantation. Our results in both heart and skin graft models clearly indicate that this type of response is tightly associated with indirect alloreactivity. This suggests that spreading of indirect alloresponse to some key autoantigens expressed by the graft may be involved in the process of acute and/or chronic rejection mediated via this pathway. The mechanisms by which indirect alloimmunity causes an autoimmune reaction are still unclear. It is likely that, similar to autoimmune diseases, antigen mimicry and release of normally sequestered autoantigens may activate some undeleted autoreactive T cells in the periphery and initiate an autoimmune pathological cascade. This implies that modulating the immune response to these key tissue-specific antigens may be necessary to achieve immune tolerance to allogeneic transplants.

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