International Immunology, Vol. 10, No. 6, pp. 711–717

Immune information, self-organization and meaning

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Keywords: context, information, language, meaning, redundancy, self-organization

Abstract

To effect the molecular integrity of the individual, the immune system has to gather antigenic information and respond in a meaningful way. Immunologists traditionally have focused their research on analyzing the component parts of the system. The achievements of immunology in its analytical enterprise have now made it possible to begin the task of synthesis. In this paper, we shall consider how the immune system combines germline and somatic information using a chemical language to establish the functional meaning of antigens.

Introduction

The affinity between neurobiology and the information sciences seems natural to both parties because the central nervous system is clearly in the information business. The central nervous system receives a wide spectrum of energies (electromagnetic, sound, pressure, gravitational, etc.) and transforms these inputs into information useful to the survival of the organism. The connections between immunobiology and the information sciences are less natural. Modern immunology arose initially from the activities of chemists and microbiologists who were not primarily concerned with questions about information; the information people, on their part, gave little thought to the immune system. Now that immunology has succeeded in establishing, at least in principle, the chemical basis of the immune system, immunologists are beginning to take a broader look at immunobiology. After all, the immune system does make sense out of the bombardment of molecular structures that constantly rains down upon the body. How does the immune system create information and meaning from this input? This article aims to place the immune system into an informational framework.

Information theory

Claude E. Shannon developed a probabilistic theory of information based on the relative frequencies of the different 'letters' in any 'alphabet' that might be used to write a set of messages (1,2). Shannon's approach stimulated thinking because it provided a way to quantitate information. Although Shannon's practical concerns were related to the engineering of telephone communications, his principles have been applied to many disciplines, including biology. Information, as defined by Shannon, involves an arrangement of elements, the string of amino acids in an antibody molecule, for example, that is 'just so' as distinct from any other possible arrangement. Indeed, the 'just-so' structure of the amino acid string compared to all other possible arrangements of the same amino acids constitutes the quantity of information in the protein. Protein synthesis can be seen as an information channel through which DNA is transcribed into mRNA; the mRNA, in turn, is translated into the amino acid sequence of the protein. If transcription and translation are free of errors, the amino acid sequence is a replica of the information in the nucleotide sequence through a deterministic rule of correspondence called the genetic code. Random perturbations in the communication process, what has been called 'noise', can disrupt the transfer of information and produce errors in the amino acid sequence. Noise, in effect, can decrease the information content of the protein, in reference to the information carried by the DNA and mRNA.

Shannon's classical formulation has helped to establish principles governing the fidelity of any transmission of information. For example, making parts of the transmission redundant can preserve information over a noisy channel of communication. When presenting ideas, our instinctual repetition of key words is for clarity, as well as for emphasis. The added cost of adding redundancy pays off in added fidelity.

Shannon's formulation is particularly robust because it holds true irrespective of the nature of the information borne by the message and is even independent of any meaning the

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Transmitting editor: B. R. Bloom

Received 30 November 1997, *accepted* 13 February 1998

message might convey to the receiver. Shannon, a scientist at the Bell Telephone Laboratories, assumed that the meaning of the message was the concern of the sender and receiver of the message; the packaging and fidelity of the transmitted information were Shannon's (and the telephone company's) concern. However, the very robustness of Shannon's theory turns out to be its major weakness for biology. As Andre Lwoff pointed out 35 years ago (3), life depends on how molecules work and not only on how much information they bear. Indeed, the way a molecule functions endows it with biological meaning. For example, two molecules of mRNA may bear the same quantity of Shannon-type information, but only one of them may be translatable into a protein. Another deficiency of Shannon's theory is that it neglects the creation of new information. Self-organizing systems like the brain and the immune system create new information and do not merely transmit or preserve existing information.

Creating new information

Obviously, a diversity of antibody molecules that can recognize a diversity of antigens contains more information than does a single mAb. So the creation of information amounts to an increase in diversity. Diversification, however, has a catch. The only way to create new information out of existing information is to disrupt the old 'just-so' order, to introduce unforeseen changes in the existing information. We say *unforeseen* changes because the expected is not really new. Mutation, a 'noisy' cause of random change, is a process that can effectively open the way for new opportunities of molecular organization. To create a new antibody molecule out of an existing antibody molecule requires a mutation of the existing antibody gene. Thus, any diversification of antibody information would seem, paradoxically, to obligate a loss of the original antibody information. One of us (H. A.) has developed a formal theory that resolves the paradoxical loss of information that seems to be required for diversification. The generation of new information is viewed as a creative process driven by noise (4–7). According to this theory, two conditions must be fulfilled if random noise is to generate useful diversity without disorganizing the system.

(i) The system must have a hierarchical, multilevel organization so that a decrease in the information transmitted in a channel at one level can actually produce an increase in the content of information at a more global level of the system. For example, a mutation in an antibody gene, which disorganizes the gene's original string of nucleic acids, could produce a new gene encoding a new antibody that could add information to the organism as a whole.

(ii) The system must feature redundancy. Redundancy refers to the existence in the system of multiple copies of the same or similar information. For example, a polyclonal antibody response to a single antigen is essentially redundant. However, having extra clones of B cells makes it possible for the system to 'experiment' by mutating some of the extra clones to fuel the process of affinity maturation. In contrast, mutation of a monoclonal response could lead to a loss of the original antibody without necessarily generating a better antibody. Thus, diversification, to be safe, requires redundancy. Redundancy makes it possible for noise to create added diversity without sacrificing all of the old information. Note, however, that successful diversification reduces the initial redundancy; the extra copies of the original antibodies get used up as the redundant clones of B cells undergo affinity maturation. Fortunately, a continuing supply of newborn B cells keeps renewing the antibody redundancy that allows continuing diversification of the specific response.

Recharging redundancy can also be seen at the evolutionary level. For example, it is now clear that a process of gene duplication, which creates redundant copies of a particular gene, is required to allow the safe generation of multigene families. Each redundant copy of the gene independently can mutate and diverge over evolutionary time to create the diversity of genetic information that produces complex organisms.

The differences between Shannon's original theory and the theory of complexity from noise can be clarified by considering the different roles each theory assigns to noise and redundancy. For Shannon, who wants to preserve the message, noise is the destroyer and redundancy of the message is a premium we pay to assure fidelity despite noise. But according to the theory of self-organization, noise (mutation) is the (blind) creator of new information and redundancy is not the cost of fidelity, but an asset, the vehicle for change. Redundancy for communication engineers is a burden. It is a bonus for biologists.

The random generation of immune diversity

The principle of complexity from noise can be seen in the creation of the immune receptor repertoire, which is fashioned by processes of genetic recombination, mutation and random insertion of nucleotides in the genes that encode the receptors. Hence, random and near-random processes create the unique specificity of the antigen combining site of each lymphocyte clone (8).

Note that randomness characterizes not only the mechanism that generates the receptors of individual clones, but also the unedited collective of receptors that arise by chance, what might be called the primordial repertoire. Quite simply, the numbers of different antigen receptors that potentially could be generated by any person's immune system is so large, perhaps 10^{10}–10^{15} different combining sites, that the chance realization of a large sample of the potential repertoire must produce an unmanageable and inefficient surplus. To be serviceable, the primordial repertoire of clones has to be organized; from the primordial repertoire, an actual repertoire has to be generated that is reduced in size and focused in a way that augments the frequencies of the more useful clones. Diversification of the redundant clones will not, of itself, produce a useful repertoire. In other words, the receptor repertoire can be made to work efficiently only by establishing a hierarchy of dominant specificities. The mechanism responsible for this reduction in initial redundancy is the selective activation of particular clones of lymphocytes, clonal selection (9). Clonal selection imposes a dynamic ordering of the receptor repertoire that reflects the actual antigenic experience of the individual with his or her particular antigen world. Thus, the frequency distribution of specific lymphocyte clones

within the immune system is a measure of the antigen-specific information inherent in the system at any given time. This clonal distribution embodies self-organization, the creation of new information that is fashioned according to actual antigenic experience. Burnet entertained the notion that some random process must precede clonal selection, although he never formalized this idea (9). The discovery of the combinatorial basis for the clonal generation of receptors has confirmed Burnet's speculation, while it has provided a living example of complexity from noise as the basis for subsequent organization of the repertoire by clonal selection. First noise, then music.

The creation of meaning

Randomness, redundancy and multilevel organization are necessary to create new information. However, adding information does not, by itself, improve function. New information is an advantage when it is meaningful. What then is meaning?

Information, as discussed above, is a property of the intrinsic organization of the message in the form of a frequency distribution of its elements. The meaning of the message, in contrast, is never intrinsic to the message; the meaning is the relationship of the message to some reference point outside of the information borne by the message. Something or somebody has to 'read' the message. *Meaning* is referential and contingent. A given immune response may mean one thing to the bacterium that bears the target antigen (death), another thing to the responding host (life) and yet another thing to certain cells within the infected tissue (activation of various genes). The meaning of an antigen, therefore, can be reduced to the type of immune response the antigen generates. Antigens bear Shannon-type information intrinsically, as a consequence of their particular molecular organization. The meaning of an antigen, in contrast to its information content, is extrinsic; the meaning depends on the response of the immune system.

Granted that a fundamental unit of information for the immune system is an antigen receptor, what reference points external to the antigen can serve the immune system to endow the antigen with meaning? An antigen is *perceived* by the immune system when an epitope of the antigen is bound by an antibody or a lymphocyte receptor; but what is the *meaning* of the antigen to the system? To reframe the question of *meaning*, how does the immune system 'know' how to respond to the antigen? After all, a processed peptide is a sample of an antigen and an antigen, possibly, is a sample of an invader. Can one depend on a sample of a sample? Is there a point of reference that could allow the immune system to vary its response to the antigen, to interpret as it were, the antigen's meaning?

The clonal selection of meaning: self–not-self discrimination

Burnet, in his clonal selection theory, offered an external reference point to solve the problem of immune meaning, although he never formulated the concept of external reference or defined meaning as such. Nonetheless, for Burnet, the meaningful reference for any antigen was essentially one: was the antigen self or was it not-self (9). The discrimination between self and not-self was seen by Burnet, and by many immunologists even today (10), as the primary function of the immune system. Molecules that originate from the body, the molecular self, are to be ignored by the system while molecules foreign to the body, the not-self, are to be rejected by an effective immune response. Thus the source of the meaning of any antigen depends on whether the antigen be self or not-self.

But how is this self–not-self distinction to be made when an antigenic epitope is merely a molecular conformation unable, by itself, to declare its origin? Inherent in Burnet's theory was an answer that, in a wondrously thrifty way, linked the creation of immune meaning (self–not-self discrimination) to the creation of immune information (the process of clonal selection): the ontogenic deletion of self-reactive clones. The reference point for self–not-self discrimination, the essence of immune meaning, was held to be a product of the lymphocyte's *history* of being born into a *context* of self-antigens. The filter of clonal suicide in ontogeny together with positive clonal selection in maturity both created information and guaranteed achievement of meaning, the discrimination between the self and the not-self. Burnet offered a view of the lymphocytes as an army that is taught during basic training what not to shoot, but when at the front, to shoot all the rest. The correspondence between antigen stimulus and immune response was seen as a reflex. The meaning was built-in. The logic and parsimony of Burnet's theory has made it the paradigm that has influenced immunological research and immunological interpretation for three decades. The problem, however, is that the immune system is more complicated than anticipated by Burnet because it must solve more complex problems than dreamed of in Burnet's philosophy.

The challenges of natural autoimmunity and positive selection

Self–not-self discrimination as the reference point for immunological meaning is rendered moot by the discovery of two facts. First, the immune repertoires of healthy individuals are filled with lymphocytes whose receptors can perceive self-epitopes (11). Indeed, the infectious invaders, which must be rejected by the system, often express epitopes identical to, or cross-reactive with self-epitopes of the host (12–14). Perhaps these matters are related; because of the evolutionary conservation of key genetic modules in multigene families, the immune system cannot afford to be blinded to epitopes that look like the self. Speculations aside, the fact is that natural autoimmunity does exist. Hence the self cannot be distinguished from the not-self solely on the basis of repertoire purging; the self is not antigenically unique and self-purging is not complete.

It may be argued that natural autoimmunity is still an aberration, though it may regularly arise through accidents natural to the deletion process. A second fact, however, suggests that autoreactivity of a type is essential to the creation of the repertoire. Developing thymic T cells will not survive to function in the body unless they have been positively selected by their ability to recognize self-epitopes (15). The molecular distinction between self-recognition that negatively selects and that which positively selects has yet to be resolved. Nevertheless, it is clear that some degree of self-recognition is a prerequisite for thymic T cell development.

Therefore, the problem of meaning is not solved by Burnetian-type deletion alone.

Second signals and idiotypes

There have been attempts to enrich the concept of clonal selection. Melvin Cohn has developed the idea of the dependency of the effector response on reception by the lymphocyte of *two* signals rather than only one signal (16). The first signal is the antigen epitope and the second signal is not an antigen, but a cytokine produced by a helper T cell that itself has been activated by an epitope. Cohn sees this two signal model as a way of achieving the goal of self–not-self discrimination (16). Cohn's model, however, suffers from the same flaw as does Burnet's theory in not being able to account for natural autoimmunity.

Niels Jerne proposed that the nature of the immune response could be regulated by a network of anti-idiotypes, clones with receptors capable of recognizing the receptors of other clones (17). The Cohn and Jerne formulations complicate the behavior of the lymphocyte repertoire in that the lymphocytes interact with each other, as anti-idiotypes or as helpers, in addition to their interactions with the antigens. However, adding diversity and complexity to the organization of the repertoire may lead to more information, but not necessarily to meaning. Meaning must be created by relating the antigens seen by the receptor repertoire to something else, something outside of the repertoire.

Danger

The concept of 'danger' has been introduced by Polly Matzinger as a way to provide meaning to the immune response independent of self–not-self discrimination (18). The danger theory proposes that the immune system is not concerned with distinguishing the difference between self and not-self antigens, but rather with the need to attack any antigen associated with a 'danger' signal. The danger theory allows natural autoimmunity to benefit the host by functioning at sites of danger. In this sense, the danger theory is truer to reality than is the insistence of classical clonal selection that autoimmunity can only be unnatural (19). Langman and Cohn have claimed that Matzinger's 'danger' still requires some form of self–not-self discrimination, and that it is not really a departure from the classical teaching (20). However, even if we were to argue with Langman and Cohn, and accept the novelty of the 'danger' idea, the concept is deceptively simple.

There is a fundamental problem with defining 'danger' as a generic property that alone could account for immune meaning. Different invading viruses or bacteria may be equally 'dangerous', yet each can require the immune system to deploy very different mixes of effector agents (13). Quite simply, there are different types of 'danger' and each type needs a different response. 'Danger' by itself cannot supply the *meaning* required to mount an optimum response; 'danger' is only the first step. 'Danger' sidesteps the problem of *appropriateness* (13,14). Foreign antigens are not all the same; we need responses tailored to the situation. Indeed, the immune system deploys many different types of response (including non-response): cytotoxic T cells, helper T cells that can secrete different mixes of cytokines, 'suppressor' cells of different types, a variety of antibody isotypes, anergy, 'programmed' cell death, to say nothing of the leukocytes and antigen-presenting cells (APC) of various kinds, and more. In other words, the meaning of an antigen to the system is discernible in the *type* of immune response produced, not merely by whether or not the antigen is perceived by the receptor repertoire (13,14,21). Because the meaning of the antigen is defined by the type of response that follows perception of the antigen (22), there is indeed a response repertoire and not only a receptor repertoire. The 'danger' concept is an innovation, but it needs elaboration. The system has to diagnose the type of 'danger' to be able to deal with it properly. 'Danger' is an *interpretation*, not an invariant *signal*.

The cognitive creation of meaning

To account for immune interpretation, one of us (I. R. C.) has proposed a cognitive paradigm of the immune system (12–14,21). The immune system, as we discussed, can respond to a given antigen in various ways, it has 'options'. Thus, the particular response we observe is the outcome of an internal process of weighing and integrating information about the antigen. In contrast to Burnet's view of the immune response as a simple reflex, the immune system is seen to exercise cognition by the interpolation of a level of information processing between the antigen stimulus and the immune response. A cognitive immune system organizes the information borne by the antigen stimulus within a given context and creates a format suitable for internal processing; the antigen and its context are transcribed internally into the 'chemical language' of the immune system.

The language metaphor

The cognitive paradigm suggests a language metaphor to describe immune communication by a string of chemical signals. This metaphor is apt because the human and immune languages can be seen to manifest several similarities such as syntax and abstraction. Syntax, for example, enhances both linguistic and immune meaning. A complete sentence, the coin of linguistic meaning, can be characterized as containing two elements: a noun phrase and a verb phrase (23). The noun phrase is the designated *subject* of the action or description; the verb phrase is the *predicate* that is connected to the subject. A sentence bears its fullest meaning when properties or actions are predicated about a subject. Although individual words and even letters can have their own meanings, an unconnected subject or an unconnected predicate will tend to mean less than does the sentence generated by their connection.

The immune system creates its 'language' by linking two ontogenetically different classes of molecules in a syntactical fashion. One class of molecules are the T and B cell receptors for antigens. These molecules are not inherited, but are somatically generated in each individual. The other class of molecules responsible for internal information processing is encoded in the individual's germline. These inherited molecules include the enzymes and organelles for antigen uptake and processing, the MHC molecules for antigen presentation, the cytokines that orchestrate inflammation and the suppression of inflammation, the cell-interaction and cell-adhesion

molecules that organize cell-to-cell interactions and cell migrations, and 'innate' receptors (24) that recognize certain molecules of infectious agents.

Just as a sentence gains meaning when it connects a subject to its predicates, an antigen gains meaning by its connection to a particular set of germline signals that elicit a specific type of immune response (see Fig. 1). Thus the antigen is like a noun serving as the subject (or address) of the immune sentence, while the germline signals are like predicates that dictate the choice of response phenotype from among a set of possible responses. Meaning, the chosen type of immune response, is the outcome of the concrete connection between the antigen subject and the germline predicate signals.

Because antibodies could 'recognize' microbial invaders, the clonal selection theory assumed that the immune system responded to antigens as they are. However, as we have noted, the immune system really responds to fragments of antigens processed and presented by the immune system within a chemical context constructed by the system according to its specifications. Thus, it may be said that infectious invaders are abstracted into a string of chemical signals manufactured by the immune system. In short, the transcription of the antigens into processed peptides embedded in a context of germline ancillary signals constitutes the functional 'language' of the immune system. Despite the logic of clonal selection, the immune system does not respond to antigens as they are, but to abstractions of antigens-in-context.

Another similarity between human language and immune 'language' is that both systems organize themselves by combining germline information with individual experience. The human species manifests an 'innate instinct' for language that is probably encoded genetically (23). This germline language information includes not only a talent for learning a language, but also a 'universal generative grammar', a primordial structuring common to individual languages (23). Actual languages are based on the combination of this innate, germline information with the actual experience of the individual within his or her particular language community. We learn words-in-context, just as we learn antigens-in-context, based on an innate infrastructure. Obviously, words and generative grammar are not processed antigens and accessory signals, but metaphorically we may see at work a similar strategy for generating meaning by combining germline and somatic experience.

Dangerous teleology

According to the cognitive immune paradigm, meaning emerges from the integration of signals by the immune system. The system, as it were, generates its own meaning. This way of looking at meaning contrasts with the 'self–not-self' and 'danger' concepts, which attribute the functional organization of the immune system to some end or aim. The immune system works the way it does, they would assert, in order to distinguish the 'self' from the 'foreign', or in order to ward off 'danger'.

The attribution of causal effects to aims or ends is called teleology. Teleology was proposed by Aristotle to be one of the primary causes for the existence of any entity. Teleology, however, has been rejected ideologically by modern science, which prefers to reduce phenomena to their underlying material and efficient causes. Nature, says science, is blind to ends, however desirable ends may seem to humans.

Now, it may be argued that the 'self–not-self' and 'danger' concepts are not real teleologies, but rather shorthand ways of saying that 'evolution' has naturally selected the immune system to be the way it is because the absence of autoimmunity, or of danger, has survival value. This explanation, however, does not exorcise the teleology demon; it merely passes the teleology on to 'evolution'. However, passing the buck will not help; if natural autoimmunity is prevalent, then autoimmunity must be compatible with the supposed 'aims' of evolution. 'Self–not-self discrimination', therefore, is an immunologist's interpretation of what is good for evolution, which, however logical, cannot be a goal of evolution. Evolution, as far as we can know, has no goals; what works, works. Indeed, some very undesirable things, from our point of view, work very well. The concept of 'danger', like that of 'self–not-self discrimination', is a human imposition on nature. If danger is so bad, why is there so much around? The process of evolution, indeed, is driven by death itself, the ultimate danger. Thus 'danger', like 'self–not-self', is a human's teleological interpretation of what evolution ought to be doing. The reader is advised, however, to keep an open mind; Aristotle may be right about teleology after all.

Talking to yourself

Medzhitov and Janeway, extending earlier ideas of Janeway, conclude, as we have done here, that the nature of the immune response is dictated by the integration of innate (germline) immunity with the adaptive (somatic) recognition of antigens (24). According to their view, the immune system cannot attack the self because the pattern recognition receptors (PRR) of the innate subsystem interact exclusively with pathogen-associated molecular patterns (PAMP), and never with self-molecules. The problem with this proposal is that many of the PRR receptors involved in innate immunity are manifestly responsive to various self-molecules, such as cytokines and cell-adhesion signals. Indeed, inflammatory responses initiated by innate immunity are key triggers of wound healing, angiogenesis, tissue regeneration and other processes essential for self-maintenance. These processes need not be related to infection or to PAMP. Contrary to the logic of Medzhitov and Janeway, the innate inflammatory response is preoccupied with the self.

One of the difficulties facing immunologists in reconciling their expectations with the actual behavior of the immune system arises from the popular conviction that the inner 'self' must be a discrete entity distinct from the 'foreign' outside world (25). Self-esteem notwithstanding, there is, in truth, no absolute way that the self can be distinguished chemically from the world of its parasites (26). We are all links in a common chain of biological evolution. Indeed, the chemical similarities between hosts and parasites can explain, at least in part, the development of the T cell repertoire based on a strategy of positive selection by processed self-peptides (15). It would seem that the immune system actually takes advantage of evolutionary conservation. However, if absolute

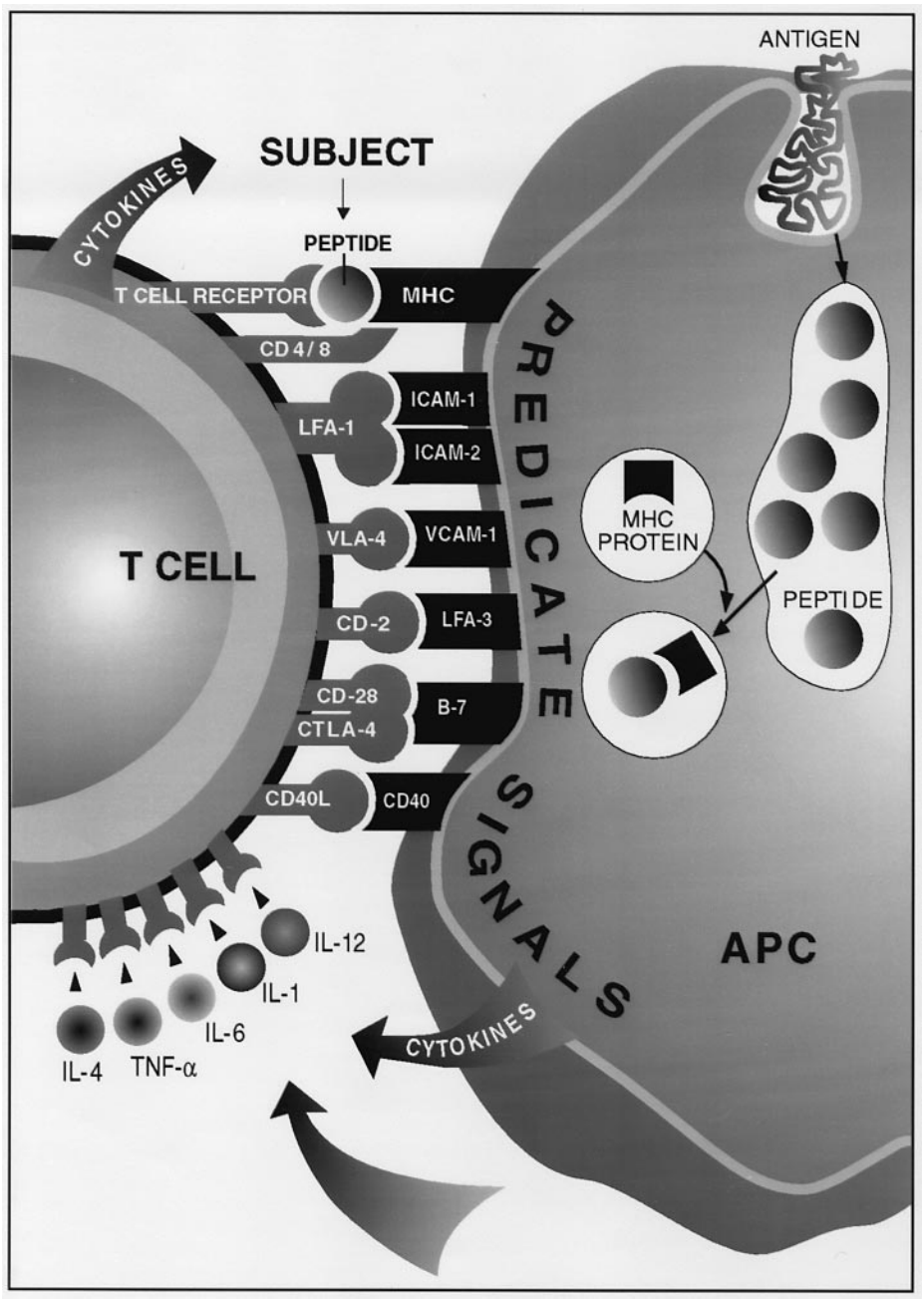

Fig. 1. The subject–predicate format of immune communication. An APC is depicted communicating an immune sentence to a T cell. The sentence describes the nature of an antigen shown as being ingested by the APC from without. (Antigen molecules may also originate from within the APC as viral molecules or self molecules.) The T cell does not recognize antigens in their native form directly; rather, a processed peptide in the MHC cleft is the subject of the immune sentence recognized by the somatically generated TCR. How the T cell responds to the peptide–MHC subject defines the immune 'meaning' of the antigen. Various response or non-response options are possible, and the particular response is predicated by the composition of a string of germline APC and tissue signals that accompany the somatic peptide–MHC subject. The germline predicate signals may include a variety of cell-interaction and cell-adhesion molecules together with a mixture of cytokines produced by the APC or by other nearby cells. The germline predicate signals reflect the state of the APC and the tissues, and indicate the type and degree of threat associated with the antigen. The T cell reads the context of the antigenic subject by integrating the germline signals with antigen recognition, and responds by producing a mixture of cytokines and other effector molecules. T cells and other leukocytes also may be triggered directly by germline signals to activate an innate inflammatory response.

self–not-self discrimination is impossible, how is the self tolerated?

The fact is that we all manifest some degree of autoimmunity to a set of dominant self antigens, but without suffering from autoimmune disease (14,27). Both the innate and adaptive arms of the system can be activated by contact with molecules

of the self. Autoimmunity is benign as long as autoimmune inflammation has the capacity to turn itself on and turn itself off as the need arises, to kill aberrant cells or to heal, repair and regenerate damaged tissues. Responsive regulation is the key to health. The immune language metaphor suits the situation. The immune self, like a conversation, is a flowing process that adjusts its responses to the requirements of the particular moment. These changing requirements are abstracted into the chemical language of the immune system. The ongoing integration of germline and somatic information in one's body is the essence of the self. The self, in other words, is more accurately described as a cognitive process than it is as a static subject. The immune self uses its language to write, as it were, its own story as it goes along. This idea of a de-centered immune self (25) should not be foreign to post-modern immunologists. The immune system seems to have discovered long ago how to implement a post-modern strategy of its own.

Acknowledgements

We thank Ms Doris Ohayon for help in preparing this paper and a reviewer for a point of information. H. A. is the incumbent of the Marc Taper Chair of Medical Biophysics at the Hebrew University and is supported by a Ishaiah Horowitz Scholarship in Residence. I. R. C. is the incumbent of the Mauerberger Chair of Immunology, the Director of the Robert Koch-Minerva Center for Research in Autoimmune Diseases and the Director of the Center for the Study of Emerging Diseases.

Abbreviations

APC	antigen-presenting cell
PRR	pattern recognition receptors
PAMP	pathogen-associated molecular patterns

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