Chapter 15

Self and Nonself

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1. Introduction

Immunology is the science that investigates how organisms defend themselves against infection, harmful substances, and foreign tissue. In order for an organism to defend itself against such threats, however, its immune system presumably must be able to discriminate self from nonself. If the immune system could not make such a discrimination, it might harm the organism it is to defend, rather than the microbes infecting it. Self–nonself discrimination thus appears to be a crucial function of the immune system. Indeed, immunology has been referred to as the "science of self–nonself discrimination" (Klein, 1982).

How self–nonself discrimination is achieved depends, among other things, on whether an organism is an invertebrate or a jawed vertebrate. Self–nonself discrimination is more rudimentary in invertebrates (and jawless fishes) because their immune systems are "innate." Innate immune mechanisms are those that do not change after repeated exposure to a given infectious agent; they do not *learn*. This contrasts with a type of immunity in jawed vertebrates – adaptive immunity – which does change after repeated exposure to pathogens. After the adaptive immune system adapts to a given pathogen, it can target the pathogen with greater precision and eliminate it more rapidly. Because of adaptive immunity, self–nonself discrimination in jawed vertebrates is specialized and precise: vertebrate immune systems are fine-tuned to differences between self and nonself.

So significant do immunologists find the evolution of adaptive immunity – both with respect to enhanced pathogen defense and self–nonself discrimination – that some refer to it as the "immunological Big Bang" (Janeway & Travers, 2005). But while the enhanced precision of the adaptive immune system is unquestionably significant, it does raise a difficult problem with respect to self–nonself discrimination: the precision of the adaptive immune system can be turned against the organism itself. Autoimmune disease occurs when the adaptive immune system targets the self, and the consequences can be disabling and deadly. Thus, one of the key questions in immunology – that of how the immune system avoids harming the organism it protects – gains special force in vertebrate immunology.

Theoretical and empirical research concerning immunological self–nonself discrimination is of interest to philosophers for at least two reasons. First, in immunology and philosophy alike, metaphysical questions exist concerning the nature of the self and its persistence over time. What are the boundaries of the self? How do we define the self? And second, self–nonself discrimination raises philosophical questions concerning explanation and reduction. Are self concepts in immunology genuinely explanatory? Is the investigation of immunology at the molecular level sufficient to explain all immunological phenomena?

In the following, I provide an overview of the different theoretical perspectives of self–nonself discrimination and some of the challenges that have been raised to those perspectives. In this overview, I focus mainly on adaptive immunity in vertebrates, given that most of the debates about self–nonself discrimination concern adaptive immunity; though, as I will suggest later, greater attention to innate immunity may be needed to resolve some of these debates. In part one, I describe three major theoretical perspectives of self–nonself discrimination: these include clonal selection theory and immunological tolerance; three-signal models; and network models. In part two, I examine challenges to contemporary thinking about self–nonself discrimination that complicate the three major theoretical perspectives described. These challenges – including questions about the genetic criterion of selfhood, the viability of the innate–adaptive distinction, and self–nonself discrimination in pregnancy – demonstrate that much conceptual work on self–nonself discrimination remains to be done.

2. Theoretical Perspectives

2.1. Clonal selection theory, tolerance and self–nonself discrimination

In the first part of the twentieth century, one of the central puzzles of immunity concerned antibody diversity. Antibodies are large soluble glycoproteins found in the blood and other fluids of the body. Vertebrate organisms develop antibodies to hundreds of millions of substances known as "antigens." Most antigens are protein fragments from microbes or cells of the organism's own body. The puzzle raised by antibody diversity is this: How does the immune system produce antibodies able to interact with such an incredibly diverse array of antigens? What accounts for the diversity of antibody conformations?

In the 1930s and 40s, proposed solutions to the puzzle of antibody diversity focused on the idea that antigens acted as templates for antibody production. In this view, antigens shape antibody structure, somewhat like a mold shapes a form, and this can generate as many different antibody conformations as there are antigens. Niels Jerne, however, showed that the template idea was flawed. Jerne was interested in natural antibodies, which are antibodies that exist in the body prior to exposure to antigens. Natural antibodies thus provided a key reason to reject template theory: if antibodies can exist prior to antigen exposure, then antigens are clearly not involved in their creation. Jerne's interest in natural antibody formation, combined with his interest in Darwinian selection processes, led to a better explanation for antibody diversity: the natural selection theory of antibody formation. In this theory, an antigen selects a

Table 15.1 Some of the main cell types of the immune system

B lymphocyte	Plasma	• Produces antibodies in response to infection • Can recognize and differentiate between different antigens
	Memory	• Circulates the body and remains quiescent until a second encounter with a given pathogen • Can recognize and differentiate between different antigens
T lymphocyte	Helper	• Stimulates B cell growth and differentiation. • Stimulates macrophages. • Can recognize and differentiate between different antigens
	Cytotoxic	• Kills virus-infected cells and tumor cells • Can recognize and differentiate between different antigens
Natural killer cell		• Kills virus-infected cells and tumor cells
Macrophage		• Presents antigen to T helper cells • Ingests and destroys microbes • Activates inflammation
Dendritic cell		• Presents antigen to T helper cells

circulating antibody and the resulting antigen–antibody complex circulates in the body until it is picked up by an antibody-producing cell. The antibody-producing cell then makes more antibodies of that type (Jerne, 1955; Söderqvist, 1994).

The idea of using natural selection to explain antibody formation was significant. But Jerne's assumption that antibody-producing cells could manufacture any configuration of antibody taken up was problematic. Each antibody-producing cell would in principle have to be able to make millions of different conformations of the antibody molecule – an implausible scenario. By 1957, David Talmage and Frank Macfarlane Burnet independently resolved this problem by shifting the selection process from Jerne's antigen–antibody complex to the antibody-producing cells themselves (Taliaferro & Talmage, 1955; Talmage, 1957; Burnet, 1957). Antigens entering the body attach themselves directly to antibody-producing cells having compatible receptors, and in so doing, they select those cells from among others. On the basis of this idea, Burnet developed his *clonal selection theory* of antibody formation. In clonal selection theory, the antibody-producing cell – a B lymphocyte cell – is selected and then proliferates by clonal expansion. (See Table 15.1.) Each of the resulting clones produces only one type of antibody molecule – the same type as the parent cell. This is a much more manageable task for an antibody-producing cell than the generation of innumerable different antibody types. Clonal selection theory thus provided a clear explanation for how vertebrate organisms produce such an incredibly diverse array of antibody conformations.

In the late 1950s, a further refinement of clonal selection theory was made with respect to the question concerning how antibodies confer immunity to pathogens that have previously caused an infection. Gustav Nossal and Joshua Lederberg (1958) found that B cells produce two different types of clones: plasma cells and memory cells. Plasma cells are the cells that generate identical copies of the antibody produced by the parent B cell. Memory cells, however, do not undergo differentiation to become antibody-producing cells. Instead, they remain quiescent in the body and persist long after the

initial infection is resolved. If, however, there is a second encounter with the microbe that caused the primary infection, memory cells will initiate a response to the microbe immediately. This fast response eliminates the threat before infection takes hold. Memory cells thus are responsible for the immunity we develop to certain infections after we have fallen ill by them.

Despite the success of clonal selection theory and the discovery of plasma and memory cells, however, fundamental questions about the genetic mechanisms behind the generation of B cell diversity and immunological memory remained. Until the early 1980s, some thought that the genetic diversity responsible for antibody diversity already existed in the germ-line of organisms. Others thought the necessary genetic diversity developed in the organism somatically; on this view, organisms are not born with the necessary genetic diversity, but develop it later.

The latter view turned out to be correct. Susumu Tonegawa (1983) found that as B cells mature into plasma or memory cells, they mix and match genes, add and delete genes, and mutate genes. This recombination, mutation, and addition and deletion of genes explains how such a diverse array of antibody conformations can be created. A similar process also occurs in another type of immune cell – the T helper lymphocyte, a cell that stimulates B cell activity. Receptors on T helper cells are very diverse and they achieve this diversity through genetic recombination (though not through mutation as in B cells). Between different antibodies and T cell receptors, the question of how the immune system recognizes such an enormous variety of antigens was more or less resolved.

The somatic rearrangement of antibody genes is responsible for the precision of the adaptive immune system: it enables the immune system to produce antibodies that are highly specific to any given antigen. Specificity means that if an antibody binds tightly to an antigen from the chicken pox virus, it will not bind well to antigens from anything else: it is specific for chicken pox. As B cells mature, those that best fit the antigen in question will last longer than those that do not, and only those that best fit will survive long enough to become plasma or memory cells. As a result of this process, plasma and memory cells are able to bind to antigens very tightly. The discovery of the somatic rearrangement of antibody genes thus helped to explain the ability of the adaptive immune system to target antigens with a high degree of precision.

But, the precision of adaptive immunity raises a problem for clonal selection theory. In adaptive immune systems, antibodies able to recognize self antigens can develop through somatic rearrangement and mutation. T cell receptors specific for self antigens can also arise through somatic rearrangement. And, we know that T and B cells are capable of mounting immune responses against the self. So, something must normally stop the immune system from targeting self tissues. But what? The principal answer – immunological *tolerance* – became a mainstay of the dominant view of self–nonself discrimination.

Immunological tolerance is a learned unresponsiveness to specific antigens: in short, it is the ability of T and B cells to tolerate or ignore self antigens. Burnet explained tolerance in the context of his clonal selection theory. He argued that B and T cells able to recognize self antigens are selected against – that is, eliminated – early in vertebrate development. Within this early window, an organism can become tolerant of any tissue, including tissue transplanted from other organisms. But if transplantation is attempted after the window closes, the transplant will not be tolerated. Key evidence

supporting this developmental account of tolerance was Ray Owen's (1945) observation that cattle that had shared a circulatory system *in utero* did not respond immunologically to each other's blood cell antigens: they were hematopoietic chimeras. Further evidence came from Rupert Billingham, Leslie Brent, and Peter Medawar's 1953 study showing that mice injected with donor cells as pups would accept skin grafts as adults from those same donors. Normally such grafts would be rejected.

It is now well established that the principal means of achieving tolerance involves the elimination of self-reactive immune cells. T cells are eliminated in the thymus if they are able to bind self antigens. An analogous process occurs in B cell development: those cells able to bind self antigens are eliminated in the bone marrow. Tolerance achieved in either of these ways is referred to as "central" tolerance. Through somatic rearrangement and tolerance-inducing mechanisms, the immune system is able to develop cells that specifically bind nonself antigens and eliminate cells that specifically bind self antigens.

The processes creating central tolerance, however, are imperfect: self-reactive cells escape the thymus and bone marrow, and some self antigens are found in tissues that are unavailable for tolerance induction in the thymus. This necessitates a means of achieving tolerance in the periphery of the body. One mechanism for peripheral tolerance is proposed in the two-signal or "associative recognition" model of Peter Bretscher and Melvin Cohn (1968, 1970) and Rod Langman and Melvin Cohn (1993). In the associative recognition model, antigen provides the first signal and this acts as an "off" signal to T cells. This induces tolerance. The second signal, delivered during infection by T helper cells known as effector T helper cells, is an "on" signal that activates the immune system's ability to destroy an infectious agent. The effector T cell recognizes the association between the T cell receiving the first signal and the antigen, hence the "associative recognition" name for the model. The delivery of both signals is thus antigen-dependent. This model is thought to explain self–nonself discrimination because self antigens, which are present continually, will provide a constant source of the first "off" signal, thus inducing tolerance. Only in the occasional instances of infection will a second signal be delivered.

But an important question remains: How is the effector T helper cell that delivers the second "on" signal itself activated? Why does it not remain in an inactive, tolerant state? Cohn (1998) refers to this as "the primer problem." In the two-signal model, this problem is solved by positing an antigen-*in*dependent pathway to T helper cell activation. Bretscher and Cohn's (1968, 1970) antigen-independent pathway holds that if T cells interact with antigen early in their development and in the absence of a stimulatory signal from a T-helper cell, their further differentiation is arrested. Because self antigens are always present, younger T cells will always be exposed to self antigen and, if they are capable of reacting with self antigen, their development will stop and they will pose no threat to the self. If, however, T cells do not react with any available self antigens, their development will slowly continue to the activation stage. Because infections occur sporadically, T cells capable of reacting to them will likely have matured to the activation stage by the time an infectious agent appears on the scene. If correct, the two-signal model offers a relatively simple way to resolve the primer problem within the context of clonal selection theory. It provides a mechanism to distinguish between self and nonself in the periphery of the body.

Self–nonself discrimination – as understood in terms of clonal selection theory – has long been the dominant model in immunology and it continues to have vigorous defenders. However, the reliance upon tolerance to establish a clear self–nonself distinction is problematic for a variety of empirical and conceptual reasons, reasons that call into question the viability of the traditional self–nonself model. Some of these problems are identified and addressed by three-signal models, to which I now turn.

2.2. Three-signal models: the end of the immune self?

One of the difficulties with the traditional model of self–nonself discrimination is that violations of the self–nonself distinction regularly occur and do not appear to cause problems for the organism. Self-reactive immune cells do escape elimination; and self-reactive antibodies known as natural *auto*antibodies exist in individuals showing no signs of autoimmune disease. Moreover, while food is nonself, it is tolerated, as are many airborne substances and species of bacteria. While the gut and respiratory surfaces may be considered the "outside" of the body and introduce the possibility that self and nonself are discriminated spatially (with nonself on the "outside"), many of the nonself substances that engage these surfaces do enter the body. These violations suggest that discrimination between self and nonself is not as straightforward as proponents assume.

A further problem for the traditional self–nonself distinction concerns the antigen-independent development of T cells in the two-signal model. Mature effector T cells could target *newly arising* self proteins in mature organisms. Because a new protein would not be present during T cell development, nothing would stop the development of effector T cells able to recognize it. As Polly Matzinger asks,

> 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 the earlier "self"? (Matzinger, 2002, p.301)

These problems suggest that the boundaries in traditional self–nonself discrimination models may need to be relaxed. Some argue that the immune system only discriminates self from *infectious nonself* (Janeway, 1992) or "*some* self from *some* non-self" (Matzinger, 1994, p.994).

Ephraim Fuchs (1992) and Polly Matzinger's (1994) "danger model," which involves three signals instead of two, is a good example of a more flexible approach to self–nonself discrimination. In the danger model, an antigen-presenting cell provides signals 1 and 2. (See Figure 15.1.) Cellular substances released in response to tissue damage or abnormal cell death emit a third signal – a "danger" signal – which is needed to activate an immune response. Without it, nothing happens. Given that healthy tissues do not emit danger signals, they will not activate the immune system. The danger model thus shifts control of tolerance from the immune system to non-immunological tissues of the body. It is the local health status of tissues, not self–nonself discrimination, that stimulates an immune response.

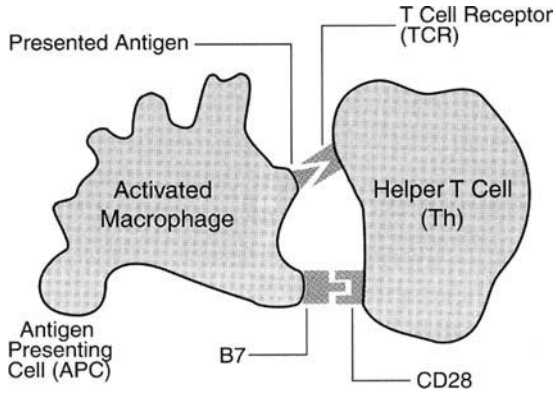

Figure 15.1 A two signal model of T helper lymphocyte activation. The first signal is the antigen presented by the macrophage (in the context of MHC class II) to the T cell receptor. The second signal is a protein (B7 in the diagram) presented to the receptor CD28. In a three signal model, an additional signal is needed to activate an immune response. Heat shock proteins spilled from damaged cells are an example of the sort of additional signal required in three signal models like the danger model. Reprinted from *How the Immune System Works*, L. Sompayrac, Blackwell Science, 1999, with permission from Blackwell

While the addition of a third signal may not seem particularly significant (Cohn, 1998), Matzinger claims that the addition of a danger signal is a small step that "drops us off a cliff, landing us in a totally different viewpoint, in which 'foreignness' of a pathogen is not the important feature that triggers a response, and 'self-ness' is no guarantee of tolerance" (Matzinger, 2002, p.302). When danger is the concern, there is no need for immune mechanisms to distinguish precisely between self and nonself. The danger model also suggests that when immunological investigations are conducted under the rubric of self–nonself discrimination, those investigations – and the treatments for cancer, organ transplantation, pregnancy, and autoimmune disease based thereupon – may target the wrong mechanisms. As Matzinger argues, questions that do not arise in the context of traditional self–nonself discrimination models do arise once selfhood is de-emphasized, including questions such as.

> why liver transplants are rejected less vigorously than hearts; why women seem to be more susceptible than men to certain autoimmune diseases . . . [and] why graft-versus-host disease is less severe in recipients that have had gentle rather than harsh preconditioning treatments . . . (Matzinger, 2002, p.301)

Despite raising these important questions, however, the extent to which the danger model really does depart from traditional self–nonself discrimination theory remains an unsettled matter. The difficulty with thinking that the danger model marks the end of immunological self–nonself discrimination is that some means of distinguishing self from nonself may still be required in the danger model – otherwise, self-reactive T cells could be activated by danger signals with harmful consequences for the organism. And, because the decision to activate the immune response at local sites of infection is not

based upon self–nonself discrimination in the danger model, there is no local way to avoid reactions against the self if self-reactive cells are present – one just has to hope that the general system has already eliminated any cells capable of self-reactivity.

Regardless of whether the danger model ultimately spells the end of the immune self, however, the questions it raises strongly suggest that self concepts in immunology require further analysis. The network theoretical perspective discussed next also suggests that analysis of self concepts in immunology remains an important task.

2.3. Network models of immunological self

The debate between clonal selection theory and the network perspective largely concerns how immune activity toward self and nonself is regulated. In clonal selection theory, regulation is achieved by self–nonself discrimination. In network models, regulation is achieved through connections amongst lymphocytes and/or between antibody molecules. Of course, in self–nonself discrimination models it is recognized that immune cells, antibodies, and immune biochemicals form a network of interactions. But in network models, "network" is meant in a more specific sense: it refers to regulatory autoimmunity. Regulatory autoimmunity, as we shall see, has consequences for understanding self–nonself discrimination.

The basis upon which contemporary network views rest is Jerne's (1974) idiotypic theory of the immune system. An idiotype is a lymphocyte antigen receptor whose unique amino acid sequence can be recognized by other lymphocyte receptors, provided they are complementary or "anti-idiotypic." (See Figure 15.2.) Jerne called these recognition interactions between lymphocytes "idiotypic." Given the diversity of lymphocyte receptors and antibodies, there must exist antibodies and lymphocyte receptors that can recognize other antibodies and lymphocyte receptors. If lymphocytes can activate other lymphocytes through idiotypic interactions, a network of interacting lymphocytes, ultimately encompassing the entire immune system, could form. In Jerne's view, this connectivity amongst lymphocytes would then serve to read the state of body and regulate the immune system accordingly, either through activation or suppression. Note that the molecular conformations involved here are all "self" in origin; hence, network perspectives are based on regulatory *auto*immunity.

Antonio Coutinho (1984, 1989) is one of the principal contemporary immunologists associated with the network approach. One interesting way in which Coutinho develops the network hypothesis, beyond Jerne's version, is his division of immune network activities into central and peripheral compartments. Coutinho holds that the immune system consists of a central immune system involving a connected network of lymphocytes that maintain tolerance to self and a peripheral immune system consisting of unconnected lymphocytes that, when stimulated by antigen, begin an immune response.

In Coutinho's model, the immune system does not regulate itself by first discriminating between self and nonself. Self–nonself discrimination is not a property or ability of an individual lymphocyte, such that it is either "turned off" if it can recognize self substances, or "left on" if it can recognize foreign substances. Rather, immune regulation is achieved by discriminating between unperturbed and perturbed states of immune

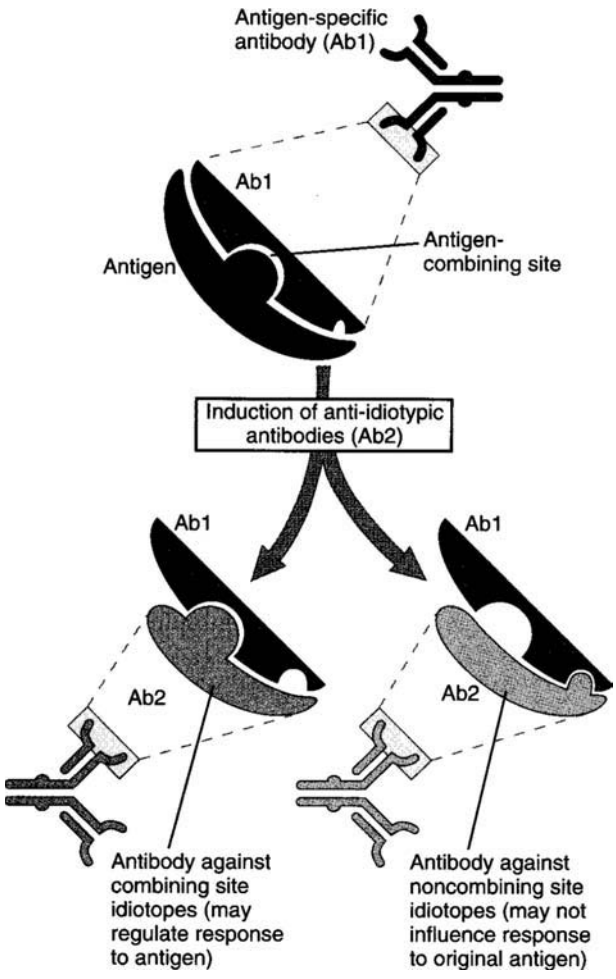

Figure 15.2 Idiotypic interactions between antibodies. Reprinted from *Cellular and Molecular Immunology*, fourth edition, A. Abbas, A. Lichtman and J. Pober, Philadelphia: W. B. Saunders Company, 2000, with permission from Elsevier

connectivity. The immune system is busy interacting with itself and with the body all of the time and the appearance of foreign antigens causes a perturbation of this activity. Because nonself is viewed as a perturbation of the system, it is not really viewed as "nonself" by the immune system. There is only "self" and its perturbations; and hence, we have a theory about how the immune system reacts to the self rather than a theory focusing on immunity to nonself.

Network approaches to the immune self thus depart from the relatively static demarcation between self and nonself found in tolerance views of self–nonself discrimination. The immune self in clonal selection theory is firmly defined: its edges may change, but the core of the self is maintained throughout life. This defined self–nonself distinction is the cause of immune activity (or inactivity, as in the case of tolerance). Unlike

traditional self–nonself discrimination, which treats the self as an entity, network views treat the self as a process. The network self does not have a stable core. In network models, self–nonself discrimination is the *outcome* of interactions between lymphocytes and not the starting point for those interactions. Self–nonself discrimination is a consequence, not cause, of immune activity.

In the network perspective,

> self is in no way a well-defined (neither predefined) repertoire, a list of authorized molecules, but rather a set of viable states, of mutually compatible groupings, of dynamical patterns . . . The self is not just a static border in the shape space, delineating friend from foe. Moreover, the self is not a genetic constant. It bears the genetic make-up of the individual and of its past history, while shaping itself along an unforeseen path. (Varela et al., 1988, p.363)

This more dynamic understanding of self also has implications for how experiments are designed in immunology. Because system-wide lymphocyte connectivity is the source of self–nonself discrimination network perspectives, Coutinho argues that *in vitro* experimental investigations of tolerance are limited in what they can tell us. Thus, the evidence provided by *in vitro* experimental studies of tolerance may not apply to naturally occurring tolerance. Similarly, evidence provided by *in vivo* studies using transgenic mice and chimeras (wherein different genetic tissues are mixed in one animal) may also fail to apply to naturally occurring tolerance. If such studies cannot provide adequate support for naturally occurring tolerance, one must return to the organism, to the lymphocyte in its bodily context, to achieve adequate understanding.

Indeed, network perspectives claim to be antireductionistic insofar as they claim that there exist some properties of the immune system that exceed description in terms of the immune system's parts and relations considered in isolation from each other. This means that complete understanding of the immune system will not be achieved by studying component functions in isolation from other immune activities. But given that immunological experimental studies must isolate mechanisms, network accounts have had difficulty finding experimental support. It is simply not possible to replicate experimentally system-wide lymphocyte behavior. Moreover, network models have not yielded much in the way of testable predictions. There are some newer experimental approaches, such as quantitative immunoblotting and multiparametric data analysis, that some immunologists are now using to investigate immune activities in a less isolated manner. However, the extent to which these experiments involve less isolated immune activities remains to be determined.

3. Challenges

Now that the three main theoretical perspectives on self–nonself discrimination have been outlined, I turn to consider several challenges that complicate these perspectives.

3.1. The major histocompatibility complex: a genetic signature of self?

The major histocompatibility complex (MHC) genes code for cellular proteins that are unique to each individual vertebrate organism. There are two classes of MHC, each of which is involved in self–nonself discrimination in a different way. MHC class I is found on all nucleated cells of the body. Its function is to sample cellular proteins and display those proteins on the cell surface, where the immune system can see and evaluate them. MHC class II is found only on antigen-presenting cells. It presents fragments of bacterial and viral substances to T helper lymphocytes and thus plays a role in establishing the first signal in lymphocyte activation.

There are at least two other respects in which MHC is relevant to self–nonself discrimination. First, MHC proteins are involved in the acceptance and rejection of transplanted tissue – indeed, they are named for this role. The immune system regards foreign MHC just as it regards viral proteins and when it targets foreign MHC in transplanted tissue, rejection results. Second, MHC plays a role in tolerance induction in the adaptive immune system. MHC is involved in the selection for and against T cells in the thymus. T cells that are aggressively reactive towards self antigens presented in the context of MHC proteins are eliminated. T cells that do not recognize self are retained.

By virtue of its involvement in transplant rejection, tolerance induction, and antigen presentation, MHC appears to provide a secure means of identifying self and nonself. Because of these functions, and because MHC proteins are unique to each individual organism, MHC has been referred to as the "genetic signature" of immunological selfhood (Tauber, 1994). On this view, MHC is a necessary, though not sufficient, element of immunological selfhood (Tauber, 1994).

It would be a mistake to settle for the view that MHC is the "genetic signature" of the self, however, if by this it is meant that the genetic criterion of selfhood is somehow more essential to selfhood than other immune factors contributing to self–nonself discrimination. By way of analogy, the claim that the human genome provides the essence of human selfhood is clearly problematic: the claim ignores biological and social development. Similarly, we should not privilege MHC genes in the development of the immune self. That the MHC contribution is genetic does not afford it some special ontological status. There may be many different routes to self–nonself discrimination, including networks and danger signals. And, and as outlined in the next section, there may also exist innate mechanisms for self–nonself discrimination.

3.2. Innate immunity: is there self–nonself discrimination without the adaptive immunity?

In vertebrates, innate immunity provides a first line of defense against infectious organisms. Cells of the innate immune system – such as macrophages and natural killer cells – prevent infection at all points of entry into the body. Macrophages engulf bacteria in a process known as phagocytosis and digest them. Natural killer cells lyse virally infected cells. And, innate immune cells produce biochemicals that stimulate the immune response. It is generally thought, however, that innate immune cells lack the specificity and immunological memory typical of the adaptive immune system and on this basis a firm distinction between innate and adaptive systems is made.

Recent findings in the area of innate immunity suggest that the innate–adaptive distinction may not be so clearly defined after all. Three-signal models, for example, challenge the innate–adaptive distinction, for non-adaptive cells like antigen-presenting cells initiate adaptive immune responses by providing danger signals or their equivalent. Problems with classifying certain immune cells as either innate or adaptive also present a challenge the innate–adaptive distinction. A type of T cell known as the gamma delta (γδ) T cell is a case in point: γδ T cells develop in the thymus like other T cells and have T-cell receptors which suggests they are part of adaptive immunity; however, they are not capable of specificity in the way that other T cells are and so they are more like innate immune cells. Moreover, γδ T cells migrate to epithelial tissues, which is characteristic of innate immune cells; in general, γδ T cells do not circulate to the lymph nodes as do other T cells. The γδ cell thus appears to resist classification as either innate or adaptive.

The classification of the macrophage as an innate immune cell – insofar as it lacks specificity – is also now being questioned. The key challenge to its classification arose during investigations in developmental biology concerning *Toll*, a maternal-effect gene responsible for embryonic dorsal–ventral polarization. A connection between *Drosophila Toll* and immunity was made when it was found that *Toll* mutants had immunological deficiencies (Rich, 2005). Macrophages were found to have many *Toll*-like receptors – "*Toll*-like" because they bear a sequence homology with *Toll* – which can recognize evolutionarily conserved microbial structures. This recognition is not that of adaptive specificity, which must be learned. However, there is some evidence that through *Toll*-like signaling, macrophage receptors gather into clusters. It is suspected that clustering introduces a form of *specificity* into the innate immune response by generating novel molecular receptor configurations. Thus, macrophage functions, long classified as non-specific and innate, may actually include the generation of novel immune specificities. It is also worth noting here that some evidence of immunological memory in invertebrates now exists (Kurtz, 2004). Despite lacking adaptive immune systems, then, invertebrate immune systems may be able to learn. Innate and adaptive systems may thus share features that are commonly used to distinguish them.

Another reason to question the innate–adaptive distinction concerns evidence that tolerance may be achievable in some cases without input from the adaptive immune system. Consider the following example. Epithelial cells lining the intestinal lumen are polarized in their expression of *Toll*-like receptors. *Toll*-like receptors are absent on epithelial surfaces facing the intestinal lumen, but present on the other side. Friendly gut bacteria only come into contact with the cell surfaces and, since there are no *Toll*-like receptors there, no immune response is initiated. But pathogenic bacteria will breach the intestinal epithelium and, in so doing, will encounter the *Toll*-like receptors. This will initiate an immune response. Here, then, tolerance to friendly bacteria, and intolerance to the unfriendly, is achieved without adaptive immunity.

These empirical challenges to the innate–adaptive distinction are intriguing, but there are also philosophical questions that need to be addressed here. Does innateness in immunology resemble notions of innateness at play in cognitive psychology, genetics, and linguistics? What exactly is an *innate* immune phenomenon? The concept of innateness generally involves notions of fixity as well as essentialist views about biological natures, but the extent to which these associations carry over into immuno-

logical innateness remains to be determined. Because innate immune recognition is thought to be germ-line encoded, immunological innateness fits these associations quite well. It seems reasonable to suppose, then, that the concept of innateness may be just as problematic for immunology as for other fields. Now that the fixity of innate immunity – its inability to learn – is being challenged, essentialist undertones may prove particularly problematic.

Given the empirical challenges posed to the innate–adaptive distinction by γδ T cells, *Toll*-like receptors, and macrophages, the distinction increasingly appears artificial. And, given the outstanding conceptual issues concerning innateness, what it is to be innate, or adaptive, in the context of immunity requires further analysis. The significance of this conclusion for vertebrate immunology is that it challenges the exclusive role of adaptive immunity and tolerance in the generation of self–nonself discrimination. Research concerning innate immunity may well provide deeper understanding of self–nonself discrimination in immunology (Janeway & Medzhitov, 2002).

3.3. Self–nonself discrimination in pregnancy immunology

Pregnancy has long been described by immunologists as a "paradox" (Medawar, 1953, 1957). Because the fetus has paternally derived MHC proteins, the fetus should appear as nonself, at least partially, to the maternal immune system. From the traditional self–nonself discrimination perspective, the fetus is akin to an organ transplant. Given this, the maternal immune system should try to reject the fetus. The objective of the fetus is presumably to try to prevent this rejection. On this view, then, a constant tension between mother (immunological self) and fetus (immunological nonself) exists at the core of immunity in pregnancy.

Indeed, in immunology, mothers and fetuses are often conceptualized as warring entities battling for control. In order to prevent maternal immune aggression from erupting, Medawar thought that either the fetus must hide from the maternal immune system or the maternal immune system must be suppressed – and updated variations of these ideas exist in the present day. Some evidence appears to support the idea that the fetus hides from the maternal immune system. For example, certain identifying cell markers derived from MHC proteins are either absent or altered in fetal trophoblast cells – the cells that interact most closely with maternal tissues. Other evidence appears to support the idea that certain maternal immune functions are downregulated. Pregnant women have increased vulnerability to certain types of infection and some experience changes in the severity of autoimmune disease.

A number of findings, however, challenge the view that self–nonself discrimination is important in pregnancy immunology and that maternal aggressiveness towards the fetus is the best (or only) way to frame maternal immunology. It may not be appropriate to treat the fetus as a nonself entity always at risk of rejection. This view is supported by the danger model, wherein the maternal immune system only responds to the placenta–fetus if danger signals are present.

Indeed, some reproductive immunologists are now exploring the idea that maternal immune recognition of the fetus is *beneficial* to fetal growth and development. The discovery of lasting microchimerism – the persistence of small numbers of cells from one individual in another – in mothers and their children also suggests that too much has

been made of maternal–fetal conflict. There is evidence that maternal immune cells present in children populate sites of infection and may lend immunological assistance (Hall, 2003). There is also evidence that persisting fetal cells contribute to tissue repair in some women long after the birth of their children (Adams & Nelson, 2004). In light of these findings, it is difficult to imagine that maternal–fetal relations should be classified simply in terms of antagonistic self–nonself relations.

Rather than being an immunological paradox or a weakened immunological state, pregnancy is probably a sensible immunological phenomenon and its study may have much to contribute to the development of more adequate models of self–nonself discrimination. Moreover, because viviparity may have been one of the selective pressures driving the evolution of adaptive immunity (Sacks, Sargent, & Redman, 1999), the fact that pregnancy receives little attention may stand in the way not just of immunological understanding, but of evolutionary understanding as well. But in order to envision alternatives to the view that pregnancy is an immunological paradox, different understandings of how selfhood relates to maternal–fetal relationship in pregnancy are needed.

4. Conclusion

As the main theoretical perspectives of self–nonself in immunology and the challenges posed to them illustrate, the issue of the self in immunology is complex and controversial. But recent challenges to immunological self–nonself discrimination should be no cause for despair: though philosophers still lack a satisfactory criterion for self identity, most have not declared the self a useless fiction. Moreover, there is much in biology to suggest that selfhood is important. It therefore seems premature to claim, as some do, that self concepts are no longer useful in immunology (Tauber & Podolsky, 1997, p.377). On the contrary, the question of immunological selfhood appears to be on the cusp of renewed and vigorous inquiry, with revised models of self–nonself relations replacing dated versions. Such revision is especially promising given growing connections between immunology and developmental biology, comparative immunology, neurobiology, and evolutionary biology. The landscape of self–nonself discrimination is changing – and philosophy has a role in coming to understand these changes.

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