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AUTOIMMUNE DISEASES

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AUTOIMMUNE diseases, with the exception of rheumatoid arthritis and autoimmune thyroiditis, are individually rare, but together they affect approximately 5 percent of the population in Western countries.[1,2] They are a fascinating but poorly understood group of diseases. In this review, we define an autoimmune disease as a clinical syndrome caused by the activation of T cells or B cells, or both, in the absence of an ongoing infection or other discernible cause. We will discuss a classification of autoimmune disease that distinguishes diseases caused by generalized defects in lymphocyte selection or homeostasis from those caused by aberrant responses to particular antigens. We will consider genetic susceptibility to autoimmune disease, environmental and internal triggers of autoreactivity, changes in pathologic processes as the disease progresses, and multiple mechanisms of tissue injury, and we will conclude with a survey of new therapeutic approaches.

For many years, the central dogma of immunology focused on the clonal deletion of autoreactive cells, leaving a repertoire of T cells and B cells that recognize specific foreign antigen. However, our present view acknowledges that a low level of autoreactivity is physiologic[3] and crucial to normal immune function. Autoantigen helps to form the repertoire of mature lymphocytes, and the survival of naive T cells[4] and B cells[5] in the periphery requires continuous exposure to autoantigens. Since there is no fundamental difference between the structure of self antigens (or autoantigens) and that of foreign antigens, lymphocytes evolved not to distinguish self from foreign, as some have speculated, but to respond to antigen only in certain microenvironments, generally in the presence of inflammatory cytokines.[6] Since autoreactivity is physiologic, the challenge is to understand how it becomes a pathologic process and how T cells and B cells contribute to tissue injury.

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CLASSIFICATION OF AUTOIMMUNE DISEASES

For clinicians, autoimmune diseases appear to be either systemic (as in the case of systemic lupus erythematosus) or organ-specific (as in the case of type 1 diabetes mellitus). This classification, although clinically useful, does not necessarily correspond to a difference in causation. A more useful division distinguishes between diseases in which there is a general alteration in the selection, regulation, or death of T cells or B cells and those in which an aberrant response to a particular antigen, self or foreign, causes autoimmunity. An example of a general defect is the absence of the Fas protein or its receptor — proteins involved in cell death — and a representative antigen-specific disorder is the demyelination syndrome that follows enteric infection with *Campylobacter jejuni*. This classification is useful in deciding on therapy, which may differ according to the pathogenic mechanism. Although this mechanistic classification can be used for animal models, we often cannot determine whether a human disease is due to a global abnormality in lymphocyte function or an antigen-specific abnormality.

Alterations that lower the threshold for the survival and activation of autoreactive B cells often cause the production of multiple autoantibodies, as in the case of the antinuclear and anti-DNA antibodies in systemic lupus erythematosus.[7-32] Low levels of these autoantibodies are the rule in all people. Other autoantibody-mediated diseases seem to reflect a loss of B-cell tolerance to a particular antigen. For example, the antiganglioside antibodies that cause the Guillain–Barré syndrome appear to arise in the face of intact general tolerance of self by B cells.[33] Genetic alterations with global effects on the function of regulatory T cells or cytokine production often lead to inflammatory bowel disease.[34-36] This process may reflect enhanced activation of T cells with an exuberant response to gut flora. Changes in the repertoire of T cells may cause a systemic illness or organ-specific abnormalities. For example, thymectomy in neonatal mice eliminates a subgroup of critical regulatory cells and causes a wasting disease or an autoimmune attack on the thyroid, gastric parietal cells, or ovaries, depending on the genetic background of the mouse.[37] This example illustrates why the distinction between systemic and organ-specific disease is not always useful for understanding mechanisms of autoimmunity.

In some organ-specific diseases, autoreactivity against a ubiquitous autoantigen develops, but the disease is restricted to a particular organ. For example, the ribonucleoprotein antigens targeted in Sjögren's

syndrome and the transfer RNA synthetases in polymyositis are ubiquitous intracellular proteins,[38] yet the pathologic effects of these diseases are relatively restricted. Presumably, the antigen has greater accessibility in affected tissues, although the patterns of lymphocyte migration may also determine sites of inflammation.[39] The differential expression of transport molecules on various subgroups of T cells was reviewed by von Andrian and Mackay.[40] The expression of many antigens is also developmentally regulated, making autoreactivity hazardous only at certain stages of growth. For example, the antibodies against the Ro (SSA) antigen in Sjögren's syndrome and systemic lupus erythematosus bind to the conducting system in the fetal heart, causing complete heart block, but they do not affect the adult heart.[41] Antibodies against desmoglein cause pemphigus in adults but not in neonates, because only one of the two desmogleins in neonatal skin is a target of these antibodies.[42]

GENETIC SUSCEPTIBILITY

Epidemiologic studies have demonstrated that genetic factors are crucial determinants of susceptibility to autoimmune disease. There is familial clustering, and the rate of concordance for autoimmune disease is higher in monozygotic twins than in dizygotic twins.[43-45] A few autoimmune diseases, such as autoimmune lymphoproliferative syndrome and the syndrome of autoimmune polyglandular endocrinopathy with candidiasis and ectodermal dysplasia (APECED), are due to mutations in a single gene. Even in these conditions, other genes modify the severity of disease and not all who possess the mutant gene manifest the disease. Autoimmune lymphoproliferative syndrome is an autosomal dominant disorder involving a defect in the Fas protein or its receptor. The Fas pathway mediates apoptosis, which down-regulates immune responses.[46] The autoreactivity in this syndrome results from an inability to trigger apoptosis of activated immune cells after encounters with microbial antigens. APECED is caused by a mutation in the gene encoding the autoimmune regulator protein (*AIRE*), which occurs predominantly in the thymic medulla but also in other tissues.[47] This protein, presumably a transcriptional regulator, has a role in the selection of T cells in the thymus[48] or in their peripheral regulation. The disease is characterized by both autoimmunity and immunodeficiency. These two abnormalities also coexist in other disorders, acquired or inherited, that are characterized by a loss of function of T cells or B cells, such as the acquired immunodeficiency syndrome, complement deficiencies, and IgA deficiency.

Most autoimmune diseases are multigenic, with multiple susceptibility genes working in concert to produce the abnormal phenotype. In general, the polymorphisms also occur in normal people and are compatible with normal immune function. Only when present with other susceptibility genes do they contribute to autoimmunity.[49,50] Some of these genes confer a much higher level of risk than others; for example, the major histocompatibility complex makes an important contribution to disease susceptibility. Most autoimmune diseases are linked to a particular class I or class II HLA molecule,[51] but this association may require linkage with another gene such as that encoding tumor necrosis factor α (TNF-α) or complement. In the case of ankylosing spondylitis, diabetes, and rheumatoid arthritis, however, the reproduction of the disease in transgenic animals expressing particular human HLA antigens strongly indicates that the class I or class II molecule itself confers susceptibility to disease.[52,53]

Some HLA alleles protect against disease even when a susceptibility allele is present.[49,50] For example, the HLA-DQB1*0602 allele protects against type 1 diabetes even if the HLA-DQB1*0301 or DQB1*0302 susceptibility gene is present,[44] and the presence of this protective allele is an exclusion criterion for current diabetes-prevention trials. The mechanism of this protection is not understood. Finally, the association of HLA alleles with a particular disease may vary among different populations. The class II HLA-DRB1*0401 and DRB1*0404 alleles are strongly associated with rheumatoid arthritis in persons of northern European ancestry,[54] but not in black or Hispanic populations.[55,56]

Genetic engineering of mice has led to the identification of at least 25 genes that can contribute to an autoimmune diathesis when they are deleted or overexpressed. These genes encode cytokines, antigen coreceptors, members of cytokine- or antigen-signaling cascades, costimulatory molecules, molecules involved in pathways that promote apoptosis and those that inhibit it, and molecules that clear antigen or antigen–antibody complexes. Two critical lessons have been learned from these models. First, whether a particular gene or mutation causes a disease depends on the overall genetic background of the host: both disease susceptibility and the disease phenotype that result from an alteration of a single gene depend on other genes. Second, some genetic defects can predispose patients to more than one autoimmune disease, so that several diseases may share common pathogenic pathways. This observation suggests the possibility of using common therapeutic strategies in different autoimmune diseases.

The findings of genetic studies in humans are consistent with these ideas. There are, for example, allelic variants of the gene encoding cytotoxic-T-lymphocyte–associated protein 4 (CTLA-4), a T-cell surface molecule that down-regulates activated T cells. One such polymorphism causes a small decrease in the inhibitory signal mediated by CTLA-4 and is associated with type 1 diabetes, thyroid disease, and primary biliary cirrhosis.[57-59] More often, however, a genetic locus

rather than a single gene has been linked to a susceptibility to autoimmune disease, and many loci are emerging as potentially important in more than one disease.[49,50] The clinical observation that different autoimmune diseases often coexist within a family strongly suggests that some genes at these loci predispose patients to more than one disease.[60,61]

It is possible that vulnerability of the target organ to immune-mediated damage is also genetically determined. A variable threshold to renal and cardiac damage has been clearly demonstrated in animal models.[62,63] Genetic variation in vulnerability to autoimmune-induced damage may underlie the clinical observation that persons with the same serologic abnormality do not necessarily have the same tissue abnormality.

In summary, the predisposition to autoimmune disease represents the net effect of enhancing and protective genes.[64,65] Since each susceptibility gene confers its own level of risk, the predisposition to autoimmunity depends on which combination of susceptibility and protective genes is present, not solely on the number of each. Genes also control the vulnerability of target organs and the accessibility of antigens in target organs.

INITIATION OF AUTOREACTIVITY

Environmental Triggers

Even in a genetically predisposed person, some trigger — an environmental exposure or a change in the internal environment — is usually required for frank autoreactivity. Studies of genetically similar populations living in different conditions strongly suggest the importance of environmental triggers. For example, the incidence of both type 1 diabetes and multiple sclerosis in a population changes as the members migrate to different regions.[66,67] That an environmental antigen elicits the antibodies against desmoglein I involved in pemphigus is strongly suggested by epidemiologic studies of pemphigus foliaceus in Brazil, where the incidence of disease declines as the distance from regions where the disease is endemic increases.[68] Such observations, along with the lower-than-expected rate of disease concordance among monozygotic twins,[69,70] suggest that an environmental factor exposes an autoimmune diathesis. In the case of most autoimmune diseases, however, the trigger is unknown.

INFECTIOUS AGENTS

Microbial antigens have the potential to initiate autoreactivity through molecular mimicry, polyclonal activation, or the release of previously sequestered antigens. Molecular mimicry has clearly been demonstrated in herpes keratoconjunctivitis in mice: T cells that react to the viral protein UL6 cross-react with a peptide derived from a corneal antigen.[71] In humans, rheumatic fever represents an autoimmune response triggered by streptococcal infection and mediated by cross-reactivity between streptococcal and cardiac myosin.[72-74] In the Guillain–Barré syndrome and its variants, antibody cross-reactivity has been demonstrated between human gangliosides and lipopolysaccharides of *C. jejuni*.[33] In autoimmune diabetes, T cells recognize both a peptide derived from the autoantigen glutamic acid decarboxylase and a highly analogous peptide from coxsackievirus P2-C protein.[75] And in multiple sclerosis, T cells react with both a peptide from the autoantigen myelin basic protein and peptides from Epstein–Barr virus, influenzavirus type A, and human papillomavirus.[76] In these examples infection could cause the initial activation of the lymphocytes that mediate these diseases and autoantigen could sustain the activation that persists even after the eradication of the infectious agent. In the case of most autoimmune diseases in humans, however, there is no compelling evidence that the antigenic cross-reactivities identified in laboratory studies are of pathogenic importance.

Microbial infection can also cause polyclonal activation of autoreactive lymphocytes. This is presumed to be the mechanism underlying the increased incidence of autoimmune disease in rodents exposed to microbial pathogens.[77] Microbes that kill cells can cause inflammation, the release of sequestered antigens, and autoimmunity.[77,78] Although nonspecific activation resulting from infection has not been proved to be a factor in humans, it is clear that inflammation, even in the absence of infection, can trigger polyclonal activation and autoreactivity. In this way, cardiac ischemia and necrosis cause heart-specific autoreactivity and myocarditis, through either the activation of anergic cells by inflammatory mediators or the activation of naive autoreactive cells in an inflammatory setting.[79]

Noninfectious Triggers

Many autoimmune diseases are much more common in women than in men, and estrogens exacerbate systemic lupus erythematosus in murine models of the disease by altering the B-cell repertoire in the absence of inflammation.[80] Drugs can also alter the immune repertoire. Procainamide regularly induces antinuclear antibodies and sometimes induces a lupus-like syndrome. Moreover, systemic lupus erythematosus is a regular feature of homozygosity for deficiencies of the C1 or C4 components of the complement cascade; and such deficiencies cause, among other problems, defective elimination of dead cells (Fig. 1).[70,81] Finally, foreign substances may act as haptens and render autoantigens immunogenic. Penicillins and cephalosporins, for example, can bind to the red-cell membrane and generate a neoantigen that elicits an autoantibody that causes hemolytic anemia.[82] Gliadin, a component of wheat gluten, is a substrate for tissue transglutaminase, an enzyme in many cells, and

the complex formed by these proteins induces antibodies against both gliadin and transglutaminase.[83]

There is mounting evidence that blockade of TNF-α, which is beneficial in Crohn's disease and rheumatoid arthritis, can induce antinuclear antibodies and perhaps even systemic lupus erythematosus and multiple sclerosis in certain persons.[84,85] TNF-α has inhibitory effects on activated T cells,[86,87] but how it induces autoimmunity is unknown.

Loss of Regulatory Cells

Several kinds of regulatory cells are important in controlling autoreactivity: CD1-restricted T cells, T cells with γ/δ receptors, CD4+CD25+ T cells, and T cells that produce cytokines that suppress pathogenic autoreactive cells. Some of these regulatory cells — for example, CD4+CD25+ T cells — must mature in the thymus[37]; others require activation by autoantigens in the periphery.

Alterations in the number and function of regulatory cells may contribute to autoimmunization. In monozygotic twins who are discordant for diabetes, for instance, levels of CD1-restricted T cells are greatly diminished in the affected twin.[88] The antigens that activate regulatory T cells in the body are unknown, and the way in which these cells exert their pressure on immune responses is only partly understood. Most important, the reason for their reduced numbers in patients with diabetes or other autoimmune diseases is unknown.

DISEASE PROGRESSION

Epitope Spreading

As an autoimmune disease progresses from initial activation to a chronic state there is often an increase in the number of autoantigens targeted by T cells and antibodies ("epitope spreading")[89,90] and, in some cases, a change in participating cells, cytokines, and other inflammatory mediators. Both autoreactive T cells and B cells contribute to epitope spreading. Activated autoreactive B cells function as antigen-presenting cells; they present novel (cryptic) peptides of autoantigens[91,92] and express costimulatory molecules. They also generate peptides that have not previously been presented to T cells; thus, T cells will not have become tolerant to such cryptic peptides. Over time, multiple novel peptides within a molecule can activate T cells.

Furthermore, if the B cell binds and takes in not a single protein but a complex of multiple proteins, epitopes from each protein in the complex will be processed and presented to naive T cells. The cascade continues, with T cells activating additional autoreactive B cells and B cells presenting additional self epitopes, until there is autoreactivity to numerous autoantigens. By then, the identity of the initiating antigen can no longer be determined.

Pathogenic Mechanisms

It has become apparent, primarily through studies in animals, that the initial mechanisms causing autoreactivity in an autoimmune disease may be superseded by different effector cells and inflammatory mediators as the disease progresses (Fig. 2). Naive lymphocytes are activated at the initiation of disease and may continue to be recruited by epitope spreading later in the disease, but it is unknown whether naive cells or memory cells cause progression and flares of disease. There are many examples of the evolution of the mechanisms as an autoimmune disease progresses. For example, antibody against Fas protein prevents the onset of multiple sclerosis in mice but blocks remission if it is given after the onset of disease because it averts the death of activated cells.[95-97] Moreover, cytokines can have different effects, depending on the stage of the autoimmune disease: transforming growth factor β, for example, suppresses autoreactivity when the disease begins,[98,99] but once the disease is established, it contributes to fibrotic organ damage.[100]

The fact that the cells and soluble mediators of injury can change over time has tremendous implications for therapy; interventions that are effective early may be less efficacious later on or may even be harmful. The unpredictability of these effects is amply illustrated by the clinical efficacy of the blockade of TNF-α in rheumatoid arthritis and Crohn's disease, at the cost of inducing antinuclear antibodies in up to 10 percent of treated patients and systemic lupus erythematosus in a few patients.[84]

TISSUE INJURY

Both autoreactive T cells and autoantibodies can damage tissues. T-cell cytolysis of target cells can be mediated through perforin-induced cellular necrosis or through granzyme B–induced apoptosis.[101] It has been suggested that type 1 helper T cells are critical to the induction of autoimmune disease through the recruitment of inflammatory cells and mediators, whereas type 2 helper T cells protect against disease.[102] However, it is now clear that cytokines produced by type 1 or type 2 helper T cells and even transforming growth factor β can cause tissue injury.[103-105]

Autoantibodies also cause damage through mechanisms that include the formation of immune complexes, cytolysis or phagocytosis of target cells, and interference with cellular physiology. Interference with cellular physiology, first identified in connection with antibodies against acetylcholine in patients with myasthenia gravis[106] and antibodies against the receptor for thyrotropin in patients with Graves' disease,[107] is a common pathway to tissue injury. In patients with pemphigus, antibodies against desmoglein induce the release of a protease that mediates the formation of blisters.[108] In patients with the antiphospholipid-antibody syndrome, antibodies bind to soluble factors in blood that prevent the activation of the clotting

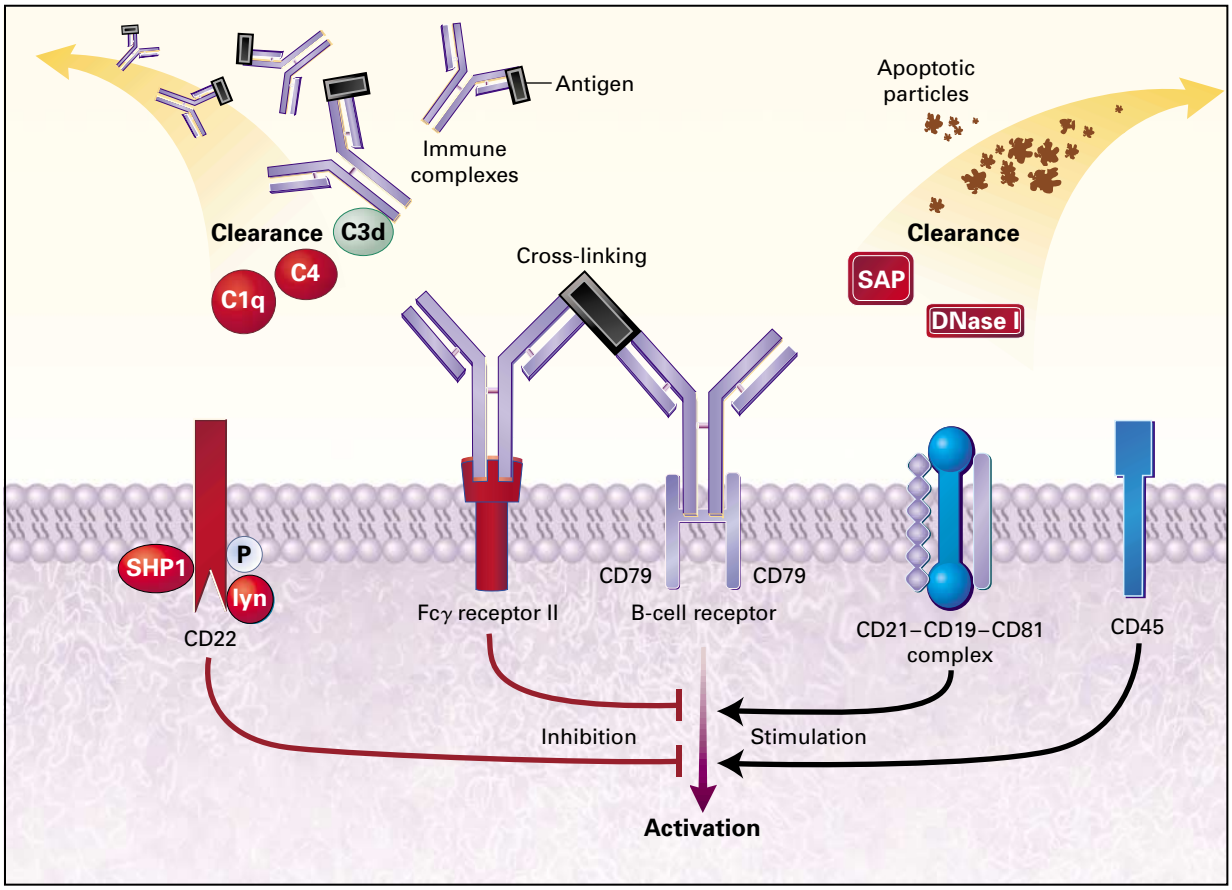

Figure 1. Defects in B-Cell Activation.

B-cell activation is mediated by antigen binding to the B-cell receptor. This results in the activation of kinases. Many other molecules affect the process; some enhance activation and some inhibit activation. The overexpression (shown in blue) of genes encoding cell-surface signaling molecules that enhance activation can result in autoimmunity. Two such defects have been described: one is a mutation of CD45 that results in the overexpression of CD45, the other is transgenic overexpression of CD19. Two defects of inhibitory signaling pathways have been described. The first is a knockout (shown in red) of the inhibitory Fcγ receptor II. This receptor recognizes the Fc region of immunoglobulin in the immune complexes, and when it is cross-linked with the B-cell receptor (which recognizes the antigen in the immune complex), it inhibits the activation of B cells. The second is a knockout of any of the components of the CD22 signaling complex — phosphorylated (P) CD22, lyn (which phosphorylates CD22), and the protein tyrosine phosphatase SHP-1 — that mediates the down-regulation of the activation of B cells. The other types of defects that can result in excessive activation of B cells are related to decreased clearance of antigen in the form of immune complexes as a result of the underexpression of C1q and C4. C1q and C4 bind to C3d, which, in turn, bind to the immune complexes. Autoimmunity can also result from defective clearance of apoptotic particles owing to the underexpression of DNase I, which breaks down apoptotic particles, and serum amyloid protein (SAP), which coats the particles and enhances their clearance. All the defects shown lead to a systemic lupus erythematosus phenotype. Systemic lupus erythematosus can also be induced by the overexpression of costimulatory molecules such as BAFF (B-cell–activating factor belonging to the tumor necrosis factor family), the underexpression of regulatory molecules such as PD-1 (programmed death 1), and the inhibition of apoptotic pathways.

cascade, thus triggering coagulation.[109,110] Moreover, some autoantibodies that bind to surface receptors are taken up by living cells.[111-113] Whether such antibodies then interfere with cellular physiology is controversial.

Increasingly, the distinction made between T-cell–mediated and antibody-mediated autoimmune disease appears inappropriate. Data showing that IgG and products of complement activation are present at sites of demyelination suggest that antibodies contribute to the lesions of multiple sclerosis.[104] Instead of dividing autoimmune diseases into those caused by effector T cells and those caused by antibodies, it seems more appropriate to assume that both antibody and effector T cells often cause tissue damage in established disease.

Cytokine or Protein	Defect	Result
Tumor necrosis factor α	Overexpression	Inflammatory bowel disease, arthritis, vasculitis
Tumor necrosis factor α	Underexpression	Systemic lupus erythematosus
Interleukin-1–receptor antagonist	Underexpression	Arthritis
Interleukin-2	Overexpression	Inflammatory bowel disease
Interleukin-7	Overexpression	Inflammatory bowel disease
Interleukin-10	Overexpression	Inflammatory bowel disease
Interleukin-2 receptor	Overexpression	Inflammatory bowel disease
Interleukin-10 receptor	Overexpression	Inflammatory bowel disease
Interleukin-3	Overexpression	Demyelinating syndrome
Interferon-γ	Overexpression in skin	Systemic lupus erythematosus
STAT-3	Underexpression	Inflammatory bowel disease
STAT-4	Overexpression	Inflammatory bowel disease
Transforming growth factor β	Underexpression	Systemic wasting syndrome and inflammatory bowel disease
Transforming growth factor β receptor in T cells	Underexpression	Systemic lupus erythematosus

Figure 2. Defects in Cytokine Production or Signaling That Can Lead to Autoimmunity.

For example, underexpression of interleukin-1–receptor antagonist leads to arthritis,[93] whereas defects in interleukin-3 lead to a demyelinating syndrome.[94] Since the substances listed are pleiotropic molecules, it is hard to predict on the basis of their known functions what will happen when they are overexpressed or underexpressed. Multiple different defects can lead to the same disease, especially in the case of inflammatory bowel disease and systemic lupus erythematosus. These molecules are starting to be exploited therapeutically, as exemplified by the use of etanercept and interleukin-1–receptor antagonist for rheumatoid arthritis. Drugs that block costimulation are also becoming available. STAT denotes signal transducer and activator of transcription.

THERAPEUTIC STRATEGIES FOR SPECIFIC DISEASES

Two major challenges lie ahead if the promise of new therapeutic approaches is to be fulfilled. First, we need reproducible and reliable serologic and clinical methods of assessing the risk of a specific disease and of identifying active disease and remission. The use of the criteria of the American College of Rheumatology for a response in patients with rheumatoid arthritis allows clinicians to compare the efficacy of various drugs in different trials.[114] The establishment of international standards for screening tests for diabetes will enhance the reliability of these assays.[115,116] Registries of patients are being established for rarer autoimmune diseases to allow clinical studies to proceed.[117,118] Nevertheless, there is an urgent need to identify markers of disease activity, remission, and impending relapse in most autoimmune diseases.

The second challenge is to determine which approach to use in each disease. Perhaps different therapeutic interventions are needed at different stages in the disease process. It is clear, for example, that the treatments that block the recruitment of naive cells differ from those that prevent the activation of memory cells. The hope is that some approaches will work in more than one disease.

Rheumatoid Arthritis

The treatment of rheumatoid arthritis has been markedly improved by the recognition that bone erosions occur early in the disease and that therapy should be instituted promptly in many patients. Although methotrexate remains the first-line disease-modifying agent, there are some promising new drugs. The fact that activated macrophages contribute to synovial inflammation in this disease has led to the development of modulators of macrophage-derived cytokines. Blockade of TNF-α by a soluble p75 TNF-α receptor–IgG1 fusion protein (etanercept) or a monoclonal antibody against TNF-α (infliximab) is highly effective in preventing erosions when it is used in combination with methotrexate. Etanercept can also be used alone, since it is not immunogenic in humans.[119,120] Blockade of TNF-α is also effective in Crohn's disease[121] and is useful in refractory psoriatic arthritis[122] and ankylosing spondylitis,[123] a disease for which no other disease-modifying therapy has been available. Leflunomide, a pyrimidine antagonist that blocks the enzyme dihydroorotate dehydrogenase, thereby blocking the synthesis of DNA, has an efficacy similar to that of methotrexate and can be used either alone or in combination with methotrexate.[124,125] Blockade of interleukin-1 receptors with a recombinant interleukin-1–receptor antagonist is less effective than blockade of TNF-α in patients with rheumatoid arthritis, but it may retard the development of bone erosions.[119] The long-term safety of these new agents, particularly with respect to the risk of infections, cancer, and other autoimmune diseases, remains to be ascertained.

Multiple Sclerosis

Advances have been made in the treatment of multiple sclerosis with the use of interferon beta-1a and copolymer I.[66] Although the indications for and timing of the use of these agents are still debated, a recent study suggests that interferon beta-1a can delay the onset of frank disease when given after a first episode of optic neuritis.[126] Copolymer I is a nonspecific inhibitor of T cells in vitro,[127] although it may also act by immune deviation from type 1 to type 2 helper T cells.[128] Treatment with altered peptide ligands derived from myelin basic protein was efficacious in murine models of the disease, but two recent phase 1 trials of such peptides were associated with clinically significant toxicity: one caused hypersensitivity reactions,[129] and the second resulted in exacerbations of multiple sclerosis.[130] Thus, studies of animal models of disease cannot substitute for clinical trials, and these must proceed with caution.

Psoriasis

Blockade of TNF-α, with or without methotrexate, has been effective in refractory psoriasis. Psoriasis responded to treatment with interleukin-10 in several small and short-term clinical trials.[131] Benefit was also achieved with the use of CTLA-4–Ig, a recombinant fusion protein in which the extracellular domain of CTLA-4 is linked to the constant region of IgG1. CTLA-4–Ig blocks the activation of most naive T cells as well as both primary and secondary antibody responses.[132] However, CTLA-4–Ig exacerbated diabetes in a mouse model in which activation of regulatory cells is thought to prevent initiation of the disease.[133] A number of other biologic agents have also been successfully used to treat psoriasis in small pilot studies. These include antibodies against CD4,[134] antibodies against the high-affinity interleukin-2 receptor CD25 (daclizumab),[135] and antibodies against the CD11a component of the adhesion molecule leukocyte function–associated antigen type 1 (also referred to as $\alpha_1\beta_2$ integrin and CD11aCD18) that mediates migration of T cells into the skin.[136,137] A humanized antibody against CD11a is currently being evaluated in a clinical trial in a large cohort of patients with psoriasis.

Type 1 Diabetes

Therapeutic efforts in type 1 diabetes have focused on prevention. Relatives of patients with diabetes who are at risk for the disease can be identified with near certainty; however, screening of the general population is associated with high false positive rates that preclude intervention studies.[44] Prevention trials are currently assessing the efficacy of inducing antigen-specific immune tolerance through the intra-

venous or subcutaneous administration of insulin in persons at risk who have evidence of decreased beta-cell mass or through the oral administration of insulin in those who have antibodies against insulin but in whom insulin secretion is normal. Initial results with oral insulin have been disappointing,[138] but the results of systemic insulin are not yet available.

Systemic Lupus Erythematosus

Clinical trials in patients with systemic lupus erythematosus are plagued by the wide range of disease manifestations; the relapsing–remitting nature of the disease, which results in high rates of response in groups given a placebo; and the lack of standardized criteria for remission. Whether or not abnormal serologic results should prompt treatment in the absence of clinical signs of the disease remains debatable. Blockade with CTLA-4–Ig or antibodies against CD40 ligand has been highly effective in the prevention or treatment of nephritis in murine models[139,140] but not in humans. Two recent clinical trials of monoclonal antibodies against CD40 ligand were unsuccessful; one did not show efficacy, and the other found unexpected toxicity.[141,142] Polymorphisms of the interleukin-10 gene are associated with systemic lupus erythematosus; a pilot study suggests that treatment of active disease with antibodies against interleukin-10 may be effective.[143]

FUTURE THERAPEUTIC APPROACHES

Four general approaches to therapy are being explored (Table 1): altering thresholds of immune activation, modulating antigen-specific responses, reconstituting the immune system with autologous or allogeneic stem cells, and sparing of target organs.

Interference with costimulation, signaling, chemokines, cytokines, and other molecules critical to immune activation is designed to restore homeostasis in the immune system and dampen the autoimmune response. It is based on the concept that small changes in the availability of proteins that control interactions between cells or participate in intracellular signaling can divert the immune system away from autoreactivity.

Antigen-specific therapies aim to induce tolerance to a particular antigen. Exposure of the immune system to autoantigens or appropriate peptides delivered either by ingestion to induce oral tolerance[147] or by injection[148] has worked well in animals but not in humans.[134,160] Perhaps this approach can only work during the initial activation of autoreactive cells, because once disease is clinically apparent, the immunologic milieu may be inflammatory and epitope spreading may have occurred. However, the rate of concordance for autoimmune disease of less than 50 percent in monozygotic twins argues against attempting preventive strategies. We may need to combine antigen-specific therapies with cytokine or costimulatory blockade to expose lymphocytes to the antigen in the absence of inflammation. Alternatively, some autoimmune diseases may be sustained by memory cells that resist the induction of tolerance.

TABLE 1. THERAPEUTIC APPROACHES.

Alteration of thresholds of immune activation
Blockade of costimulatory factors[132]
Antagonism of inflammatory cytokines[144,145] or protective cytokines[126,131]
Inhibition of signaling cascades by small molecules[146]
Modulation of antigen-specific cells
Induction of regulatory cells (intravenous, subcutaneous, or oral delivery of antigen)[147,148]
Alteration in peptide ligands[129,130]
Formation of complexes of peptide and major-histocompatibility-complex molecules[149]
Development of T-cell receptor vaccines[150,151]
Induction of B-cell tolerance[152]
Immune deviation from type 1 to type 2 helper T cells[128,153,154]
Reconstitution of the immune system[155]
Bone marrow ablation with autologous stem cells
Bone marrow ablation with donor stem cells
Bone marrow ablation without stem cells
Sparing of target organs
Antagonism of complement[156]
Antagonism of chemokines[157]
Use of antiinflammatory agents
Inhibition of matrix metalloproteases[158]
Inhibition of nitric oxide synthase[159]

An approach involving stem-cell transplantation has engendered much excitement recently. Pilot studies of reconstitution with autologous and allogeneic stem cells are proceeding in patients with systemic lupus erythematosus, rheumatoid arthritis, scleroderma, and multiple sclerosis.[155,161-163] The hope is to restore homeostasis with regulatory cells. The efficacy and safety of this approach are unknown.

The complex causes of autoimmune diseases not only present a challenge to the development and testing of new therapies but also offer a framework that allows the identification of subgroups of patients who might benefit from particular approaches. Although we will encounter both successes and setbacks, continued studies of autoimmune diseases in humans and animals are necessary to help identify the most appropriate strategies for each disease.

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