ACADEMIC PRESS

Cellular Immunology 216 (2002) 23–30

Cellular Immunology

www.academicpress.com

Simplicity belies a complex system: a response to the minimal model of immunity of Langman and Cohn

Sol Efroni[a,b] and Irun R. Cohen[a,*]

[a] *Department of Immunology, The Weizmann Institute of Science, Rehovot 76100, Israel*
[b] *Department of Computer Science and Applied Mathematics, The Weizmann Institute of Science, Rehovot 76100, Israel*

Received 30 June 2002; accepted 15 July 2002

Abstract

Langman and Cohn have written a paper entitled "If the immune repertoire evolved to be large, random, and somatically generated, then..." This paper uses reductionist logic to prove that the minimal model of immunity proposed by Langman and Cohn is the only reasonable description of the workings of the immune system. Here we analyze the logic behind this model and show that the complexity of the real immune system contradicts the teachings of Langman and Cohn.

Keywords: Self–non-self discrimination; Specificity; Reductionism; Complex systems; Immunological Homunculus; Emergence

1. Introduction

Immunologists would like to understand how the immune system understands what it should preserve and what it should attack. These two types of understanding are not necessarily the same. The first type of understanding, ours, depends greatly on the clarity of our reasoning from first principles, observations, and experiments. The second type of understanding, that of the immune system, is bereft of clarity, reasoning, and first principles; the immune system operates solely by observations and experiments. The difference between the two types of understanding arises because we understand using our cognitive brains and the immune system, in contrast, understands using molecular receptors; it has no brain—each lymphocyte and each macrophage does its own thing in the light of its own information. This is obvious; why bother to mention it?

We bother to mention it because the human brain sometimes confuses the two types of understanding. The human brain sometimes confounds its understanding of the immune system by endowing the immune system with clarity, reasoning, and first principles. This imposition of human reason on the immune system is illustrated by the paper by Rodney Langman and Melvin Cohn, "If the immune repertoire evolved to be large, random, and somatically generated, then..." [1]. The title of the paper is formatted in the style of a logical syllogism that sets the stage for clarity, reasoning, and first principles. The problem is that the clear reasoning of Langman and Cohn is not matched by the observed behavior of the system. The immune system does not act in accord with either the reasoning or the first principles of Langman and Cohn. Each system has a different mind, metaphorically, that is. In this response to Langman and Cohn, we do not try to explain the content of their argument; you can read their paper for that. Rather, we analyze the way Langman and Cohn try to represent the immune system logically—what might be called the form of their argument. The clear logic of Langman and Cohn, we believe, is not appropriate to the manifest complexity of the immune system they, and we, are trying to understand. The divergence between the logic of Langman and Cohn and that of the actual immune system can help to clarify the difficulties in thinking about complex systems.

* Corresponding author. Fax: +972-8-9344103.
E-mail addresses: sol.efroni@weizmann.ac.il (S. Efroni), irun.cohen@weizmann.ac.il (I.R. Cohen).

0008-8749/02/$ - see front matter
PII: S0008-8749(02)00504-X

2. The paper

In their paper "If the immune repertoire evolved to be large, random, and somatically generated, then..." Langman and Cohn propose to demonstrate that they have solved the problem of self–non-self discrimination. They do not present new data, but convince the reader of the virtue of their "Minimal Model" [1] by showing the logical flaws inherent in any alternative theory that tries to explain how the immune system operates. Langman and Cohn analyze the mechanism at the heart of a competing theory, outline the conclusions this mechanism imposes, add assumptions derived from their theory and then demonstrate that the competing theory arrives at a logical contradiction or entails a conclusion that is not allowed or that cannot exist. In this way, all theories other than the Minimal Model reach a dead-end. The ideas of Langman and Cohn stand on logic, symmetry, reduction, and deduction. But the immune system, one of the most complex of biological systems, is not founded on logical simplicity. The immune system is a paragon of complexity and needs the tools of complex systems research to understand it.

2.1. The logic of Langman and Cohn

The attempt to turn complexity into logic seems to be inspired largely by the thinking of classical physics. Physics, through reductionism, has proved very successful in discovering the basic mechanisms and underlying principles governing all matter and all dynamics. The reductionist approach is clearly stated by Albert Einstein:

> The grand aim of all science is to cover the greatest number of empirical facts by logical deduction from the smallest number of hypotheses or axioms [2].

True to Einstein, Langman and Cohn propose a theory that is logical, concise, simple, inclusive, and above all, minimal. Scientists feel fulfilled when they succeed to formulate explanations with such properties. Yet physicists dealing with complex systems know that it is not productive to try and apply the criteria of concise simplicity at the level of single interactions within a complex system. Such approaches are applicable only at the level of the whole system, or perhaps at the level of functionally distinct modules within a complex system. Complex systems are complex precisely because they resist reduction; their properties of interest are emergent properties. Reduction to simple subunits does not provide understanding. Strangely, Langman and Cohn are faithful to classical notions that even physicists are now questioning.

The authors apply a minimal approach to immunology. They build for themselves a new lexicon and apply it to dismantle the processes of the immune system.

2.2. To-Be-Ridded or Not

The new lexicon replaces the term "self" with the term "Not-To-Be-Ridded" and replaces the term "non-self" with "To-Be-Ridded". Langman and Cohn claim that this new terminology resolves the question of "... what we mean by the self–non-self discrimination." They say that ambiguity is not a problem for the immune system, but only for us, who wish to understand what confronts the system. Once we use the right words, which describe what the immune system has to do, the ambiguity vanishes. The immune system needs only to determine what is To-Be-Ridded and what is Not-To-Be-Ridded.

2.3. Antigen-by-antigen

A key concept in the paper is the distinction between interactions that are "antigen-by-antigen" and interactions that are "epitope-by-epitope." Any interaction that falls into the category of "antigen-by-antigen" is an interaction based on functional recognition either of some general or specific property of the antigen, or of some kind of knowledge of the meaning of the antigen as a whole. We will return later to the biological materialization of this conceptual distinction. The second term, "epitope-by-epitope," can be understood simply as the interaction between a peptide (or other chemical subunit of an antigen) and an antigen receptor (paratope).

Throughout the paper, the authors use the two interactions—antigen-by-antigen and epitope-by-epitope—as exclusive attributes: an immunological process or mechanism may either be "antigen-by-antigen" or "epitope-by-epitope," but not both. Using these distinctions, the authors examine competing theories—suppression, self-markers, localization, and peripheral regulatory mechanisms—and uncover their logical flaws. The reasoning is proof by contradiction; we are left with only one conceivable theory—the minimal model.

3. The minimal model

The minimal model is illustrated schematically in Fig. 1. The model belongs to the long tradition (extensively reviewed in [3]) of two-signal models. Antigen stimulates the naïve immune cell to enter an initial state (i), but the cell will undergo apoptosis unless it receives a second signal from a T-helper cell. The authors report that they have resolved the long-standing question of how the first T helper cell gets activated without help, but do not elaborate. Support for the minimal theory rests mainly on proof by contradiction of the competing theories. The only time the minimal model is used in the

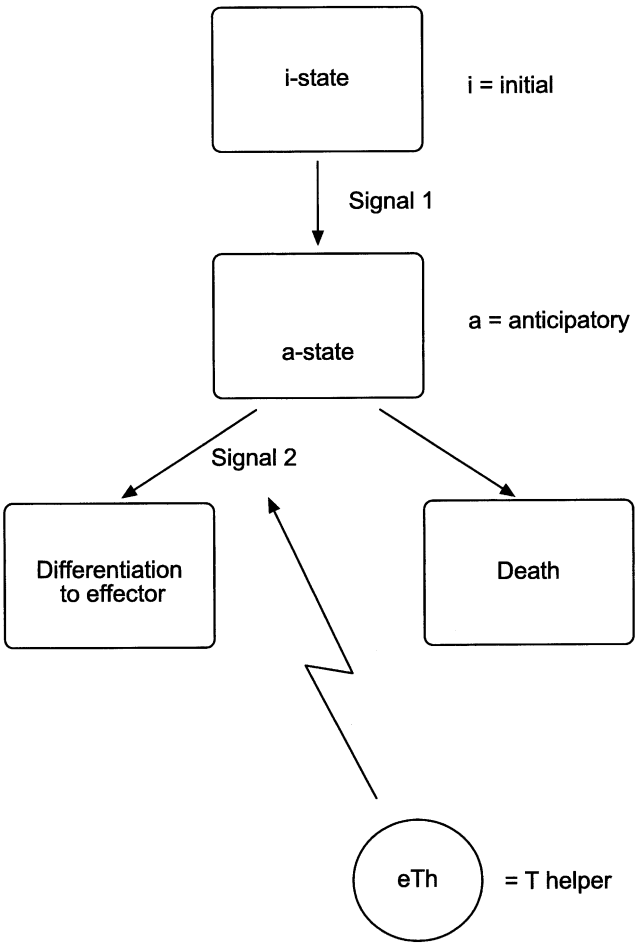

Fig. 1. The "Minimal Model" proposed by Langman and Cohn.

argument is when Langman and Cohn disprove regulation by suppressor mechanisms.

Fig. 2 schematically summarizes the argumentation for disqualifying alternative theories or mechanisms of immune behavior. Each alternative proposition is stated simply and its implications are developed. During analysis, further assumptions are added to the path of reasoning. Some assumptions are covert and some are overt; we have color-coded each type. All the argumentations reach a dead-end, marked in red. Only one theory survives this reduction to logic—the minimal model.

The propositions rejected by the logic of Langman and Cohn are as follows:

Proposition 1. *Autoimmunity is controlled by self-markers.*

As the figure shows, the existence of self-markers implies that effectors are selected by a sorting mechanism that works at the antigen level. But if sorting works antigen-by-antigen, then the whole system works antigen-by-antigen. Now, according to the minimal model, immune recognition leads to immune attack. Any antigen the system recognizes it will kill. This axiom entails two possible outcomes: if self and non-self antigens would never share epitopes, it would be possible to use self-markers to prevent autoimmunity. Unfortunately, Langman and Cohn acknowledge the fact self and non-self do share epitopes and this would lead to destruction of self-antigens, which is unacceptable. Therefore, autoimmunity cannot be controlled by self-markers.

Proposition 2. *Suppression controls autoimmunity.*

If suppression controls autoimmunity, then suppression as defined by Langman and Cohn is at the antigen level ("recognition of one epitope on the antigen by the suppressor cell dictates the response of any cell interacting with that antigen"). To sort suppressor cells that respond to antigens rather than epitopes, sorting must be done at the antigen level. On the other hand, Langman and Cohn's minimal model implies that helper T-cells should also be selected at the antigen level. If we add to this the (hidden) assumption that only one mechanism is responsible for both the selection of helper cells and suppressor cells, then we are left with the unacceptable conclusion of a selecting mechanism that operates at the antigenic level. Therefore, suppression cannot control autoimmunity.

Proposition 3. *Autoimmunity is controlled by peripheral mechanisms.*

We assume an antigen A with two arbitrary properties α and β. If we have two "competing" mechanisms—central (enclave) and peripheral—and we further assume that each of them works on a different property of A, then one of them might tell us to remove the antigen while the other commands us to ignore it. This would result in a contradiction between the two mechanisms. Therefore, autoimmunity cannot be controlled by peripheral mechanisms.

Proposition 4. *Anatomical site regulates immunogenicity.*

Since a self–non-self decision must be made, and since this decision is made at the epitope level, the proposition that anatomical location determines immunogenicity requires decision epitope-by-epitope. But there is no way to tell the location of an antigen through its epitopes. We therefore arrive at a contradiction. Therefore, the anatomical site cannot regulate autoimmunity.

4. Reality bites

Langman and Cohn base their argumentation on four assumptions: antigen receptors (paratopes) are

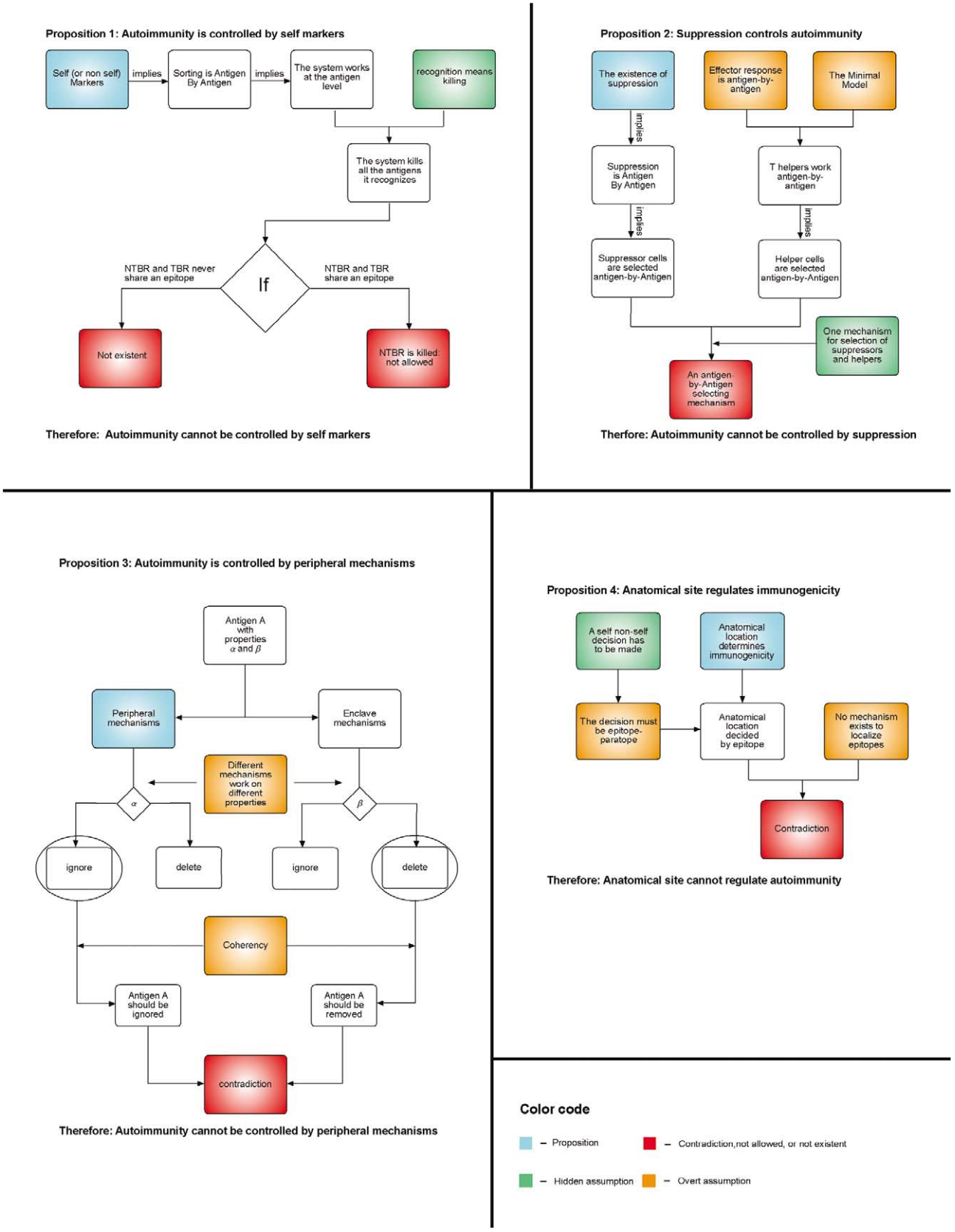

Fig. 2. Langman and Cohn's arguments against alternative theories: a schematic representation.

specific for specific epitopes; the response to different epitopes on the same antigen must be coherent; the repertoire is random; and evolution guarantees that a more fit mechanism will always replace a mechanism less fit to solve a biological problem. All four assumptions are problematic; they are contradicted by the data. Let us examine each of these assumptions.

4.1. Specificity

The antigen receptors are assumed capable of discriminating between self and foreign (or NTBR and TBR, as Langman and Cohn prefer). The problem with immunological specificity is that antigen receptors are demonstrably degenerate. This degeneracy has been analyzed mathematically to show that a single antigen receptor might recognize up to 10^6 different antigens [4,5]. Recently, actual experiments show that a single T-cell clone can respond to many different peptides [6,7]. Indeed, studies using positional scanning synthetic combinatorial libraries indicate that a T-cell clone can respond to any of 30×10^6 different peptides [8]. The T-cell receptor has been shown to be physically flexible and not as rigid as previously assumed [9]. Crystal structures of TCR p/MHC complexes show the chemical basis underlying this degeneracy [10] and give unmistakable evidence that the interaction cannot be strictly specific. Observing that antibodies of lower affinity may make better distinctions between two antigens than antibodies with higher affinity, Van Regenmortel [12] has concluded that, "Immunology shares with the whole of empirical science the need to handle fuzzy sets and concepts..."

A one-to-one relationship between a paratope and an epitope does not exist and cannot exist. Without specificity, how can a self–non-self decision be made on the *one epitope–one paratope* interaction?

4.2. Coherence

The concept of immune coherence assumed by Langman and Cohn is not intuitively clear and needs some explanation. Coherence, is the requirement that the "... response to each epitope on the antigen must be in the same effector class." Although Langman and Cohn do not detail the different effector classes in this paper, they do so in another paper [12], where they refer to the effectors as: biodestructive (B cells and cytotoxic T cells), regulatory (T-helper cells) and APC's (cells with no antigen-specific receptors). Rephrasing the principle of coherence, we suppose it to mean that different cells reacting to different epitopes on the same antigen should functionally produce the same effect.

But, the principle of coherence is contradicted by the facts. Experimental results show that different epitopes on the same antigen are treated differently by the immune system. Antigens are degraded into separate epitopes by proteolytic events within the APC and are presented as individual MHC-peptide complexes; how can responding T cells recognize whether or not different processed peptides have originated from a common source? Even the same peptide can elicit different immune responses when administered at different sites, with or without various accessory signals [13]. A T-cell interaction involves the organization of multiple molecules into the *immunological synapse*, where the TCR, as one of the receptors on the T-cell's surface, interacts only with a fragment of the antigen in the MHC cleft. Many other molecules—cytokine receptors, chemokine receptors, integrins and others—have a critical influence on the outcome of the T cell–APC interaction. There is no way by which this array of signals can be reduced to any kind of intrinsic knowledge of the whole antigen. The only way the immune system makes sense of the antigen is through its functional representations in the system, which are the chemical dynamics of the process. If we take the word *coherence* to mean *agreement*, then the components of the immune system certainly do not uniformly agree how to handle an antigen. Immune cells mine the data available to each of them and respond to the array of signals they see at the moment: cells migrate, proliferate, differentiate, secrete, undergo apoptosis, cluster synapses, or perform other cellular functions. There is no systemic decision of bio-destruction of a specific antigen at the scale of the whole system and there is no such decision at the scale of the single cell. Coherence is logical for minds, but non-existent for lymphocytes.

4.3. Randomness

Although it is still unknown how large the actual immune repertoire really is, various findings show it is clearly not as large as its potential of 10^{12} different T-cell clones [14]. The repertoire can still be called large. Calling the immune repertoire random is something that has to be proven. Although the process of recombination that generates the repertoire is random, the repertoire itself is not. Indeed, thymic selection, positive and negative, ensures that the repertoire will not be random. Many, if not most clones do not even reach the stage of selection [15]. Moreover, maturing thymocytes are presented with only a relatively small number of peptides at high concentration: 5–10% of all MHC's on a presenting cell will present the same peptide [16]. Reconstitution of the T-cell repertoire after irradiation or viral destruction, shows repopulation on the basis of a small group of self-antigens [17]. Negative and positive selection on self-peptides provide a window of selection that is not only limited in size, but also biases all T cells to recognize self-like epitopes. It is no wonder that various studies show the immune repertoire to be biased. Also

significant is the fact that autoimmune diseases in different individuals attack a uniform set of possible self-peptides [13]. In general, although the bias and the reason for the bias are still unknown, it is clear the immune system does not choose lymphocytes from a random set of possible affinities, but rather selects only certain of them. It is also unknown whether this selection is simply a filter or whether it directs the lymphocytes to evolve into some particular pattern [11].

4.4. Survival of the fittest logic

In many instances, Langman and Cohn justify their argument based on the power of evolution to guarantee the extinction of the less fit immune mechanism by the more fit. Their reasoning goes like this: assume the existence of two specified mechanisms responsible for performing some desired biological function. They conclude that only the one "better" mechanism will survive selection pressure. The one superior mechanism will take over all the tasks that could be performed by the less efficient mechanism.

The problem with this argument, like others invoked by Langman and Cohn, is that it is not applicable to biological phenomena. One organism does not become extinct upon the appearance of an organism that deploys a "better" solution for the same survival task, and one physiological mechanism does not simply disappear upon the arrival of a more reasonable solution to the problem. Mechanisms do not survive only because evolution found them to be "better" than other mechanisms; mechanisms remain because they fit their environment. Our immune system is not superior to that of invertebrates. It is not even superior to that of plants. Trees live longer than do vertebrates. Does the ability to recognize every possible molecule, an ability only the vertebrate immune system has, give the shark any superiority over the squid who has no lymphocytes? The evolution of any organism involves the use and re-use of almost identical molecules and mechanisms present in preceding organisms. Humans re-use genes and molecules present in *Caenorhabditis elegans* and *Drosophila*, but in more complex ways. These molecules and mechanisms exist because they create the equilibrium we call the creature's niche in the biosphere. A new physiological mechanism is never the next level of development of its predecessor, but is the reshuffling of building blocks in a way that perturbs the system into a new equilibrium. An unsuccessful mechanism is not an inferior mechanism; it is an unfitted mechanism. Survival is not of the *fittest*; survival is of the *fitted* [13].

In their introduction, Langman and Cohn attempt to portray the different views of what is self to the immune system as exclusive: self might be defined by self-markers, non-self markers, or other means, but not by all at once. They assume that the immune system cannot contain different views of the self because only one view, the "best," must have been selected over evolutionary time to replace the other, less efficient views. In fact, however, the immune system does hold different views of the self, simultaneously. Different views of the self persist because the immune system scans different properties of the tissues in the course of regulating inflammation. Self-markers do exist, but other ways to regulate homeostasis exist as well.

4.5. Self-markers exist

Langman and Cohn prove that self-markers cannot exist because if self-markers did exist, evolutionary pressure would have considered them sufficient for self–not-self discrimination and would not have needed to evolve a somatically generated repertoire. But self-recognition does exist in the form of self-markers. NK cells provide an example. NK cells respond rapidly to self-cells infected by viruses or other intracellular pathogens and to transformed cells [18]. The cytokine production and cytotoxic activities of NK cells are regulated by a family of receptors that recognizes self-MHC class I (or similar) structures [19]. This regulation is based on signals from inhibitory and activating receptors, and one can clearly see the ability of NK cells to make distinctions based on the presence or absence of self-MHC class I molecules on target cells [20–22]. The NK cell asks other body cells a simple question: "do you express a self marker?" if the answer is anything but "yes," the NK cell attacks.

Such a solution alone, according to Langman and Cohn, would solve the problem of self–non-self discrimination and an adaptive immune response would be unnecessary. But does a self-marker really dismantle the difficulties facing the immune system? Will an NK cell, the perfect cell in a reductionist's world, know how to intensify the response, to diminish the response, to make an immune response of the proper phenotype, memorize the antigen it met and integrate all this to provide self-maintenance [13]? The magnitude, duration, location, and dynamically adjusted consequences of inflammation are the responsibility of the immune system. The NK cell triggers one kind of inflammation and is probably also involved in the outcomes of triggering, but does not solve the problem. The immune system is a complex system because its function is complex. Seemingly redundant mechanisms are needed and cannot be dispelled by simple logic.

4.6. Complex systems

The paper by Langman and Cohn is an enlightening example of an attempt to apply reductionism to a complex system. Complex systems [23] are composed of many autonomous agents that interact in parallel to

achieve properties such as measurable emergence, robustness, multi-scale organization, and intricate networks. The new science of complexity [24], also called self-organized criticality [25], complex adaptive systems, and other names [26] investigates such systems. Complex systems are characterized by networks. Consider the brain: 10^{12} separate neurons do not create a system, but 10^{12} well-connected neurons make a brain.

The immune system is a complex system. Reductionism has produced much information about the agents comprising this system through their autonomous interactions. We now know who the different cellular agents are; we have ways of telling them apart; we have ways to follow them through their lifetimes and through their interactions; we can count, see, and tell apart the molecules inside these cells and on their surface. We even know, with various degrees of understanding, how to make them work for us and how to alter their behavior in pathology and health. Jenner saved millions of lives without any knowledge of virology or of vaccines other then the observation that vaccination works [27]. Penicillin was discovered by an innocent mistake, and even grandmother's advice works [28].

We enjoy the same magnitude and scope of knowledge regarding other complex systems too. For example, we know almost everything we need to know about the subunit ingredients that interact to create an economy, about the gases and heat sources that comprise the weather, about the CPU's, hard disks, and network cables that make up the internet, and about the neurons and their axons and supporting cells that make up the brain. Still, we never presume to reduce inflation to two individuals making a transaction. We do not think about a storm as the sole result of gas-gas and gas-solid interactions. Web transport or channel robustness over web communication is by definition a non-reducible property. Emergence of new qualities by the interactions of many subunit agents is realized in the human brain: can human understating be reduced to its component neurons? Can knowledge, vision or passion be attributed to any number of underlying components? Can logic be broken down into two contradicting neuronal connection? Certainly not.

The immune system is as complex as the nervous system. There is no way to derive its functions by dismantling its subunit fractions.

Today, when scientific reduction has given us so much knowledge of the cells and molecules of the immune system, we can start to try and build our knowledge from the bottom up and see how networks are formed and how novel properties emerge at the level of the system as a whole. Our database is sufficient to the task, but we are lost in its complexity. To understand complex systems, we need to build models of its networks. To build such models, we can no longer treat models as we treat hypotheses. Models will have to be dynamic and capable of being simulated with mathematical precision. The models will have to be tested using the computational machines that store the database. The models will have to be measured and adjusted to changes in the database. The immune system, as other complex systems, will have to be understood as a subject for dynamical mathematical analysis.

The complexity of immune reactions renders the traditional self–non-self disputations obsolete. What could be the dynamics of self and not self? Let us suppose the immune system does know, by some mechanism, a certain cell to be non-self. Does that help us understand the resulting immune reaction: the inflammatory response? Inflammation is where immune complexity leaves reductionism speechless. Inflammation is the result and the cause of many cells working as cohorts through the exchange of countless molecules. Single cells make experiments and single cells make observations. Intensifying the reaction and stopping it are complex enough, even without the need to recruit new cells, orchestrate the appearance of the proper molecules, etc. Analyzing the network that materializes from the experiments and observations the cells make is where understanding may be found. The immune system is about inflammation. The ridding of the dangerous or the unwanted is the result of inflammation. The fact that a certain antigen is self or non-self does not bring us, or the immune system any closer to understanding inflammation.

The time has come to uncover the properties the immune system shares with other complex systems. Universally shared properties, such as robustness [29], internal patterns [30], hidden power laws [31], and others [32–36] might lead to the laws of emergent self-organization. Emergent self-organization is the heart of the immune system; minimal models miss the mark.

Acknowledgments

Sol Efroni is a doctoral student in the Department of Immunology and in the Department of Computer Science and Applied Mathematics at the Weizmann Institute of Science; his fellowship is supported by The Feinberg Graduate School and by the Minerva Foundation.

Irun R. Cohen is the incumbent of the Mauerberger Chair of Immunology and the Director of the Robert Koch-Minerva Center for Research in Autoimmune Diseases at the Weizmann Institute of Science and the Director of the Center for the Study of Emerging Diseases, Jerusalem.

References

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

[2] Simpson's Contemporary Quotations, Houghton Mifflin Company, Boston, 1988.
[3] A.G. Baxter, P.D. Hodgkin, Activation rules: the two signal theories of immune activation, Nat. Rev. Immunol. 2 (2002) 439–446.
[4] D. Mason, A very high level of crossreactivity is an essential feature of the T-cell receptor, Immunol. Today 19 (1998) 395–404.
[5] V. Detours, R. Mehr, A.S. Perelson, Deriving quantitative constraints on T-cell selection from data on the mature T-cell repertoire, J. Immunol. 164 (2000) 121–128.
[6] J.J. Marchalonis, M.K. Adelman, I.F. Robey, S.F. Schluter, A.B. Edmundson, Exquisite specificity and peptide epitope recognition promiscuity, properties shared by antibodies from sharks to humans, J. Mol. Recog. 14 (2001) 110–121.
[7] Z.J. Chen, C.J. Wheeler, W. Shi, A.J. Wu, C.H. Yarboro, M. Gallagher, A.L. Notkins, Polyreactive antigen-binding B cells are the predominant cell type in the newborn B cell repertoire, Eur. J. Immunol. 28 (1998) 989–994.
[8] 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 (2002).
[9] 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.
[10] M.G. Rudolph, I.A. Wilson, The specificity of TCR/pMHC interaction, Curr. Opin. Immunol. 14 (2002) 52–65.
[11] M.H. Van Regenmortel, From absolute to exquisite specificity. Reflections on the fuzzy nature of species, specificity and antigenic sites, J. Immunol. Methods 216 (1998) 37–48.
[12] R.E. Langman, M. Cohn, A minimal model for the self–nonself discrimination: a return to the basics, Semin. Immunol. 12 (2000) 189–195 (discussion 257–344).
[13] I.R. Cohen, Tending Adam's Garden: Evolving the Cognitive Immune Self, Academic Press, London, 2000.
[14] T.P. Arstila, A. Casrouge, V. Baron, J. Even, J. Kanellopoulos, P. Kourilsky, A direct estimate of the human αβ T-cell receptor diversity, Science 286 (1999) 958–961.
[15] M. Merkenschlager, D. Graf, M. Lovatt, U. Bommhardt, R. Zamoyska, A.G. Fisher, How many thymocytes audition for selection?, J. Exp. Med. 186 (1997) 1149–1158.
[16] G.M. Barton, A.Y. Rudensky, Evaluating peptide repertoires within the context of thymocyte development, Semin. Immunol. 11 (1999) 417–422.
[17] A.W. Goldrath, Maintaining the status quo: T-cell homeostasis, Microbes Infect. 4 (2002) 539–545.
[18] L.L. Lanier, On guard—activating NK cell receptors, Nat. Immunol. 2 (2001) 23–27.
[19] K. Natarajan, N. Dimasi, J. Wang, R.A. Mariuzza, D.H. Margulies, Structure and function of natural killer cell receptors: multiple molecular solutions to self, nonself discrimination, Annu. Rev. Immunol. 20 (2002) 853–885.
[20] J.C. Ryan, C. Naper, S. Hayashi, M.R. Daws, Physiologic functions of activating natural killer (NK) complex-encoded receptors on NK cells, Immunol. Rev. 181 (2001) 126–137.
[21] M. Vales-Gomez, H.T. Reyburn, R.A. Erskine, M. Lopez-Botet, J.L. Strominger, Kinetics and peptide dependency of the binding of the inhibitory NK receptor CD94/NKG2-A and the activating receptor CD94/NKG2-C to HLA-E, EMBO J. 18 (1999) 4250–4260.
[22] Y.M. Vyas, K.M. Mehta, M. Morgan, H. Maniar, L. Butros, S. Jung, J.K. Burkhardt, B. Dupont, Spatial organization of signal transduction molecules in the NK cell immune synapses during MHC class I-regulated noncytolytic and cytolytic interactions, J. Immunol. 167 (2001) 4358–4367.
[23] Y. Bar-Yam, Unifying Themes in Complex Systems: Proceedings of the First Necsi International Conference on Complex Systems, Perseus Book Group 2000, 2000.
[24] S.A. Kauffman, Investigations, Oxford University Press, Oxford, 2000.
[25] P. Bak, M. Paczuski, Complexity, contingency, and criticality, Proc. Natl. Acad. Sci. USA 92 (1995) 6689–6696.
[26] M. Gell-Mann, What is complexity, Complexity 1 (1995) 16–19.
[27] H. Bazin, Eradication of Smallpox: Edward Jenner and the First and Only Eradication of a Human Infectious Disease, Academic Press, New York, 2000.
[28] G.R. van den Brink, D.E. van den Boogaardt, S.J. van Deventer, M.P. Peppelenbosch, Feed a cold, starve a fever?, Clin. Diagn. Lab. Immunol. 9 (2002) 182–183.
[29] J.M. Vilar, H.Y. Kueh, N. Barkai, S. Leibler, Mechanisms of noise-resistance in genetic oscillators, Proc. Natl. Acad. Sci. USA 99 (2002) 5988–5992.
[30] S.S. Shen-Orr, R. Milo, S. Mangan, U. Alon, Network motifs in the transcriptional regulation network of Escherichia coli, Nat. Genet. 31 (2002) 64–68.
[31] N.M. Shnerb, Y. Louzoun, E. Bettelheim, S. Solomon, The importance of being discrete: life always wins on the surface, Proc. Natl. Acad. Sci. USA 97 (2000) 10322–10324.
[32] A.J. Noest, Designing lymphocyte functional structure for optimal signal detection: voila, T cells, J. Theor. Biol. 207 (2000) 195–216.
[33] Meier-Schellersheim, M. SIMMUNE, a tool for Simulating and Analyzing Immune System Behavior, 99, DESY.
[34] N. Kam, I.R. Cohen, D. Harel, The immune system as a reactive system: modeling T-cell activation with statecharts, Bull. Math. Bio. (in press).
[35] D. Harel, Statecharts: a visual formalism for complex systems, Sci. Comput. Program. 8 (1987) 231–274.
[36] D. Harel, in: On Modeling and Analysing System Behavior: Myths, Facts and Challenges, Proceedings of the 20th International Conference on Software Engineering, vol. 2, IEEE Press, New York, 1997, pp. 8–10.