seminars in **IMMUNOLOGY**, Vol. 12, 2000: pp. 215–219
doi: 10.1006/smim.2000.0234, available online at http://www.idealibrary.com on IDEAL

Discrimination and dialogue in the immune system

Irun R. Cohen

This paper presents reasons for concluding that the immune system maintains the individual body throughout the vicissitudes of life without the need to make an absolute distinction between self and nonself. Self-maintenance and defence against parasites both require measured inflammation, and the immune system, in both its innate and adaptive arms, regulates inflammation. The intensity, dynamics and orchestration of inflammation emerge from an ongoing dialogue.

Key words: autoimmunity / maintenance / inflammation / self / homunculus

© 2000 Academic Press

In their introduction, the editors of this issue of Seminars in Immunology, Langman and Cohn, suggest that the various essays on self and nonself discrimination could be organized coherently around an algorithm of reasoning that begins with the question:

> 'Is a self-nonself discrimination obligatory?'

A 'yes' answer leads one through a series of yes-no nodes down a decision tree in the figure provided by Langman and Cohn. A 'no' answer is a dead-end limb in the figure, so I suppose Langman and Cohn believe that 'no' is an answer not worth pursuing. However, let us suspend beliefs for a brief moment and examine some observations about the actual behaviour manifested by the immune system towards the body that houses it. In the light of these observations, I will reason that it is not self-nonself discrimination that is obligatory, but judgement; not verdict, but dialogue.

From the Department of Immunology, The Weizmann Institute of Science, Rehovot 76100, Israel. E-mail: Irun.Cohen@weizmann.ac.il.
©2000 Academic Press
1044–5323/00/030215+ 05/$35.00/0

Observations

1. Body maintenance. We may define body maintenance as the implementation of processes critical to wound healing, tissue repair, angiogenesis, cell regeneration, and the disposal of abnormal cells and nonfunctional molecules. These processes, to a large degree, are triggered or performed by immune cells and by the molecular products of immune cells: antibodies, cytokines, chemokines and adhesion molecules. Body maintenance, in short, depends on the immune activity that we call inflammation. Body maintenance would seem to require inflammation regulated according to need.[1,2]

2. Autoimmune T cells contribute to body maintenance. It is usually assumed that body maintenance is carried out exclusively by cells of the innate (germline) arm of the system. However, my colleagues and I now have evidence that autoimmune T cells have an important role in maintaining at least one organ: the central nervous system (CNS). Autoimmune T cells directed to myelin antigens, notorious for mediating the autoimmune disease EAE,[3] were found to protect the CNS against the secondary degeneration that follows traumatic injury.[4,5] In other words, a single population of autoimmune effector T cells can be seen to attack the body or, alternatively, to protect it, depending on the state of the tissue. Thus, the agents of a CNS disease can also be the agents of CNS salvation. The difference between autoimmune protection and autoimmune disease, it appears, is a matter of the intensity and the timing of the autoimmune inflammation; the autoimmune T cells are the same. The relevant point here is that autoimmune inflammation can be advantageous.[1,2,6] I suspect that autoimmune maintenance of additional tissues will be seen if sought.

3. Autoimmunity can be activated spontaneously by tissue damage.[7] This autoimmunity does not usually lead to spontaneous autoimmune disease, and so it is probably regulated. Point 2 above suggests that the natural autoimmune response to injury might function to help maintain damaged tissue.[8]

4. Healthy individuals are populated naturally with autoantibodies[9] and autoimmune T cells.[10] Natural autoimmunity is structured and directed to a limited set of dominant self-antigens. I have called this natural regularity of autoimmunity the immunological homunculus.[11]

5. Natural autoimmunity to a self antigen such as hsp60 can up- or down-regulate immune responses to foreign antigens to which hsp60 is linked or co-expressed.[12,13]

6. Autoimmunity regulates itself to prevent autoimmune disease. This is evident in various transgenic models. For example, mice bearing an autoimmune T cell receptor transgene specific for myelin basic protein do not develop EAE spontaneously. The presence of a functional rag gene appears to allow the emergence of a small number of regulatory T cells that suffice to block the pathogenic effects of the millions of anti-myelin T cells flooding the body.[14]

7. Tumor antigens, for the most part, are normal self antigens, and tumor immunity is mostly autoimmunity.[15]

8. Autoimmune disease often involves the dysregulated activation of natural autoimmunity.[2,10,11] Disease can result from unregulated processes usually associated with healing, and not only from the direct killing of self-target cells: Scleroderma, for example, results from the inappropriate formation of scar tissue; the destructive pannus of rheumatoid arthritis is scar tissue; excess angiogenesis can destroy the retina in autoimmune uveitis.

Interpretations

One may argue about the relevance or the solidity of some of the observations cited above, but, viewed in their totality, these observations are not compatible with the idea that self-nonself discrimination is obligatory. True, the immune system discriminates between antigens, and that is what antigens are: molecules or fragments of molecules that are distinguished from one another by antigen receptors. The system, however, discriminates between antigens, as antigens, but not on the basis of a self-nonself dichotomy. The healthy immune system recognizes both self-antigens and foreign antigens, without class discrimination. Contrary to the assertion of Langman and Cohn, the job of the immune system is not to pronounce a verdict distinguishing 'that which is to be destroyed' from 'that which is not to be destroyed'. The data suggest that the immune system, in both its germline and somatic (adaptive) arms, is continuously busy recognizing the states of the tissues and responding to them with corrective inflammation. Self-nonself discrimination is not what the immune system is about. The immune system is about fitness.[10] Autoimmune maintenance suggests that the answer to the introductory question, to my mind, is 'no'; self-nonself discrimination is not obligatory. That leaves us with the 'dead-end question' of Langman and Cohn: What discrimination is obligatory? The answer is not a single discrimination, but a series of ongoing discriminations.

Look at it this way: physiological autoimmunity serves to help maintain the body. The task of the immune system is to append the right type of inflammatory response to the needs of the moment: Is new connective tissue needed here? Are new blood vessels required there? Does a fractured bone need mending? How should we best rid the body of these aged, or abnormal, or infected cells? The problem is not only to make the appropriate response,[10,16] the problem is to orchestrate the spectrum of responses dynamically over time according to the shifting needs of the tissue.[2,17] Inflammation keeps the body fit, and physiological autoimmunity helps fine-tune inflammation.

But, you may ask, what about immune defence against pathogens? Defence against pathogens is a critical function of the immune system, and it has been argued that the essential immune discrimination is the discrimination between infection and non-infection, or between danger and non-danger.[18] Simple dichotomies, however, conceal the depth of immune maintenance. To keep a body fit, the immune system must select and regulate the repertoire of inflammatory responses in concert with the needs

of the situation, be the challenge one of self maintenance or of nonself confrontation. Just as different body maintenance problems need different solutions (compare a broken bone with a poisoned liver), so do different types of infection, or danger, need different types of attention (compare Mycobacteria with Meningococci, or with influenza virus or *E. coli*).

Actually, defence against infection can be seen as a special case of body maintenance. Note that defence against infection does not always depend on the immediate destruction of the infectious agent. Indeed, the immune system, for the good of the body, exchanges signals with the normal flora (and with the normal viruses) and helps vouchsafe their orderly existence within us. The immune system maintains the normal parasites as part of the healthy body; normal flora can preempt niches within us that could otherwise provide a foothold for more virulent pathogens.[19] Rejection of infectious agents depends more on the site and circumstances of the infected tissue than it does on the identity of the infectious agent. However, the host–parasite relationship is a complexity beyond our present consideration.

The bottom line for now is that the concept of self-nonself discrimination may be clear and catchy, but it is inadequate, and also misleading. Graded immune inflammation is required for self-maintenance. Simple discrimination between this or that entity will not suffice for day-to-day maintenance; the immune system has to judge the circumstances surrounding the antigens it sees, the self and the nonself equally.

Mechanisms

So what mechanisms does the immune system use to interpret the state of the body and provide the appropriate inflammatory response? Langman and Cohn caution us to 'be suspicious of unnecessary complexity'; science has done well by habitually preferring the clear and simple to the dark and complicated. However, there is nothing darker than a clear concept that is faulty. The immune system is a complicated system because the regulation of inflammation requires complicated judgement. Accordingly, its mechanisms are commensurately complex; however, it is not so bad. The mechanisms of immune judgement are actually known to us in fair detail; it is just that we have to see them for what they are in synergy. Among these mechanisms are the *immune dialogue* and *corespondence*.

Immune dialogue

I shall discuss the immune dialogue briefly; interested readers can find more detail elsewhere.[20] A dialogue can be characterized, for our purposes, by two elements: its continuous activity and its give and take. I think it is fitting to talk about an immune dialogue because the immune system continuously exchanges molecular signals with its interlocutor, the body. Additionally, both the body and immune system adjust their behavior in the light of the signals each receives and sends to the other. There is nothing magical about these signals; they are merely antigens, antibodies, accessory molecules, cytokines, chemokines, adhesion molecules, inflammatory mediators, enzymes, free and bound receptors, complement factors, clotting factors, glycosaminoglycans, lipid molecules, steroid and protein hormones and all the rest of the agents that influence the mutual behavior of immune cells and tissue cells. Obviously, some of the signals are one-way, such as antibodies, and some are two-way, such as cytokines. The immune system integrates these signals at the cellular level and continuously updates its activities. The immune system is a *reactive system*,[21] just like a dialogue. Immunologists know much about these molecules and their effects; by working all together, the molecules create a reactive mechanism by which the immune system makes its judgements. What we do not understand very well is how, at the intracellular level, signal transduction sensibly negotiates among all these signals, many of which are contradictory and simultaneous.

Corespondence

Corespondence is another mechanism from which immune judgement emerges.[2] Corespondence refers to a way the immune system constructs its picture of the objects it sees. Corespondence arises because different classes of immune cells respond to different aspects of any single immune object, self and nonself. T cells, for example, see processed peptides presented by MHC molecules; B cells see pieces of conformation; and macrophages and other germline leukocytes see the context—the state of the tissues. Each class of immune cell, by expressing cytokines and other signal molecules informs its fellows about its own response to what it has seen. Each immune system cell coresponds by modifying

its own response in the light of the information it receives from its fellow cells. Yet, each type of cell continues to see its own world: T cells go on seeing processed peptides and MHC molecules, B cells see conformation, and macrophages sense context. However, each cell type is led by the responses of the other cell types to respond with more or less vigor, and with different response molecules and behaviors. The immune system, in short, responds to its own responses as it orchestrates inflammation. This is corespondence. Corespondence is decision-making by committee.[10,22]

We can look at corespondence in yet another way: A bacterium, a virus or a broken bone is not a processed peptide, a piece of conformation, or an inflammatory context. These different fragments constitute an abstraction, a useful artefact as it were, that replaces the reality of the bacterium, virus or injury. The immune response, in essence, emerges from the de-construction of a real infection or injury, and from the re-construction of new immune information. Again, the processes of immune de-construction and re-construction are not mere philosophy. They are the molecular processes that immunologists tend to study in isolation. Put the processes together simultaneously, and you have another mechanism of immune judgement. A fuller description of corespondence can be seen in my book *Tending Adam's Garden: Evolving the Cognitive Immune Self*.[2]

Proof

The root meaning of the word proof is probing, testing, or trying, like in the saying 'the proof of the pudding is in the eating'. How then are we to decide which ideas about self-nonself discrimination are more to our taste? The test, I believe, is now being done in the clinic. Will we succeed in curing autoimmune disease by abolishing self-recognition in favor of nonself-recognition, or will we do better leaving self-recognition intact, but physiologically regulated?[23] The results of the trials will soon be in hand.[24]

Acknowledgements

I am the incumbent of the Mauerberger Chair in Immunology, Director of the Robert Koch Minerva Center for Research in Autoimmune Disease, and Director of the Center for the Study of Emerging Diseases. I thank my students and colleagues for the pleasures of thinking and doing together, and the Weizmann Institute for being a good place for doing and thinking otherwise.

References

1. Schwartz M, Moalem G, Leibowitz-Amit R, Cohen IR (1999) Innate and adaptive immune responses can be beneficial for CNS repair. Trends Neurosci 22:295–299
2. Cohen IR (2000) Tending Adam's Garden: Evolving the Cognitive Immune Self, Academic Press, San Diego
3. Ben-Nun A, Wekerle H, Cohen IR (1981) The rapid isolation of clonable antigen-specific T lymphocyte lines capable of mediating autoimmune encephalomyelitis. Eur J Immunol 11:195–199
4. Moalem G, Leibowitz-Amit R, Yoles E, Mor F, Cohen IR, Schwartz M (1999) Autoimmune T cells protect neurons from secondary degeneration after central nervous system axotomy. Nat Med 5:49–55
5. Hauben E, Nevo U, Yoles E, Moalem G, Agranov E, Leibowitz-Amit R, Mor F, Pevsner E, Akselrod S, Neeman M, Cohen IR, Schwartz M Autoimmune T cells: a potential neuroprotective therapy for spinal cord injury. The Lancet 355:286–287
6. Schwartz M, Cohen IR Autoimmunity can benefit self-maintenance. Immunol Today 21:265–268
7. Popovich PG, Stokes BT, Whitacre CC (1996) Concept of autoimmunity following spinal cord injury: possible roles for T lymphocytes in the traumatized central nervous system. J Neurosci Res 45:349–363
8. Grossman Z, Herberman RB (1986) 'Immune surveillance' without immunogenicity. Immunol Today 7:128–131
9. Fesel C, Coutinho A (1998) Dynamics of serum IgM autoreactive repertoires following immunization: strain specificity, inheritance and association with autoimmune disease susceptibility. Eur J Immunol 28:3616–3629
10. Cohen IR (1992) The cognitive principle challenges clonal selection. Immunol Today 13:441–444
11. Cohen IR (1992) The cognitive paradigm and the immunological homunculus. Immunol Today 13:490–494
12. Birk OS, Gur SL, Elias D, Margalit R, Mor F, Carmi P, Bockova J, Altmann DM, Cohen IR (1999) The 60-kDa heat shock protein modulates allograft rejection. Proc Natl Acad Sci USA 96:5159–5163
13. Konen-Waisman S, Cohen A, Fridkin M, Cohen IR (1999) Self heat-shock protein (hsp60) peptide serves in a conjugate vaccine against a lethal pneumococcal infection. J Infect Dis 179:403–413
14. Olivares-Villagomez D, Wang Y, Lafaille JJ (1998) Regulatory CD4(+) T cells expressing endogenous T cell receptor chains protect myelin basic protein-specific transgenic mice from spontaneous autoimmune encephalomyelitis. J Exp Med 188:1883–1894
15. Pardoll DM (1999) Inducing autoimmune disease to treat cancer. Proc Natl Acad Sci USA 96:5340–5342
16. Segel LA, Bar-Or RL (1999) On the role of feedback in promoting conflicting goals of the adaptive immune system. J Immunol 163:1342–1349
17. Grossman Z (1992) Contextual discrimination of antigens

by the immune system: towards a unifying hypothesis, in Theoretical and Experimental Insights into Immunology (Perelson A, Weisbuch G, eds) pp. 71–89. Springer-Verlag
18. Matzinger P (1994) Tolerance, danger, and the extended family. Annu Rev Immunol 12:991–1045
19. Rosenberg E, Cohen IR (1983) Microbial Biology, Saunders, Philadelphia, PA
20. Atlan H, Cohen IR (1998) Immune information, self-organization and meaning. Int Immunol 10:711–717
21. Manna Z, Pnueli A (1992) The Temproral Logic of Reactive and Concurrent Systems, Springer-Verlag, Berlin
22. Grossman Z (1989) The concept of idiotypic network: deficient, or premature? in Theories of Immune Networks (Atlan H, Cohen IR, eds) pp. 38–52. Springer-Verlag, Berlin
23. Cohen IR (1995) Treatment of autoimmune Disease: to activate or to deactivate? Chem Immunol 60:150–160
24. Elias D, Cohen IR (1994) Peptide therapy for diabetes in NOD mice. The Lancet 343:704–706