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Cutting Edge Commentary:
A Copernican Revolution?
Doubts About the Danger Theory[1]

Russell E. Vance[2]

The immune system is often said to function by "self-nonself" discrimination. Recently, some have argued that it actually detects "danger" or "strangers." There are problems with all of these points of view. Given that the immune system has been cobbled together throughout evolution and uses a diverse array of innate and adaptive defense mechanisms, it may not be possible to account for immunity within one "paradigm" or another. *The Journal of Immunology,* **2000, 165: 1725–1728.**

The provocative suggestion that the immune system does not distinguish "self" from "nonself" but instead responds to "danger" has generated considerable attention in prominent scientific journals (1–3) and in the lay press (4–7). More telling, "danger" has even begun to creep into the everyday immunological vernacular (8, 9). Now that the dust is settling a little, perhaps the time has come to assess the state of immunological theory, to determine the role (if any) for "danger" in that theory, and, perhaps most importantly, to ask whether a discipline as increasingly complex as immunology needs or can even have "a theory."

Its proponents have portrayed the danger theory as a bold new "paradigm" in immunology that accounts for the "anomalies" of earlier theories. Some danger theorists have even gone so far as to compare the danger theory to the Copernican Revolution of the 16th century, in which a heliocentric view of the solar system came to replace the ancient geocentric view (10). There is a growing consensus (11–14) that the danger theory is emphatically not a Copernican Revolution. I concur, and in this article I offer some new doubts about danger. Nevertheless, immunology is a changing discipline. In particular, as is reviewed below, there is an ever-growing recognition of the critical role that innate immune mechanisms play in shaping adaptive responses. The question addressed here is to what extent the recognition of the importance of innate immunity forces us to abandon "self-nonself" theories in favor of alternative approaches such as "danger."

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What Is the Danger Theory?

Although the notion that the immune system has evolved to recognize (dangerous) pathogens is not new (15), recent discussions of "danger" have revolved around one particular characterization of the notion, which is summarized as follows:

> For many years, immunologists have been well served by the viewpoint that the immune system's primary goal is to discriminate between self and non-self. I believe that it is time to change viewpoints. . . I discuss the possibility that the immune system does not care about self and non-self, that its primary driving force is the need to detect and protect against danger, and that it does not do the job alone. . . (16)

In more recent work, danger theorists have gone on to equate "danger" with unprogrammed "tissue destruction," necrosis, or other signs associated with cellular distress (17, 18). Despite its vagueness, I will explain later how narrow this definition of danger actually is. Nevertheless, as it is advanced above and elsewhere (17), the danger thesis is controversial because it emphasizes two points: 1) the notion of an immune "self" should be abandoned, and 2) the notion of "danger" is central to understanding immunity. Moreover, the danger theory incorporates the underlying assumption that 3) because the immune system should be viewed as having a primary goal or driving force, "danger" and "self-nonself" discrimination cannot both be true. In what follows, I argue in turn that all three tenets are problematic. But more significantly, I want to suggest that reductionist approaches to immunity, such as the danger theory, should be distinguished from profitable attempts to integrate what is known about the innate and acquired immune responses.

The Trouble with "Self"

The idea that the immune system functions by discriminating "self" from "nonself" has a long history in immunology. Its conceptual underpinnings have been traced to Elie Metchnikoff's turn-of-the-century work on the phagocyte (19), but its modern formulation is generally credited to the work of Talmage (20), Burnet (21), and Medawar (22). As is by now well known, their work established the idea that during the neonatal period the immune system can learn to tolerate Ags that are normally present in the self. This education process—usually referred to as "central tolerance"—is now said to occur (at least with respect to T cells) throughout life in the thymus, where developing T cells strongly reactive with self-Ags are eliminated (23). Of course, not every possible "self"-Ag is believed to be present in the thymus (but see

Ref. 24). Consequently, there must also be "peripheral" mechanisms that prevent mature, circulating T cells from attacking non-thymic self-Ags. (Here I ignore B cell tolerance, though in many respects it resembles T cell tolerance; for a thorough discussion, please see Ref. 25.) Although the distinction between central and peripheral tolerance is generally accepted, it is not known what fraction of self-reactive cells is inactivated in the thymus as opposed to the periphery; nor is it known whether a breakdown in central tolerance would lead to autoimmune disease or to what extent peripheral mechanisms could compensate.

The above understanding of tolerance emphasizes the importance of the Ag-specific signal received through the TCR, a signal often called "signal one." In the simplest scenario, the tolerance mechanisms that eliminate "self"-reactive cells ensure that signal one can only originate from a "foreign" Ag, i.e., signal one is a self-nonself discriminator. However, immunologists are increasingly framing questions of tolerance in terms of a two-signal model of lymphocyte activation (26–29). Signal two, or "costimulation," is a more generalized signal that is required to ensure self-tolerance in cases where, for some reason, central tolerance fails and a self-reactive T cell is not inactivated before functional maturity. The idea is that the second signal is required to properly activate T cells, but will only be provided during genuine infections and not to autoreactive T cells in healthy individuals.

In this context, then, what do danger theorists mean when they attack the idea of "self"? One mild interpretation is that they are simply questioning the relative importance of both signal one and central tolerance. When explaining why T cells generally respond only to infected and not normal tissue, danger theorists tend to downplay the idea that the thymus selects self-restricted T cells that can respond specifically to "foreign" peptides presented on the surface of infected tissue. Instead danger-theorists prefer to emphasize the requirement for second signals induced on APCs by the infected tissue (one recurring suggestion is that necrotic or infected tissue expresses heat-shock or other "stress" proteins that induce second signals on APCs). There are problems with such a mild interpretation of the danger theory. For one, it seems too mild for a theory that is supposed to be an immunological revolution. For another, there is the question of how danger theorists propose to assess the relative importance of signal one vs signal two. Most immunologists seem to think both signals are important (11). Finally, while one of the tenets of the danger theory involves the rejection of the concept of "self," any acceptance of the two signal model implicitly involves some acceptance of signal one, a signal that can easily be understood, in many cases, as a self-nonself discriminator (see above).

In all their writings, danger theorists clearly support a two-signal model (16–18). So what are their difficulties with the concept of self? There are at least three (16). First, the central concept of "self" is ill-defined. Indeed, "self" has been variously understood as 1) the sum of genome-encoded Ags, 2) the body, 3) the total set of MHC/peptides, or 4) simply the subset of MHC/peptides expressed on APCs. Second, there are many exceptions. For instance, normal individuals produce Abs to self-Ags (such as DNA or keratin); there are T cells in the periphery that are specific for self-Ags (such as myelin basic protein). Third, the self-nonself model fails to account for a wide enough range of phenomena. For example, why are B cells particularly strongly activated by LPSs? Why is "complete" adjuvant, containing microbial products, required to elicit an immune response against soluble foreign Ags?

These criticisms are hardly new, and indeed immunologists have always been a bit suspicious of the idea of "self." Even Burnet tended to surround the word in quotation marks, as a caution to anyone who tried to take the idea too literally (19). The truth is that no serious immunologist today really believes, for example, that "self" is defined solely in the thymus during the neonatal period; yet in discussions of danger, it has often been this vulnerable conception of "self" that is trotted out as the reigning "paradigm" and then demolished with a triumphant fanfare (17, 30). While it may be true that immunologists have shifted their attention to signal two, this does not mean that signal one lacks importance. "Self-nonself discrimination" was never intended to be an exceptionless law of nature (or else, why would there be autoimmune disease at all?). Rather, "self" was—and continues to be—a useful heuristic device that helps explain phenomena as diverse as MHC restriction (31), positive (32) and negative (23) selection, and the rejection of allogeneic but not syngeneic skin grafts, bone marrow grafts (33), and tumors. So the question is: why should we discard the idea of "self" when really all that is needed is to recognize—as immunologists already do—that it cannot be the whole story.

In fact, while they might avoid the word, it seems that danger theorists cannot and do not actually discard the concept of self. In a recent discussion of negative selection, for instance, two danger theorists claim that "any thymocyte that recognizes the normal surface MHC/Ag profile of a dendritic cell would thus be eliminated. . ." (17). Rhetoric aside, is there really much that separates "normal surface MHC/Ag profile" from most immunologists' idea of "self"? Are danger theorists rejecting the concept of "self" entirely, or are they seeking its redefinition? While the former strategy exhibits the bold sweep of simplicity, it seems that the latter may in fact describe more accurately the modest extent of the danger program.

The Real Trouble with Self

Thus, I venture that danger theorists might secretly agree that self-nonself discrimination does occur on some level. Their real complaint seems to be that the APCs that provide the critical second signal seem themselves to have no basis for distinguishing self from nonself. APCs present Ags irrespective of the Ags' self or foreign origin. This is a deep if obvious point. Danger theorists are, in effect, asking about the signals that control the presence, absence, or effectiveness of the second signal. The importance of these "third" signals has long been recognized (15), but only recently have immunologists begun to unearth their molecular basis. As is reviewed briefly below, it is now clear that at least some of these "third" signals are diverse and evolutionarily ancient signals that are closely tied to the innate immune response.

Thus, the novelty of the danger theory, if any, can only derive from the proposal to unify the signals of the innate immune system under the rubric of danger. However, as I argue below, this strategy seems not only pointless, but potentially misleading, as there is no reason to think these signals have much in common with each other. In addition, I suggest that the notion of danger curiously fails to live up to the same three criteria used in rejecting the concept of "self," namely 1) it isn't well defined, 2) it has many exceptions, and 3) it doesn't account for a wide enough range of immunological phenomena.

What Is Danger?

On first glance, the danger theory may seem both sensible and plausible. The idea that the immune system's purpose is to prevent attack from harm provides a simple answer to the problem of how such a system could evolve. But a simplistic understanding of danger, while intuitive, can come uncomfortably close to conceptual emptiness. One is tempted to agree that of course the immune system protects against danger: so do eyes, legs, teeth, and practically every other feature of anatomy and physiology (one could

even argue that the stomach protects against the danger of starvation). As immunologists, the crucial issue we want to understand is what kinds of danger the immune system detects, and how does it detect them? Without specifying these features, the notion of danger would lack critical depth.

Therefore, it is essential to realize that danger theorists are really talking about something quite limited. They suggest that the immune system detects as dangerous "anything that causes cell stress or necrotic cell death" (16, 17). (Others have made similar proposals (34).) While such a definition of "danger" is unfortunately vague, it is at least clear that the "danger" signal is not considered to be delivered directly by infectious agents themselves, but by host tissues that are damaged in the course of an infection. This is a surprisingly narrow construal. The danger theory would thus seem to exclude all signs of infection of exogenous origin, perhaps including potent immunostimulatory compounds such as bacterial LPSs, bacterial DNA, or mimics of viral RNA such as poly(I:C). At least some of these compounds apparently need not cause damage to exert their effects, i.e., they are not, by definition, strictly "dangerous." Rather, they are evolutionarily conserved signs of infection that are detected directly by specialized receptors on cells of the immune system (Refs. 35 and 36 and see below). These signs have been dubbed "pathogen-associated molecular patterns" (35) or "strangers" (14) and are distinct from the concept of "danger" as it has been proposed (16, 17).

Moreover, though they are often conflated, a clear distinction must also be drawn between "danger" and inflammation. Inflammation, which is mediated by immune effectors, is proposed by danger theorists to arise as a consequence of danger signals, which themselves arise as a direct consequence of host cell necrosis, induced by pathogens. Although inflammation does cause damage, which may in turn expand immune responses, the purpose of "danger" is primarily to explain the initiation of immune responses, not simply their expansion.

The Diversity of Innate Immune Detectors

It would of course be a mistake to ignore the important role that endogenous signs of cellular distress might play in provoking immune responses. Recent evidence has suggested that stressed cells are capable of producing a wide variety of signals to the immune system. For example, the MHC class I-like molecule MIC is induced on the surface of heat-shocked or otherwise stressed cells, and has been shown to bind to an activating receptor called NKG2D, which is expressed by $\gamma\delta$ T cells, CD8$^+$ T cells, and NK cells (37). Heat shock proteins themselves appear to have properties of adjuvant (38), as does complement (39). And although its molecular mechanism remains unclear, the apparent ability of dendritic cells to distinguish infection-associated damage (necrotic cells) from normal cell death (apoptotic cells) may also be important (40).

So while it might be agreed that the immune system can sense endogenous signs of distress (danger), the question is whether immunology should be limited, a priori, to the study of these endogenous signs—especially as the molecular mechanisms that the immune system uses to detect "strangers" is becoming increasingly understood. Perhaps most important are the mammalian Toll-like receptors (TLR) that recognize a variety of conserved microbial-associated products such as LPS (on Gram-negative bacteria), lipoteichoic acid (on Gram-positive bacteria), or mannans (on fungi). Interestingly, different TLR can distinguish between different classes of pathogens. For example, TLR2 and TLR4 are essential for the detection of Gram-positive and Gram-negative bacteria, respectively (41, 42). Particular forms of nucleic acids specifically associated with undesirable "strangers" are also apparently immu-

nostimulatory. Of recently renewed interest is the pleiotropic immune response stimulated by double-stranded RNA (43), a nucleic acid associated with numerous viruses, and mimics of which (e.g., poly(I:C)) are potent stimulators of type I IFNs. Particular unmethylated CpG dinucleotides, found preferentially in prokaryotic DNA, also exhibit a wide array of immunostimulatory properties (44). Finally, GPI protein anchors, abundantly expressed by some pathogenic protozoa, may bind the MHC class I-like CD1 molecule and stimulate NK T cells (45).

However, in some cases the immune system may be tuned neither to danger nor strangers. Zinkernagel, for instance, argues that it is the repetitive pattern of Ag (as found for example on viral coats) or Ag localization kinetics that govern immunogenicity (46). In the case of NK cells, which express inhibitory receptors that recognize MHC class I, cytotoxicity is enhanced when a target cell down-regulates self-MHC due to viral infection or transformation (33). And so on. The moral is that if the diversity of immune detectors is to be appreciated, it becomes necessary to speak not of a single "danger" signal, but of multiple "danger + stranger + other" signals. But if we're going to appreciate the plurality of immunogenic signals, why not discuss the signals directly, and dispense with the monolithic and misleading label of "danger"?

Can the Danger Theory Be Tested?

It is often claimed that a theory is only as good as its ability to be tested. Experiments explicitly designed to test the danger theory have been proposed (13), and in some cases conducted, with results that apparently either confirm (40) or elegantly refute (47) the danger theory. But it seems highly unlikely that any single experiment will ever settle the debate between danger and self-nonself theories. Those who insist on experimental verification miss the point of these theories, which are essentially metaphorical generalizations, far abstracted from the gritty but testable details of immunity. The theories' value, if any, lies in their ability to help us organize our thoughts about how all the details might fit together. Because they are generalizations, there are bound to be exceptions or "anomalies" that the theories will be unable to explain (a point danger theorists selectively ignore in their discussions of self-nonself discrimination). The danger vs self debate will thus not be settled by a direct experiment, but by the community of immunologists, who will assess whether the usefulness of the generalization outweighs the problems associated with the anomalies. I and others (11, 13) have tried to suggest that, because of its explanatory power, immunologists are right to retain the generalization of "self-nonself," despite its flaws. I have also argued that "danger" may be less useful, and might even be misleading. But to suggest that the danger theory should be "tested" in a winner-takes-all experiment is to mistake "danger" for a bold "Copernican" hypothesis, which it distinctly is not.

Let's Abandon Paradigms for Pluralism!

The popularity of the idea that great science proceeds by the revolutionary overthrow of reigning paradigms is due to Thomas Kuhn, a historian and philosopher of science (48). Danger theorists even cite Kuhn in a defense of their radicalism (10) (the irony is that one of Kuhn's most infamous suggestions was that new paradigms are not necessarily superior to their predecessors). Nevertheless, immunologists have traditionally had a tendency to propose grand unified theories, or "paradigms." I am thinking here not only of the danger theory, but of Jerne's Network Theory, "suppressor" cell theories of tolerance, and even theories of "self-nonself" discrimination. Such conceptual frameworks have been important to the history of immunology, but to varying degrees all sacrifice accuracy for generality.

So perhaps we should resist the Kuhnian ideal. After all, his ideas are based largely on examples from physics and chemistry, and contemporary philosophers question to what extent the Kuhnian model applies to biology and other sciences. As quoted above, one prominent danger theorist appears to think that the immune system should be viewed as having a primary driving force (16). This belief chimes with Kuhn's notion that disciplines are governed by "incommensurable" paradigms and forces danger theorists to choose between self and danger. The underlying delusion is that immune responses obey a small set of laws like the movements of the planets obey the law of gravity. The danger theory even proposes to encompass immunity in just three "Laws of Lymphotics." This is absurd. Why not, rather, think of the immune system as a much more diverse collection of mechanisms and processes that have been cobbled together during the course of evolution? If I am right, it will be the details of these mechanisms and their interactions that will ultimately be of interest to immunologists, and not whether they conform to one "paradigm" or another.

Acknowledgments

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