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Modulation of alloreactivity to MHC-derived peptides and transplantation tolerance

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1. ABSTRACT

The recognition by T cells of intact foreign MHC molecules at the surface of transplanted cells (direct pathway) was originally thought to represent the driving force behind acute rejection of allogeneic transplants. Over the past decade, however, a body of evidence has been provided demonstrating that T cell recognition of donor peptides presented by recipient APCs (indirect pathway) is sufficient on its own to ensure both acute and chronic rejection of allografts. While the direct allorecognition leads to an exceptionally vigorous inflammatory T cell response, it is thought to be short lived due to the rapid depletion of donor professional APCs and it can be controlled with a short course of immunosuppressive drugs including calcineurin inhibitors. In contrast, while the indirect alloresponse is oligoclonal and much weaker, it is long-lived and tends to spread to formerly cryptic determinants on donor and self-tissue specific antigens. This feature of indirect alloreactivity is presumably associated with the sustained presence of recipient professional APCs that can maintain a chronic inflammatory response similar to that observed in autoimmune diseases. Consequently, the indirect alloresponse may be more difficult to suppress than its direct counterpart. On the other hand, there is accumulating evidence showing that administration of alloantigen in a "tolerogenic fashion" mediates allograft acceptance via the activation of regulatory T cells recognizing donor antigens via the indirect allorecognition pathway. Apparently, these regulatory T cells can suppress both direct and indirect inflammatory T cell responses to donor antigens. This suggests that modulation of indirect alloreactivity may represent the best strategy to achieve long-term donor-specific tolerance to allotransplants.

2. INTRODUCTION

Historically, allorecognition was thought to be exclusively mediated by T lymphocytes recognizing determinants bound to intact donor MHC molecules displayed on the surface of transplanted cells (*direct allorecognition*). However, in the early 1980s, R Lechler's group published some results suggesting the relevance in T cell alloreactivity of alloantigen presentation by recipient APCs (1). The observation that activation of allospecific T cells can occur in the absence of passenger leukocytes following retransplantation of kidney allografts in rats suggested the involvement of an alternative "indirect" pathway of allorecognition as the trigger for host T cell sensitization. In 1992, we and others reported that after transplantation of allogeneic tissues, peptides derived from donor MHC molecules are regularly processed by host APCs and presented to alloreactive T cells, a phenomenon referred to as *indirect allorecognition (2-4)*. It is now firmly established that the presentation of alloMHC-derived peptides elicits vigorous $CD4^+$ T cell responses and represents an essential element of T cell immunity to transplanted tissues. The presence of T cells activated in an indirect fashion is sufficient to cause acute rejection of skin grafts and is thought to play a pivotal role in the initiation of chronic rejection of allotransplants. This underscores the need for selective immune therapies designed to prevent or suppress indirect T cell alloresponses in transplant recipients. It is important to note that evidence has been provided supporting the involvement in indirect alloreactivity of other non-MHC determinants including those derived from minor histocompatibility proteins and tissue-specific autoantigens (5-9). However, while a

number of studies have clearly demonstrated the role of MHC peptide determinants in allograft rejection, the precise contribution of indirect presentation of non-MHC antigens to this process remains unclear. This explains why most attempts to modulate indirect alloreactivity have focused on MHC peptides. In the present article, we review different studies describing the modulation of indirect alloreactivity in vivo using peptides derived from polymorphic and conserved regions of donor MHC class I and II molecules. Based upon this information, we briefly discuss the mechanisms by which T cell indirect allorecognition can drive the recipient immune system towards rejection or tolerance of transplants.

3. THE CONTRIBUTION OF INDIRECT ALLORECOGNITION TO THE ALLORESPONSE AND ALLOTRANSPLANT REJECTION

Following allotransplantation, indirect presentation of donor antigens induces the rapid expansion of allospecific $CD4^+$ Th1 cells producing pro-inflammatory cytokines i.e. IL-2, γ-IFN, IL-12 (10-16). These activated T cells provide help for the differentiation of anti-donor $CD8^+$ cytotoxic T cells (17-19), for the production of allospecific antibodies by B cells (20-22) and that they mediate DTH reactions (23). This suggests that this type of alloresponse can contribute to the rejection of allogeneic transplants. In support of this view, Fangmann et al. initially reported that sensitization of recipients to allo-MHC peptides results in accelerated kidney graft rejection in rats. Subsequently, studies in Auchincloss's laboratory showed that MHC class II-deficient skin transplants that are theoretically incapable of inducing a $CD4^+$ T cell direct alloresponse, are acutely rejected (17-19, 24). In another study, A. Valujskikh and P. Heeger isolated and characterized a Th1 T cell line from BALB/c recipient mice ($H\text{-}2^d$) of B10.A ($H\text{-}2^a$) skin transplant that was specific for a defined immunodominant, self-restricted MHC class II allopeptide, $I\text{-}A^k$ beta 58-71. When transferred into BALB/c SCID mice recipients of B10.A skin allografts, this cell line specifically induced rejection of previously acccepted skin grafts characterized by the presence of Th1 cytokines, macrophage infiltration, and extensive fibrosis. Recall immune responses and histological examination of the rejecting skin revealed only the presence of the peptide-specific $CD4^+$ T cells within the recipient animals, with no evidence of a direct pathway alloresponse (25, 26). Finally, our laboratory reported that the rejection of corneal transplants, naturally devoid of MHC class II expression at the time of transplantation, is mediated exclusively by $CD4^+$ T cells recognizing donor antigens in an indirect manner (27). Taken together, these studies demonstrate that indirect allorecognition by $CD4^+$ T cells is sufficient to initiate an alloimmune response leading to acute graft rejection.

Two lines of evidence support the view that indirect allorecognition may represent the driving force behind the chronic form of allograft rejection: 1) after transplantation, the frequency of T cells recognizing intact alloMHC declines with time regardless of the presence of chronic rejection and, 2) the presence of chronic rejection in heart, kidney and lung transplant models is generally correlated with raised frequencies of T cells with indirect anti-donor specificity, a phenomenon thought to result from antigen spreading (28-39). It is possible that slow and progressive deterioration of the graft tissue could result in shedding of donor- and self-proteins, thereby promoting chronic inflammation via induction of indirect alloresponses to newly presented, formerly cryptic, determinants. Until now, the actual contribution of indirect alloreactivity to chronic rejection remains hypothetical. The most compelling evidence in support of the potential involvement of indirect alloreactivity in chronic rejection has been provided by J. Madsen's group (40). In this study, induction of an indirect alloimmune response via immunization of pigs with an immunodominant donor MHC class I peptide accelerated the onset and increased the severity of cardiac allograft vasculopathy (CAV) of transplanted hearts.

4. INDIRECT ALLORECOGNITION OF MHC DETERMINANTS: THE RULES OF IMMUNODOMINANCE

The vast majority of the MHC molecules are filled with peptides of self-origin, as revealed by chemical elution and analysis of the peptides bound to the groove of MHC molecules (41, 42). It is important to note that a large proportion of these self-peptides are derived from MHC glycoproteins themselves (43). Indeed, there is a body of evidence showing that self-MHC class I and II molecules are regularly processed and presented in peptide form in a MHC context at the surface of Aantigen presenting cells (APCs) (44-48). While a few dominant self-MHC peptides induce central tolerance in the developing thymus, many self-MHC peptides (cryptic self-peptides) are not presented efficiently enough to ensure deletion of corresponding T cells (46-48). Studies by Moudgil et al. indicate that these cryptic self-peptides play an important role in positive selection (49). This implies that thymic positive selection of T cells to self-MHC peptides during ontogeny may be essential to the shaping of the T cell repertoire to related peptides on allogeneic MHC molecules. This may explain the bias of indirect allorecognition toward determinants derived from MHC molecules. In this scenario, one would expect that T cell responses to donor MHC peptides induced by allotransplantation could be associated with simultaneous priming of T cells to cross-reactive self i.e. recipient-derived cryptic MHC peptides. Alternatively, host T cell response to self-MHC determinants could result in sensitization to some other peptides on allogeneic, donor MHC molecules. In support of this view, T cell-mediated indirect alloresponse to a dominant donor MHC determinant in skin-grafted mice has been shown to induce a concomitant disruption of tolerance to a cross-reactive peptide on recipient (self) MHC (50). In this model, immunization of recipients with the donor MHC peptide was sufficient to disrupt T cell tolerance to a dominant self-MHC determinant. Alternatively, Soares et al., have shown that immunization of mice with a self-MHC derived peptide can prime their T cells toward cross-reactive determinants on an allogeneic MHC molecule, thereby sensitizing them to an allograft (51). These two examples suggest that the T cell repertoires to self- and allo-MHC

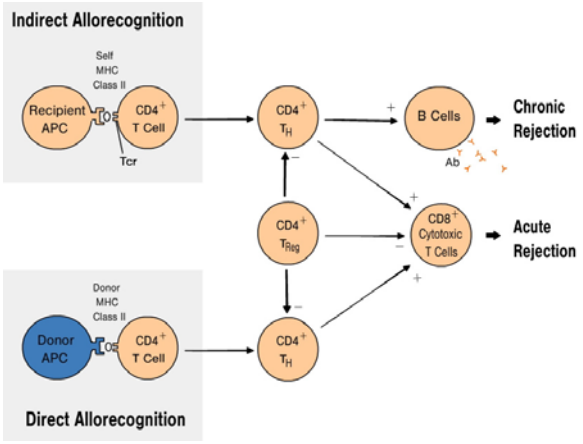

Figure 1. Schematic view of a model for T cell allorecognition in allotransplant rejection

determinants are closely related. Therefore, cross-recognition by T cells of recipient and donor MHC determinants may represent an essential element of the thymic selection and peripheral sensitization of T cells in indirect allorecognition.

We and others have investigated the extent of heterogeneity of specificity involved in the indirect allorecognition of allogeneic MHC molecules. To address this, a series of overlapping MHC peptides progressing along the sequence of different mouse MHC class I and II proteins by single amino acid steps was synthesized. We then systematically mapped all potential determinants on donor MHC to which indirect T cell responses were generated *in vivo* following skin transplantation. Host's MHC-restricted T cell alloresponses were invariably directed to a single or a few dominant determinants on donor MHC antigen. It is noteworthy that depending upon the donor/recipient combination, different regions of MHC were found immunogenic. These allo-immunogenic determinants were, however, systematically located in polymorphic regions of donor MHC molecules (47, 52). Liu et al. reported similar restriction of T cell responses via the indirect allorecognition pathway to a dominant determinant on HLA DR1 molecule (53-55). Furthermore, in this human model, a limited usage of T cell receptor (TCR) V_β genes by T cells responding to allopeptides (53) was observed. Collectively, these studies show that while direct allorecognition is characterized by its heterogeneity, indirect allorecognition follows the rules of immunodominance in that it is restricted to a few dominant determinants on donor MHC. It is noteworthy, however, that at late time points after transplantation, the hierarchy of determinants on donor MHC can be altered, (32, 36, 56, 57) a phenomenon resulting in the induction of T cell response to formerly cryptic determinants on the donor MHC molecule. Therefore, antigen spreading, a phenomenon previously described in autoimmune diseases (58-60), is also a feature of indirect T cell allorecognition during transplant rejection. Diversification of indirect allorecognition to new determinants on donor MHC has been regularly detected in patients undergoing chronic allograft rejection (36, 56). This suggests that antigen spreading of indirect alloreactivity may contribute to the induction and/or maintenance of a chronic form of transplant rejection (32, 56).

5. INDIRECT ALLORECOGNITION AND TRANSPLANTATION TOLERANCE

Some studies support the view that tolerance to alloantigens may arise from regulatory T cells activated via the indirect pathway of allorecognition and capable of suppressing direct alloresponses. There is accumulating evidence from studies in autoimmune disease models, that $CD4^+$ T cells expressing high levels of CD25 can promote tolerance *in vivo* (61). In mouse models, elimination of innate $CD4^+CD25^{high}$ T cells (also called Tregs) results in the spontaneous development of autoimmune pathologies (61). These innate Tregs initially generated in the thymus are not antigen-specific and require cell-cell interaction with their "target". On the other hand, peripherally activated adaptive regulatory T cells called Tr1/TH3 cells are specific for their antigen and suppress inflammatory T cells via the secreting of soluble factors including TGFβ2 and IL-10 cytokines. In transplantation, it has been known for some time that tolerance generated to an alloantigen can suppress the response to another alloantigen presented on the same APCs; a phenomenon called linked suppression (62-64). Both indirect allorecognition and type 2 cytokines have been implicated in this phenomenon. In another study by Yamada et al it was observed that survival of cardiac allografts induced by anti-CD40L/CTLA4-Ig costimulation blockade requires the presence of $CD4^+$ T cells activated via indirect allorecognition (65). Taken together, these studies suggest that activation/differentiation of some regulatory T cells via the indirect allorecognition pathway can induce immune tolerance to alloantigen and achieve long-term graft survival. However, the mechanisms underlying this form of T cell regulation are unclear, and the nature of the antigen peptides recognized by regulatory T cells is still unknown.

6. MODULATION OF ALLOIMMUNITY AND ALLOGRAFT REJECTION VIA ADMINISTRATION OF RECIPIENTS WITH SYNTHETIC MHC-DERIVED PEPTIDES

Donor antigen-specific tolerization of T cells mediating a direct alloresponse may be difficult to design owing to the polyclonal and polyspecific nature of this response. In contrast, the indirect alloresponse is thought to involve a limited set of alloreactive T cells expressing selected TCR genes and recognizing a few dominant determinants on allogeneic MHC molecules (4, 66-68). This feature of indirect alloreactivity suggests that peptide-based strategies could be designed to manipulate this type of alloresponse *in* vivo similarly to what is being attempted in autoimmune disease models. Based upon this principle, a number of laboratories have administered transplant recipients with synthetic peptides derived from MHC class I and II molecules in order to modulate the alloimmune response and subsequent allograft rejection.

6.1. Peptides from polymorphic regions of MHC class I proteins

Significant prolongation of allograft survival has been accomplished upon intrathymic injection of MHC class I antigens (69-71) and allopeptides (72-75) in rats. This was associated with predominant expression of Th2 cytokines in the graft, whereas control animals expressed Th1 cytokines, a result suggesting that this phenomenon was caused by immune deviation (76). These peptides were more efficacious in promoting long-term allograft survival when coadministered along with a single dose of anti-lymphocyte serum (ALS). Donor-specific tolerance was confirmed by acceptance of a second cardiac transplant from the same donor, while third-party grafts were acutely rejected (74). In another study, ACI rats were injected intravenously with syngeneic dendritic cells (DCs) previously pulsed with a dominant alloMHC class I (P5, RT1.A(u)) peptide of Wistar Furth (WF) origin. T cells from these rats were then inoculated intrathymically to a naïve ACI rat. This treatment resulted in a permanent and donor specific acceptance of pancreatic islets from WF donors (77). Intravenous injection of donor MHC class I P5 peptide-activated T-cells combined with transient ALS immunosuppression also induced transplant tolerance. In the same model, intravenous administration of P5 peptide-pulsed DCs was also shown to ensure tolerance to WF transplanted hearts (78). Other investigators (79, 80) also achieved permanent graft survival when other peptides of the same MHC class I molecule ($RT1.A^a$) were administered in conjunction with a single dose of anti-lymphocyte serum prior to cardiac transplantation in a DA to LEW rat model. In addition, oral feeding of peptide P5 in combination with a short course of Cyclosporin A (CsA) prolonged graft survival of DA cardiac allografts in Lewis recipient rats (81). More recently, intratracheal delivery of a peptide derived from a variable region of the mouse MHC Class I molecule K^b (region 54-68) was shown to induce reduce inflammatory responses to and long-term survival of allogeneic cardiac grafts presumably via the generation of regulatory T cells (82). In another set of studies, human MHC class I-derived peptides (HLA-B7.75-84 and HLA-B2702.75-84) referred to as ALLOTRAP, displayed some immunomodulatory effects in different animal models (83-85). D-isomers of these peptides (more resistant to proteolytic degradation in vivo) displayed more potency than their L-isomers counterparts (86). Apparently, these peptides produced their effect by preventing the differentiation of precursor $CD8^+$ T cells into effector cytotoxic T cells (CTLs), by inhibiting lysis by established CTLs, and by suppressing natural killer cell–mediated cytotoxicity (87). Apparently, these MHC Class I peptides could bind to two proteins of molecular weights 70 and 74 Kd (88) and mediated their immunomodulatory effects by interacting with natural killer cell inhibitory receptors and heme oxygenase-1, an inducible heat shock protein (HSP) (89).

6.2. Peptides from polymorphic regions of MHC class II proteins

Administration of peptides derived from MHC Class II polymorphic sequences have also been shown to exert some suppressive effects on alloimmunity when administered via either intrathymic or oral route (20). Seminal studies by M. Sayegh et al. have shown that intrathymic injection of a single immunodominant MHC Class II peptide could result in specific inhibition of primed T-cell proliferative responses to the corresponding determinant in vitro (90) as well as inhibition of delayed-type hypersensitivity (DTH) responses in vivo (91). Here again oral tolerance was associated with a state of "immune deviation" characterized by a predominance of Th2 cytokine production (92). Similarly, preoperative administration of LEW recipients with the WF-specific MHC Class II peptides RT1.B2 in combination with low-dose CsA induced prolongation of allograft survival of WF small bowel transplantation (93). In another set of studies by C. Leguern's and our group, intracellular expression of previously transduced donor MHC class II molecules in recipient bone marrow cells was shown to induce transplant tolerance in pigs and mice. Animals that received these transgenic bone marrow cells were tolerant to allotransplants displaying this MHC class II transgene. Apparently, tolerance in this model was associated with processing of the transgenic alloMHC class II molecule and its presentation as peptides on host APCs' MHC class II molecules. The mechanisms by which the indirect presentation of donor MHC class II peptides induces transplant tolerance in this model are extensively described in C. Leguern's article in this issue.

6.3. Peptides from conserved regions of MHC modecules

Many naturally processed peptides found in the grooves of cell surface MHC class II molecules are derived from non-polymorphic regions of both MHC class I and class II amino acid sequences (42, 43). Three peptides derived from a conserved region of the MHC class II chain inhibited rat MLR in a dose-dependent manner (94, 95). The human HLA-DQA1*0101 peptide was shown to inhibit both human and mouse MLRs (96). Finally, MHC-derived peptides corresponding to CD4 and CD8 interacting regions have also been used to modulate immune functions. For example, peptides corresponding to the CD4 interacting regions of MHC class II molecules could directly interfere with CD4 interactions thereby suppressing T helper responses (97). Peptide analogues that mimic the putative interaction sites of CD8 and the MHC class I molecule prolonged skin allografts in a MHC class I–mismatched mouse model. (98). Additionally, a synthetic peptide with a sequence derived from the MHC class II–associated invariant chain peptide inhibited antigen-specific T-cell response in vitro and in vivo following immunization (99). Apparently, this peptide inhibited the loading of antigenic peptides onto MHC class II molecules and the subsequent expression of the MHC molecule-peptide complexes at the cell surface.

7. FUTURE PERSPECTIVES

The studies described in this paper show that indirect recognition of donor-derived peptides plays a critical role in the initiation and regulation of alloimmune T cell responses in vivo. Actually, the inflammatory T cell

response to allogeneic MHC peptides presented by recipient APCs is sufficient to ensure acute and chronic rejection of most allotransplants. On the other hand, several lines of evidence have been provided showing that transplantation tolerance via DST or costimulation blockade is mediated by regulatory T cells activated in an indirect fashion. Taken together, these observations suggest that manipulation of indirect T cell alloresponses may be used to prevent allotransplant rejection. Compelling evidence that tolerance induction of the indirect pathway favors graft survival was obtained from experiments in which recipients were treated with donor MHC peptides. The mechanisms by which these MHC-derived peptides mediate their tolerogenic effects are still ill defined. There is, however, increasing evidence suggesting that, under appropriate conditions, the presentation of MHC-derived peptides to T cells may play a critical role in the activation of regulatory T cells that can reduce and maintain robust tolerance to allotransplants. A number of studies show that tolerance to key allodeterminants can spread to other donor antigens present on the same transplant. This suggests that administration of recipients with a single or a few dominant allopeptides given in a "tolerogenic fashion" may be sufficient to accomplish immunological tolerance to allogeneic transplants.

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