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Network Regulation of Autoimmunity: An Automaton Model

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Four classes of regulatory T lymphocytes have been implicated in the control of experimental autoimmune diseases: a pair of helper and suppressor T lymphocytes that recognize the self-antigen (antigen-specific); and a pair of helper and suppressor T lymphocytes that recognize the autoimmune effector lymphocytes (anti-idiotypic). The anti-idiotypic pair of regulators was detected following vaccination against autoimmune disease using autoimmune effector T clones as vaccines.

To learn how the anti-idiotypic regulatory lymphocytes might function in concert with the antigen-specific regulatory lymphocytes, we devised a network in which the cell populations could be viewed as interconnected automata. Analysis of this novel network model suggests how self-tolerance may operate, how progressive autoimmune disease may develop, and how T-cell vaccination can control autoimmune disease.

Introduction

Widely prevalent and serious diseases such as rheumatoid arthritis, juvenile onset (or Type I) diabetes mellitus, and multiple sclerosis, despite their marked clinical differences, can all be classified as autoimmune diseases. These diseases are autoimmune because each is thought to be caused by clones of activated effector lymphocytes whose antigen-recognizing receptors direct them to attack specific target tissues in the individual. A rational and natural therapy for autoimmune disease would exist if one could abrogate the activities of the relatively few clones of autoimmune lymphocytes without compromising the ability of the immune system to deal with foreign invaders [1]. In the course of pursuing this goal, observations were made which provide an insight into the fundamental organization of the immune system. The purpose of this article is to formulate that insight.

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T-cell vaccination

Experimental autoimmune diseases in laboratory animals have been controlled using potentially virulent autoimmune T lymphocytes as vaccines [2]. For example, activated autoimmune T lymphocytes were rendered avirulent by gamma irradiation [3] or by modification of their surface membranes [4]. Administration of the treated T cells to recipient rats or mice endowed them with resistance to attempts to induce the specific autoimmune disease. T-cell vaccination was also found to induce permanent remission of already established disease [4]. Thus, both treatment and prevention was attained.

A widely studied model of autoimmune disease is experimental autoimmune encephalomyelitis (EAE). This disease can be induced in many mammalian species by immunization to the basic protein of myelin (BP) in a suitable adjuvant [5]. The disease is expressed clinically by paralysis and histologically by infiltration of lymphocytes and other white cells into the myelinated areas of the central nervous system. EAE in rats is usually an acute disease from which the animal either dies or fully recovers [6]. Recovery from a first bout of EAE is associated with permanent resistance to future EAE [7].

T-cell vaccination against EAE was first demonstrated using lines of anti-BP T lymphocytes rendered avirulent by irradiation [3]. More recently it was observed that resistance to lethal doses of anti-BP T clones (10^6–10^7 cells) could be induced by first exposing rats to low (subencephalitogenic) doses of the activated, potentially virulent T lymphocytes (10^2–10^4 cells) [8–10]. Since 10^2–10^4 cells is a number likely to be attained by T lymphocyte clones expanding during EAE *in vivo*, the mechanisms of resistance induced by such vaccination might teach us about the physiological processes set into motion by the activation of virulent autoimmune T cells.

Using low-dose T-cell vaccination, we discovered that resistance to EAE was associated with the development of anti-idiotypic T lymphocytes [8–10], T lymphocytes that recognized specifically the receptors of the pathogenic autoimmune T-lymphocytes [11]. Cloning of the anti-receptor T lymphocytes uncovered anti-idiotypic T lymphocytes of two classes, $CD4^+$, $CD8^-$ helpers that stimulated the proliferation of the autoimmune effector T lymphocytes and $CD8^+$, $CD4^-$, and suppressors that inhibited the response of the autoimmune effector T clones to their specific antigen [8]. Clones of $CD8^+$ anti-idiotypic T cells have been found to protect rats against EAE [12]. The anti-idiotypic $CD8^+$ T cells were specifically cytolytic *in vitro* suggesting that lysis of the autoimmune effector T cells might aid resistance to disease. However, acquired resistance to EAE does not depend wholly on the death of the effector cells; virulent anti-BP line cells could be isolated from resistant rats that had recovered from EAE months earlier [13]. Therefore, EAE effector T cells can persist in a suppressed state.

Regulatory T lymphocytes specific for antigen

Contrasting with the T-helper and T-suppressor cells reactive to the effector lymphocyte idiotype, are the regulatory helper (inducer) and suppressor T lymphocytes discovered originally to be reactive to the inciting antigen [14]. Indeed, it has been postulated that EAE (and other autoimmune diseases) are regulated by the

balance between antigen-specific helpers and suppressors [15, 16]. Although the existence of antigen-specific suppressor T cells at the clonal level has been questioned, we would argue that antigen-specific suppression certainly exists as a phenomenon attributable to a population of T cells. This by itself justifies inclusion of the class of antigen specific suppression within our model.

Thus there may be two sets of regulatory lymphocytes, an antigen-specific pair and an anti-idiotypic pair. Intuitively, it would seem that each pair alone ought to be sufficient for regulation, with any positive activation signal supplied by helper T cells being balanced by a negative, anti-activation signal provided by suppressor T cells.

However, is the anti-idiotypic pair of T lymphocyte regulators independent of antigen-specific T helper and suppressor cells, or might both sets of regulatory T cells function together? In other words, are the anti-idiotype and the antigen-specific regulatory systems redundant or fail-safe alternatives, or must they interact as a unit to control autoimmunity? Moreover, what might be the role of each of the regulatory cell types in preventing (the suppressors?) or in perpetuating (the helpers?) autoimmune disease?

A network of five automata

Our task was to understand how autoimmune disease could be regulated by a system composed of the self-antigen and five cell classes: the disease-causing autoimmune-effector lymphocytes, and four classes of regulatory T cells, i.e., the antigen-specific helper and suppressor cells previously described [14], and the anti-idiotypic helper and suppressor cells induced by T-cell vaccination [8].

Initially we attempted to formulate a model system using differential equations, as have others. But in the absence of quantitative information about key parameters (cell multiplication and death rates, affinity constants, etc.), it was impossible to construct such equations without making *ad hoc* suppositions. We therefore turned to an automaton network model to see what could be learned about regulation of autoimmunity, despite limited information about the cell types. Automata models of relatively great complexity and scale have been used to simulate learning and associative memory in neural networks [17]. They have also been applied to evolution theory [18, 19] and used to provide a general framework for understanding structural and functional self-organization [20]. The present work is an extension of automata concepts into immunology.

We pictured the five types of cells as a five-membered network of inter-connected automata in which each automaton represented a distinct population of cells. We simply assumed that each of the cell types could be in either of two states: *on* (activated) or *off* (not activated). Therefore, at a given time, the state of the network as a whole could be defined by the set of the current states, (*on* or *off*), of each of the five automata. The five cell network, therefore, has 32 possible states (2^5). Table 1 shows each of the 32 states in which the term '0' designates *off* and '1' designates *on*. The cells are designated by numbers as follows: I is the antigen-specific helper (inducer) T cell, II is the autoimmune effector T cell, III is the anti-idiotypic T suppressor, IV is the anti-idiotypic T helper, and V is the antigen-specific suppressor T cell.

We assumed that autoimmune disease might result from any of the 16 states in which the autoimmune effector cell II is *on*, while health (absence of autoimmune

Table 1. *The 32 states of the five-cell network*

State Number	State of cell population				
	I	II	III	IV	V
0	0	0	0	0	0
1	1	0	0	0	0
2	0	1	0	0	0
3	1	1	0	0	0
4	0	0	1	0	0
5	1	0	1	0	0
6	0	1	1	0	0
7	1	1	1	0	0
8	0	0	0	1	0
9	1	0	0	1	0
10	0	1	0	1	0
11	1	1	0	1	0
12	0	0	1	1	0
13	1	0	1	1	0
14	0	1	1	1	0
15	1	1	1	1	0
16	0	0	0	0	1
17	1	0	0	0	1
18	0	1	0	0	1
19	1	1	0	0	1
20	0	0	1	0	1
21	1	0	1	0	1
22	0	1	1	0	1
23	1	1	1	0	1
24	0	0	0	1	1
25	1	0	0	1	1
26	0	1	0	1	1
27	1	1	0	1	1
28	0	0	1	1	1
29	1	0	1	1	1
30	0	1	1	1	1
31	1	1	1	1	1

Cell population: (I) Antigen-specific helper; (II) Autoimmune effector; (III) Anti-idiotypic suppressor; (IV) Anti-idiotypic helper; (V) Antigen Specific Suppressor.

disease) is associated with any of the remaining 16 states in which the autoimmune effector cell is *off*.

The connections that tie the network together are the interactions between the cell types. These connections, represented by the arrows in Figure 1, transmit the state of activity (0 or 1) of one cell population to others in the network. A connection is positive (Figure 1, solid arrows) if the connecting cell is a helper, and negative (Figure 1, broken arrows) if the connecting cell is a suppressor. Consequently, the effects of a cell type on other cell types were represented by three values: '0' if the

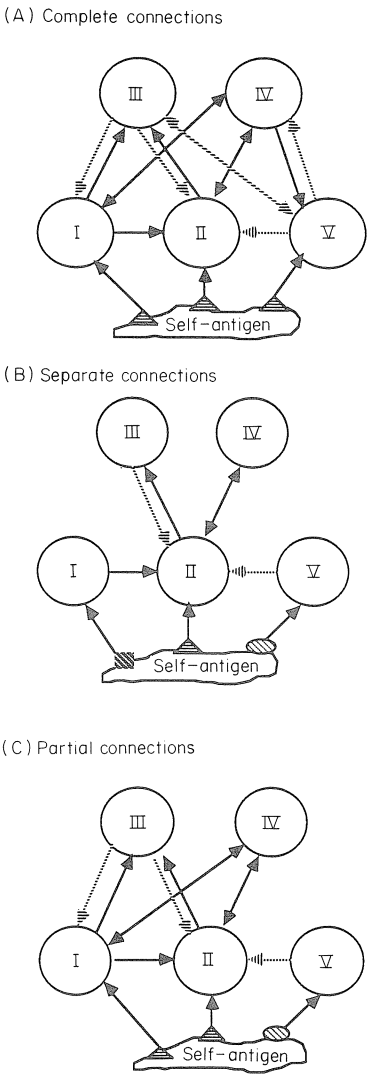

Figure 1. The network connection structures. The circles designate the cell types as follows: (I) antigen-specific helpers; (II) autoimmune effectors; (III) anti-idiotypic suppressors; (IV) anti-idiotypic helpers; (V) antigen-specific suppressors. The arrows designate functional connections between the elements; solid arrows represent a $+1$ input, and broken arrows a -1 input, when the connecting cell is activated. The arrows leading from the epitopes of the self-antigen (triangles, circles or squares) represent recognition of the epitope by the cells. They add a $+1$ (external) input to the automata which receive them. Suppressogenic self-antigen activates only automaton V. Immunogenic self-antigen activates both automaton I and V. Automaton II, the effectors, recognize the antigen but are activated by the antigen only when helped by a positive signal for automation I. Three connection structures are depicted: (A) Complete connections—populations I, II and V recognize the same epitopes and share idiotypes. (B) Separate connections—populations I, II and V each recognize a different epitope and do not share idiotypes. (C) Partial connections—populations I and II recognize common epitopes and share idiotypes, while V recognizes a different epitope and has a unique idiotype.

connecting cell was *off*, '$+1$' if the connecting cell was an *on* helper cell, and '-1' if the connecting cell was an *on* suppressor cell.

It may be argued that the connections between the various elements might have different weights due, for example, to differences in cell number or affinity. Nevertheless, for the present we chose to ignore these differences simply because we had no exact information about them. However, as we shall discuss below, changes in quantitation of the connections may be key elements in the evolution and function of the real network.

The state of a given cell population (automaton) at a given time was determined by a law amounting to an arithmetic summation of all of its inputs at a preceding time, and the comparison of the value of this sum to a threshold of '0'. The law states that if the sum of the inputs is greater than '0', then the next state of the automaton is *on*, designated by a value of '1'; if the sum is equal to or less than '0' then the next state of the automaton is *off*, designated by a value of '0'. In other words, a cell population will revert to inactivity unless it receives a net positive activation signal. Thus, given any initial condition, the future states of the system as a whole are determined to a significant degree by the mutual influences of the interacting elements. Defining the behaviour of the system means recording the states of the individual cell populations as they flash *on* and *off* in response to the signals received from their neighbors. As long as the flashing (*on* and *off*) persists, the network is in flux. A state of the system when the flashing tends to stop or become periodic is called an *attractor*.

Attractors

The term attractor is used in system dynamics to describe the stable state (or the oscillations between a defined, limited set of states) into which a system will spontaneously evolve from a variety of initial conditions [17]. For example, the attractor of an ideal, friction-free pendulum jostled into motion is the oscillation of the pendulum defined by Newton's laws. The attractor of the pendulum in the real world of friction is the state of rest dictated by the law of gravity, the oscillations of the pendulum marking its transition from initial motion to rest.

The attractors in our system could be any one or more of the 32 possible states of the network, or the oscillations between a limited number of states. Attractors are generated by the postulated connections, which determine the transition laws governing the behaviour of the network. Once an attractor is reached, any subsequent change (*on* or *off*) in any of the cell populations will automatically lead to a return to the same or a different attractor state. A system has no attractor if, once set into motion, it roams indefinitely through all possible states.

Computation

Computation of the system's dynamics involves updating the state of each of the five-cell populations as each population undergoes a change of state (*on* or *off*). For the sake of completeness, the computation was done in each of three possible ways: (1) in series—the antigen-specific regulatory T cells and effector cell were assumed to change their states before the anti-idiotypic cells changed theirs; (2) in parallel—all five cell populations were imagined to compute and update their new states simultaneously, and; (3) at random—the cell populations computed and updated one after the other without any fixed order.

The random mode of computation appeared to us to be the most apt in principle because it assumes no *a priori* constraints. Moreover, it is likely, that, in practice, cell populations in the immune system undergo a degree of random activation independent of contact with their antigen or their anti-idiotype as individual cells wander into sites of inflammation or chance to be hit by interleukins or other activating molecules.

All the attractors demonstrable using random computation were also found using computation in parallel or series, although the latter modes of computation, by ordering the computation process, occasionally generated a few additional attractors. However, we chose to present the random mode of attractor computation because it provided us with the most fundamental order, one created solely by the connections between the cell populations.

Connection structures

The organizing principle of the network is the connections between the cell populations, who speaks to whom and how. Figure 1 depicts three different connection structures we examined for attractors. These connection structures were chosen for their immunological plausibility. The total number of connection structures that could be constructed using five automata and three types of connections is very large (3^{25}).

(1) *Complete connection*—Cells I and V (the antigen-specific regulators) were assumed to recognize the same epitope and to feature the same idiotype as does cell II (the effector). Therefore, the anti-idiotypic T cells (III and IV) were connected to I and V, as well as to cell II [Figure 1(A)].

(2) *Separate connection*—Cells I and V were assumed to recognize specific helper and suppressor epitopes, and so were not recognized by the anti-idiotypic cells (II and IV) which were connected only to the autoimmune effector cell (II) [Figure 1(B)].

(3) *Partial connection*—Cells I and II (the T helper and T effector) were assumed to recognize the same epitope, while V (the T suppressor) recognized a distinct suppressor epitope. Thus, cells III and IV were connected to cells I and II, but not to cell V [Figure 1(C)].

In all three cases, cells I and V, the antigen-specific regulators, were assumed to be connected to cell II by helper or suppressor molecules elaborated by the cell [21].

The self-antigen

We postulated that the self-antigen could have two forms of input into the system: suppressogenic or immunogenic [22]. Immunogenic self-antigen was assumed to be that presented to the system in association with ancillary signals such as Class II MHC molecules of antigen-presenting cells, products of inflammation, or foreign carriers. Self-antigen in this form activated both helper (II) and suppressor T cells (V). In contrast, self-antigen seen without ancillary signals, which we have termed suppressogenic self-antigen, activated suppressor T cells (V). (Suppressogenicity is not an attribute limited to self-antigen. Even foreign molecules administered in a

Table 2. *Automata network generates self-tolerance*

Network connection structure	Form of self-antigen	Attractor state number	Attractors population state				
			I	II	III	IV	V
Complete	Suppressogenic	16	0	0	0	0	1
	Immunogenic	17	1	0	0	0	1
Separate	Suppressogenic	16	0	0	0	0	1
	Immunogenic	17	1	0	0	0	1
Partial	Suppressogenic	16	0	0	0	0	1
	Immunogenic	29	1	0	1	1	1

Attractors were detected by random computation using transition laws outlined in the text, according to the connection structures depicted in Figure 1.

soluble, unaggregated form without adjuvants tend to induce suppression [23].) Presentation of self-antigen to the autoimmune effector cell (II) was assumed to be constant. However, the self antigen could only activate the effector when the inducer cell (I) provided help.

Generation of self-tolerance

Table 2 shows the attractors obtained by random computing of the three connection structures (complete, separate and partial) of the network. Suppressogenic self-antigen was found to induce only a single attractor, number 16 in the list of attractors shown in Table 1. In this attractor state the antigen-specific suppressor cell remains *on* while the four other cell classes remain *off*. Since this single attractor dominates the three connection structures, it would seem to represent self-tolerance in its most basic form, self-tolerance that is relatively insensitive to variations in the connection structure of the network.

Immunogenic self-antigen generated two different attractors, states 17 or 29, depending on which of the three connection structures was in force (Table 2). The complete and separate connection structures each generated state 17, self-tolerance in which the antigen-specific helper and suppressor were both *on*. The partial connection structure produced a more interesting attractor, state 29. In this case all the automata were *on*, except for the autoimmune effector which was *off*. These attractors constitute stable self-tolerance; random activation of any of the *off* cells, including the autoimmune effector, will automatically return the system to these attractors.

Aberrant expression of MHC Class II molecules leading to activation of auto-immune effector cells has been postulated as a cause of progressive autoimmune disease [24]. However, the continued presence of self-antigen in an immunogenic form could not account for progressive autoimmune disease in the present network. Even if the autoimmune effector cells were to become activated, non-activation of the

Table 3. *Deletion of regulatory cells generates autoimmune disease in response to immunogenic self-antigen*

Network connection structure	Cell population deleted	Attractor state number	Attractors population state I	II	III	IV	V
Complete	None	17	1	0	0	0	1
	III	17 and	1	0	0	0	1
		27	1	*1*	0	0	1
	IV	17	1	0	0	0	1
	V	15	1	*1*	1	1	0
Separate	None	17	1	0	0	0	1
	III	17 and	1	0	0	0	1
		27	1	*1*	0	0	1
	IV	17	1	0	0	0	1
	V	15	1	*1*	1	1	0
Partial	None	29	1	0	1	1	1
	III	27	1	*1*	0	1	1
	IV	16–17–21–20			cycle		
	V	15	1	*1*	1	1	0

The laws of computation were carried out and attractors were detected as described in the legend to Table 2, except that the indicated cell populations (automata) were deleted. A cycling attractor was defined as a short sequence of network states in which one state is necessarily driven into the next state in the sequence, whatever the order of computation happens to be. The last state in the sequence of the cycle leads back to the first state.

effector cells (self-tolerance) will remain the stable attractor. Thus the system is guaranteed by its structure to return to self-tolerance. Autoimmune disease, in this network, would require some defect or change in the cells or connections of the network itself.

Disease follows cell deletion

Which changes in the network could generate persistent or cyclical activation of an autoimmune effector? To ascertain how such pathogenic attractors might emerge, we weakened specific connections by assigning a value of '0' to each of the four regulatory cells in turn and tested the effect on the network response to immunogenic self-antigen. In the present network of unweighted connections, this constituted functional deletion of the particular cell population. Table 3 shows the changes in attractors produced by deleting cells III, IV or V. Deleting I, the helper cells, left the network unresponsive. The absence of either automaton III or V (the suppressors) enhanced the likelihood of autoimmune disease, irrespective of which of the three network connections were tested. Deletion of III from either the complete or separate connection structures introduced attractor state 27 (II activated) along with state 17 (II not activated). This means that random fluctuations (noise) could push the system from one attractor to the other, that is, from tolerance to disease and back. The partially connected system had only disease as its attractor when III was deleted

(state 27). Deletion of V in each of the three connection structures produced a single attractor (state 15), disease only. Therefore, the activities of both sets of suppressor cells, the antigen-specific and the anti-idiotype seem to be required for optimal self-tolerance. Hence, the antigen-specific and the anti-idiotypic regulators are not redundant but apparently are required to function together.

Deletion of IV (the anti-idiotype helper) affected only the partially connected structure, making the system continually cycle through four states: 16, 17, 21 and 20. Each of these states features the autoimmune effector in the *off* configuration. Thus, the absence of the anti-idiotypic helper did not lead to loss of self-tolerance. However, the anti-idiotypic helper did contribute to stability of the network. As we shall discuss elsewhere, the anti-idiotypic helper T cell could perform a major function in generating memory for reactivity in the cellular network regulating immunity to foreign antigens.

A rationale for T-cell vaccination

The well-connected five-cell network displays different attractors in response to self-antigen in its suppressogenic and immunogenic forms. These different attractors would appear to represent two different levels of self tolerance discernible both experimentally and clinically. In other words, each of the levels is the primary responsibility of a different set of cells. The first level of regulation is proof against self-antigen encountered without ancillary immunogenic signals, what we have termed suppressogenic self-antigen. We propose that this level of regulation is mediated by antigen-specific suppressors (automaton V) that function to deactivate potentially virulent circulating effector cells (II). For example, anti-BP T lymphocytes have been isolated from healthy rats [25, 26] and humans [27], yet these cells do not seem to produce disease spontaneously.

Nevertheless, this first level of self-tolerance is not proof against immunogenic self-antigen. Immunization with BP together with complete Freund's adjuvant induces active EAE in rats [3–8]. However, after an acute disease of several days the rats recover spontaneously and are no longer susceptible to repeated attempts to induce a second bout of active EAE [7]. Recovery from EAE and resistance to future EAE was found to be associated with the development of cells capable of recognizing and suppressing virulent anti-BP effector T lymphocytes [7]. As described above, anti-idiotypic suppressor T cells were also detected following vaccination with relatively small numbers of some anti-BP clone cells [8]. Development of these anti-idiotypic suppressor cells was associated with resistance to disease produced by preformed, activated, virulent anti-BP effector T lymphocytes. Therefore, a second, more advanced level of resistance to activated effector cells is probably mediated by the anti-idiotypic T cells, particularly by anti-idiotypic suppressors (III) [12].

Similar to rats in the laboratory, humans are also confronted from time to time by self-antigens associated with immunogenic signals. As has been suggested, this may come about by aberrant Class II MHC gene expression resulting from viral infection [24]. Bacteria and viruses presenting antigens cross-reactive with host antigens abound [28, 29], and the invaders could easily supply immunogenic adjuvants for self-mimicking epitopes. These and other inopportune events are probably regular occurrences. Accordingly, we suspect that many individuals endure episodes of

autoimmune disease when their autoimmune effector lymphocytes become activated by immunogenic self-antigen. However, the attractors of an adequately connected network containing both antigen-specific and anti-idiotypic suppressors lead to inactivation of the effectors and tolerance to subsequent contact with self-antigen in an immunogenic form. This more advanced state of self-tolerance prevents incipient autoimmune disease from progressing or recurring. The bane and the hallmark of autoimmune disease are progression and recurrence. Autoimmune disease expressed, for example, as a single, transient episode of rheumatoid arthritis, or the asymptomatic death of a few insulin-secreting beta cells in the pancreatic islets would go undiagnosed.

The minority of instances in which clinical autoimmune disease does become manifest may be blamed on inadequate development of network connections. The problem is not that autoimmune disease is triggered, which happens in everybody, but that the immune system fails to shut it off properly by developing a solid second stage of self-tolerance. The reason and aim of T-cell vaccination is to strengthen the connections required for advanced tolerance. Obviously, experiments must be done to measure the changes in connections (numbers and affinities of cells) responsible for the second stage of self-tolerance, a kind of distributed memory [30].

The substance of this paper relates to the regulation of autoimmunity. Other features of the immune system, notably the response to foreign antigens and the character of immunological memory, will be dealt with elsewhere.

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