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REVIEW

The Immune Tolerance Network and Rheumatic Disease

Immune Tolerance Comes to the Clinic

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Autoimmune diseases pose some of the most baffling scientific questions and daunting clinical challenges in internal medicine. With rare exception, we do not know what causes these diseases, and we have neither safe nor sufficiently effective therapies. Thus, in rheumatoid arthritis (RA), we define success as a 20% improvement in 50% of patients. In systemic lupus erythematosus (SLE), we define success in treating nephritis as prevention of end-stage renal disease, often at the cost of producing iatrogenic Cushing's syndrome, infertility, or worse. Although these definitions of success leave much to be desired, they do represent substantial progress in recent decades. Crippling disability is now less likely in patients with RA, and death is less likely in patients with SLE. This progress is a consequence of many factors, including advances in general medical care and orthopedic surgery, new antiinflammatory drugs, more judicious and effective use of immunosuppressive agents, and better antibiotics. Yet, all these advances relate to improved immunosuppression and require ongoing medication to suppress autoreactivity.

Thus, the ultimate goal of research in these diseases remains elusive. In clinical terms, that goal is to prevent or selectively ablate pathologic immune responses without damaging protective immune responses. In scientific terms, that translates into maintaining or restoring immune tolerance. The goal of achieving tolerance will be met when patients remain well without requiring ongoing intervention.

Dramatic recent advances in our understanding of the basic mechanisms of the immune system have led many to believe that the ability to achieve immune tolerance in patients with autoimmune disease may be close at hand. In recognition of this exciting prospect, the National Institutes of Health established the Immune Tolerance Network (ITN) on September 30, 1999 (see http://www.immunetolerance.org). The ITN is funded as a joint effort by the National Institute of Allergy and Infectious Diseases, the National Institute of Diabetes and Digestive and Kidney Diseases, and the Juvenile Diabetes Foundation International. The Network is mandated to initiate and oversee clinical trials of new therapies designed to produce long-lasting immune tolerance in situations where the immune response is harmful, such as in autoimmune diseases, allergic responses, and transplant rejection. To accomplish this goal, the ITN has established a steering committee of more than 70 world leaders in immune tolerance, both basic scientists and clinicians, whose charge is to solicit, review, and coordinate clinical trials of new, biologically based strategies to achieve immune tolerance.

An additional innovative feature of the ITN is that all trials will be coupled to mechanistic studies so that we can better understand how clinical protocols designed to induce tolerance actually alter the function (both the protective and the pathogenic responses) of the immune system. The mechanistic studies will also advance other important goals, including development of markers for a tolerant state and identification of genes that are associated with a therapeutic response or lack of response to a particular immunologic intervention.

Immune activation

The development of rational strategies to promote immune tolerance requires a thorough under-

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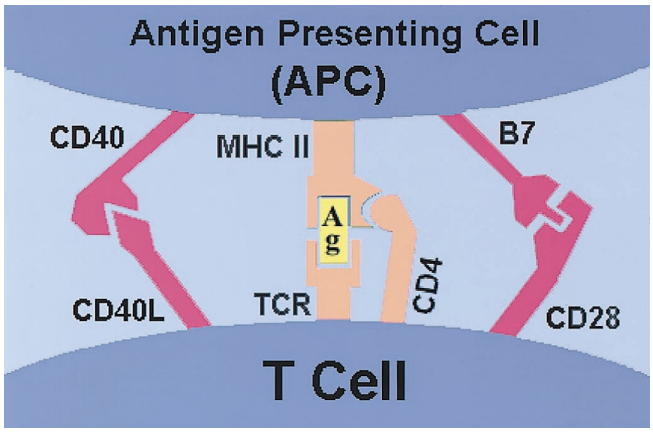

Figure 1. Mechanism of immune activation whereby following interaction with antigen, lymphocytes may be activated or they may be rendered inactive ("tolerant"). In the case of T cells, for example, antigen recognition occurs via the T cell receptor (TCR), which recognizes antigenic peptides (Ag) in the context of major histocompatibility complex class II (MHC II) antigens on antigen-presenting cells (APC), such as B cells or macrophages. Whether this interaction leads to T cell activation or T cell tolerance depends on other receptor–ligand pairs that provide "costimulation" to the T cell. In the presence of T cell costimulation, Ag recognition leads to T cell activation. Conversely, in the absence of T cell costimulation, Ag recognition may lead to tolerance. Many receptor–ligand pairs on the surface of T cells and APC contribute to T cell costimulation. Two particularly important costimulation pathways are shown, involving interactions between B7 molecules (on APC) and CD28 (on T cells) or between CD40 (on APC) and CD40 ligand (CD40L) (on T cells).

standing of the mechanisms involved in immune activation. As we have learned about the immune system, it has become clear that antigen alone does not activate an immune response. As Bretscher and Cohn postulated years ago (1), 2 signals are required to activate T and B lymphocytes, and this has been confirmed in recent studies (2). For activation to occur, lymphoid cells must engage antigen through an antigen receptor, either a T cell receptor (TCR) or a B cell receptor (BCR), as well as receive costimulation through other receptor–ligand pairs (3–6) (Figure 1). A major recent advance has been the identification of the critical costimulatory molecules on T and B cells and their interacting ligands on antigen-presenting cells and T cells, respectively. CD28 on T cells interacts with B7 molecules on antigen-presenting cells (3,4), while CD40 on B cells interacts with CD40 ligand on T cells (5,6). These costimulatory pairs must be engaged for cellular activation to proceed.

Activation involves both proliferation and effector function. In the case of T cells, various effector functions exist. It is well established that there are both CD4+ helper T cells and CD8+ cytotoxic T cells (7). In addition, helper T cells may at times be classified as Th1 or Th2, depending on the panel of cytokines secreted (8,9). It is becoming increasingly evident that additional T cell subsets also exist, although their phenotypic and functional characterization is as yet incomplete. B cells are more limited in effector function, secreting antibody molecules of different isotypes.

Progress toward immune tolerance

As our knowledge of the immune system has increased, much attention has focused on the regulation of autoreactivity. It has become clear that all individuals generate autoreactive, potentially pathogenic T and B cells (10–21). Why are these cells not activated? Mechanisms exist within both primary and secondary lymphoid organs to eliminate, inactivate (anergize), or otherwise render nonpathogenic these cells. These mechanisms include deletion and anergy of autoreactive cells (14,22–27) and suppression by interacting cells or soluble factors (28–37). In the case of B cells, an additional mechanism, called receptor editing, constitutes a first defense against autoreactivity, since this mechanism provides for the generation of a new BCR to replace an autoreactive one (38,39).

Some of the mechanisms that lead to deletion and anergy are now well understood. For example, if a lymphocyte encounters antigen in the absence of a costimulatory signal, that cell will be subjected to tolerance induction, either by deletion or by induction of anergy (3–6). For autoreactive B cells developing in the bone, self tolerance may be maintained by receptor editing. Receptor editing is the process whereby an autoreactive B cell will rearrange a second light chain to generate a BCR that lacks autoreactivity (38,39). Should receptor editing not occur or fail to eliminate autoreactivity, the B cell will then be deleted or anergized (14,16,21). Autoreactive T cells similarly are deleted or anergized during thymic development (13,14). There are recent data demonstrating the existence of receptor editing for T cells also (40).

Not all autoreactive cells are tolerized as they develop in primary lymphoid organs, since not all self antigens are present in the bone marrow or the thymus. Thus, there must be mechanisms to induce tolerance of lymphocytes that encounter self antigen in the periphery. Both deletion and anergy occur in the periphery (12,16,22), but whether receptor editing occurs in the periphery remains somewhat controversial. There is in

the periphery, however, a unique mechanism of tolerance that involves the activation of regulatory cells that, through a variety of mechanisms, limit the activation of pathogenic autoreactive cells (28–37).

Despite the existence of these central and peripheral mechanisms to restrict the T and B cell repertoires and avoid autospecificity, autoreactive cells still exist in all individuals. T or B cells that elude tolerance induction may do so because of exposure to a low concentration of self antigen, too low to signal anergy or deletion, or because of a complete lack of exposure to self antigen when the antigen is sequestered away from lymphoid cells. Sometimes, the presence of autoreactive cells is masked, either because the cells have no pathogenic consequence or because there are regulatory cells that keep the autoreactive cells in check (41,42).

Immune tolerance is the normal state of an organism and is characterized by the absence of activation of pathogenic autoreactivity. As stated above, we now know that potentially pathogenic lymphocytes are generated in all individuals. These cells can be activated in an inflammatory milieu and often are activated during microbial infection due to antigenic cross-reactivity (43–45). Since activation of autoreactive cells is routine, it is evident that mechanisms are needed not only to establish tolerance, but also to restore tolerance after inflammation. Deletion of autoreactive cells is the only fail-safe mechanism of tolerance induction; however, other mechanisms can provide effective regulation under most circumstances. It is a goal of immunologists and clinicians alike to draw upon our understanding of tolerance induction of naive cells and of activated cells to devise new strategies for the treatment of autoimmune disease.

Achieving tolerance

To improve upon current immunosuppressive therapy, T and B cells must be targeted for deletion based on their antigenic specificity. Our current understanding of the ontogeny of the immune repertoire is that naive lymphoid cells encountering high concentrations of antigen in the absence of costimulation will be tolerized. It is currently thought that strong cross-linking of membrane TCR or BCR will lead to deletion, whereas less cross-linking will lead to anergy rather than deletion. This mechanism, however, does not apply to memory cells. Memory cells do not require costimulation for activation and are activated on exposure to antigen alone (46–50). Thus, soluble antigen can delete or anergize only naive autoreactive cells. Administration of antigen, however, requires a knowledge of the antigen targeted by the pathogenic lymphocytes. The appropriate antigens for such antigen-based interventions are still unknown in the rheumatic diseases. Thus, administration of soluble antigen is a desirable strategy for tolerance induction, but the lack of identified antigens and the inability to affect memory cells limit this approach.

Just as antigen alone in the absence of a costimulatory signal can cause deletion or anergy, exposure to antigen in the context of costimulatory blockade can also induce tolerance. Animal models of SLE and RA as well as nonrheumatic autoimmune disease demonstrate that costimulatory blockade can block induction of disease (51–54). In some situations, costimulatory blockade can also abort or diminish ongoing disease. These models have generated enthusiasm for exploring the use of immune modulators that interfere with costimulatory interactions in human disease. The limitation of costimulatory blockade in lupus and RA is similar to the problem with soluble antigen as a therapeutic reagent. This approach can only tolerize naive cells. Thus, the limitations of costimulatory blockade will help teach us the extent to which disease activity relies on the continual recruitment of naive cells to an autoreactive response and the degree to which memory cells are engaged.

Some autoreactive responses are pathogenic because the cytokines that are secreted either directly mediate tissue injury or activate other cells to destroy tissue. There is substantial evidence that the autoreactive T cells in multiple sclerosis, for example, must secrete a Th1 panel of cytokines for the autoreactivity to have pathologic consequences. Autoreactive T cells of the Th2 phenotype do not cause disease (55). The effort to alter the cytokine profile of antigen-specific T cells is termed “immune deviation” and provides an approach to therapy for certain autoimmune diseases. The T cell phenotype is determined by the antigen-presenting cell and the cytokine milieu at the time that the T cell confronts antigen. Thus, strategies to present antigen in a controlled context have been proposed. This approach has, in fact, been part of the therapeutic armamentarium of the allergist for years, since desensitization involves changing the nature of T cell help such that IgG rather than IgE antibodies are produced.

Finally, autoreactive cells may be rendered nonresponsive in the presence of regulatory cells. Regulatory cells that diminish the activation of autoreactive

cells clearly exist. Some time ago, these cells were termed "suppressor cells," but difficulties in their analysis led investigators to doubt their existence for a time. Recently, refinements in our characterization of T cell subsets have brought new life to this area of immunology. The exact nature of these regulatory cells remains somewhat controversial, but CD25+ cells and CD1-restricted T cells have been suggested to play a regulatory role (56,57). Transforming growth factor β appears to be a cytokine secreted by regulatory cells (58). Although studies of the activation of regulatory cells are still in their infancy, it can be anticipated that future strategies for treatment of autoimmune disease will include the selective activation of such cells.

Application to rheumatic disease

Autoimmune rheumatic diseases may reflect organ-specific autoreactivity or generalized autoreactivity. For example, RA is most commonly limited to inflammation of the joints, and myositis to muscle inflammation. SLE, in contrast, is characterized by a much broader spectrum of autoreactivity involving more autoantigens and leading to inflammatory damage in many organs. Whether different therapeutic interventions will be necessary to restore immune tolerance in organ-specific and generalized autoimmune diseases is not known. It is tempting to speculate that antigen-specific approaches may be beneficial in diseases where the target autoantigens are limited in number. In a disease like SLE, where many autoantigens are targeted by the immune system, a better approach might be a generalized dampening to thresholds for immune activation. Although this dichotomy is intellectually appealing, proof of its utility awaits successful clinical interventions in rheumatic disease that lead to disease-free periods which persist in the absence of continuous therapy.

Goals of the Immune Tolerance Network

The ITN is committed to exploring new therapeutic interventions that will lead to the cessation of unwanted, tissue-damaging immune responses. The ITN solicits and reviews proposals for clinical trials and for tolerance assays. Members of the ITN work with investigators to ensure that adequate preclinical data are available to proceed to human studies. In general, the ITN hopes to support efficacy studies, but it will fund phase I safety studies when necessary.

The ITN is also interested in learning how to identify a state of immune tolerance. To that end, it is establishing core facilities to analyze patterns of gene expression and cellular phenotypes that characterize states of tolerance and that are altered during times of disease activity. It is hoped that these studies will provide clues to disease pathogenesis and identify surrogate markers for disease remission or flare that can be used in clinical decision-making. As yet, neither clinicians nor immunologists know the profile of the patient who has been "cured" of rheumatic disease. It is a goal of the ITN to define that profile.

Summary

The development of effective, new, biologically based therapies for RA has created real excitement and justifiable optimism in recent years among rheumatologists and among patients with rheumatic diseases. Recent advances in our understanding of the mechanisms of immune activation and immune tolerance provide further cause for optimism. Against this background, the establishment of the ITN is an important step. However, significant hurdles remain to be cleared. First, despite dramatic scientific progress, restoration of immune tolerance in the face of an established autoimmune response is still an elusive goal, even in the laboratory. Not only does the ITN face this fundamental scientific challenge, but it also faces daunting practical and political challenges. For example, can the ITN influence the research agenda of the pharmaceutical and biotechnology industries? This question and other important questions will only be answered as the ITN matures.

Autoimmune disease, although individually uncommon, affects more than 2% of Americans. The rheumatologist is especially aware of the devastating potential of autoimmune diseases. If the ITN succeeds in linking basic research into the mechanisms of autoimmunity with clinical trials of promising new therapies, it can be expected to play a critical role in advancing the practice of clinical rheumatology.

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