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Spreading of T Cell Responses to Autoantigens after Allotransplantation and Its Potential Involvement in the Rejection Process

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Peripheral T lymphocytes recognize protein antigens in the form of peptides bound to self–major histocompatibility complex (self-MHC) molecules expressed on the surface of antigen-presenting cells (APCs). During ontogeny, thymic T cells interacting with efficiently processed/presented dominant self-peptides with high affinity are either deleted or inactivated.[1] In contrast, thymocytes, which recognize poorly processed peptides (i.e., cryptic determinants), escape clonal elimination and presumably undergo positive selection.[2] In addition, it is possible that certain self-proteins may be initially cryptic altogether because they are sequestered or not expressed at the time of thymic selection. Hence, it is likely that some T cells displaying low affinity for some dominant self-peptides differentiate into mature T cells and contribute to the establishment of the peripheral T cell repertoire in adults. It is therefore clear that thymic selection is insufficient to remove all potentially harmful autoimmune T cells and that this process is only a component of the multiple mechanisms designed to prevent autoimmune pathology in the periphery. Indeed, a number of phenomena, including peripheral deletion through activation-induced cell death and anergy, are thought to contribute to the maintenance of tolerance to self-antigens in the periphery. However, there is a body of evidence showing that any combination of events that may lower the threshold of activation of some low-affinity T cells specific for dominant self-determinants or promote the processing and presentation of formerly cryptic self-peptides can result in the initiation of an autoimmune T cell response in adult individuals.[3,4] Yet induction of an autoreactive T cell response is necessary but not sufficient for the initiation of an autoimmune pathology.

It is firmly established that infection by certain microorganisms can trigger an autoimmune process presumably via the presentation of some microbial peptides mimicking self-determinants on autoantigens. It is, however, increasingly evident that activation of T cells by these peptides is not sufficient on its own to initiate an autoimmune pathology. It is likely that local inflammation, associated with massive release of inflammatory cytokines by infiltrating phagocytes and T cells, is also an essential element of the induction/perpetuation of an autoimmune disease. This is especially true in the case of chronic inflammatory autoimmune diseases such as multiple sclerosis and autoimmune diabetes.[5]

During the past years, our laboratory has published a series of papers that described the activation of autoreactive peripheral T cells after transplantation of allogeneic tissues. Initially, we showed the breakdown of T cell tolerance to a dominant MHC class I peptide derived from self-MHC molecules after injection of allogeneic splenocytes. In this model, we obtained strong circumstantial evidence indicating that this autoimmune response resulted from the presentation of a cross-reactive determinant on donor MHC by recipient APCs (i.e.,

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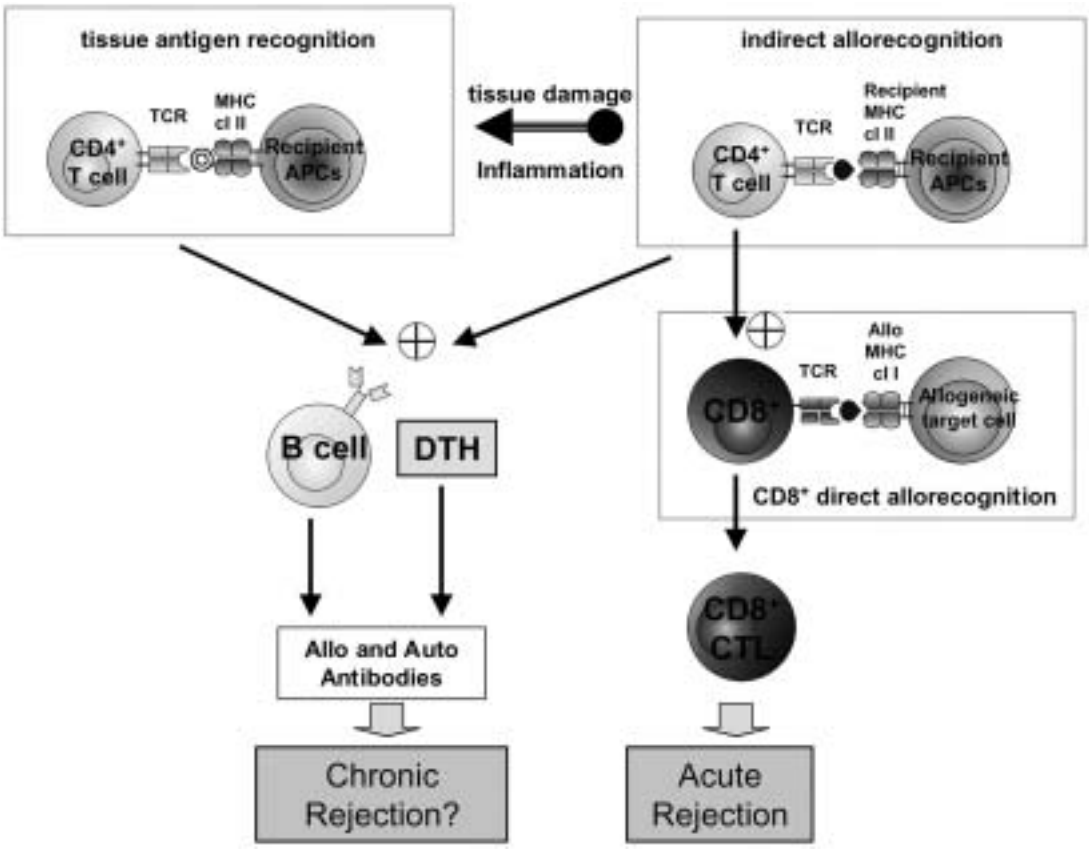

Figure 1. Potential roles of indirect allorecognition in acute and chronic allograft rejection.

via indirect allorecognition; Fig. 1).[6] In a subsequent study, we showed the induction of autoimmunity to cardiac myosin (CM) protein after transplantation of allogeneic hearts in mice. Importantly, T cell reactivity to CM is known to cause cardiac tissue injury and trigger autoimmune myocarditis.[7] This suggested that the autoreactivity to CM found in cardiac transplanted individuals could mediate heart tissue injury in a fashion similar to that observed in the autoimmune pathology, thereby contributing to the rejection of these grafts. In support of this view, we showed that modulation of anti-CM response in recipients could prolong the survival of cardiac allografts in the absence of any immunosuppressive treatment.[8] It is noteworthy that induction of $CD4^+$ T cell–mediated CM autoreactivity was dependent on the presence of an indirect alloresponse.[8] Most important, we observed that a syngeneic heart transplant was rejected in mice presensitized to CM.[7] This result demonstrated that in the absence of an alloresponse, CM autoimmunity is sufficient to ensure the rejection of a cardiac allograft. In turn, surprisingly, in allografted mice displaying a CM response, we never detected any sign of infiltration and autoimmune injury in their native heart. Indeed, the absence of trauma and of local inflammation in the nontransplanted heart may have resulted in the lack of chemokine and inflammatory cytokine production and of adhesion molecule upregulation, thereby accounting for the absence of infiltration by immunocompetent cells. This observation further supports the view that induction of a T cell response to the target autoantigen is required but not sufficient to lead to an autoimmune pathology.

Since our initial description of autoreactive T cell response in allotransplanted mice, a number of groups have reported similar findings in lung, skin,

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and heart transplant models studied in mice, rats, miniswines, and humans.[7-12] This suggests that post-transplantation autoimmunity may represent a general phenomenon in allotransplantation. Strikingly, in the lung transplant model studied by D. Wilkes's group, the modulation of T cell response to collagen type V autoantigen resulted in long-term survival of these allografts.[12] Together with our results, this observation strongly suggests that this type of response is an essential element leading to the rejection of allogeneic solid transplants. Yet the mechanisms by which indirect alloimmunity causes an autoimmune reaction remain unknown. It is possible that similar to autoimmune diseases, antigen mimicry and/or release of formally "sequestered" tissue/organ-specific proteins/peptides could stimulate some undeleted autoreactive T cells in the periphery and trigger an autoimmune pathological process. Our results in both heart and skin graft models[13] clearly indicate that this type of response results from indirect alloreactivity. This suggests that spreading of indirect alloresponse to certain tissue antigens expressed by the graft may be involved in the process of acute and/or chronic rejection mediated via this route of allorecognition. This further emphasizes the need for novel strategies designed to prevent or block the indirect alloresponse and subsequent spreading of T cell alloreactivity to transplant-tissue-specific antigens.

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