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The heuristics of biologic theory: the case of self–nonself discrimination

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Abstract

Mel Cohn has responded to our critique of the minimal model of self–nonself discrimination proposed by Langman and him. In this response to Mel Cohn, we summarize the essential differences between our points of view and highlight one criterion (of many) for preferring one theory to another in the complex field of biology: a preferred theory, rather than solving a problem, is heuristic. A good theory is one that activates a scientist to perform experiments that are novel and productive.

1. Essential agreement

Mel Cohn states [1],

> If one wishes to argue that the immune system is not a biodestructive protective mechanism but instead carries out its major role as a regulatory system for a variety of normal physiological functions [2] then of course, an NTBR-TBR discrimination is not required; in fact, it is irrelevant.

This statement bears the core of the difference between our opposing points of view [3]. Langman and Cohn focus on the ''biodestructive'' decisions that have to be made by a primarily ''protective'' immune system [4]. We, in contrast, see the immune system as the ''regulatory system'' responsible for dispensing the ''physiological function'' called *inflammation* [5]. The rest of the argument really emerges from this basic difference in point of view.

Before proceeding, let us note that Langman and Cohn are not alone: for at least half a century, mainstream immunology has taught that the primary role of the immune system is to protect the body from foreign invaders. And so discrimination between the self and the foreign is the beginning of immune wisdom [6]. The *minimal model*, which assumes the capacity of adaptive antigen receptors to distinguish self from nonself, is a logical expression of this wisdom.

Likewise, we, Efroni and Cohen, are not alone: the founding fathers of immunology, who preceded the era of self–nonself discrimination, focused on the varied expressions of inflammation as the cause of health and disease [7]. Our preference for the explanatory *complexity* of inflammation over the *simplicity* of self–nonself discrimination can be said to mark a return of immunology to its historical roots [7]. The specificity of the immune system is not in what it recognizes, but in how it responds.

The middle ground—positioned between Langman and Cohn and us—has been defended by Silverstein: self–nonself discrimination is only a peripheral implication of the classic clonal selection theory (CST), and so can be jettisoned without endangering the essential CST [8]. Parnes thinks otherwise: receptor specificity and self–nonself discrimination are equally central to the CST [9]; one cannot abandon self–nonself discrimination by antigen receptors and still maintain CST orthodoxy. But that issue is beyond our present discussion.

2. Understanding

Mel Cohn states [1],

> When I say that I 'understand' a biological system, in the end I mean that I can place it in an evolutionary context that defines the selectable steps that resulted in its emergence.

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This statement marks the aim of theory and here too we agree with Cohn: the aim of theory is *understanding*; a good scientific theory helps us understand how nature works. But we don't agree with Cohn when he writes that "the selectable steps" of the "evolutionary context" constitute *understanding*. Evolution is certainly one of the greatest of ideas, perhaps the greatest, in biology. But "survival of the fittest" is a concept that is really not falsifiable, and so some have questioned whether the theory of evolution can be considered a genuine scientific theory [10]. (In fact, some have questioned whether a simple two-signal model of the immune response is itself falsifiable; [11].) Whether or not such claims are meaningful, we don't think that we can ever refute another person's favored evolutionary context merely by asserting our own favorite evolutionary context; each to his or her own tastes in evolutionary contexts. In fact, the evolutionary context is the disputed issue—does one favor the evolutionary context of self–nonself or that of inflammation? *Understanding* evolutionary context is thus a matter of one's *subjective* psychology and that is not an issue worth pursuing here. What we seek is an *objective* criterion for deciding whether simple self–nonself discrimination or complex inflammation is the more fit concept, at present, for the advance of immunology.

3. Heuristics

The fitness of a scientific theory cannot be judged by its long-term survival; scientific theories, especially in fields as complex as biology, are bound to be superceded and replaced by new theories [12]. Biology, like evolution itself, does not come to an end.

Cohn points out that a good theory should provide a "heuristic solution" [1]. Now the word *heuristic* means "serving to find out or discover" (Oxford English Dictionary). Thus, a good biologic theory is a theory that serves the process of discovery; the preferred theory motivates the biologist to undertake experiments that uncover new facts about the system under study. A preferred theory is heuristic—a prod to new research. Note that a heuristic theory does not cap a field of research by solving a problem. On the contrary, a good heuristic theory makes problems; a good heuristic theory opens the way to otherwise unthinkable research. We would argue that Cohn's usage of the term "heuristic *solution*" is a contradiction of sorts; *questions* are more heuristic than are *solutions*.

We can now reframe the disputation between self–nonself simplicity and inflammatory complexity: What has been the past heuristic harvest of each point of view, and which point of view is likely to be productive in the near future?

4. The self–nonself harvest

The past harvest of self–nonself discrimination (which we would like to equate to the CST) has been very great, even miraculous (if a scientist may ever use such a word). One could argue that the concept of self–nonself discrimination drove the research that has uncovered the molecular realities of the antibody, the B-cell receptor, and the T-cell receptor and that has elucidated the molecular biology of antigen-receptor somatic recombination. The concept of self–nonself receptor specificity has been so heuristic that it may have finally driven itself into obsolescence; it appears that antigen receptors operate with an immense degree of molecular degeneracy [13–15]. A single T-cell receptor can recognize perhaps millions of different peptide ligands. Self–nonself discrimination simply is not achievable by a T-cell receptor at the molecular scale.

One might argue that the concept of self–nonself discrimination has not been very successful in the field of autoimmune disease. According to the CST, claimed Burnet, no two persons could ever suffer from the same autoimmune disease; no two persons would ever be expected to harbor the same forbidden clone [16]. Thus, the CST obscured the nosologic order inherent in the major clinical autoimmune diseases [17] and denied the very existence of physiological autoimmunity [18]. Moreover, the CST theory of self–nonself discrimination led to autoimmune disease therapies aimed at blocking specific self-recognition or designed to destroy self-reactive lymphocytes [19]. This therapeutic strategy, regrettably, has thus far failed. Worse, the self–nonself notion discouraged any alternative approaches that might involve treating autoimmune disease by activating autoimmune regulation. As Langman and Cohn assert, there is no need for any kind of peripheral immune regulation; the *minimal model* alone solves the problem of regulation [4]. Cohn invokes the AIRE gene as an example of how the loss of negative selection in the thymus can lead to autoimmune disease [1]. That interpretation, however, is only one of many alternative ideas that could be related to the multiple actions of a very complex gene [20]; perhaps AIRE influences the positive selection of regulatory networks?

5. The harvest of physiological autoimmunity

Physiological autoimmunity is a complex idea that stems from the view that the immune system regulates inflammation—what Cohn calls a "variety of normal physiological functions" [1]. The notion of physiological autoimmunity is not a simple explanation; but it has served to drive productive research programs in immune physiology and pathophysiology. T-cell vaccination [21] and self-peptide vaccination [22] therapies for autoim-

mune diseases are currently in phase II clinical trials. These therapeutic strategies arose from the complex idea that the healthy immune system does indeed recognize the self in an ordered and regulated way. The demonstrated role of autoimmunity in neuroprotection is another heuristic achievement of physiological self-recognition [23]. The physiology of self-recognition is key to current research into the functions of CD25 positive T cells [24,25], and it is a factor in the thinking behind oral tolerance therapy for autoimmune disease [26]. Research into regulatory networks of self-recognizing lymphocytes continues to be heuristically productive [27,28]. The interaction of self-molecules with both innate immune receptors and adaptive immune receptors is yet another heuristic output of physiological self-recognition [29]. We believe that self–nonself discrimination has done its molecular job to the point of exhaustion. The future is physiology—putting the parts together to make a working system. The heuristic debate is left to the judgment of the reader.

References

[1] M. Cohn, Does complexity belie a simple decision—on the Efroni and Cohen critique of the Minimal Model for a self–nonself discrimination, Cell. Immunol. 221, 138–142.

[2] I.R. Cohen, Tending Adam's Garden: Evolving the Cognitive Immune Self, Academic Press, London, 2000.

[3] S. Efroni, I.R. Cohen, Simplicity belies a complex system: a response to the minimal model of immunity of Langman and Cohn, Cell. Immunol. 216 (2002) 23–30.

[4] R.E. Langman, M. Cohn, If the immune repertoire evolved to be large, random, and somatically generated, then..., Cell. Immunol. 216 (2002) 15–22.

[5] I.R. Cohen, Discrimination and dialogue in the immune system, Semin. Immunol. 12 (2000) 215–219 (discussion 257–344).

[6] J. Klein, Immunology: The Science of Self–Nonself Discrimination, Wiley, New York, 1982.

[7] O. Parnes, "Trouble from within": allergy, autoimmunity and pathology in the first half of the twentieth century, Studies in History and Philosophy of Biological and Biomedical Sciences (in press).

[8] A.M. Silverstein, The clonal selection theory: What it really is and why modern challenges are misplaced, Nat. Immunol. 3 (2002) 793–796.

[9] O.S. Parnes, The specificity of the clonal selection theory, Nat. Immunol. 4 (2003) 95.

[10] K.R. Popper, P.A. Schilpp, The Philosophy of Karl Popper, Open Court, La Salle, IL, 1974.

[11] R.N. Germain, The art of the probable: system control in the adaptive immune system, Science 293 (2001) 240–245.

[12] T.S. Kuhn, The Structure of Scientific Revolutions, University of Chicago Press, Chicago, 1970.

[13] E. Borras, R. Martin, V. Judkowski, J. Shukaliak, Y. Zhao, V. Rubio-Godoy, D. Valmori, D. Wilson, R. Simon, R. Houghten, C. Pinilla, Findings on T cell specificity revealed by synthetic combinatorial libraries, J. Immunol. Methods 267 (2002) 79–97.

[14] M. Jacobsen, S. Cepok, W.H. Oertel, N. Sommer, B. Hemmer, New approaches to dissect degeneracy and specificity in T cell antigen recognition, J. Mol. Med. 79 (2001) 358–367.

[15] E. Maverakis, P. van den Elzen, E.E. Sercarz, Self-reactive T cells and degeneracy of T cell recognition: evolving concepts-from sequence homology to shape mimicry and TCR flexibility, J. Autoimmun. 16 (2001) 201–209.

[16] F.M. Burnet, Self and Not-Self, Cambridge University Press, Cambridge, 1969.

[17] I.R. Cohen, The cognitive principle challenges clonal selection, Immunol. Today 13 (1992) 441–444.

[18] I.R. Cohen, The cognitive paradigm and the immunological homunculus, Immunol. Today 13 (1992) 490–494.

[19] J.F. Bach, Immunosuppressive therapy of autoimmune diseases, Immunol. Today 14 (1993) 322–326.

[20] J. Pitkanen, P. Peterson, Autoimmune regulator: from loss of function to autoimmunity, Genes Immun. 4 (2003) 12–21.

[21] V. Kumar, E. Sercarz, J. Zhang, I. Cohen, T-cell vaccination: from basics to the clinic, Trends Immunol. 22 (2001) 539–540.

[22] I. Raz, D. Elias, A. Avron, M. Tamir, M. Metzger, I.R. Cohen, Beta-cell function in new-onset type 1 diabetes and immunomodulation with a heat-shock protein peptide (DiaPep277): a randomised, double-blind, phase II trial, Lancet 358 (2001) 1749–1753.

[23] M. Schwartz, I.R. Cohen, Autoimmunity can benefit self-maintenance, Immunol. Today 21 (2000) 265–268.

[24] S. Sakaguchi, N. Sakaguchi, J. Shimizu, S. Yamazaki, T. Sakihama, M. Itoh, Y. Kuniyasu, T. Nomura, M. Toda, T. Takahashi, Immunologic tolerance maintained by CD25+ CD4+ regulatory T cells: their common role in controlling autoimmunity, tumor immunity, and transplantation tolerance, Immunol. Rev. 182 (2001) 18–32.

[25] E.M. Shevach, CD4+ CD25+ suppressor T cells: more questions than answers, Nat. Rev. Immunol. 2 (2002) 389–400.

[26] Y. Komagata, H.L. Weiner, Oral tolerance, Rev. Immunogenet. 2 (2000) 61–73.

[27] V. Kumar, E. Sercarz, An integrative model of regulation centered on recognition of TCR peptide/MHC complexes, Immunol. Rev. 182 (2001) 113–121.

[28] H. Jiang, N.S. Braunstein, B. Yu, R. Winchester, L. Chess, CD8+ T cells control the TH phenotype of MBP-reactive CD4+ T cells in EAE mice, Proc. Natl. Acad. Sci. USA 98 (2001) 6301–6306.

[29] C. Habich, K. Baumgart, H. Kolb, V. Burkart, The receptor for heat shock protein 60 on macrophages is saturable, specific, and distinct from receptors for other heat shock proteins, J. Immunol. 168 (2002) 569–576.