FORUM: Links between Autoimmunity and Alloimmunity

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Introduction

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By convention, autoimmunity and alloimmunity are treated as separate subdisciplines of immunologic study. The presumption is that the 2 immune response systems operate independently via unrelated mechanisms. To the informed immunology enthusiast, this ought to be a curious presumption. Clearly, both self-reactive and alloreactive T cells are distributed throughout the periphery of the body, where they would have access to relevent antigens. Furthermore, tissue damage, also known as "danger," is a strong stimulus for T cell responses to antigens that may be present at a site of inflammation. Finally, to the cells of the immune system, an antigen is an antigen. Given these facts, why isn't autoimmunity commonly associated with alloimmunity (or any other destructive immune response within tissues)?

Perhaps it is. Perhaps our time-honored presumptions regarding the lack of relationship between autoimmunity and alloimmunity are simply incorrect. Data to support this possibility are provided by the independent studies of at least 4 investigators, whose work is highlighted in this forum. David Wilkes has demonstrated that immune responses to allogeneic lung tissues involve concurrent responses to a monomorphic matrix protein, collagen V. Gilles Benichou, who recently reviewed his studies in *Graft* (Vol. 5, 2002), has demonstrated that immune responses to allogeneic cardiac tissues involve concurrent responses to myosin, a monomorphic protein that is critical for myocyte function. Indeed, manipulation of the antimyosin response can have a strong influence on the progression of the alloimmune response in cardiac allograft recipients. Reciprocally, Jake Demetris has demonstrated that the induction of allograft tolerance can protect recipients from the development of autoimmune responses induced by an unrelated stimulus, HgCl2. Peter Heeger, another active investigator in this arena, will discuss the immunologic issues highlighted by these experimental observations.

The common denominator of all these studies is the poorly understood phenomenon of immunologic tolerance. Among the cast of players in the tolerance story are regulatory T cells, and the behavior of these T cells appears to provide a link between autoimmunity and alloimmunity. Regulatory T cells are emerging as key players in many immune responses, ranging from the active immune indifference toward self-proteins that marks homeostatic immune conditions to the array of immune dispositions that develop toward antigens under conditions of immunologic challenge. This array includes the destructive, IFNγ, and TNF-associated immune disposition that is adopted toward alloantigens in rejecting allografts, as well as the permissive, TGF-β and IL-10-associated immune disposition that is adopted toward them in accepted allografts.

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The integration of regulatory T cells into working models of immune reactivity requires a philosophic shift away from traditional conceptualizations that promote on-off, light-switch-like mechanisms of proinflammatory immune activation, toward newer conceptualizations that invoke adjustable, rheostat-like mechanisms of counterbalanced proinflammatory and anti-inflammatory immune activation. In this scheme, antigen simultaneously induces various degrees of both proinflammatory and anti-inflammatory immune activity, and the apparent immune response reflects the balance between these activities. For autoantigens, the balance commonly favors a net anti-inflammatory disposition. For alloantigens, the balance usually favors a net proinflammatory disposition. Similar counterbalanced immune activation mechanisms can develop concurrently for several antigens, and it should be expected that the balanced immune responses directed at one antigen may influence the balances developed for other colocalized antigens. In allograft tissues, colocalized antigens would include both unique alloantigens and shared autoantigens. Under these conditions, when opposite immune dispositions are displayed toward the 2 colocalized antigenic systems, immune responses become especially interesting.

Thus, the information in this forum may illustrate how the anti-inflammatory disposition toward self-antigens and the proinflammatory disposition toward colocalized alloantigens may affect one another. These experimental observations hint at a conceptual adjustment that integrates previously isolated subdisciplines of immunology, that is, autoimmunity and alloimmunity. Furthermore, these studies move toward the frontier of immunologic understanding by exploring how immunity operates beyond the commonly explored intracellular level and within the relatively unexplored intrasystems level sometimes referred to as systems biology. For these reasons, the information presented in this forum should be of particular interest not only to transplant immunologists but to immunologists in general.