Autoimmunity, microbial immunity and the immunological homunculus

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Clonal deletion and anergy are believed by many immunologists to be the fundamental mechanisms responsible for self tolerance. Nevertheless, as Irun Cohen and Douglas Young point out, such notions of nonreactivity cannot explain certain key features of immune behaviour: the immunological dominance of microbial antigens that mimic self, the uniformity of autoimmune diseases and the prevalence of natural autoimmunity among the healthy. The theory of the immunological homunculus is presented here as a unifying principle.

The healthy immune system is tolerant to the molecules comprising the body in which it resides. Why this should be so is obvious; how it is so is obscure. The demonstration of negative selection of T cells during their differentiation in the thymus[1] provides experimental support for the venerable idea that the source of self tolerance is the cleansing filter of clonal deletion[2]. Some will argue that healthy individuals have lymphocytes that recognize self antigens but most would agree that self antigens are poor immunogens. To state the idea in operational terms, the closer a molecule is to self, the less immunogenic it should be. It is surprising, therefore, to find that among the major antigens recognized during a wide variety of bacterial and parasitic diseases many belong to conserved protein families sharing extensive sequence identity with the host's molecules.

The immunogenicity of self-like microbial molecules is strikingly illustrated in the case of antigens that belong to heat shock protein (hsp) families (Table 1). Hsps were first identified by their increased synthesis in response to elevated temperature, but it is now clear that these proteins are in fact inducible by almost any form of cellular stress in any type of cell, from prokaryotic to human[3]. Members of hsp families are remarkably conserved: there is more than 50% sequence identity between bacterial and mammalian counterparts[4]. Moreover, hsp molecules contain significant stretches of complete sequence identity. Thus, every microbial hsp is studded with self epitopes for any animal with an immune system.

Nevertheless, as listed in Table 1, dominant antibody responses to members of hsp families are associated with infection by many protozoan and helminthic parasites.

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Table 1. Heat shock proteins and the immune response to infection

Heat shock protein family	Pathogen	Disease	Ref.
hsp70	*Plasmodium falciparum*	Malaria	5–7
	Trypanosoma cruzi	Chagas disease	8
	Leishmania donovani	Visceral leishmaniasis	9
	Schistosoma mansoni	Schistosomiasis	10,11
	Brugia malayi	Lymphatic filariasis	12
	Onchocerca volvulus	Ocular filariasis	13
	Mycobacterium tuberculosis	Tuberculosis	14
	Mycobacterium leprae	Leprosy	15
	Chlamydia trachomatis	Blinding trachoma	16
hsp60 (GroEL)	*Mycobacterium tuberculosis*	Tuberculosis	14,17
	Mycobacterium leprae	Leprosy	14,17
	Coxiella burnetii	Q fever	18
	Treponema pallidum	Syphilis	19
	Legionella pneumophila	Legionnaires' disease	20
	Chlamydia trachomatis	Blinding trachoma	21
	Borrelia burgdorferi	Lyme disease	22
hsp90	*Plasmodium falciparum*	Malaria	23
	Trypanosoma cruzi	Chagas disease	24
	Schistosoma mansoni	Schistosomiasis	25
small hsps	*Schistosoma mansoni*	Schistosomiasis	26
	Mycobacterium leprae	Leprosy	27
GroES	*Mycobacterium tuberculosis*	Tuberculosis	28

Table 2 shows that hsps are not the only conserved proteins identified as major antigens during infection. These microbial antigens have from 40% to greater than 70% amino acid homology with self molecules. Their strong immunogenicity contradicts our expectations. As students of mycobacterial hsp65, we have learned that immunity to this antigen is associated with autoimmune arthritis in rats[38] and in humans[39], and with autoimmune diabetes in nonobese diabetic (NOD) mice[40]. Immunity to hsp70 (Ref. 41) and to hsp90 (Ref. 42) is associated with systemic lupus erythematosis (SLE). Such dangerous antigens should not be immunologically dominant.

There is yet another paradox: if immunity to hsp molecules is involved in autoimmune diseases, how is it that natural immunity to such antigens is present in healthy individuals[43–46]?

Science, in contrast to the outside world, welcomes unfulfilled expectations; the search for an explanation has motivated this article. As in all biological matters, useful explanations are two fold: how (mechanistic) and to what advantage (teleological). In other words, what is the point of the immune system focusing its attention on the very molecules that the parasite shares with the host; how is this focus of attention encoded in the machinery or structure of the system; and how is the danger of autoimmune disease reduced or abrogated?

Autoimmune responses are to dominant self antigens

Autoimmunity is like microbial immunity in that the target antigens are usually predictable; they are dominant. Although the target autoantigens involved in many autoimmune diseases have not been identified, the autoimmune responses characterized to date show uniformity (see Ref. 47, Chapter 2): humans and mice with SLE have more or less the same spectrum of autoantibodies; patients with primary biliary cirrhosis all respond to the same mitochondrial enzymes; autoimmune thyroiditis is characterized by immunity to thyroglobulin and to the thyroid peroxidase enzyme; individuals with myasthenia gravis have antibodies to the α chain of the acetylcholine receptor; patients with insulin-dependent diabetes mellitus (IDDM) have autoantibodies to insulin and to a 64 kDa islet cell antigen; pemphigus patients react to particular skin cell antigens; and arthritis sufferers respond to the hsp65 molecule. Whether or not multiple sclerosis (MS) is caused by autoimmunity to myelin basic protein (MBP)[48], the MBP molecule dominates other antigens in the central nervous system; any species immunized to whole brain or spinal cord tissue responds predominantly to MBP.

Along with the regularity of autoimmune responses, one can observe a regularity in the expression of autoimmune diseases; about twenty can be diagnosed[47]. Of course, one may claim that the regularity of diagnosis is due more to the constraints of nosology than to any inherent standardization of autoimmunity itself. Nevertheless, it is apparent that the relatively limited spectrum of autoimmune responses and autoimmune diseases argues against the notion that autoimmunity is caused by random mutations of lymphocytes into 'forbidden clones', as suggested by Burnet[2]. The 'forbidden clones' arising by chance in each individual ought to differ from those arising in others. Autoimmunity due to unstructured events ought to be individualized. On the contrary, even the T-cell receptor genes used by autoimmune T cells seem to be relatively restricted, at least in rodents[49,50]. Indeed, the regularity of autoantigens, disease entities and T-cell receptors is the opposite of

Table 2. Highly-conserved proteins and the immune response to infection

Protein	Pathogen	Characteristics of antigen	Ref.
Aldolase	*Plasmodium falciparum*	p41; protective antigen in animal models, target of human antibody response	29
Glyceral-dehyde-3-phosphate dehy-drogenase	*Schistosoma mansoni*	p37; antibody response in sera of individuals with low disease susceptibility	30
Glutathione S-transferase	*Schistosoma mansoni*	p28-1; protective antigen in several animal models	31,32
	Schistosoma japonicum	Sj26; strong antibody response in resistant mouse strain	33
Myosin	*Schistosoma mansoni*	Strong antibody response in infected mice, rats and humans	34
Cathepsin B	*Schistosoma mansoni*	Sm31/32; antibody response in infected patients	35
Mn superoxide dismutase	*Myco-bacterium leprae*	28 kDa antigen; identified by monoclonal antibodies	36
Cyclophilin	*Echinoccus granulosis*	Cyclosporin A receptor; identified by patient's antibodies	37

randomness and implies a degree of order and even the existence of ordering principles.

One ordering principle for autoimmunity is the major histocompatibility complex (MHC) gene products whose molecular clefts trap and present peptide antigens to T cells[51]. Only peptide epitopes associated with MHC molecules become immunogens. This filtering function of the MHC may explain the dominance of particular epitopes within the entire sequence of a protein antigen, and so the MHC cleft can clearly influence susceptibility to an autoimmune disease[52]. Nevertheless, the MHC cannot explain the immunological dominance of the antigen as a whole.

Another way that MHC molecules can influence the function of the immune system is via their role in the development of the mature T-cell repertoire during T-cell differentiation in the thymus[1]. However, positive or negative selection of T cells in the thymus sets the stage only for the immune responses and their regulation that take place in the periphery. Peripheral contact with antigen and peripheral regulation are critical to the expression of autoimmunity.

The immunological homunculus

I. Cohen[53] has proposed elsewhere that the immunological dominance of selected self antigens can be explained by cellular networks. This hypothesis was conceived after the observation that the dominant immune responses to MBP, to hsp65 and to insulin[54] are associated with preformed sets of interacting lymphocytes. Preformed networks would also appear to be involved in the family of antibodies characteristic of SLE[55], myasthenia gravis[56] and other major autoimmune responses (see Ref. 47, Chapter 4B).

The idea is that some, perhaps all, major autoantigens are indeed dominant because each one of them is encoded in the organizational structure of the immune system. Each dominant self antigen is served by an interacting set of T and B cells that includes cells with receptors for the antigen (antigen-specific) and cells with receptors for the antigen-specific receptors (anti-idiotypic). Some of these lymphocytes suppress and others stimulate. The detailed structure and behavior of a T-cell network automaton has been presented formally elsewhere[57] and the connectivity among T cells and between T cells and B cells has recently been reviewed[58]. For the present discussion, it is sufficient to note that, owing to the mutual connections between the various interacting lymphocytes in the network, some lymphocytes become activated even without being driven by contact with specific antigen in an immunogenic form[59]. The state of autonomous activity defined by a pattern of interconnected lymphocytes constitutes a functional representation of the particular self antigen around which the network is organized. In other words, the picture of the self antigen is encoded within a cohort of lymphocytes.

This limited set of dominant self antigens, each encoded in a cellular network, comprises the immune system's picture of the self. This picture was termed the immunological homunculus (little man)[53] by its analogy to the picture of the body encoded in the central nervous system by a series of neural networks. The neurological homunculus is a functional picture of the body in which the space occupied by a particular network is directly associated with the neurological importance of the organ encoded by the network, and not by its relative mass in the body. For example, the speech organs in humans and the olfactory organs of dogs are prominently represented. In other words, the neurological homunculus encodes neurological dominance. Likewise, the immunological homunculus, composed of immune networks centered around a relatively selected few self antigens, encodes the dominance of these antigens. These antigens are dominant, therefore, because the response to them is already anticipated by preformed lymphocyte networks, a distributed picture of the immunological self.

An open question is why some self antigens are included in the immunological homunculus whereas others

seem to be excluded. Is it accidental that many dominant self antigens are enzymes or hsps? Does the physiological function of a molecule contribute to its immunological delineation within the homunculus?

Irrespective of the ontogeny and specificity of the immunological homunculus, the advantages of the immunological dominance that it generates are three fold.

(1) Inherent in the essentially open-ended repertoire of the immune system is chaos – the capacity to respond to everything. To process information and to distinguish signals from noise, the immune system, like the nervous system, makes use of a predetermined set of categories. By encoding immunological dominance, the immunological homunculus allows the immune system to deal with self molecules efficiently and predictably. It establishes law and order. Every organ system in the body seems to have its own set of dominant antigens that can attract any errant autoimmune responses to themselves.

(2) The dominance of a few selected self antigens blinds the system to the many other competing self molecules and so creates self tolerance to these recessive self antigens by inattention, passively and automatically. Focus relegates the unfocused into the background. The system is thus spared the need actively to tolerize itself to the enormous number of possible epitopes on all possible self antigens – an unattainable achievement that if ever attained would leave the system with very little repertoire for foreign defense.

(3) The ultimate benefit of the immunological homunculus is that it connects immunological dominance to immunological control. The self molecules chosen for, and thus attracting, autoimmune responses are precisely those for which regulatory networks already exist. The regulatory elements channel the autoimmune response to controlled pathways that prevent the development of disease. As a result, the autoimmune response is graded, guarded and often transient. For example, while an unregulated aggressive immune response to cardiac myosin can lead to fatal autoimmune myocarditis[60], myocardial infarction triggers, in the vast majority of patients, a regulated and therefore transient and harmless autoimmune response to myosin[61].

Microbial immunity and autoimmunity

In the past decade it has become clear that a significant proportion of the B cells present in healthy humans or other animals spontaneously produce autoantibodies (Ref. 62 and Ref. 47, Chapter 3). Prominent among the natural autoimmune B cells is the class of $CD5^+$ B cells that may specialize in producing autoantibodies[63]. These natural autoantibodies react with a wide variety of self antigens, but perhaps predominantly with those self antigens that are immunologically dominant such as the spectrum of antigens characteristic of SLE, thyroglobulin, tubulin, actin, myoglobin, albumin, collagen and hsps. The origin and physiological functions of these natural autoantibodies has been obscure and controversial. Coutinho and his colleagues[58] have proposed that network connections between these autoreactive B cells dynamically locks them into a safe state of controlled, low-grade reactivity. Thus self tolerance is maintained, not by elimination of autoreactive lymphocytes, but by their continuous preoccupation with themselves – 'self assertion'[64]. Accordingly, the immune system is two: a connected network of controlled autoreactive lymphocytes and an unconnected, unfettered population of non-autoreactive lymphocytes ready to behave aggressively upon contact with foreign antigen. Kocks and Rajewsky[65] also proposed the existence of two immune systems – an autonomous 'natural' immune system and an immune system 'acquired' by contact with foreign antigens.

Cohen and Cooke[66] reasoned that the natural autoantibodies must have a beneficial role to account for their universality and suggested that they might function by binding to and obscuring microbial antigenic epitopes that are crossreactive with self epitopes. The natural autoantibodies were seen as blocking potentially dangerous immune responses to self mimicking antigens.

It is now proposed that natural anti-self B cells and their autoantibodies originate as members of the lymphocyte networks that constitute the immunological homunculus[53]. Low-grade activation of the natural anti-self B cells can be maintained by their connections to the network, even in the absence of overt autoimmunization to self antigens. These natural autoantibodies create a built-in bias towards microbial molecules that mimick the host's dominant self antigens.

Macrophages or dendritic cells that have bound natural autoantibodies and the B cells that make the autoantibodies are very efficient presenters of antigens to T cells[67]. Natural autoimmune T cells, too, can enhance immunogenicity, by providing ready-made help; the T-cell self epitopes can function as carriers for responses to other epitopes[68]. Thus self-like microbial molecules recognized by autoimmune T cells and B cells or by autoantibodies have a marked advantage over competing nonself antigens in attracting the attention of the immune system. We believe that this priming-for-self explains why conserved, self-like microbial antigens are dominant over exotic microbial antigens.

Regulated autoimmunity

How, then, is autoimmune disease avoided by this built-in preference for the self-like? Note that once the conserved microbial molecule is taken up and processed, the B cell or macrophage will present two classes of peptide fragment: those representing shared self epitopes and those representing microbe-specific epitopes. The T cells recognizing the self epitopes are part of the immunological homunculus. These autoreactive T cells are therefore regulated by the network connections of the immunological homunculus. Thus, the autoimmune response to these self epitopes will be tightly controlled and no aggressive reaction or autoimmune disease will develop. In contrast, the T cells bearing receptors for the microbe-specific epitopes of the conserved molecule are not under such regulatory constraints. Hence an aggressive, protective response can develop aimed at these foreign epitopes (Fig. 1). The homunculus generates dominance. However, the same homunculus operates to channel aggressive T-cell responses away from the self epitopes and towards the foreign epitopes specific for the microbe.

Conserved molecules such as hsp molecules are dependable targets. They are conserved because they are essential; neither the host nor the parasite can do without

them. As the products of stress produced by both the host and the parasite, hsp molecules faithfully and unfailingly signify invasion, inflammation and tissue damage[69]. Their homunculus-encoded dominance directs the effector immune response to the parasite as long as the stress persists. Indeed, it has been shown that an hsp T-cell epitope covalently bound to a viral antigen can markedly enhance the immune response to the virus[70]. Thus the host can count on exploiting the very same homunculus for self tolerance and for microbial intolerance. We are healthy, not despite autoimmunity, but because of autoimmunity. Is this not the best of all possible worlds?

Autoimmune disease

Unfortunately, there is no free lunch. A few per cent of the population pays the price of the autoimmune disease that must surface when the homunculus falters. In fact, the uniformity of autoimmune disease can be viewed as a by-product of the homunculus. The autoimmune T or B cells, channeled to respond to the dominant self antigen by the homunculus, may produce an aggressive immune reaction if not properly regulated by the suppressing control elements of the homunculus. Thus the type of effector response appropriate for the rejection of an invading microbe may be misdirected to the self. In this case, the antigenic mimicry between a microbe and a host organ-specific antigen that determines immunological dominance may also determine a specific autoimmune disease. This seems to be the case in adjuvant arthritis[71].

Moreover, perpetuation of autoimmune damage may be related to a failure to regulate the autoimmune response to self hsp molecules. It is conceivable that a virus infection or even physical or metabolic insult could induce the augmented expression of hsp molecules in any particular target organ such as the joints or the thyroid. Inadequate regulation of the ensuing anti-self-hsp response might lead to 'autoimmune' destruction of the organ by an escalating cascade in which heightened expression of hsp produces more immune damage which in turn induces more hsp expression, and so on. Thus, one kind of antigenic mimicry could initiate an autoimmune disease while another kind of antigenic mimicry (hsp?) could perpetuate an autoimmune disease.

Microbial disease

Just as the misdirection towards the self of the effector immune response appropriate to a parasite can lead to autoimmune disease, so misdirection of network regulation to a parasite can produce inadequate defense against infection. Lepromatous leprosy does not occur because of a total lack of immunity to *Mycobacterium leprae*; a response occurs that is tightly regulated, non-aggressive and more appropriate to the self than it is to *M. leprae*[72]. Microbial disease can thus occur through inappropriate regulation (too much) just as autoimmune disease can occur through inappropriate regulation (too little).

Therapy

The natural answer to inappropriate regulation of anti-microbial immunity would seem to be vaccination of the host against the microbial epitopes for which self-like regulation does not exist. The response might then be redirected to epitopes that permit an aggressive immune response. Obviously, the physiologically ideal therapy for autoimmune disease is to restore the regulatory powers of the immunological homunculus by strengthening the connections between autoimmune effector cells and regulatory cells in the natural network[53]. T-cell vaccination, the use of attenuated autoimmune effector T cells to stimulate and augment anti-idiotypic[73,74] and anti-ergotypic[75] control mechanisms, seems to do just that. To argue in a circle – how could treatment with a single T-cell clone turn off adjuvant arthritis[73] unless some form of immunological homunculus actually did exist?

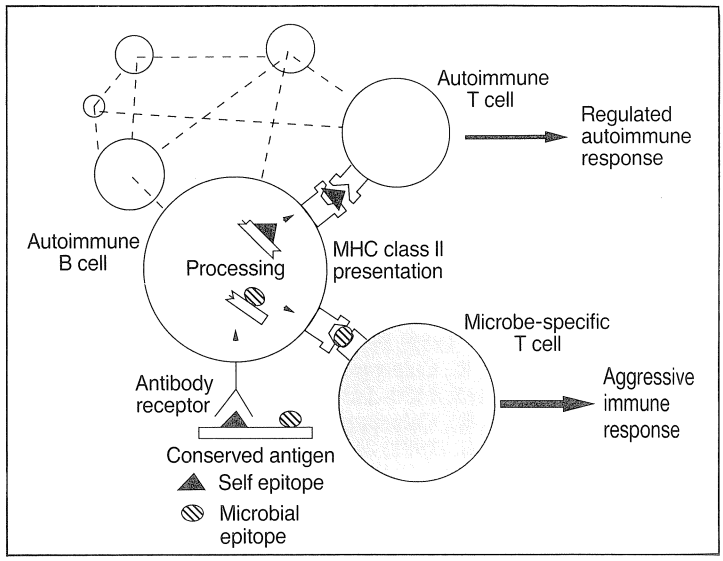

Fig. 1. *The immunological homunculus lymphocyte network connects regulated autoimmunity with effective microbial immunity. A natural autoimmune B cell (or macrophage that has bound natural autoantibody) recognizes the self epitope present on a conserved microbial antigen using the specific autoantibody. This receptor-linked uptake and processing renders the conserved molecule immunologically dominant over other antigen molecules for which there are no preformed natural autoantibodies. The antigen-presenting B cell (or macrophage) then presents both the shared epitope and the foreign microbial epitope. The response to the self epitope is safely regulated by the lymphocyte network (dashed lines) controlling the autoimmune T cells while the T cells recognizing the microbe-specific epitope are free to react aggressively. Note that the immunological dominance of conserved antigen molecules may also be served by autoimmune T-cell help.*

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