Review Articles

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TOLERANCE AND AUTOIMMUNITY

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THE immunologic specificity of the antigen receptors of T cells and B cells is the result of random shuffling of the many genes that form the DNA code for the antigen-binding site of these receptors.[1-3] Theoretically, this process could generate 10^9 different T-cell receptors, including some that can bind to autoantigens (these cells are often called self-reactive T cells). Tolerance is the process that eliminates or neutralizes such autoreactive cells, and a breakdown in the working of this system can cause autoimmunity.

B-CELL TOLERANCE

Autoantibodies are characteristic of many autoimmune diseases and may be the direct cause of the lesions in some of these disorders. In Graves' disease, autoantibodies bind to and stimulate the receptor for thyrotropin, and in pemphigus vulgaris, autoantibodies against the epidermal adhesion molecule desmoglein 3 disrupt the epidermis. In contrast, autoantibodies against intracellular antigens are not usually pathogenic[4] but, instead, have been viewed largely as secondary consequences of the autoimmune process. This view has been challenged recently: in a murine model of autoimmune arthritis, the transfer of IgG from diseased animals induced arthritis in healthy recipients.[5] These pathogenic autoantibodies bind to glucose-6-phosphate isomerase, a ubiquitous intracellular antigen.[6]

Several mechanisms are available to filter autoreactive B cells out of the B-cell repertoire: the clonal deletion of immature B cells in the bone marrow,[7] the deletion of autoreactive B cells in the T-cell zones of the spleen or lymph nodes,[8] functional inactivation (anergy),[9] and "receptor editing," a mechanism that changes the specificity of the B-cell receptor when an autoantigen is encountered.[10] How important these mechanisms are in preventing autoimmune disease is unclear. There is evidence that B-cell tolerance is predominantly due to a lack of help from T cells. Mice that were genetically manipulated to express a foreign antigen (hen's-egg lysozyme) on the surface of their thyroid epithelial cells produced numerous B cells with receptors for hen's-egg lysozyme. Yet these animals showed no signs of thyroiditis, presumably as a result of T-cell tolerance.[11] There is also evidence that under some circumstances, B cells can overcome tolerance in the absence of help from T cells, but it is inconclusive.[12,13] More about B-cell tolerance can be found elsewhere[10,13-17]; in this review we focus on the dominant role of T cells in immune tolerance and autoimmunity.

CENTRAL T-CELL TOLERANCE

The chief mechanism of T-cell tolerance is the deletion of self-reactive T cells in the thymus. Immature T cells migrate from the bone marrow to the thymus, where they encounter peptides derived from endogenous proteins bound to major-histocompatibility-complex (MHC) molecules.[3] T cells whose receptors have very low affinity for these peptide–MHC complexes do not receive signals that would prevent spontaneous apoptosis, and these cells therefore die in the thymus. T cells with high-affinity receptors for these complexes undergo apoptosis and die in a process called negative selection. The remaining T cells, which have receptors with an intermediate affinity for such complexes, mature in the thymus and migrate to the periphery, a process referred to as positive selection (Fig. 1). The induction of central tolerance requires the presence of autoantigens in the thymus.[18-21] Not all self-antigens occur in the thymus, which necessitates the existence of peripheral mechanisms that participate in T-cell tolerance.

PERIPHERAL T-CELL TOLERANCE

Ignorance

Since immunization of normal animals with certain self-antigens in an adjuvant induces autoimmune diseases, it follows that autoreactive T cells must be present in normal animals. Indeed, B cells and T cells that recognize insulin or myelin basic protein can be isolated from persons without diabetes or multiple sclerosis, respectively.[22,23] Naive T cells, which cannot enter normal tissues other than lymphoid organs,[24] do not induce tissue damage. Evidently, under normal

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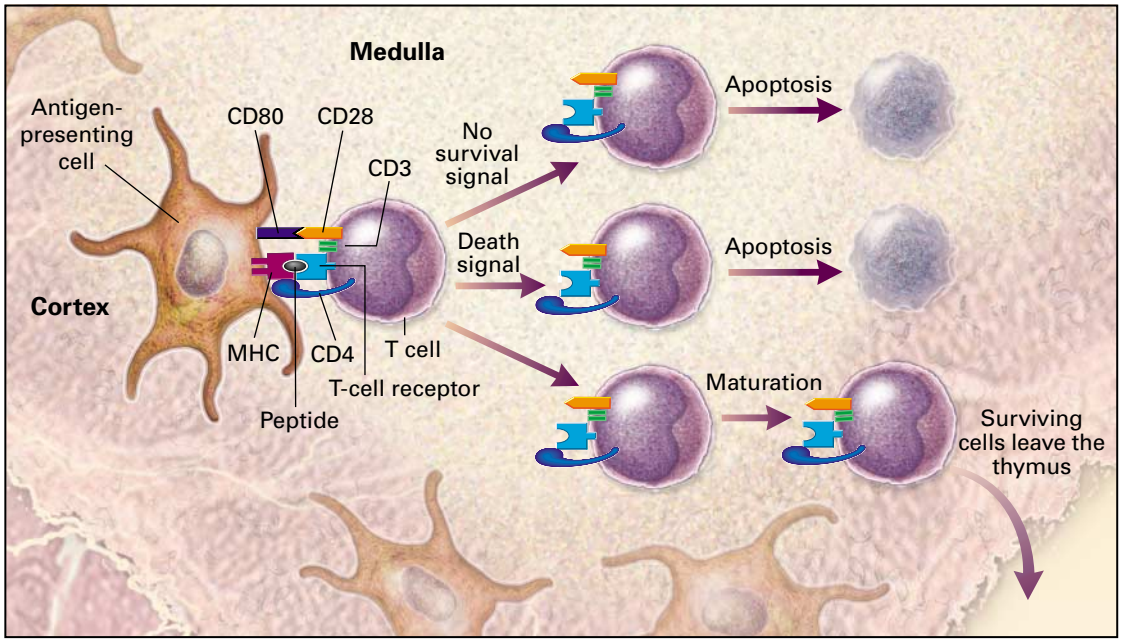

Figure 1. Central Mechanisms of the Induction of Tolerance.

Immature T cells migrate to the thymus, where they encounter antigen presented by thymic epithelial cells. Cells whose T-cell receptors have a low affinity for the complex of self peptide and a self major-histocompatibility-complex (MHC) molecule do not receive a signal to switch off the process of spontaneous apoptosis and therefore die in the thymus. Cells whose T-cell receptors have a high affinity for such complexes are also eliminated by means of apoptosis. The remaining T cells have an intermediate affinity for these complexes, and these mature in the thymus and migrate to the periphery, where they can become activated.

conditions, potentially autoreactive T cells ignore their antigens, thereby maintaining self-tolerance (Fig. 2).

The importance of immunologic ignorance was demonstrated in mice that were genetically engineered to express a T-cell receptor that recognizes a particular viral peptide (transgenic mice). These mice were bred with another transgenic strain that expressed the viral peptide on the surface of their pancreatic islet cells. Surprisingly, diabetes did not develop in the offspring even though in vitro their T cells could kill cells that displayed the viral peptide.[25,26]

The T cells in these double-transgenic mice were therefore not tolerant in vivo, they simply ignored their target cells. Several mechanisms can cause immunologic ignorance: the level of the antigen may be below the threshold required to induce the activation or deletion of T cells,[20,27] antigens may be physically separated from T cells (e.g., by the blood–brain barrier) (Fig. 2),[28] and antigens presented by MHC molecules in the absence of costimulation cannot induce T-cell responses.[29] Furthermore, in the absence of help from CD4+ T cells, CD8+ T cells cannot damage tissue.[30] Thus, self-reactive T cells do not lead to disease as long as they ignore or are kept away from self-antigens. Nevertheless, immunologic ignorance is not always beneficial. Pathogens with exclusively peripheral-tissue tropism (such as papillomavirus) and low levels of harmful antigens may also be ignored.[31]

Deletion

The presentation of antigens in the absence of costimulation not only fails to prime T cells but can also delete them.[20,27,32] Another mechanism of peripheral deletion results from the lack of growth factors for which all activated T cells compete.[33] The death of T cells is also mediated by the pathway involving Fas (also called CD95) and its ligand. Engagement of the Fas receptor induces apoptosis in Fas-positive cells.[34] Since T cells express both Fas and its ligand on activation, the interaction between the two molecules can induce apoptosis.[35-37] The importance of this mechanism is illustrated by the fact that patients with defective Fas have a severe lymphoproliferative disease.[38,39] Some tissues, such as the anterior chamber of the eye, normally express Fas ligand.[40] Consequently, when CD95+ T cells enter these tissues, they undergo apoptosis without damaging the tissue (Fig. 2). The human immunodeficiency virus subverts this mechanism by increasing the expression of Fas ligand by the macrophages it infects, thereby inducing apoptosis in T cells that come into contact with such

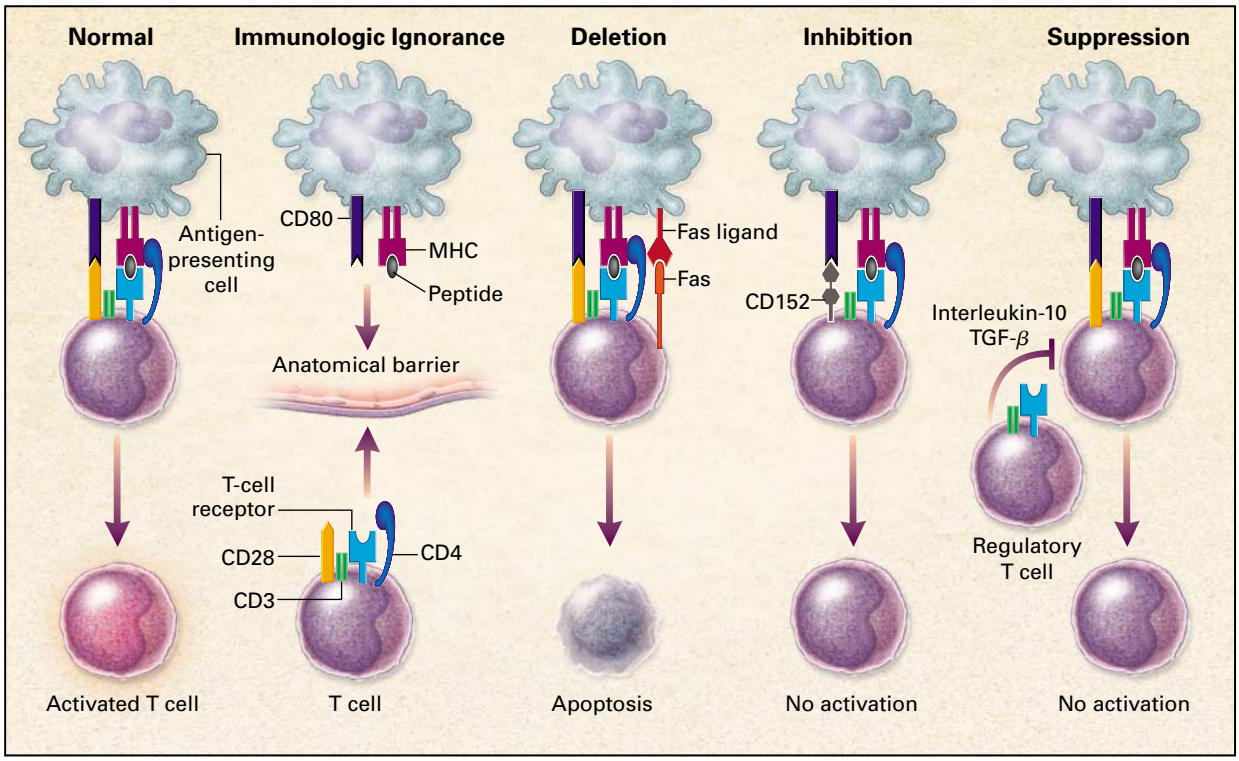

Figure 2. Peripheral Mechanisms of the Induction of Tolerance.

T cells that are physically separated from their specific antigen — for example, by the blood–brain barrier — cannot become activated, a circumstance referred to as immunologic ignorance. T cells that express the Fas (CD95) molecule on their surface can receive their signals from cells that express Fas ligand and undergo apoptosis, a process known as deletion. One example of inhibition is as follows: CD152 binds CD80 on antigen-presenting cells, thereby inhibiting the activation of T cells. Regulatory T cells can inhibit, or suppress, other T cells, most likely through the production of inhibitory cytokines such as interleukin-10 and transforming growth factor β (TGF-β).

macrophages.[41] The same mechanism may allow tumor cells to escape immune surveillance.[42]

Regulation

Anergy

T cells that do not produce interleukin-2 on encountering their antigen (and that therefore cannot be completely activated) are called anergic.[43-46] Anergy may have widespread consequences, because certain anergic T cells produce interleukin-10, which suppresses the activation of T cells.[47] No specific phenotypic markers of anergy have yet been discovered, but the availability of DNA-microarray analysis may lead to the identification of such markers.[48,49]

Inhibition

CD152 (also referred to as cytotoxic-T-lymphocyte–associated protein 4, or CTLA-4) on T cells binds CD80 (B7-1) and CD86 (B7-2) on B cells with a higher affinity than the costimulatory receptor CD28. In this way, CD152 inhibits the activation of T cells[50] (Fig. 2). For example, blockade of CD152 accelerates the progression of autoimmune diabetes in mice.[51] Furthermore, the type 1 diabetes susceptibility locus *IDDM5* in humans and mice cannot be dissociated in mice from the *ctla4* and *cd25* loci.[52]

Suppression and Deviation

Transgenic mice with T cells that bear a T-cell receptor for myelin basic protein are usually healthy, because the autoreactive T cells do not cross the blood–brain barrier (immunologic ignorance).[53] However, encephalitis develops after they receive an injection of myelin basic protein in an adjuvant. Several weeks later the disease often spontaneously remits. When these transgenic mice were genetically modified to prevent the development of normal T cells, the encephalitis that occurred after immunization with myelin basic protein did not remit. The protective T cells that caused remission of the encephalitis are CD4+,[54,55] but their mechanism of action is unknown. It is likely that more than one type of cell and a variety of mol-

ecules[47,56-58] participate in regulating and modifying[59-61] susceptibility to autoimmune diseases and inflammation (Fig. 2).

BREAKDOWN OF TOLERANCE

How can T-cell tolerance, induced in the thymus and then reinforced by multiple extrathymic mechanisms, be overcome and thus give rise to autoimmune diseases? One reason is that the extent of intrathymic deletion of autoimmune T cells varies.[21] For example, the genes that confer susceptibility to autoimmune diabetes include one that determines the intrathymic level of insulin.[18,19] Another mechanism is the activation of potentially self-reactive T cells in the normal repertoire by infectious agents.

Considerable evidence implicates infection as a cause of autoimmune diseases, such as multiple sclerosis and type 1 diabetes.[62] Mechanisms that could lead from infection to autoimmunity include the release of sequestered autoantigens through tissue damage,[63] the activation of a large fraction of the T-cell population by superantigens,[64] and the induction of inflammatory cytokines and costimulatory molecules by microbial products.[65-69] In mice, so-called bystander activation of this type can precipitate autoimmune diabetes.[70]

Alternatively, a structural similarity between microbial and self-antigens ("molecular mimicry") could have a key role in activating autoreactive T cells.[71,72] Indeed, some T cells can recognize both a microbial peptide and a self-peptide with a similar amino acid sequence.[73-75] However, in vivo evidence that molecular mimicry precipitates autoimmune disease is lacking. Actually, a single T-cell receptor can recognize many peptides, not all of which show strong sequence homology.[76-79] The idea that cross-reactivity between a microbial peptide and a self-peptide causes autoimmunity may therefore be simplistic.[80,81] Infections may be capable not only of triggering autoimmunity but also of activating a protective cell population. Multiple infections during the first year of life are associated with a significant reduction in the risk of autoimmune diabetes.[80]

Occasionally, the activation of self-reactive T cells induces only transient autoimmunity, an indication that there are additional "checkpoints" that can lead to measures to prevent autoimmune disease. Optic neuritis is a common initial manifestation of multiple sclerosis and one from which patients often recover. Yet both patients with a single episode of optic neuritis and those in whom multiple sclerosis is eventually diagnosed have T cells that recognize central nervous system antigens.[82] In murine models of autoimmune diabetes, insulitis can be detected several weeks before the onset of diabetes as frequently in male mice as in female mice, yet diabetes rarely develops in male mice. Insulitis without progression to diabetes also occurs in mice with certain polymorphisms,[83] and candidate genes that influence the progression from insulitis to diabetes have been identified in mice and humans.[52,84,85] In mice with autoimmune diabetes, T cells that enter the pancreatic islets are initially kept in check by their inhibitory receptor CD152.[51] Similar observations have been made in animal models of autoimmune thyroiditis[20] and arthritis.[6] Table 1 summarizes the various mechanisms that can help prevent progression to autoimmune disease.

TABLE 1. FACTORS THAT INFLUENCE THE PATHOGENESIS OF T-CELL–MEDIATED AUTOIMMUNE DISEASES.*

FACTOR	EXAMPLES
Genetic susceptibility	HLA haplotype, polymorphisms in immunologically important molecules (e.g., cytokines and receptors), homeostasis of T-cell populations
Activation of autoreactive T cells	
Antigen-specific	Presentation of autoantigen or cross-reactive microbial antigen by antigen-presenting cells
Antigen-nonspecific	Bystander activation
Infiltration of target organs by T cells	Expression of adhesion molecules on T cells and endothelial cells, activation status of local antigen-presenting cells
Damage to target organ, overt autoimmune disease	Presence of T-cell–effector molecules (including cytokines), collaboration of different cell populations (e.g., T and B cells), sensitivity of target organ to damage mediated by T cells

*The clinical manifestations of T-cell–mediated autoimmune disease depend on many factors in addition to the breakdown of T-cell tolerance. All the listed factors are subject to immunologic regulation.

GENETIC SUSCEPTIBILITY TO AUTOIMMUNITY

Linkage analysis of the human genome has revealed candidate loci for susceptibility to multiple sclerosis, type 1 diabetes, systemic lupus erythematosus, and Crohn's disease. The chromosomal regions identified in this way include some that span genes for cytokines, cytokine receptors, and other immunoregulatory molecules.[86] Suggestive as these data are, there were major differences in the results of two studies that attempted to identify susceptibility genes for autoimmune diabetes.[87,88] Moreover, in these studies and in similar studies of multiple sclerosis[89] the only unambiguous links identified were to the HLA complex, a finding that merely confirmed previous knowledge.

The genetic analysis of a rat model of rheumatoid arthritis showed that different loci were associated with the onset of arthritis, the severity of joint erosion, and the chronicity of the disease.[90] And genes were identified in a murine model of systemic lupus

erythematosus that conferred resistance to the disease.[91] A more focused approach led to the identification of point mutations in the gene coding for a hitherto unknown transcription factor (*AIRE*) that causes the autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED) syndrome.[92,93] Other well-defined genetic lesions occur in primary immunodeficiency[94] and complement deficiency[95] that increase the likelihood of autoimmunity.[96]

"Background" genes, which are unrelated to genes of the immune system, are important in the development of type 1 diabetes[83] and autoimmune encephalitis. For example, two inbred strains of mice have the same MHC haplotype and have T cells that recognize the same epitope on myelin basic protein, yet one of the strains is susceptible to autoimmune encephalitis and the other is not.[97,98]

THERAPEUTIC IMPLICATIONS

In animal models, literally hundreds of therapies prevent type 1 diabetes, experimentally induced arthritis, chronic inflammatory bowel disease, and experimental autoimmune encephalitis.[99] Yet very few, if any, of these interventions cure established disease. Therapies are needed that not only prevent T-cell reactivity but also reestablish tolerance once the autoreactive T cells have been activated and an autoimmune disease is diagnosed (Table 2). One example of immunomodulation is the treatment of patients with hemophilia. In about 30 percent of patients with hemophilia A who receive infusions of factor VIII concentrates, antibodies against factor VIII develop. To overcome the effects of these antibodies, tolerance can be induced by long-term daily infusions of large amounts of factor VIII.[119] This treatment induces tolerance that lasts for years in approximately 80 percent of patients.[120]

Systemic injection of deaggregated antigen induces tolerance in helper T cells[121] and can prevent experimentally induced autoimmune encephalitis.[122] Clinical investigations of parenteral administration of peptides derived from the autoantigens thought to be involved in diabetes, various allergies, and multiple sclerosis have been performed. Whereas the prophylactic treatment of persons at risk for autoimmune diabetes yielded encouraging results,[102] the beneficial effects of such treatments in patients with established disease were limited.[103-105]

In 1911, Wells reported that anaphylaxis could be prevented in guinea pigs by first feeding them the offending antigen.[123] Oral administration of soluble collagen has prevented collagen-induced arthritis in mice,[124] and oral administration of myelin basic protein and insulin has induced tolerance and prevented disease in murine models of encephalitis and diabetes, respectively.[125,126] However, in another murine model oral administration of autoantigen induced autoimmune diabetes.[110] Moreover, mucosal application of an autologous heat-shock protein induced uveitis in rats,[111] and feeding of the central nervous system autoantigen myelin oligodendrocyte glycoprotein induced a delayed, yet exacerbated, form of encephalitis in monkeys.[127] Clinical trials of oral antigen for the treatment of multiple sclerosis,[106] uveitis,[107] rheumatoid arthritis,[108,109] and autoimmune diabetes[128] have not yielded beneficial effects. The oral delivery of DNA coding for allergens has shown promising results in mice,[129] as has the nasal delivery of peptides.[130]

A peptide that inhibits the activation of a T-cell clone is called an antagonist.[131] Some viruses escape the host's immune response by producing such antagonistic variants of important antigens,[132] and the administration of antagonist peptides has prevented autoimmune encephalitis in mice.[133] A drawback to this therapeutic approach is that the immune response to autoantigens in humans is polyclonal. A peptide that inhibits one clone may stimulate another. A recent phase 2 clinical trial of an altered peptide for the treatment of multiple sclerosis was halted because of exacerbations of the disease in three patients.[134]

IMMUNOMODULATION

Because treatment with antibodies against molecules important for T-cell function induced T cells to become unresponsive in rodents, several of these antibodies have been evaluated in clinical studies.[100] A soluble form of CD152 inhibits the interaction of the costimulatory molecules CD80 and CD86 on antigen-presenting cells with their shared receptor, CD28, on T cells. Treatment with this form of CD152 prevented or ameliorated lupus,[112] autoimmune encephalitis,[135] and arthritis[136] in mice. In a phase 1 study, this form of CD152 decreased disease activity in patients with psoriasis.[113]

Such an approach can, however, have unexpected effects. Blocking CD28-mediated costimulation in mice with autoimmune diabetes exacerbates rather than ameliorates the disease, seemingly because CD28-mediated signals are essential for the survival of CD4+CD25+ T cells that have been implicated in the down-regulation of T-cell–mediated immune responses.[60]

T cells can be categorized according to the cytokines they produce. Type 1 helper T (Th1) cells produce mainly interferon-γ, tumor necrosis factor β, and interleukin-2, whereas type 2 helper T (Th2) cells produce mainly interleukin-4, interleukin-5, and interleukin-13.[137] Since multiple sclerosis and type 1 diabetes are mainly mediated by Th1 cells and allergic diseases by Th2 cells, alteration of the cytokine balance is an appealing therapeutic possibility. There is already evidence that the shift in the balance between Th1-type cytokines and Th2-type cytokines that occurs during pregnancy alleviates the symptoms of rheumatoid arthritis.[138] Such changes in the cyto-

TABLE 2. IMMUNOMODULATORY MECHANISMS AND AGENTS FOR THE TREATMENT OF AUTOIMMUNE DISEASE.*

MECHANISM	TREATMENT	COMMENT
Antigen-specific tolerance	Parenteral application of antigen	Allergen desensitization works well in many cases of allergy.[101] The subcutaneous or intrathecal application of peptide antigens, however, has had very limited success in allergic[102-104] or autoimmune[105] diseases.
	Mucosal application of antigen	Although the results were promising in many animal models, clinical studies have had only limited success.[106-109] In a small minority of animal models, oral application of antigen caused an exacerbation of the disease.[110,111]
	Administration of altered peptide ligands	Results were promising in some animal models, but there was an exacerbation of the disease in one clinical trial.[112]
	Vaccines	Vaccines may be effective in a minority of persons at high risk for autoimmunity against a known self antigen (e.g., the siblings of patients with autoimmune diabetes).
Immunomodulation	Inhibition of costimulation	Results were very promising in animal models. Good results were obtained in a phase 2 study of soluble CD152 in patients with psoriasis.[113] Treatments that block other costimulatory molecules (e.g., CD40), which are currently being evaluated in clinical trials, may not be as safe and effective.
	Change in the cytokine balance	
	Administration of agents that suppress regulatory cytokines (interleukin-10, transforming growth factor α)	Results were mixed in animal models, depending on the timing and the location of the cytokine injection. Results of a phase 2 trial of interleukin-10 in patients with psoriasis were promising.[114]
	Administration of agents that antagonize inflammatory cytokines (TNF-α)	This approach is effective in rheumatoid arthritis[115,116] and Crohn's disease[117] and has been approved by the FDA; however, it induced exacerbations in patients with multiple sclerosis.[118] The long-term safety and efficacy of treatment with TNF-α antagonists are unknown.
	Change in the Th1–Th2 balance	This approach is theoretically appealing but may be difficult to achieve, partly because the phenotype of Th1 or Th2 cells may become unalterable. Exacerbations of disease have been observed in animals in which the Th1–Th2 balance has been altered.
	Other approaches	Interferon beta-1a and interferon beta-1b have been approved by the FDA for the treatment of multiple sclerosis.
	Stem-cell transplantation	Stem-cell transplantation is currently being evaluated in many centers for the treatment of patients with severe autoimmune disease that is refractory to other treatments. This approach may be more successful for some diseases (e.g., systemic lupus erythematosus) than for others (e.g., scleroderma and rheumatoid arthritis).

*A variety of other treatments have been tested in animals and patients with autoimmune diseases.[99,100] FDA denotes Food and Drug Administration, and TNF-α tumor necrosis factor α.

kine profile may be responsible for the beneficial effects of allergen desensitization[101] and of glatiramer acetate, a polypeptide used to treat multiple sclerosis.[139]

Rectifying imbalances between Th1-type cytokines and Th2-type cytokines will not be a simple matter, in part because Th2 cells can mediate effects that are usually attributable to Th1 cells, such as demyelination[127,140] and the destruction of islet cells.[141] Moreover, in animal models of autoimmune arthritis and multiple sclerosis, in which Th1 cells predominate, antibodies mediate tissue damage.[5,142] Conversely, Th1 cells can exacerbate rather than counterbalance Th2-mediated allergic responses.[143]

Clinical trials that are evaluating the immunoregulatory cytokine interleukin-10 in chronic inflammatory diseases have reported encouraging initial results in patients with psoriasis.[114] Antagonizing the inflammatory cytokine tumor necrosis factor α with monoclonal antibodies or soluble "decoy" receptors has proved remarkably effective in the treatment of rheumatoid arthritis[115,116] and Crohn's disease.[117] In stark contrast, neutralization of tumor necrosis factor α exacerbated multiple sclerosis.[118] Clearly, we still have much to learn about the pathogenesis and treatment of chronic inflammatory diseases.

PURGING AUTOREACTIVE T CELLS FROM THE T-CELL REPERTOIRE

Purging autoreactive cells from the immune repertoire is an option in severe cases of autoimmunity. Autologous stem-cell transplantation has been tried in patients with rheumatoid arthritis, psoriasis, and systemic lupus erythematosus with variable success.[144,145] It is not yet possible to judge the long-term efficacy and safety of this approach, and it is unclear whether patients who receive such treatment can generate a completely new repertoire of T cells.[146] Nevertheless, purified CD34+ hematopoietic progenitor cells that are depleted of autoreactive lymphocytes and inflammatory leukocytes may be a way to reinduce tolerance.

CONCLUSIONS

The past decade has witnessed an enormous expansion in the knowledge of lymphocyte physiology

and the mechanisms that induce and maintain self-tolerance. In large part this new understanding is due to technical advances such as the development of transgenic and "knockout" mice, the ability to detect and isolate rare lymphocyte populations, and "high-throughput" analysis of genetic information. Oligonucleotide arrays, which can detect several thousand genes that are expressed in healthy or diseased tissue, have been used to elucidate molecular mechanisms of the activation, tolerance, and autoimmunity of T cells.[48,49,66] Several genes that were hitherto not suspected to participate in chronic inflammatory processes have already been identified through the use of this technique.[147] Gene-mapping studies have demonstrated that allergy and autoimmunity must involve not only the recognition of antigen by T cells, but also the crucially important immunoregulatory effects of cytokines, inhibitory receptors, and survival factors.[85,86,90,91] The challenge is to make therapeutic use of this new knowledge.

It is easy to point out disappointments encountered when treatments based on animal models were transferred to the clinic.[103,105,106,108,109,128] But by no means does this end our hope for clinical applications of novel strategies that are emerging from the laboratory. Notably, interferon beta for multiple sclerosis[148,149] and tumor necrosis factor α antagonists for rheumatoid arthritis[115,116] and Crohn's disease[117] are the first new treatments for autoimmunity approved by the Food and Drug Administration in 20 years. Moreover, a wealth of recent data points to the importance of the innate immune system in determining whether T cells become activated and functional.[150] This information has already been used to improve immunization strategies[151] and should also lead to new approaches to the reinduction of immune tolerance. Finally, the characterization of self antigens that threaten high-risk groups (e.g., siblings of patients with autoimmune diabetes) could result in the development of an effective vaccine.

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