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Homeostasis and Self-Tolerance in the Immune System: Turning Lymphocytes off

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The immune system responds in a regulated fashion to microbes and eliminates them, but it does not respond to self-antigens. Several regulatory mechanisms function to terminate responses to foreign antigens, returning the immune system to a basal state after the antigen has been cleared, and to maintain unresponsiveness, or tolerance, to self-antigens. Here, recent advances in understanding of the molecular bases and physiologic roles of the mechanisms of immune homeostasis are examined.

The immune system has a remarkable capacity to maintain a state of equilibrium even as it responds to a diverse array of microbes and despite its constant exposure to self-antigens. Immunologists have focused largely on defining the stimuli that induce the growth, differentiation, and effector functions of lymphocytes, and over the last two decades, the essential features of lymphocyte activation and immune responses have been defined in considerable detail. Less is known about the mechanisms that terminate immune responses. These mechanisms are important in two main situations. First, after a productive response to a foreign antigen, the immune system is returned to a state of rest, so that the numbers and functional status of lymphocytes are reset at roughly the preimmunization level. This process is called homeostasis, and it allows the immune system to respond effectively to a new antigenic challenge. The size and content of the preimmune lymphocyte repertoire are also closely regulated, as new emigrants from the generative lymphoid organs compete for "space" with resident cells. The mechanisms responsible for maintaining homeostasis before antigen exposure have been the subject of other reviews (*1*) and are not discussed here. Second, lymphocytes with receptors capable of

recognizing self-antigens are generated constantly, yet normal individuals maintain a state of unresponsiveness to their own antigens, called self-tolerance. In this article, we review the principal control mechanisms for maintaining homeostasis after active immune responses to foreign antigens and for preventing or aborting responses to self-antigens. Our emphasis is on T lymphocytes, because many of the recent advances have come from studies of T cells, but it is likely that the general principles are applicable to all lymphocytes. Elucidating the nature of these homeostatic mechanisms may lead to better strategies for suppressing harmful immune responses and for augmenting and sustaining beneficial responses to microbial vaccines and tumors.

Signals for Lymphocyte Maintenance, Growth, and Differentiation

Phenotypically and functionally naïve lymphocytes may survive for long periods, up to several months in mice, in the absence of overt antigen exposure (*2*). The basal survival of naïve B cells requires the expression of antigen receptors (*3*), and that of T cells requires the presence of major histocompatibility complex molecules, which are essential components of the ligands that the T cells recognize (*4*). Thus, the maintenance of the pool of naïve lymphocytes, before immunization, is dependent on antigen receptor–mediated signals (Fig. 1). These signals might be

generated by spontaneous aggregation of antigen receptors or by the engagement of these receptors by extracellular ligands. The requisite ligand or ligands have not been identified; they may include environmental antigens or even self-antigens that are recognized with low affinities by mature lymphocytes.

For an immune response to occur, lymphocytes must be exposed to two types of stimulus. The first signal, an antigen, ensures the specificity of the response. "Second signals" are elicited by microbes, either directly or by the initial innate immune response, which identifies the antigen as a potential pathogen (*5, 6*). Second signals for T lymphocytes include costimulators and cytokines that promote clonal expansion of the specific T cells and their differentiation into effector and memory cells (Fig. 1). The best defined costimulators for T cells are the two members of the B7 family, B7-1 (CD80) and B7-2 (CD86), which are induced on antigen-presenting cells (APCs) by microbes and by cytokines produced during innate immune reactions (*7*). The CD28 receptor on T cells recognizes B7 molecules and delivers activating signals; a second receptor for B7, called CTLA-4, functions to terminate T cell responses and is discussed later. The engagement of CD28 by B7 results in the expression in T cells of antiapoptotic proteins of the Bcl family, notably Bcl-x$_L$ (*8*), and the production of cytokines, such as interleukin-2 (IL-2) (*9*). Thus, costimulation promotes the survival of T cells that encounter an antigen, allowing autocrine cytokines to initiate clonal expansion and differentiation. A second system of costimulation may be the CD40 molecule on antigen-presenting cells, which interacts with its ligand on T cells (*10*). Neither the biochemical consequences of CD40L engagement in T cells nor the ability of CD40-CD40L interactions to replace B7-CD28 signals has been established. The best defined second signal for B cells is a breakdown product of complement activation, called C3d, which engages its receptor, CD21, on B cells and functions in concert with an antigen to trigger B lymphocyte proliferation and differentiation (*5, 11*). Microbes may directly activate the complement cascade by the alternative pathway, generating C3d, or an initial immunoglobulin M antibody re-

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sponse may activate the classical pathway, also leading to the generation of C3d. The critical role of complement as a second signal for B cells is demonstrated by the virtual absence of antibody responses in mice lacking C3 or the CD21 receptor (*11*). It is not known if CD21 engagement activates antiapoptotic genes and promotes B cell survival, allowing helper T cell–derived cytokines to then stimulate B lymphocyte expansion and differentiation, but the parallel with the requirement for T cell costimulation is striking.

Some of the progeny of antigen-stimulated lymphocytes develop into long-lived, functionally quiescent memory cells. Memory cells may be capable of surviving for long periods without stimulation; alternatively, and more likely, they may be maintained by low-level stimulation by a persisting fraction of the antigen that initiated the response or by environmental or self-antigens that cross-react with the initiating antigen (*12*). Thus, the maintenance of mature lymphocytes in lymphoid tissues is an active process that requires continual stimulation. We do not know the differences between stimuli that keep naïve and memory cells viable but in a noncycling state without overt immunization and those that drive specific lymphocytes into proliferation and differentiation upon exposure to an antigen.

Mechanisms for Preventing and Terminating Lymphocyte Responses

Maintaining homeostasis in the face of rapid and dynamic alterations in lymphocyte populations and avoiding autoimmune reactions to continuously present self-antigens require effective mechanisms for preventing and terminating lymphocyte responses. These mechanisms fall into two broad categories. First, the absence or loss of stimuli that provide necessary survival and growth signals to lymphocytes leads to a failure to initiate immune responses and functional inactivation or programmed death of lymphocytes. Second, lymphocyte activation itself triggers regulatory systems whose primary function is to control lymphocyte proliferation and differentiation. We will first discuss the mechanisms that prevent and terminate immune responses and then the roles of these mechanisms in lymphocyte homeostasis and self-tolerance.

Failure of lymphocyte activation. Lymphocyte activation requires both antigen and second signals and will not occur when either is absent. The review by Ploegh in this issue discusses how microbes can elude the immune system by blocking antigen presentation, thus eliminating the first signal needed for lymphocyte activation (*13*). In other situations, an antigen may be pre-

sented to lymphocytes in the absence of second signals, again failing to activate them. For instance, if T cells are exposed to an antigen in the presence of B7 antagonists, or if CD28-deficient T cells encounter an antigen, the cells do not expand and rapidly undergo apoptosis (*8, 14, 15*). As we shall discuss later, self-antigens may be ignored by the immune system in part because they do not trigger innate immunity or induce the expression of second signals. Foreign antigens administered without adjuvants may also fail to stimulate immune responses, for the same reason. This concept has been exploited to develop strategies for preventing allograft rejection, by blocking costimulation at the time of organ transplantation in animals (*16*). Clinical trials of costimulator antagonists for blocking pathologic immune responses are currently under way.

Lymphocyte anergy. Antigen recognition by lymphocytes without second signals may lead to a state of functional unresponsiveness, also called anergy. This state was first demonstrated with cloned lines of CD4$^+$ helper T cells, in which antigen receptors were engaged without costimulation (*17*). It is thought that anergy is induced by foreign antigens administered without adjuvants or by autologous tissue antigens that are recognized by T cells without costimulation, because such antigens do not stimulate inflammation or activate APCs (*18*); why these antigens are not simply ignored by the immune system is not clear. Essentially the same phenomenon occurs in self-reactive B cells chronically exposed to a self-antigen in the absence of T cell help (*19*). The major limitation of these studies is that the T cell experiments have been done mainly in vitro with cell lines and the B cell experiments rely on transgenic systems in which large numbers of identical B cells are exposed to high concentrations of self-antigens. To what extent these findings may be extrapolated to normal lymphocyte populations exposed to tolerogenic foreign or self-antigens in vivo remains unanswered. Some studies suggest that in some models of T cell anergy, the unresponsive state is induced not because of the absence of B7-mediated costimulation but because T cells use the CTLA-4 receptor to recognize B7 molecules (*20*); the importance of CTLA-4 is discussed below. T cell anergy may also be induced under conditions at which adequate costimulation is available but at which the antigen receptor signal is suboptimal, for example, when a T cell encounters an altered peptide ligand, which does not bind to the T cell receptor optimally (*21*).

Loss of activated lymphocytes due to "death by neglect." The frequency of mature lym-
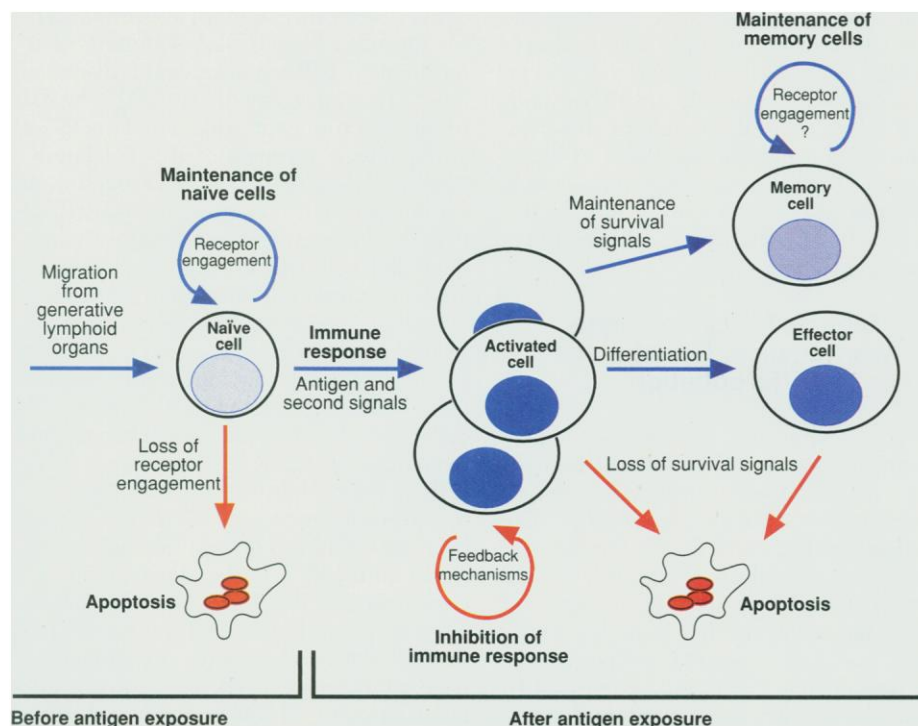

Fig. 1. Stages in the development and homeostasis of an immune response. The signals that maintain lymphocyte populations and induce their proliferation and differentiation are indicated in blue and those that terminate immune responses and maintain homeostasis are shown in red.

phocytes specific for any one antigen is on the order of 1 in 10^6. Upon exposure to the antigen under conditions that elicit specific immune responses, this frequency can increase to 1 in 1000 or more within a week and return to baseline levels within 4 to 12 weeks (2, 22). This rapid decline in cell number is due to the elimination of lymphocytes by apoptosis. Lymphocytes that are deprived of survival stimuli, such as costimulators and cytokines, lose expression of antiapoptotic proteins, mainly of the Bcl family, and die "by neglect" (23). We refer to this pathway of apoptosis as "passive cell death" to distinguish it from "activation-induced cell death," which will be discussed later. Although both pathways of apoptosis share the same terminal effector phase and show the same morphologic and biochemical manifestations, their induction, molecular controls, and physiologic functions are largely distinct (Table 1).

Active termination of T cell immune responses. A unique feature of lymphocytes is that their activation itself triggers feedback mechanisms that limit their proliferation and differentiation. Three such regulatory pathways have recently been identified in T cells (Fig. 2), and mutations in the critical molecules are providing important insights into the physiologic importance of such mechanisms and the pathologic consequences of their disruption.

1) CTLA-4–mediated T cell inhibition. The discovery of the B7-CD28 pathway of costimulation provided a much sought after explanation for the requirement for second signals for T cell activation. It, therefore, came as a surprise when a second T cell receptor for B7 molecules, called CTLA-4, was shown to function primarily to shut off T cell activation (24). CTLA-4 is induced on T cells after activation, and upon binding B7 it transduces signals that inhibit the transcription of IL-2 and the progression of T cells through the cell cycle (25). The biochemical basis of negative signaling by CTLA-4 is not clearly defined. It is known that CTLA-4 blocks signals transduced by CD28, suggesting that these two B7-recognizing molecules function as mutual antagonists (25).

2) Fas-mediated activation-induced cell death. Activation of T cells also leads to coexpression of the death receptor, Fas (CD95), and its ligand, FasL, resulting in death of the same and neighboring cells (23, 26). The biochemistry of Fas-mediated apoptosis has been the subject of numerous reviews (27). In T cells, this pathway of apoptosis is induced by repeated activation, is potentiated by IL-2, and is not prevented by constitutive expression of Bcl-2 or Bcl-x_L (see Table 1). It is likely that Fas-mediated death of T lymphocytes is most important

for eliminating cells that repeatedly encounter persistent antigens, such as self-antigens. This hypothesis is supported by the observation that mice with mutations in Fas or FasL develop autoimmune disease (discussed below) but do not exhibit abnormally prolonged responses to viruses or immunization with foreign antigens (28, 29).

3) IL-2–mediated feedback regulation. IL-2 is the prototypical T cell growth factor and functions in an autocrine and paracrine manner to stimulate clonal expansion of antigen-stimulated lymphocytes and "bystander" cells. This role of IL-2 is so well
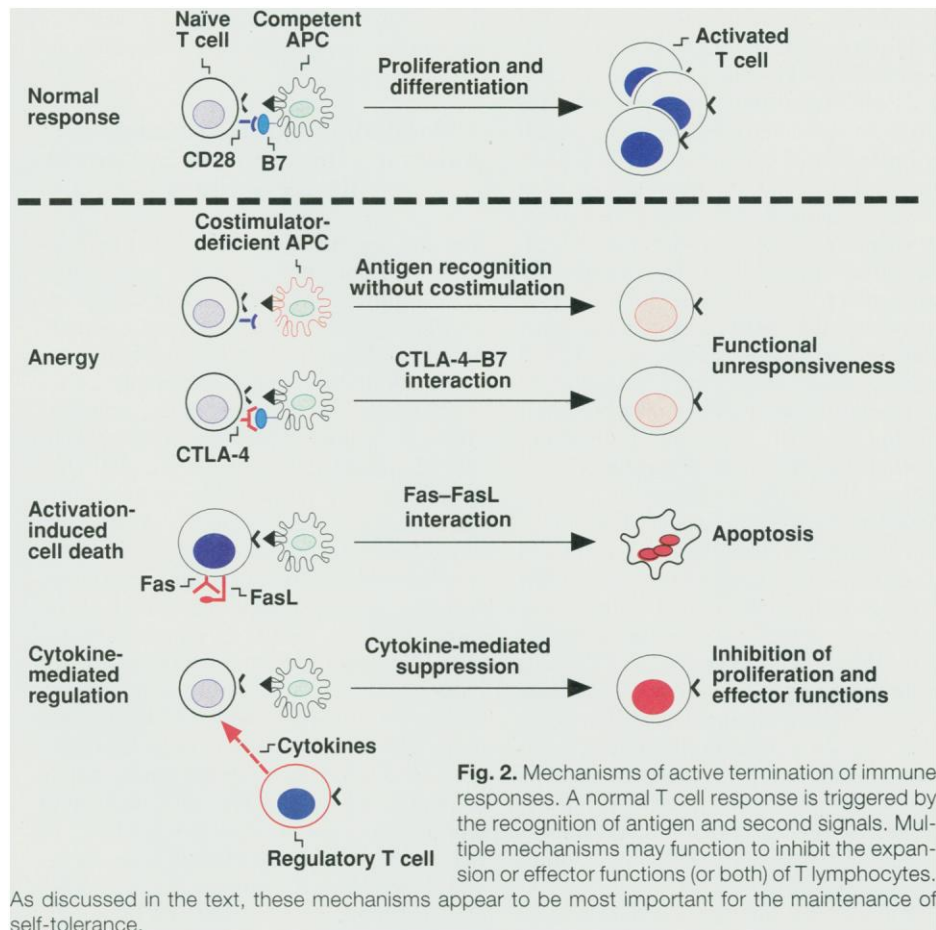

Fig. 2. Mechanisms of active termination of immune responses. A normal T cell response is triggered by the recognition of antigen and second signals. Multiple mechanisms may function to inhibit the expansion or effector functions (or both) of T lymphocytes. As discussed in the text, these mechanisms appear to be most important for the maintenance of self-tolerance.

Table 1. Pathways of apoptotic death of mature CD4$^+$ T lymphocytes. The comparative features of apoptotic pathways in mature CD4$^+$ T lymphocytes are summarized. Note that these pathways of apoptosis may serve other functions in immature lymphocytes and in B cells, which are not included.

Feature	Passive cell death ("death by neglect")	Activation-induced cell death
Induction	Inadequate stimulation [absence of antigens or costimulators (or both)]	Repeated antigenic stimulation
Sensitivity of naïve and activated T cells	Both sensitive	Only activated cells sensitive
Role of IL-2	Protects	Enhances
Role of Fas	None	Obligatory
Role of Bcl-2 and Bcl-x	Protects	None
Physiological roles	Elimination of mature cells that do not encounter antigens and costimulation	Elimination of mature self-reactive T cells (peripheral tolerance)
	Homeostatic control of lymphocyte pool: loss of activated cells that do not receive continued stimulation or growth factors	Homeostatic control?

established that it came as a surprise to discover that targeted disruption of the *IL-2* gene leads not to profound immunodeficiency but to uncontrolled accumulation of activated lymphocytes and manifestations of autoimmunity (*30*). Mice lacking the high-affinity IL-2 receptor show the same phenotypic abnormalities (*31*). These results suggest that IL-2 is a necessary feedback inhibitor of lymphocyte responses and its role as a growth factor can be replaced by other cytokines. How IL-2 functions to control T cell expansion is not yet fully resolved. One possibility is that IL-2 potentiates Fas-mediated apoptosis, and in the absence of this cytokine the Fas signaling pathway is silenced (*32*). It may also interfere with other activation-dependent feedback control mechanisms. The growth-promoting effect of IL-2 and its inhibitory effect could well be active at different phases of immune responses: Early in a T cell response, when IL-2 concentrations are low, the proliferative effect may be dominant, but when the cytokine accumulates and other stimuli change, it may function to terminate the response (*15*).

Cytokine-mediated regulation. The stimulation of naïve T lymphocytes by antigen and second signals leads to their differentiation not only into effector cells whose function is to eliminate the antigen but also into regulatory cells. Such regulatory T cells may function by producing cytokines whose net effect is immunosuppressive. Examples of such cytokines are transforming growth factor–β1 (TGF-β1) (*33*), which inhibits lymphocyte proliferation, and IL-10, which inhibits macrophage activation and the expression of costimulators (*34*). These inhibitory cytokines limit the expansion of specific lymphocytes and return activated macrophages and other inflammatory cells to their normal resting state.

The existence of multiple mechanisms for feedback inhibition of immune responses raises several important issues. First, it is striking that the same molecules or pathways may function to both amplify and terminate immune responses. The best examples of such dual functions are the B7 costimulators and IL-2, both of which are capable of delivering activating and inhibitory signals. In the case of B7, the net functional effect is determined by which T cell receptor (CD28 or CTLA-4) is engaged, but IL-2 mediates both types of functions by interacting with the same multimeric receptor. This raises the important, and as yet unresolved, problem of how the opposing functional effects of the same extrinsic stimuli are regulated. Second, we do not know if all the feedback mechanisms work together to terminate all immune responses or if, as seems more likely, different

mechanisms become operative after different types of antigen exposure. If the latter, then we need to define the nature of the antigen (its form, concentration, and persistence) and other concomitant stimuli that determine which mechanism is involved in terminating the response. This question is important not only for elucidating the biology of homeostasis in the immune system but also for developing approaches for manipulating immune responses.

Mechanisms of Homeostasis: Returning the Immune System to Its Basal State

Immune responses are self-limited and decline with time after antigenic stimulation. This decline is characterized by a precipitous fall in lymphocyte numbers accompanied by a diminution in effector functions, leaving long-lived but functionally quiescent memory lymphocytes as the only surviving indicators of previous antigen exposure (*2, 12, 22*). This loss of antigen-stimulated lymphocytes probably occurs mainly because of passive cell death. As the immune response eliminates the antigenic stimulus and the innate immune reaction to antigen (microbe) exposure subsides, the stimuli that are needed for lymphocyte survival (including costimulators and cytokines) gradually wane, resulting in reduced expression of antiapoptotic Bcl family proteins. The importance of Bcl-regulated passive cell death in lymphocyte homeostasis is demonstrated by the loss of lymphocytes seen in mice that are deficient for Bcl-2 or Bcl-x (*35*), by the correlation between reduced Bcl-2/Bcl-x$_L$ expression and the decline of lymphocyte numbers after immunization (*36*), and by studies showing that constitutive expression of Bcl-2 as a transgene in B or T lymphocytes results in enhanced survival of antigen-stimulated lymphocytes and prolonged immune responses (*29, 37*). These results also suggest that lymphocytes that are recruited to the memory population may reexpress antiapoptotic Bcl proteins. Perhaps the stimuli that maintain quiescent naïve and memory lymphocyte populations are sufficient to induce the expression of antiapoptotic proteins but are incapable of inducing production of the cytokines that trigger lymphocyte proliferation and differentiation. It is also possible that the viability of naïve and memory cells is less dependent on survival stimuli than that of activated lymphocytes, so that the disappearance of antigen and second signals leads to the loss of recently activated cells but does not eliminate naïve and memory populations.

The role of actively induced feedback

mechanisms in returning the immune system to its basal state after antigen exposure is being investigated in numerous laboratories. The control of potentially harmful T cell and macrophage reactions by immunosuppressive cytokines is important for limiting the inflammatory consequences of immune responses, because mice with targeted disruptions of IL-10 or TGF-β1, the two best defined antiinflammatory cytokines, develop uncontrolled leukocyte activation and tissue injury (*38*). Much less is known about the functions of T cell anergy or CTLA-4– or Fas-mediated regulation in normal homeostasis. In fact, T cells lacking CTLA-4 or Fas show normal kinetics of expansion and decline after exposure to an antigen in vivo (*29, 39*). Such results raise the possibility that CTLA-4– and Fas-mediated regulation is more important for the maintenance of self-tolerance than for the regulation of responses to foreign antigens.

Mechanisms of Self-Tolerance: Preventing Autoimmune Reactions

The mechanisms that prevent immune responses against self-antigens fall into three broad groups. Central tolerance is due to the death of developing lymphocytes when they encounter self-antigens in the generative lymphoid organs and is important for tolerance to self-antigens that are present at high concentrations in the bone marrow and thymus. The genes involved in regulating the development of lymphocytes are discussed by Fischer and Malissen (*40*). Peripheral tolerance is maintained by mechanisms that act on mature lymphocytes that have left the generative organs and encounter self-antigens in peripheral tissues; the mechanisms of peripheral tolerance are discussed below. Some self-antigens may induce neither central nor peripheral tolerance but are simply ignored by the immune system. Such "clonal ignorance" (*41*) may be because the self-antigen is anatomically sequestered from immunocompetent lymphocytes or because the antigen is presented to lymphocytes in the absence of the second signals that are needed to trigger effective immune responses. Because self-antigens do not normally elicit innate immune reactions, it is not surprising that they may be ignored by the immune system. A continuing problem in our understanding of self-tolerance is that we do not know which or how many self-antigens induce central or peripheral tolerance or are ignored and which characteristics of self-antigens determine which of these mechanisms of self-tolerance is operative.

Self-antigens may induce tolerance in the mature B or T lymphocyte compart-

ment if these cells encounter the antigens in the absence of second signals or if the self-antigens trigger mechanisms that actively block lymphocyte activation or induce apoptosis (Fig. 2). Although it is widely believed that self-antigen recognition without costimulation induces functional anergy, we do not know what factors determine whether a self-antigen is functionally ignored or induces anergy. The frequently noted association between infections and autoimmunity has been attributed to the activation of anergic self-reactive lymphocytes by adjacent cells reacting to microbial antigens but may also result from the activation of autoreactive lymphocytes that have remained ignorant of the antigen until second signals are up-regulated as a consequence of the infection.

The maintenance of self-tolerance may not simply reflect the lack of lymphocyte responses to self-antigens but may be because the responses of lymphocytes to self-antigens are tightly regulated by specific molecular interactions. This concept is best illustrated by the autoimmune diseases that develop in knockout mice lacking proteins that are critical for terminating immune responses (Table 2). Thus, mutations in Fas or FasL result in lupuslike autoimmune disease (26), which is due to abnormally prolonged survival of autoreactive helper T cells (29) and an inability to eliminate self-reactive B lymphocytes by apoptosis (42). Mutations in the *fas* gene are associated with an autoimmune syndrome with lymphoproliferation in humans as well (43). The regulatory function of CTLA-4 is most markedly illustrated by targeted disruption of the *CTLA-4* gene in mice, which results in massive accumulation of activated lymphocytes in the spleen and lymph nodes, manifestations of autoimmunity, and infiltration of multiple tissues by activated lymphocytes, with attendant injury that is usually fatal by 3 to 4 weeks of age (44). These lesions are suggestive of autoimmune disease, but to date, there is no direct demonstration that the infiltrating lymphocytes actually recognize and respond to self-antigens. Mice lacking IL-2 and the α or β chain of the IL-2 receptor develop lymphadenopathy and various manifestations of autoimmunity, including autoimmune hemolytic anemia (30, 31). Polymorphisms in the *IL-2* gene are linked to insulin-dependent diabetes mellitus (IDDM) in mice (45) and humans (46), and another susceptibility locus for IDDM maps close to the *CTLA-4* gene (46). The role of regulatory T cells in preventing autoimmunity is best illustrated in animal models, in which selective depletion of T cells with an activated phenotype allows the development of multiorgan autoimmune lesions (47). Such

results imply that a subset of T cells responds to self-antigens (hence the "activated" phenotype) and keeps in check other, potentially pathogenic autoreactive lymphocytes. The regulatory function may be mediated by immunosuppressive cytokines, but the critical molecules have not yet been identified.

These single gene models are providing valuable information about the mechanisms of T cell–mediated autoimmune disease. In these models, central tolerance, or negative selection of developing T cells in the thymus, is unaffected, so the abnormality must be in peripheral tolerance. All the genes involved play roles in T cell regulation, leading to the conclusion that defects in lymphocyte regulation may result in autoimmunity without any change in the way self-antigens are displayed to the immune system. This conclusion also implies that specific recognition of self-antigens is a normal phenomenon and that key to the maintenance of self-tolerance is the control imposed on specific lymphocytes after they have encountered self-antigens. In fact, regulatory mechanisms dependent on Fas-FasL interactions, CTLA-4, and IL-2 are actually triggered by antigen recognition, suggesting that self-tolerance develops if responses to self-antigens are initiated and then aborted. Finally, and perhaps most intriguing, is the finding that, despite the existence of multiple mechanisms of self-tolerance, disruption of any one pathway leads to autoimmunity. In other words, these mechanisms are not redundant and cannot compensate for one another. The available evidence indicates that Fas-FasL interactions are responsible for activation-induced apoptotic death of mature T lymphocytes in vivo (48), CTLA-4 plays a role in inducing functional inactivation or a form of anergy (20), and IL-2 potentiates Fas-mediated cell death (32, 49) and possibly other regulatory mechanisms. The roles of these regulatory proteins may be nonredun-

dant because different self-antigens may induce peripheral tolerance by different mechanisms. For instance, tissue-restricted self-antigens present at low concentrations may induce anergy, and widely disseminated and abundant self-antigens may trigger activation-induced cell death. Such a hypothesis can be experimentally tested by expressing "self"-antigens as transgenes in different tissues and at different concentrations, an approach that has been enormously valuable for analyzing B cell development and self-tolerance (50). If different self-antigens induce tolerance by different mechanisms, for example, CTLA-4–dependent anergy or Fas-mediated apoptosis, then one can predict that the autoimmunity seen in the various gene knockout models (Table 2) will be toward distinct types or classes of self-antigens. We do not know if this is true, because the failure to clearly identify target antigens has been a major problem in elucidating the mechanism of autoimmune diseases in humans and experimental models.

Conclusions

Terminating lymphocyte activation is important for the normal decline, or homeostasis, of responses to foreign antigens and for maintaining tolerance to self-antigens. The mechanisms that terminate or prevent immune responses fall into two broad categories: "passive" control mechanisms due to the decline or absence of activating stimuli and active mechanisms induced by the processes of lymphocyte activation.

Elucidation of these homeostatic processes raises the following question: Do different regulatory mechanisms serve distinct physiologic functions, or can they all function to maintain both homeostasis and self-tolerance? Although definitive answers are not yet possible, the available data suggest that the return of the immune system to rest after it has responded to foreign antigens is mainly

Table 2. Autoimmunity caused by single-gene defects. Mutations in regulatory molecules (either spontaneous or created by targeted gene disruption) lead to autoimmune diseases with distinct phenotypes in mice. AICD, activation-induced cell death.

Fas-FasL	IL-2–IL-2Rα, β	CTLA-4
	Autoimmune disease	
Multiple autoantibodies; nephritis	Hemolytic anemia; anti-DNA antibodies; inflammatory bowel disease (due to infection?)	Tissue infiltration; autoantibodies?
	Lymphoproliferation	
Yes; accumulating cells are inert double-negative T cells	Yes; accumulating cells are phenotypically normal, activated T and B cells	Yes; accumulating cells are phenotypically normal, activated T and B cells
	Postulated immunologic defects	
Failure of AICD in CD4$^+$ helper T cells; failure to eliminate anergic B cells	Failure of AICD in CD4$^+$ helper T cells; other defects in regulation?	Failure of T cell anergy

due to passive death of activated lymphocytes. In contrast, self-tolerance is maintained either because self-antigens are ignored by the immune system or because they actively terminate immune responses. If the mechanisms that maintain homeostasis and self-tolerance are indeed largely distinct, then the next question that arises is what are the features of foreign and self-antigens that trigger these distinct regulatory processes. This question, too, cannot be answered with certainty. It is tempting to speculate that the key differences are that most foreign antigens, such as microbes, are short-lived and responses to them are often accompanied by innate immune reactions, whereas self-antigens are permanent, and their recognition is not associated with innate immune responses. Therefore, the type of homeostatic processes that terminate an immune response may vary according to the nature of the antigen and attendant stimuli and may not be strictly related to whether the antigen is foreign or self. Indeed, it is possible that responses to some foreign antigens, for example, viruses, that are able to persist in the absence of substantial inflammation may be limited by the same mechanisms that normally function to maintain self-tolerance and that tolerance to certain self-antigens may result from the elimination of activated lymphocytes by passive cell death.

Future studies should start to define the types of immune responses, conditions of antigen exposure, and forms of foreign and self-antigens that trigger different mechanisms of homeostasis and self-tolerance, as well as the biochemical basis of these regulatory processes. The ability to combine transgenic and gene knockout animal models with in vivo and biochemical analyses holds great promise for providing valuable answers to these fundamental questions.

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Viral Strategies of Immune Evasion

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The vertebrate body is an ideal breeding ground for viruses and provides the conditions that promote their growth, survival, and transmission. The immune system evolved and deals with this challenge. Mutually assured destruction is not a viable evolutionary strategy; thus, the study of host-virus interactions provides not only a glimpse of life at immunity's edge, but it has also illuminated essential functions of the immune system, in particular, the area of major histocompatibility complex–restricted antigen presentation.

The immune system is commonly divided into two major branches: innate and adaptive immunity (Fig. 1). The innate response to an invading pathogen involves the rapid recognition of general molecular patterns such as carbohydrates or other posttranslational modifications present on the pathogens themselves or in the infected cell. Eosinophils, monocytes, macrophages, natural killer cells, and soluble mediators—such as components of the complement cascade and acute phase reactants—are either bactericidal or activate cellular functions that eradicate pathogens. Viral infections also induce a potent antiviral response mediated by interferons. Confrontation of the innate immune system with pathogens leads to its activation and prepares the adaptive arm of the immune system to respond appropriately. Adaptive immunity is conveyed by both cellular and humoral elements. Through their antigen specific receptors, B and T lymphocytes interact with pathogens or fragments derived from them, presented on antigen-presenting cells. The activated

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