T Cell Autoreactivity by Design: A Theoretical Framework for Understanding Tolerance, Autoimmunity, and Transplant Rejection

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Graft 2003; 6; 33
DOI: 10.1177/1522162802239755

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Self-reactive T lymphocytes are largely but not entirely eliminated from the host's T cell repertoire during development through central thymic deletion. Standard immunologic paradigms suggest that the residual autoreactive T cells represent a threat to the host as they have the potential to initiate autoimmune disease. An alternative viewpoint is that the autoreactive T cells are released into the periphery by design and that they participate in the maintenance of self-tolerance through regulatory mechanisms. This theoretical framework is consistent with many of the experimental observations made in tolerant allograft recipients and provides a foundation through which one can make sense of the recently described interrelationship between autoreactive T cells and alloreactive T cells in transplantation immunobiology.

Keywords: allograft rejection; autoimmunity; T lymphocytes; tolerance; regulatory cells

During development in the thymus, T lymphocytes initially undergo positive selection so as to be able to preferentially recognize peptides expressed in the context of self-major histocompatibility complex (MHC) molecules.[1-4] Subsequently, the process of intrathymic negative selection results in deletion of T cell clones with "high affinity" for many self-antigens. The end result is that the mature T cell repertoire is capable of responding to an enormous variety of foreign antigens that it has not previously encountered.[1-4] Nonetheless, central deletion of self-reactive T cells is incomplete, and many relatively low-affinity autoreactive T cells "escape" into the periphery.[5] Standard paradigms in immunology view these escapees as an unwanted consequence of T cell development and as problematic to the host. In this view, the immune system must make use of a variety of peripheral tolerance mechanisms, including deletion, ignorance, anergy, suppression, and end organ resistance, to control these potentially pathogenic T cells. Autoimmune disease results under rare circumstances in which such tolerance mechanisms are overcome. Although this paradigm can explain many experimental observations, it falls short of providing a comprehensive basis for our understanding of natural tolerance to self-antigens and of experimentally induced tolerance, particularly in light of some recent observations regarding the development of autoreactive T cells following allograft transplantation. It is the goal of this commentary to provide an alternative framework within which one can incorporate the known experimental findings and potentially better account for them. It is hoped that the model will provoke thought and discussion.

Emerging results from multiple laboratories showing that autoreactive T cells can exhibit regulatory properties (reviewed in ref. 6) raise the possibility that one function of the T cell repertoire selection process is to seed the periphery with

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DOI: 10.1177/1522162802239755

Table 1 | **KEY FEATURES OF AUTOIMMUNITY BY DESIGN THEORY**

Autoreactive T cells are released from the thymus by design
Autoreactivity is not equivalent to autoimmune disease
Autoreactive T cells usually prevent inflammation through dominant regulatory mechanisms but can be corrupted into becoming pathogenic
The lack of inflammation is an active process involving autoreactive regulatory T cells interacting with parenchymal tissues
The inflammatory (or quiescent) states of individual microenvironments are regulated independently
The phenotypic expression of inflammation at a given site is dependent on the presence or absence of proinflammatory versus tolerogenic signals expressed by cells of that organ and the relative numbers of pathogenic versus regulatory T cells at that site

autoreactive T cells. Based on this postulate, one can then hypothesize that autoreactive T cells are present by design and play an active role in the maintenance of self-tolerance through dominant, interactive regulatory mechanisms (Table 1 and Fig. 1A). This concept stands in contradistinction to the standard view that autoreactive T cells represent an unwanted side effect of T cell ontogeny that must be controlled to prevent autoimmune disease. The "autoimmunity by design" model assumes that autoreactivity is not equivalent to autoimmune disease; the specificity of a T cell does not define its functional capabilities. Implicit in the model is the concept that a naive T cell has the ability to differentiate into an effector cell with proinflammatory features (e.g., an IFNγ-producing TH1 cell) or into one with a protective phenotype (e.g., a TGF-β- or IL-10-producing Tr1 cell) depending on the specific environmental conditions encountered by the lymphocyte. In this view, the process of T cell ontogeny has evolved such that a small number of positively selected, autoreactive T cells are released from the thymus rather than escape from the thymic deletion process. The T cell receptors (TCRs) expressed by the autoreactive T cells are likely to have relatively low affinities for their ligands (as the T cells expressing the highest affinity TCRs are presumably deleted centrally). There are some data to suggest that a proportion of these autoreactive T cells can be preconditioned centrally to have a regulatory or suppressor phenotype after encountering self-antigens on thymic antigen-presenting cells (APCs).[6,7] However, as all self-antigens are not expressed in the thymus, some autoreactive T cells are likely to be released into the periphery as naive precursors. These latter autoreactive T cells are hypothesized to home to secondary lymphoid tissues, where they have the opportunity to interact with self-APCs expressing self-antigens. If and when the naive autoreactive T cells encounter their antigenic ligand on a nonactivated (or immature) APC, they have the potential to differentiate into a regulatory or suppressor cell.

Activated, regulatory T cells (either deriving directly from the thymus or after priming in the periphery) would then circulate widely where they could reencounter their antigenic ligands expressed on normal tissues. These interactive events are hypothesized to result in reciprocal down-regulatory signals: The autoreactive T cells are hypothesized to encounter self-antigen in the absence of proinflammatory stimuli (i.e., no costimulation) and thereby maintain and reinforce their anergic/suppressive phenotype. The induced regulatory characteristics would prevent activation or effector function of small numbers of other potentially pathogenic T cells that infiltrate the organ, either through direct cell-cell contact or through bystander (possibly cytokine-mediated) effects. At the same time, signals from the regulatory T cells delivered to vascular cells, parenchymal cells, and/or bone marrow–derived APCs of the organ would theoretically maintain their quiescent, tolerogenic state (possibly through upregulation of protective genes or inducing APCs to differentiate into a tolerogenic phenotype). The end result would be a self-perpetuating, protective microenvironment that is dependent on the interaction between the regulatory T cells and the induced protective state of the organ. It is hypothesized that the autoreactive regulatory T cells are required to induce the tolerant state but may not be sufficient to maintain it; induced alterations

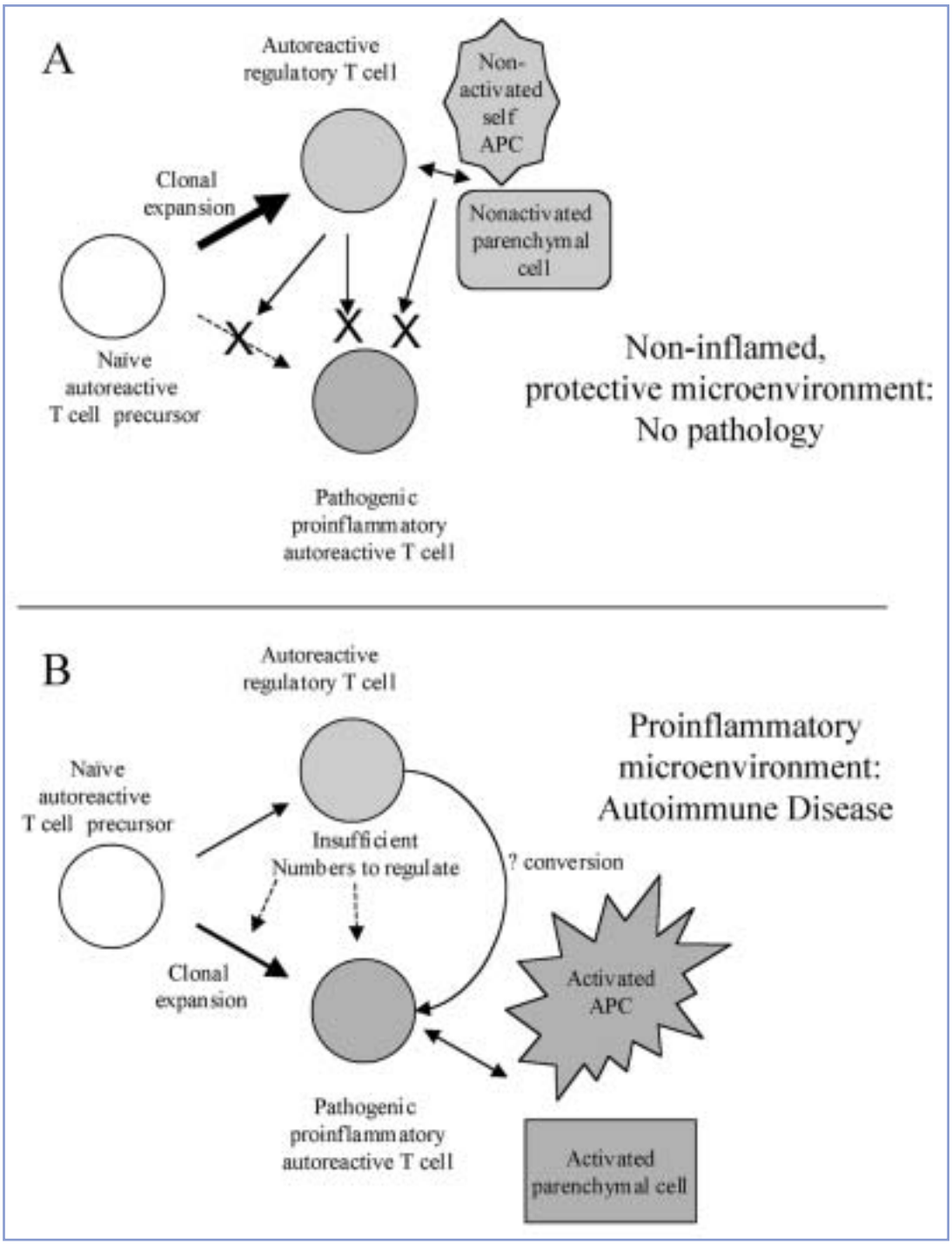

Figure 1. Schematic depiction of autoimmunity by design in the absence (A) or the presence (B) of autoimmune disease. (A) Naive autoreactive T cell precursors emerge from the thymus and differentiate into regulatory T cells. These regulatory T cells interact with quiescent or immature antigen-presenting cells (APCs) and normal parenchymal cells to create a protective microenvironment. This interactive process prevents activation and effector function of any potentially pathogenic autoreactive T cells. (B) Under unusual proinflammatory conditions, pathogenic, autoreactive T cells expand in a proinflammatory microenvironment (composed of activated APCs, chemoattractant signals, and the absence of protective signals) to an extent that cannot be controlled by regulatory cells and results in autoimmune disease.

in the peripheral organ tissue cells and/or APCs such that they have protective or tolerogenic properties would be necessary for maintenance. In contrast to standard paradigms, the hypothesis suggests that the lack of inflammation is an active process, involving an ever-evolving interaction between autoreactive (regulatory) T cells and the "normal" tissues of the peripheral organs. The immune system must overcome these active, protective processes to mediate local inflammation. Further implicit in this paradigm is the concept that individual microenvironments are regulated independently—how the immune system behaves in one location may not be identical to how it behaves at a different site in the organism (i.e., inflammation can be localized to a single site with the remainder of the host being unaffected).

Is the autoimmunity by design framework consistent with experimental observations made in tolerant animals? Certainly, normal hosts, presumably tolerant to self-antigens, have T cell repertoires containing autoreactive T cells, some of which are naive and others of which seem to have regulatory properties.[6-8] Increasing evidence is accumulating to show that regulatory T cells are detectable in both mice and humans and that depletion of certain subpopulations of regulatory T cells (i.e., CD25+ and CD4+) can result in autoimmune pathology (although the specificity of these cells has not been defined in most studies; see the review in ref. 9). Studies from at least 1 transplant model show that normal, donor organs contain T cells with regulatory potential that have the capability of repopulating an immunodeficient recipient and can mediate tolerance.[10] In vivo expansion of autoreactive T cells can be elicited experimentally and can result in either pathogenic autoimmunity or protective tolerance, depending on the experimental protocol utilized.[11,12] Some induced regulatory populations of T cells can transfer tolerance to naive animals.[13-15] There is also evidence that transfer of regulatory T cells alone may not be sufficient to mediate tolerance in naive animals but that tolerogenic APCs may be required.[16,17] Finally, tolerance can be associated with end organ resistance, mediated by expression of protective gene products (i.e., heme oxyengase, indoleamine 2,3-dioxygenase, FasL) that in turn can be upregulated by interactions with primed T cells (some of which have been shown to be tolerogenic) or their secreted cytokines.[18-20] Thus, in a broad sense, the autoreactivity by design hypothesis is consistent with many experimental observations regarding tolerance.

How would the conceptual framework of autoreactivity by design explain the development of pathologic autoimmune disease? First, it is notable that the development of autoimmune disease is a relatively rare event and that it is difficult to induce autoimmune disease in animal models using even the most potent proinflammatory stimuli (e.g., complete Freund's adjuvant).[12] This observation, in conjunction with the fact that autoreactive T cells are detectable in normal hosts, suggests that there are potent regulatory mechanisms controlling or preventing the development of pathogenic autoreactive T cells under normal conditions. The autoimmunity by design paradigm suggests that naive or regulatory autoreactive T cell emigrants, designed to be protective, can be subverted into a pathogenic phenotype under unusual potent proinflammatory conditions (Fig. 1B). As an illustrative hypothetical example, a pulmonary viral infection can result in increased local expression of MHC and costimulatory molecules (among others), thereby altering the microenvironment of the lung (but not of other noninfected organs) from a permissive/tolerogenic phenotype to a proinflammatory phenotype. This would be entirely appropriate to cure the infection. Virus-specific T cells activated in the secondary lymphoid organs by APCs expressing processed viral determinants are then preferentially attracted to the infected organ where they reencounter their antigenic ligands, leading to tissue destruction and, ultimately, control of the virus. It is possible that some viral antigens could exhibit cross-reactive features to certain autoantigens such that priming of proinflammatory antiviral T cells could inadvertently result in activation of cross-reactive, pathogenic autoreactive T cells. The number of autoreactive T cells primed under these conditions would be dependent, in part, on the genetic composition of the individual (including the T cell repertoire and a number of other genes that determine responsiveness) and specific characteristics of the infectious agent. Circumstantial evidence for this type of cross-reactivity has indeed been de-

tected in a number of models of autoimmune disease.[21,22] An additional consequence of the local tissue destruction aimed at curing the viral infection would be the release, endocytosis, processing, and presentation of peptides derived from a large number of self-proteins found in the normal cells (as well as foreign, virus-derived proteins). Although the majority of these self-peptides would be innocuous, rare self-peptides expressed in the context self-MHC on activated APCs may act as cryptic antigens and elicit priming of naive autoreactive T cell precursors into pathogenic autoreactive T cells. Such a scenario would be consistent with the well-established concept of epitope spreading, in which an initially focused immune response (in this case, antiviral) spreads to involve additional antigens (in this case, self-antigens) presented to the immune system in the context of the proinflammatory microenvironment.[23] The local inflammatory phenotype of the infected organ would support and potentially accelerate attraction of these pathogenic autoreactive T cells and perpetuate the autoimmune reactivity. If sufficient numbers of these autoreactive T cells are activated and if the target organ expressing the self-antigen maintains the proinflammatory state (due to the ongoing viral infection), the proposed regulatory, autoreactive-T-cell-dependent mechanisms that maintain tolerance may be overwhelmed and the newly primed pathogenic autoreactive T cells could contribute to organ damage (and in fact could contribute to the cure of the infection). Resolution of the inciting infection should lead to a down-regulation of the virus-specific immune repertoire such that only a few residual antivirus, memory T cells remain in the host. It is hypothesized that normally, the number of autoreactive T cells activated during such infections is limited and that this response also resolves despite the fact that persistent self-antigens are always present (perhaps due to the persistence of the autoreactive regulatory repertoire already present in the host). Under extremely rare conditions, again determined by genetic predispositions of the host and various environmental factors, the autoreactive component of the proinflammatory immune repertoire may not fully resolve or may reactivate. In these latter instances, the target organ would not resolve back to the normal, quiescent, but actively protective state, with the end result being the development of self-perpetuating, organ-specific autoimmune disease.

It is intriguing to note that pathologic autoimmune reactions are generally organ specific and do not spread to involve other organs despite the fact that many normal tissues likely express some of the same autoantigens (although organ-specific autoimmunity can be directed toward antigenic targets specifically found in a given organ and not another). The autoimmunity by design framework suggests a plausible explanation to account for this, based on the assumption that the various microenvironments of the host can differentially influence the autoimmune repertoire. The model would suggest that the noninvolved host tissues maintain a tolerant phenotype, consisting of infiltrating, autoreactive, regulatory T cells; a nonpathogenic microenvironment; and an absence of chemoattractant signals to attract pathogenic T cells. If small numbers of activated pathogenic T cells spill over into these tissues, they would be controlled by the permissive microenvironment (just as outlined above for organs of the normal, noninfected host), thus preventing spread of the autoimmune disease to additional organs.

The development of pathogenic and protective autoreactivity within the conceptual context of autoimmunity by design can account for some recent observations in transplantation immunobiology as well. Emerging data, summarized in the accompanying articles by Benichou, Demetris, and Wilkes, provide convincing evidence that autoreactive T cells can contribute to destruction of a transplanted organ. Work by these investigators and by others showed that allograft transplantation primes pathogenic, recipient-MHC-restricted T cells specific for peptides derived from cardiac myosin (heart grafts), collagen V (lung transplants), heat shock proteins (skin grafts and heart grafts), and some unknown autoantigens.[11,24-30] The primed autoreactive T cells were not simply innocent bystanders because (1) they could be isolated from allografts undergoing rejection, (2) immunization with these autoantigens prior to transplantation could accelerate allograft rejection, and (3) induction of a pathogenic immune response to these autoantigens through experimental immunization

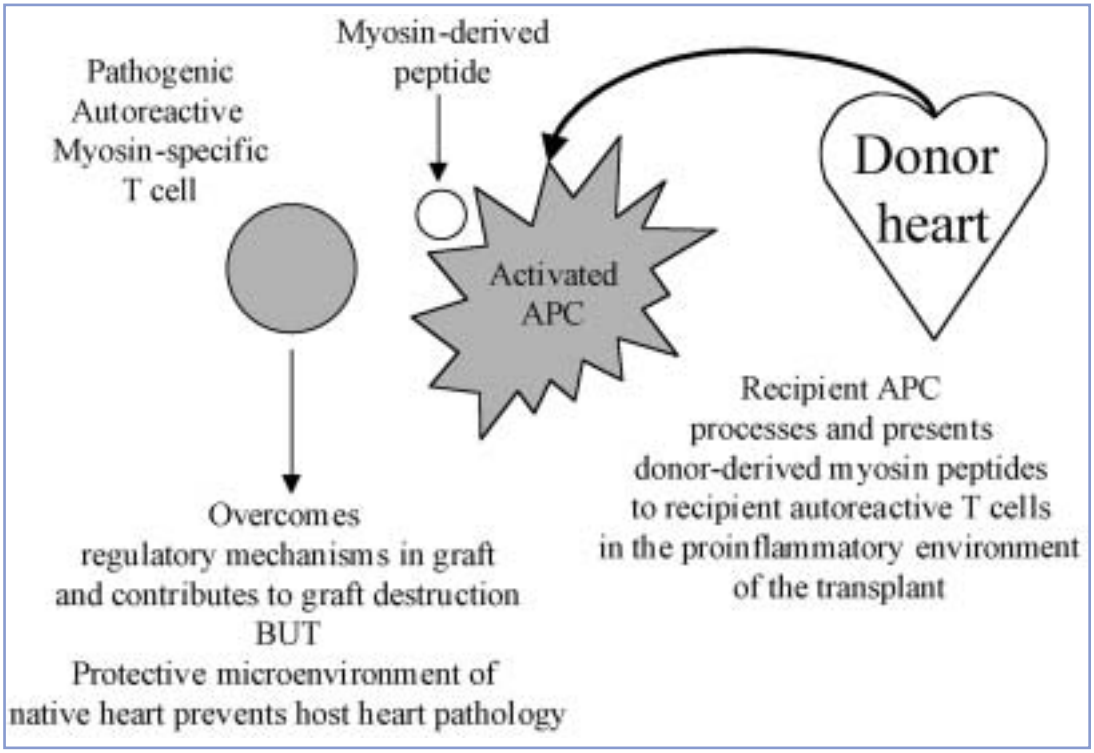

Figure 2. Schematic depiction of the development of pathogenic autoreactive T cells following heart transplantation. See text for details.

could precipitate rejection of an isograft. Interestingly, the primed, autoreactive T cells capable of rejecting a transplanted isograft did not seem to cause injury to the native organs of the recipient.

The detection of autoreactive T cells following transplantation should be anticipated (Fig. 2). In addition to direct recognition of donor cells, recipient T cells recognize donor-derived antigenic determinants complexed to recipient MHC molecules expressed on recipient APCs.[31] This indirect pathway of allorecognition represents the usual method of immune recognition by T cells: The exogenous antigen is engulfed by the host's APCs, processed into peptide fragments, shunted through the MHC processing pathways, and expressed on the APC surface. Although many of the indirectly presented peptides derive from donor MHC molecules, any antigen found in donor cells (including so-called minor antigens and even nonpolymorphic antigens common to both donor and recipient) could theoretically be processed and presented by recipient APCs. The proinflammatory state of the transplanted organ (due in part to surgical trauma and ischemia reperfusion injury), along with the enormous antiallograft T cell immune response focused toward donor MHC molecules (direct pathway), could easily overcome the hypothesized tolerogenic state of the donor organ, permitting priming of autoreactive T cells and facilitating/accelerating the migration to and pathologic function of these autoreactive T cells in the transplant. The ability of such primed T cells to contribute to destruction of an allograft would also be anticipated, as the autoreactive T cells infiltrating the donor allograft could reencounter self-antigens expressed on infiltrating self-APCs and mediate local tissue injury through release of proinflammatory cytokines, induction of delayed-type hypersensitivity reactions, and initiation of other, secondary, macrophage-mediated effector mechanisms.

The experimental data show that despite the development of pathogenic autoimmunity directed toward transplanted organs (including isografts), the autoreactive T cells do not cause injury to the

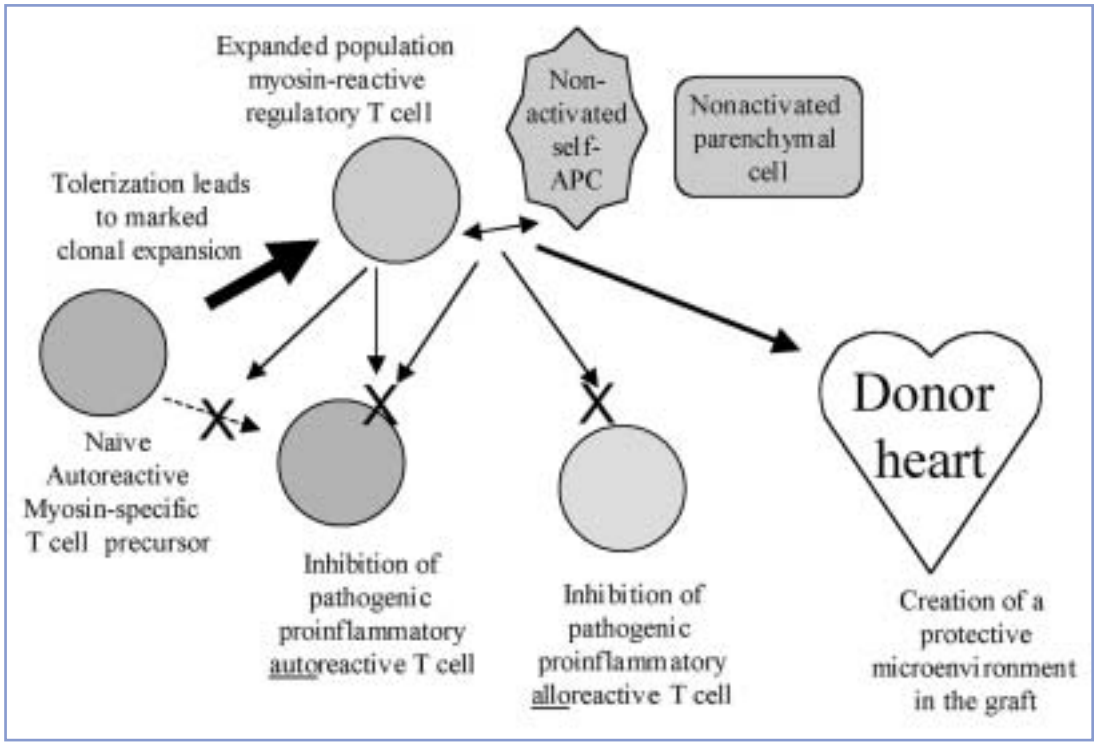

Figure 3. Schematic representation of how tolerance induction to autoantigens might prevent or delay graft rejection. See text for details.

native organs of the recipient (see accompanying articles in this issue). The endogenous host tissues seem to maintain a nonpathogenic microenvironment (theoretically due to the reciprocal interactions between regulatory T cells and the host tissue) and an absence of chemoattractant signals to attract pathogenic T cells. Although pathogenic autoreactive T cells are activated as a component of the alloimmune response, these cells seem to be preferentially attracted to the transplanted graft and do not accumulate in the native organ in large numbers. Small numbers of rogue, activated T cells that enter the normal tissue could theoretically be controlled by the permissive/tolerogenic microenvironment, preventing the development of diffuse autoimmune disease in the native tissues. If this hypothesis is true, then expression of inflammatory signals within an otherwise normal organ could precipitate organ-specific autoimmune disease. Indeed, studies in which TNFα was genetically overexpressed in islet cells confirmed that local production of this proinflammatory molecule could result in islet inflammation and diabetes.[32] Another potential test of the hypothesis would be to induce injury of the native heart (e.g., by ischemia reperfusion via tying off a coronary vessel) at the time of heart allograft placement, with the premise being that the induced injury would result in attraction of primed, autoreactive (i.e., myosin-specific) T cells and thereby precipitate myocarditis of the native heart.

The autoimmunity by design hypothesis additionally provides a potential explanation for the intriguing observation that induction of tolerance to the organ-specific autoantigen prior to transplantation can delay or even prevent rejection of a subsequently placed allograft (Fig. 3). Experimental tolerization (e.g., by administration of antigen in incomplete Freund's adjuvant) would expand the population of endogenous autoreactive regulatory T cells, creating a permissive microenvironment in the host through interaction with normal host tissues, and may be dependent on T cell–mediated induction of "tolerant" APCs. Following transplant

Table 2 | **Questions Raised by the Autoimmunity by Design Theory**

Can naive T cell precursors differentiate into multiple phenotypes of proinflammatory versus regulatory cells? If so, what influences the decision?
Can one routinely isolate autoreactive regulatory T cells from normal organs?
Do autoreactive, regulatory T cells proliferate and alter expression of cell surface markers upon activation?
What signals attract regulatory cells to normal organs, and do these signals differ from those that attract proinflammatory cells? Do regulatory T cells cross endothelial cell barriers, and if so, how?
Can autoreactive regulatory T cells be converted into pathogenic proinflammatory T cells or are they at an end-differentiated stage of development?
Can one alter the expression of protective genes in parenchymal cells and affect the proinflammatory versus tolerant state of the organ?
Do the relative numbers of regulatory versus proinflammatory autoreactive T cells contribute to the development of inflammation at a given site?
What are the mechanisms employed by regulatory T cells? Bystander suppression? Prevention of precursor differentiation into proinflammatory effectors? Upregulation of protective genes on parenchymal cells?
Can certain cells, other than T cells, transfer tolerance? If so, what are the phenotypic markers that define these cells, how are they induced, and how do they function?

surgery, the expanded repertoire of tolerant APCs and regulatory T cells would inhibit priming or effector function of any pathogenic alloreactive T cells (functioning either in the secondary lymphoid organs and/or in the graft). In addition, this increased number of regulatory cells would partially restore the microenvironment of the inflamed graft toward a protective state, thereby raising the threshold number of pathogenic T cells required to mediate graft rejection. Prevention of graft rejection would be thus be dependent on the relative numbers of regulatory cells versus pathogenic T cells infiltrating the graft as well as the phenotype of the graft itself. In some cases (as outlined in the accompanying articles), tolerance induction may sufficiently raise the number of regulatory cells to fully prevent rejection of an allograft. In other situations, the induced tolerance to autoantigens may expand the number of regulatory cells but not to a sufficient degree to prevent the eventual effects of a potent alloimmune response (and thus only delay, not prevent, rejection). The hypothesis is again supported by recent results in the models of skin graft tolerance,[15] autoimmune diabetes,[33] and experimental autoimmune encephalomyelitis,[34] in which expanded populations of regulatory T cells (in some cases shown to be autoreactive) can localize to the target organ and can inhibit the development and effector function of pathogenic T cells, thereby preventing tissue injury. Overall, the experimental data suggest that one can harness the naturally developing, autoreactive regulatory cell repertoire and that expansion of these T cells to a sufficient degree can result in a regulatory immune repertoire capable of controlling or preventing the development of a pathogenic alloimmune response.

Autoimmunity by design, as outlined, does not account for the presence of autoantibody-mediated processes, although analogous regulatory features could be envisioned (through controlling complement activation or signaling through inhibitory Fc receptors expressed on macrophages). Overall, although the idea of protective, autoimmunity by design is consistent with much of the published literature, there remain a number of unanswered questions (Table 2). The hypothesis would be bolstered by more experimental data clearly identifying the phenotypes, mechanisms of action, and origins of regulatory T cells, and of autoreactive, regulatory T cells in specific. Experiments designed to better test whether the numbers of pathogenic versus tolerogenic, autoreactive T cells affect the threshold for the expression of organ pathology/rejection, as well as experiments focusing on further isolation, characterization, and mechanistic analysis of tolerogenic APCs, are also needed.

The autoimmunity by design paradigm provides a conceptual framework through which to consider experimental results and requires a shift in thinking about why autoreactive T cells are present in a host.

Instead of functioning as escaped prisoners that are dangerous to the community, this hypothesis suggests that autoreactive T cells act more like your friendly, local police department, constantly patrolling the neighborhood for signs of commotion, reinforcing the walls of protection against intruders, and quenching any local disturbances. Under certain stimulatory conditions, additional members of the department can be recruited into active duty, affording a more potent protective police force. It is only under the most unusual combination of circumstances in which such protective T cells are corrupted into criminal behavior that results in tissue destruction and true autoimmune disease. I hope that the readership will consider the merits (and the shortcomings) of this conceptual framework, and I look forward to your thoughts and to your feedback.

Acknowledgments

I wish to especially thank Rob Fairchild, Anna Valujskikh, and Charley Orosz for their helpful discussions, input, and feedback.

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