The Danger Model: A Renewed Sense of Self

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For over 50 years immunologists have based their thoughts, experiments, and clinical treatments on the idea that the immune system functions by making a distinction between self and nonself. Although this paradigm has often served us well, years of detailed examination have revealed a number of inherent problems. This Viewpoint outlines a model of immunity based on the idea that the immune system is more concerned with entities that do damage than with those that are foreign.

First, do no harm.
      –Hippocratic oath

Of all the mysteries in modern science, the mechanisms of self versus nonself recognition in the immune system ranks at or near the top.

–D. E. Koshland Jr. (*1*)

As a graduate student, I was taught that the immune system functions by discriminating between self (defined early in life) and nonself (anything that comes later), tolerating self and attacking nonself. Although this elegantly simple idea seemed to make a lot of sense, it had problems from the beginning and has failed over the years to explain a great number of findings. For example, what happens when "self" changes? How do organisms go through puberty, metamorphosis, pregnancy, and aging without attacking newly changed tissues? Why do mammalian mothers not reject their fetuses or attack their newly lactating breasts, which produce milk proteins that were not part of earlier "self"? Why do we fail to make immune responses to vaccines composed of inert foreign proteins unless we add noxious substances, collectively known as "adjuvants"? Why do we fail to reject tumors, even when many clearly express new or mutated proteins? Why do most of us harbor autoreactive lymphocytes without any sign of autoimmune disease, while a few individuals succumb?

To answer some of these questions, I proposed the Danger model, which suggests that the immune system is more concerned with damage than with foreignness, and is called into action by alarm signals from injured tissues, rather than by the recognition of nonself (*2*, *3*). In the intervening 7 years, in conversations with a wide variety of people, I discovered that this simple idea not only offers answers to broad immunological questions, it also covers many details that had not

been incorporated into previous models [for example, why major histocompatibility complex (MHC)–mismatched kidney transplants from living donors often perform better than MHC-compatible kidneys from cadavers (*4*); why liver transplants are rejected less vigorously than hearts; why women seem to be more susceptible than men to certain autoimmune diseases; why Rh disease of the newborn is a problem in the second pregnancy, but not the first; why graft-versus-host disease is less severe in recipients that have had gentle rather than harsh preconditioning treatments (*5*, *6*); and so on] without adding special new situation-specific assumptions.

This Viewpoint will first trace the history of the self-nonself (SNS) model, showing how it had to be modified over the years to accommodate new data, then give a brief description of the Danger model, and show how it is leading us to a new way of thinking about self-recognition. Those readers who may already have encountered some of these concepts (*2*, *7–9*) will find more details in the supplementary Web material on *Science* Online (*10*).

The Self-Nonself Models

Burnet's original model (*11*) suggested (Fig. 1) that (i) each lymphocyte expresses multiple copies of a single surface receptor specific for a foreign entity, (ii) signaling through this surface antibody initiates the immune response, and (iii) the self-reactive lymphocytes are deleted early in life [based on Owen's discovery that nonidentical cattle twins were mutually tolerant of each other's blood cells (*12*)]. This straightforward model gained general acceptance when Medawar *et al.* found that adult mice would accept foreign skin grafts if they had been injected as babies with cells from the donors (*13*). In 1960, Burnet and Medawar shared the Nobel Prize for their work, and the SNS discrimination model has dominated the field ever since.

The original SNS model has changed, however, to accommodate incompatible new findings. It was first modified in 1969, after

the discovery that activated B lymphocytes hypermutate, creating new, potentially self-reactive cells. Realizing that autoimmunity would be rare if immunity required the cooperation of two cells, Bretscher and Cohn (*14*) added a new cell (the helper, later found to be a T cell) and a new signal (help), proposing that the B cell would die if it recognized antigen in the absence of help (Fig. 1B). In 1975, Lafferty and Cunningham (*15*) dealt with the finding that T cells respond more strongly against foreign cells of their own species than against cells of another species, by adding another cell and another signal. They proposed that T cells also need a second signal (named "costimulation"), which they receive from "stimulator" cells [now called antigen-presenting cells (APCs)], and suggested that this signal is species specific (Fig. 1C).

The Infectious-Nonself (INS) Model

The need for costimulation posed a major problem for SNS models. If, as they assumed, the decision to respond is made by antigen-specific cells, and if self-reactive ones are deleted, then immunity can be directed against nonself. If, however, responses are initiated by APCs, which are not antigen specific (they capture all sorts of self and foreign substances), then immunity cannot be directed only against nonself. The concept of costimulation was therefore essentially ignored until it was rediscovered experimentally by Jenkins and Schwartz in 1986 (*16*). In 1989, Janeway offered an ingenious solution (*17*), suggesting that APCs have their own form of SNS discrimination and can recognize evolutionarily distant pathogens. He proposed that APCs are quiescent (a very important and previously unappreciated point) until they are activated via a set of germ line–encoded pattern recognition receptors (PRRs) that recognize conserved pathogen-associated molecular patterns (PAMPs) on bacteria. On activation, APCs up-regulate costimulatory signals, process the bacterial antigens, and present them to passing T cells (Fig. 1D). The PRRs, he wrote, allow APCs to discriminate between "infectious-nonself" and "noninfectious-self" (*18*).

Although the essence of SNS recognition was temporarily saved, Janeway's infectious-nonself (INS) model created new complexities while solving old problems. It could not explain why viruses stimulate immunity, why transplants are rejected, what induces autoim-

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munity, why tumors are sometimes spontaneously rejected, or how nonbacterial adjuvants, such as alum, work. Over the years, Janeway's model has been modified to account for some of these issues (see Viewpoint by Medzhitov and Janeway in this issue) (*19*), suggesting, for example, that viral double-stranded mRNA is a signature of foreignness. What then of viruses that do not generate double-stranded RNA, adjuvants that do not incorporate bacterial products, transplants, and autoimmunity? Even with all of the modifications that SNS/INS models have undergone over the years, they still have difficulty with some of these fundamental processes.

The Danger Model

Standing on the shoulders of the SNS models, the Danger model added another layer of cells and signals (*2*), proposing that APCs are activated by danger/alarm signals from injured cells, such as those exposed to pathogens, toxins, mechanical damage, and so

forth (Fig. 1e). Although purely theoretical at the time (*20*), many alarm signals have since been empirically revealed (*9*). Alarm signals can be constitutive or inducible, intracellular or secreted, or even a part of the extracellular matrix. Because cells dying by normal programmed processes are usually scavenged before they disintegrate, whereas cells that die necrotically release their contents, any intracellular product could potentially be a danger signal when released. Inducible alarm signals could include any substance made, or modified, by distressed or injured cells. The important feature is that danger/alarm signals should not be sent by healthy cells or by cells undergoing normal physiological deaths.

Although this may seem to be just one more step down the path of slowly increasingly complex cellular interactions, this small step drops us off a cliff, landing us in a totally different viewpoint, in which the "foreignness" of a pathogen is not the important feature that triggers a response, and "self-ness" is no guarantee of tolerance. The surprising explanatory and

predictive power of this model provides insight into many of the things that the immune system does right, as well as many of the things it seems to get wrong (*21*).

Danger Signals: Common Ground for the INS and Danger Models?

Although they differ greatly in detail, both the INS and the Danger models assume that resting APCs can be activated by signals from their immediate environment. The INS model has found support in the recent discovery of the evolutionarily conserved membrane-bound Toll-like receptors (TLRs), which act as PRRs for components of bacteria and fungi, and initiate immune responses in organisms as distant as flies and mammals (*22–26*). There are presently 10 known mammalian TLRs, which bind a wide range of biological molecules and awaken resting APCs (*27*).

The Danger model has been supported by the discovery of endogenous, nonforeign alarm signals (*9*), including mammalian DNA (*28*), RNA, heat shock proteins (Hsps), interferon-α

a) 1959, original SNS model said that lymphocytes are activated by recognition of foreign things.

b) 1969, 1st modification: B cells die when they see antigen (signal one) unless rescued by help (signal two).

c) 1975, 2nd modification: T helper cells die when they see antigen unless rescued by co-stimulation (signal two) from APCs.

d) 1989, 3rd modification (INS): APCs do not co-stimulate unless activated via PRRs (receptors for evolutionarily distant infectious non-self).

e) 1994, 4th modification (Danger model : major change) APCs are activated by endogenous cellular alarm signals from distressed or injured cells.
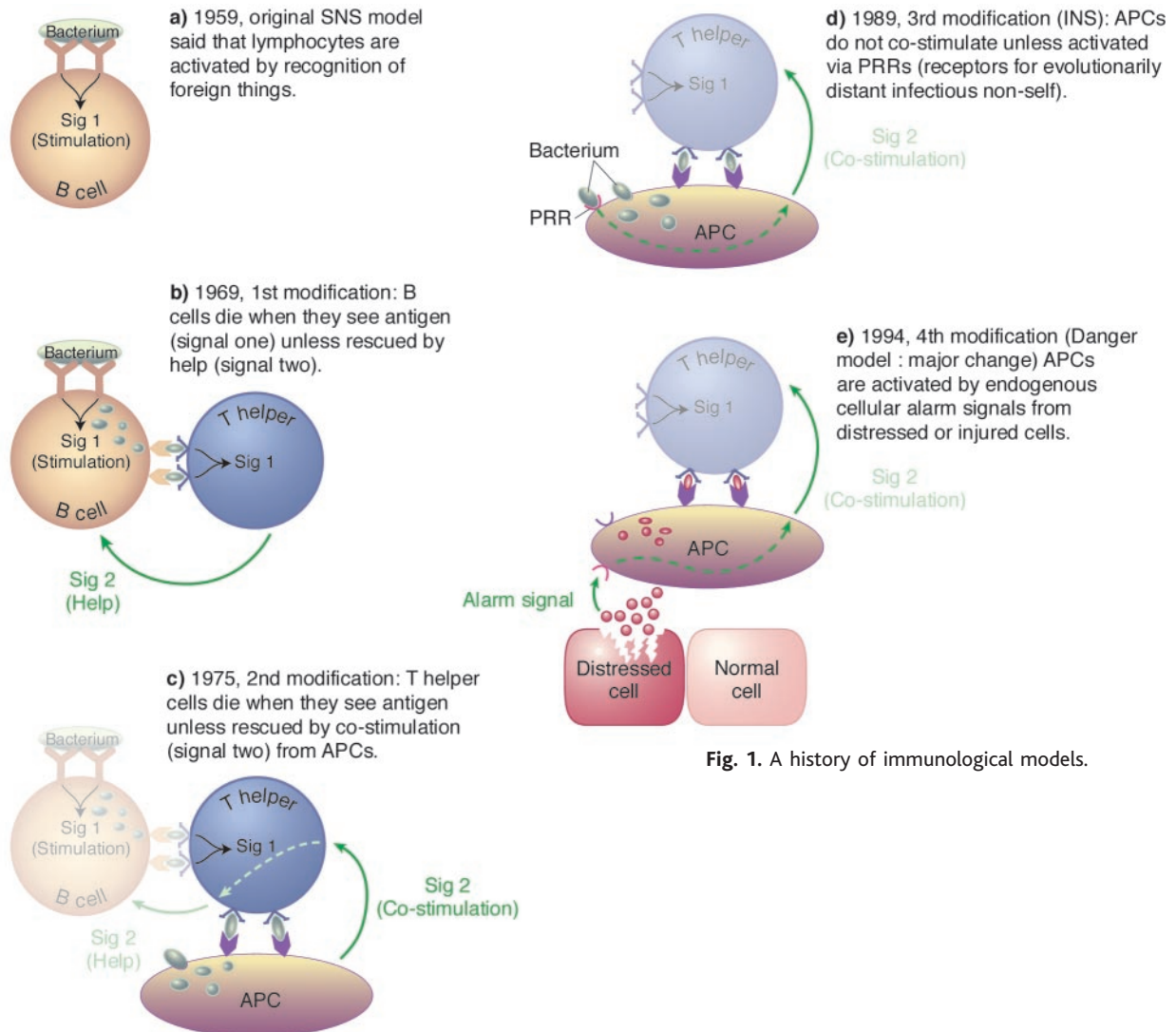
Fig. 1. A history of immunological models.

(an inducible protein often made by virus-infected cells), interleukin-1β, CD40-L (a surface molecule on activated platelets and activated T cells), and breakdown products of hyaluron (made when vessels are damaged).

There is no reason why APCs should not respond to both endogenous and exogenous signals. Vertebrates and bacteria have shared eons of evolutionary time and space, and thus receptors for endogenous and exogenous signals may have evolved simultaneously. Indeed, there is evidence that these receptors are often the same molecules. For example, TLR4 is a receptor for the bacterial product lipopolysaccharide (LPS), the endogenous cellular molecule Hsp70, and the extracellular breakdown products of hyaluron; TLR2 binds bacterial lipoproteins and Hsp 60; and TLR9 binds to DNA CpG sequences (found in all living creatures). Thus, it appears that the TLRs can recognize both endogenous and exogenous molecules. The binding characteristics of a newly discovered family of intracellular proteins, called nucleotide-binding oligomerization domain (NOD) receptors, are not yet as well worked out, but it is beginning to appear that they too can respond to both injury/pathogen-related signals and normal physiological signals involved with apoptosis (29). Indeed, one of the puzzling features of TLRs and NODs is that each one can bind to many different kinds of molecules. How can one receptor—TLR4, for example—be specific for a bacterial LPS, cellular Hsp70 protein, and hyaluron?

One possibility is that we may be looking at the PRRs completely backwards (7). Perhaps PRRs have not evolved to bind to pathogens at all. Perhaps the pathogens have evolved to bind to them! Many cell surface molecules involved in normal physiological functions are targeted by pathogens. Human immunodeficiency virus, for example, binds to CD4, CCR5, and CxCR4, and *Toxoplasma* also seems to bind to CCR5 (30), whereas *Staphylococcus* and *Streptococcus* bind to a conserved loop on T cell receptors and to the Fc portion of antibodies. Coxsackie virus binds to intracellular cell adhesion molecule–1 (ICAM-1), rabies to N-CAM, and Epstein-Barr virus to complement receptor 2, thus activating a B cell as it enters. No one suggests that these molecules have evolved to act as receptors for pathogens. We assume instead that the pathogen's ability to bind to these molecules serves the pathogen's agenda, not ours. Similarly, the PRRs may be misnamed. For example, CD14, which recognizes apoptotic cells (31), has been called a PRR because it also binds to bacterial LPS (32). However, mice lacking CD14 resist Gram-negative bacteria more vigorously than their normal littermates (33), suggesting that the LPS-CD14 interaction is more favorable to the bacterium than to the host.

Thus, perhaps TLRs and NODs originally evolved as receptors for injury-related signals, and the microbes subsequently evolved mechanisms to use these receptors to enhance their own survival. From this vantage point, it may no longer be surprising that the TLRs bind to so many different kinds of molecule, as each type of pathogen will have evolved its own way of binding to a TLR.
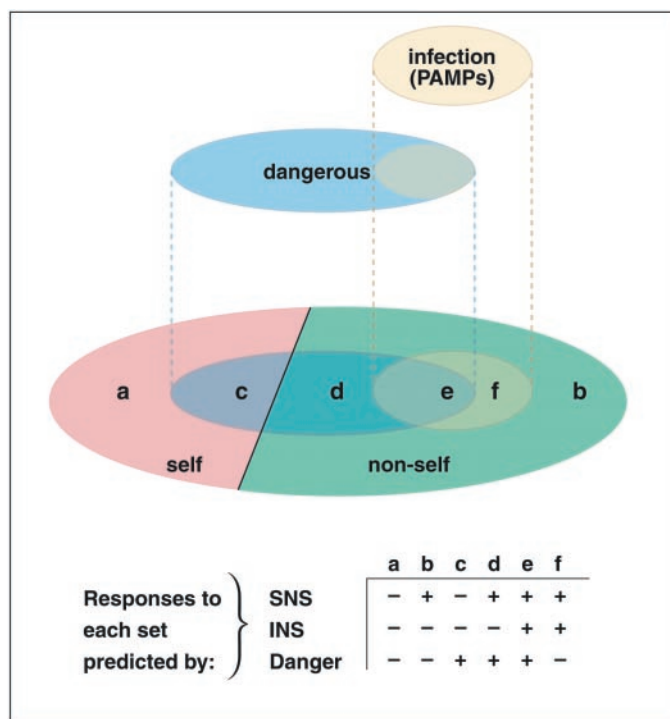
S. Y. Seong has suggested the even more intriguing possibility (34) that the same alarm signals may be used by many different organisms. Because life evolved in water, any hydrophobic portion (Hyppo) of a given molecule is usually buried in the depths of that molecule, or hidden in the lipid membrane of the cell, and could act as an alarm signal if exposed (34). For example, the hydrophobic part of LPS is crucial for its immunostimulating properties, yet LPS is normally an integral bacterial membrane molecule and its Hyppos are hidden in the membrane. However, when released by damaged or dead bacteria, the newly exposed Hyppos could act as a bacterial alarm signal (or perhaps a type of quorum sensor (35), perhaps signaling the surviving bacteria to sporulate or otherwise change their behavior. Plant and animal cells also have an abundant supply of hidden Hyppos in their membranes and cytoplasm. During protein synthesis, Hsps and other chaperones bind to the Hyppos of nascent proteins to prevent their aggregation. Should a cell be disrupted, the Hyppos of both the nascent proteins and their chaperones would be exposed. Future evidence may show that our immune systems may thus be using TLRs and other receptors to respond to truly ancient multipurpose signals of distress that cross species barriers.

Dangerous Self and Harmless Foreign: The Uncommon Ground Between the Two Models

Although the INS version of the SNS models and the Danger model have some common features, their basic assumptions about what initiates immunity are fundamentally different. Is it microbial nonself or is it danger? As nonself is sometimes dangerous, the definitions overlap, but they are not identical (Fig. 2). For dangerous foreign pathogens (Fig. 2, sets d and e) or harmless self (Fig. 2, set a), the two models make the same predictions. However, some things (Fig. 2, sets b and f) are foreign but harmless (e.g., fetuses), whereas others (Fig. 2, set c) are self but harmful (e.g., some mutations). For these entities lying outside the overlapping sets, the INS and Danger models make different predictions, and these are therefore the interesting test cases. Below I will briefly cover a few of these (10).

Foreign entities that are not associated with microbes include transplants and fetuses. Why should the former be rejected and the latter not? Although the INS model would suggest that

Fig. 2. Partitioning the universe of antigens. SNS models split all antigens into two sets: self and nonself (sets a and b). The INS model divides antigens into "noninfectious self" (set a) and "infectious nonself" (set f), suggesting the existence of pathogen-associated molecular patterns (PAMPs) that are evolutionarily conserved on pathogens that are evolutionarily very distant from their hosts, and that the host APCs can therefore have germ line–encoded pattern recognition receptors (PRRs) to detect them. It tends to ignore the subsets b and f. The Danger model partitions antigens into those associated with dangerous entities or harmless ones, defining as dangerous anything that induces stress or nonphysiological death of a cell. Dangerous entities may be self (set c), such as mutations that lead to stress or inappropriate cell death or inefficient scavenging; or nonself, such as pathogens (set e), environmental toxins (set d), and such. Set f would contain evolutionarily distant organisms that have PAMPs, but that are not dangerous (e.g., symbiotic organisms, well-adapted viruses).

Figure labels: infection (PAMPs); dangerous; self; non-self; a, c, d, e, f, b

Responses to each set predicted by:	a	b	c	d	e	f
SNS	−	+	−	+	+	+
INS	−	−	−	−	+	+
Danger	−	−	+	+	+	−

neither should be rejected because they are not associated with microbial stimulators, and the old SNS models would suggest that both should be rejected because they are nonself, the Danger model suggests that healthy fetuses should not be rejected because they do not send alarm signals. Transplants, however, cannot be performed without surgical and/or ischemic damage. Thus, to induce the acceptance of transplants without lifelong immunosuppression, we should mimic the body's own way of inducing tolerance, i.e., by blocking the endogenous alarm and/or costimulatory signals. Most of the current immunosuppressive drug protocols endeavor to block Signal One (antigen recognition). Although this effectively blindfolds the lymphocytes, it also prevents them from becoming tolerant, and consequently the drugs must be given for life. In contrast, studies in rodents and monkeys (36–38) have shown that short-term treatment with costimulation blockers, or blockers of alarm signaling (39), can lead to long-term graft acceptance in the absence of long-term immunosuppression. Perhaps the lower extent of damage can explain why kidneys from living donors are accepted more easily than those from cadavers (4). Similarly, fetuses should not elicit immunity, in spite of being foreign, as long as they are healthy and do not send alarm signals (10).

Tumors are entities for which both the INS and the Danger models have the same prediction, namely, that tumors should not stimulate immunity, either (INS) because they are not associated with microbial stimulators, or (Danger) because they are healthy growing cells that do not send alarm signals. Thus, to eradicate a tumor, we should infect it (40), or cause it repeated damage to alert the local APCs [as Bill Coley did in the late 1800s (41, 42)], or we should vaccinate repeatedly with a tumor vaccine that stimulates immunity.

For autoimmunity, the Danger model offers a unique suggestion that would not arise from the SNS or the INS models. Starting with the view that "bad" death or cell stress can elicit an immune response, the model suggests that some autoimmune diseases may be caused by mutations in genes governing the normal physiological death and clearance processes, or by environmental pathogens or toxins that cause cellular stress or death. In these cases, the immune system is not at fault; it is doing its job of responding to alarm signals (but, in these cases, to the detriment of the host). If we could pinpoint these mutations or environmental agents, we might be able to reduce the incidence of autoimmune diseases.

A Renewed Sense of Self: Expanding the Horizons of the Danger Model

There is inherent beauty in a model that uses very few assumptions to explain a wide variety of phenomena. However, for me, the most interesting aspect of the Danger model has been a deep-rooted shift in thinking that it inspired. The shift came in two phases that abruptly expanded the model's explanatory range. Originally conceived to answer the first question the immune system must consider when faced with a potential threat—namely, whether to respond—the model now also offers a suggestion for the next question—having decided to respond, what kind of response should it make? How does the immune system know whether to generate killer T cells to eliminate a virus or immunoglobulin E (IgE) antibody to catch a worm? In immunological terms, how does it determine the effector "class" of the response?

The first shift came from the realization that the immune system may not be the ultimate controller of immunity. Like most immunologists, I had thought that immunity is controlled by the cells of the "adaptive" immune system (lymphocytes) or the more ancient "innate" immune system (such as macrophages, dendritic cells, and the complement system). I now believe that the ultimate power lies with the tissues. When healthy, tissues induce tolerance. When distressed, they stimulate immunity, and (continuing down this path) they may also determine the effector class of a response. Although it has long been thought that the effector class is tailored to the targeted pathogen (e.g., virus or worm), I now think that it is tailored to the tissue in which the response occurs.

Different tissues seem to have different means of determining the effector class of a response. For example, the class of response that occurs most often in the skin (e.g., after exposure to poison ivy, TB tests, or subcutaneous vaccinations), called "delayed type hypersensitivity" (DTH), is characterized by swelling, redness, an influx of macrophages, and the production of tumor necrosis factor (TNF) and interferon-γ (IFN-γ). Unlike skin, however, both the gut and the eye can be destroyed by DTH responses, and the most common response in these organs is the production of IgA, an antibody found at high levels in tears, saliva, milk, and gut secretions. To ensure that IgA is made, and TNF and IFN-γ are not, the cells of the anterior chamber of the eye produce vasoactive intestinal peptide (VIP) and transforming growth factor-β (TGF-β), two cytokines that are also made by the gut and that promote a switch to IgA and suppress the DTH response (43, 44). Thus, local tissue cells strongly influence the local immune response.

The second shift came from the realization that tossing out the idea that the immune system uses SNS discrimination to decide whether to respond leaves us free to use self-recognition in a positive way to control other aspects of the response. Many organs harbor special populations of lymphocytes that appear to be evolutionarily old, often have limited receptor diversity, and have been called "innate lymphocytes" because they respond to stress-induced self molecules rather than to the foreign entities seen by the "adaptive" lymphocytes (45). These cells have no place in the SNS and INS models, and they have remained on the fringe of respectability. But, seen from the standpoint that immunity is governed by the tissues, these self-reactive cells do not seem so odd (7), and Bendelac calls this "autoimmunity by design" (45). For example, the dendritic epidermal T cells ($\gamma\delta$ T cells) found in mouse and bovine skin all express exactly the same receptor (46), arise late in fetal life, and emigrate in one wave to the skin, where they settle quietly. When stimulated by the appearance of stress-induced molecules on keratinocytes (47), they produce epidermal cell growth factor, IL-2, and IFN-γ. These cells are clearly not the kind of lymphocytes we are accustomed to. They seem to be there to produce cytokines that heal damaged skin by inducing cell growth and nudging local immunity toward a DTH. In human gut, T cells expressing self-reactive Vδ6 receptors also respond to stress-induced molecules (48). Many other $\gamma\delta$ T cells may be similar, responding to endogenous stress signals rather than to foreign antigens.

T cells bearing α/β receptors can also be usefully self-reactive. The thymus, bone marrow, and liver contain NK1 T cells specific for the ancient MHC-like molecule, CD1, which is expressed by activated but not resting APCs (49). Activated NK1 T cells from the thymus produce copious amounts of IL-4, a cytokine that skews local immune responses away from a DTH and toward the production of IgG1 and IgE. Furthermore, T cells specific for brain proteins can lessen the secondary damage that follows neural injury (50).

All of these tissue-localized cells appear to be useful self-reactive cells involved in local immunity, and there may be many other localized and/or circulating cells doing similar jobs. For example, a lot of effort has gone into the search for the foreign ligands recognized by circulating $\gamma\delta$ T cells. After more than a decade, very few have been found, and these include such ubiquitous cellular molecules as polyprenyl pyrophosphate (51) and phosphorylated nucleotides (52).

Perhaps, if we move from the idea that every lymphocyte should be directed against non-self antigens whose appearance stimulates the response, and consider instead the possibility that immunity is controlled by an internal conversation between tissues and the cells of the immune system (53), we may regain a renewed sense of the self that we have lost.

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20. Like physicists, who deduced the need for a new particle based on the behavior of the system, Bretscher and Cohn (*14*) and Lafferty and Cunningham (*15*) postulated cells and/or signals for which, at the time, there was no evidence. Later experiments showed resoundingly that they were correct. In a similar vein, Janeway postulated a new state for a previously known cell, the APC. Up to that time, APCs were thought to be constitutively active, but a seemingly small glitch in the behavior of the system (the need for adjuvant) led him to suggest that they were normally quiescent and needed to be activated. These insights showed that theoretical biology and physics may have more in common than is sometimes thought.
21. Allergy, for example, is a partial conundrum. Many allergens are dangerous substances. Der-p1, the major allergen in house dust mite, is a protease that attacks the surface of B cells and lung epithelium. Likewise, bee venom is not an innocuous substance. From the standpoint of the Danger model, it is not surprising that the immune system responds to allergens. What is not clear, however, is why some individuals make IgG whereas others make IgE (the antibody associated with allergy).
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53. The Network model, which proposed that "self" is defined in a positive way, also emphasized the idea of connectedness. The idea was that lymphocytes react against each other's antigen-specific receptors and maintain a balance of self-reactive and foreign-reactive cells (*55*). The proponents of the network have been arguing for years that the study of single lymphocytes is an inappropriate way to study the immune system, but that we should study the connectivity between cells (*56*) Finally, after years of finding the model intriguing, but narrow, I agree. However, I think that we should not limit the study to interactions between lymphocytes but expand it to include their conversations with all the bodily tissues, which have the ultimate say.
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57. I thank past and present members of the ghost lab (S. Gallucci, J. Wright, S. Wolf, K. Abdi, E. Bachelder, O. Alpan, P. Rohwer-Nutter, A. Perez, R. Massey, and D. Culp), as well as H. Arnheiter and Y. Rosenberg for comments on the manuscript. I would also like to send a kiss to the anonymous referee who placed a heavy but appropriate boot in the right place.

VIEWPOINT

Recognition and Rejection of Self in Plant Reproduction

June B. Nasrallah

Plant self-incompatibility (SI) systems are unique among self/nonself recognition systems in being based on the recognition of self rather than nonself. SI in crucifer species is controlled by highly polymorphic and co-evolving genes linked in a complex. Self recognition is based on allele-specific interactions between stigma receptors and pollen ligands that result in the arrest of pollen tube development. Commonalities and differences between SI and other self/nonself discrimination systems are discussed.

The concept of self/nonself discrimination was elaborated by Burnet (*1*) as a way to describe specificity in the immune response and is most often associated with the field of immunology. It is perhaps less well known that, in the plant kingdom, sophisticated self-recognition systems have evolved that allow plants with perfect (hermaphroditic) flowers to avoid inbreeding. These intraspecific prefertilization mating barriers are collectively known as self-incompatibility (SI). This term encompasses several systems that are mechanistically distinct but have the same outcome, namely the inhibition of self-related pollen tube development and, consequently, the prevention of sperm cell delivery to the ovules.

SI systems are said to discriminate between self and nonself because they produce different outcomes in self- and cross-pollinations. Specificity in SI is typically controlled by one or more highly polymorphic genetic loci. In the context of SI, self and nonself mean, respectively, genetic identity and nonidentity at the SI locus (or loci) in pistils and pollen. The outcome of this discrimination is the converse of that of the immune response, in which case self has been classically defined as those elements that are tolerated and do not elicit a response. In SI, self is the condition that elicits the response and is inhibited, whereas nonself is the condition that is ignored and does not elicit a response.

A Variety of Plant SI Systems

As an advantageous outbreeding device, SI is widely distributed in flowering plants (*2*). It evolved independently in several lineages, and the SI systems adopted by different plant families vary with respect to site and mechanism of self inhibition. In self-incompatible species of the crucifer family (e.g., *Brassica* species and close relatives of *Arabidopsis thaliana*), SI disrupts hydration and germination of a pollen grain on the stigma epidermis, thus preventing growth of pollen tubes into the subepidermal tissues of the pistil. In other families, SI acts after pollen germination and pollen tube ingress into the pistil, either within the stigmatic zone (as in the poppy family), or later, within the style (as in the tobacco, rose, and snapdragon families).

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