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The cognitive paradigm and the immunological homunculus

Irun R. Cohen

In last month's issue of Immunology Today, *Irun Cohen discussed the inadequacies of the clonal selection paradigm and proposed a cognitive paradigm in which preformed internal images guide and restrict the process of clonal activation. Here he clarifies the nature of these internal images, drawing on concrete examples from the image of infection and the image of self, the immunological homunculus.*

Contrary to the expectations of clonal selection, the germ-line effectively encodes a primitive internal image of bacteria, viruses, and the context of inflammation[1]. These images do not depend on the antigen receptors of lymphocytes. Components of complement can recognize some microorganisms directly, targeting them for phagocytosis or lysis[2]; natural killer (NK) cells can respond to bacteria[3]; macrophages and other white blood cells have invariant germ-line receptors for lipopolysaccharides, muramyl dipeptide cell wall elements, and other distinctly bacterial molecules; many different cells recognize viral nucleic acids and the interferons that are elaborated as a consequence of viral infection. This primitive information arms cells with the capacity to recognize and respond to invaders: to secrete cytokines; to migrate, adhere, and penetrate tissues; to engulf bacteria and viruses; to activate enzyme systems and generate toxic molecules and free radicals that can kill invaders[3].

The germ-line picture also encodes the organ or site in the body in which invasion has taken place. The patterns of lymphocyte migration, determined by molecules encoded in the germ line, compartmentalize the body[4]. Specialized types of monocytes are resident in various tissues – skin, liver, lungs, gut, eye, nervous system – and each type of monocyte processes the information of invasion in specialized ways.

The germ-line picture of infection and infectious agents developed over evolutionary time as a result of the fact that parasites are not only packages of antigenic variation; they are constrained by invariant structures and programs dictated by their ecology – their need to exist in defined anatomical and biochemical niches, to reinfect new hosts, and so forth. These obligatory manifestations of parasitic life were exploited by the germ-line to evolve an internal picture of infection. Charles Janeway[5] reasons that the immune system evolved to discriminate infectious nonself from noninfectious self.

Figures 1 and 2 illustrate the main features of the clonal selection and cognitive paradigms. The diagram of the clonal selection paradigm (Fig. 1) shows its appealing simplicity. The diagram of the cognitive paradigm is more complicated (Fig. 2) but it serves as an outline and a summary of this article.

Sensing context

Processing and presentation

Antigen presenting cells (APCs) can, according to the context, modify expression of cell interaction molecules, major histocompatibility complex (MHC) molecules, and adhesion molecules; these molecules determine how antigen signals are heeded by T cells[6]. The presence or absence of stress or inflammation influences the uptake of external molecules and the degradation, processing, and presentation of both external and self epitopes. Indeed, immunologists discovered empirically that the immunogenicity of most antigens

including self antigens is augmented by the presence of bacteria. Complete Freund's adjuvant (killed mycobacteria in oil) empowers self antigens to induce experimental autoimmune diseases[7]. Apparently, a destructive effector response to the self is legitimate when the self antigen is in the context of infection staged by the adjuvant. In this case, the immunologist has learned how to lie to the immune system. Note, however, that the healthy immune system usually can be fooled only once. Autoimmune diseases often go into remission spontaneously and cannot be induced a second time[8]. The system can learn to interpret context.

The importance of context is, likewise, illustrated by immunization in the absence of an adjuvant signal. A foreign protein molecule administered without adjuvant usually induces no immune response, and may even induce tolerance to the antigen: there will be little or no response in the future to the antigen administered with an adjuvant. Indeed the immune system may be tolerant of a viral antigen when it is expressed as a self antigen (early in development and no sign of infection) in a transgenic mouse[9]. But tolerance to that pseudo-self antigen is lost when the mouse is later infected with the virus. The context of infection can be more decisive for the response than the foreign or self identity of the antigen; the 'second' signal may be more fundamental than the epitope[5]. Thus, the immune system is driven not by antigens, but by antigens-in-context. The intentionality of the system, expressed by the signals accompanying antigen presentation, is to fight infection[1].

Filtering and focusing

The APCs[6] report the context of the antigenic encounter and, by processing and presenting, they serve as a filter and a lens: a filter that destroys molecular noise, and a lens that focuses the attention of lymphocyte receptors on particular molecular signals. Stable binding of the processed peptide fragments of antigens to MHC molecules requires that the peptides contain certain amino acid motifs at particular positions in the peptide sequence[10]. Thus, only a fraction of any antigen is preserved as a potential signal for lymphocytes. The APC is the germ-line's way of focusing attention on priority objectives. Like the retina[11], the APC acts as a feature detector; it processes information with intent.

Priming the repertoire in the thymus

The germ line, as we have seen, deals with the problems of focus and context; on this basis the receptor repertoire, generated somatically, is now able to act. However, before it confronts the outside world, the receptor repertoire is primed by the self. During the maturation of T cells in the thymus, the thymic environment drives some clones to expand (positive selection) while it activates other clones to die a programmed death (negative selection). (Many clones are thought to die a neutral death because of lack of positive selection.) The clonal selection paradigm has led to the supposition that these processes, negative selection in particular, exist to produce self tolerance, that is to rid the T-cell repertoire of potentially self-recognizing lymphocytes[12]. The cognitive paradigm suggests that the shaping of the lymphocyte repertoire during ontogeny is to help inscribe internal images for recording later antigenic experience; it may include the positive selection of some self-recognizing T cells, along with the negative selection of others. Some T cells that do not recognize self may die a neutral death. Analysis of the specific molecular environment in the thymus, the peptidic self[13], will clarify the thymic contribution to a selective image of the self, the immunological homunculus.

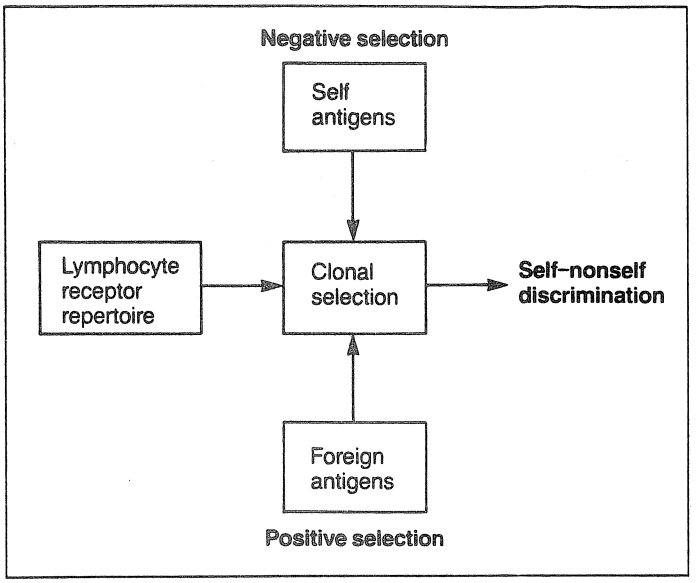

Fig. 1. *The clonal selection paradigm. This paradigm proposes that the receptor repertoires of B and T cells are organized by two antigenic forces: the self antigens, which negatively delete or anergize potentially autoimmune clones, and the foreign antigens, which positively select the remaining clones that have complementary receptors. The output of the system is the discrimination between the self antigens, which are ignored, and the foreign antigens impinging on the system, which are rejected.*

Help from mother

Antibodies binding to a particular antigen greatly enhance the uptake and processing of that antigen; preformed antibodies thus flag specific antigens for special attention[14]. Mother effectively primes her offspring's immune system by transferring a sample of her antibodies[15]. Her antibodies to infectious agents protect the baby during the early period of parasitization; newborn ungulates deprived of maternal antibodies die of infection[16]. Since Mother has experienced and survived the local parasitic environment, her image of that environment carries a warranty. Mother thus provides a more detailed image of the immediate external environment to augment the primitive image of infection carried by the germ line. Moreover, her natural autoantibodies can also help the child develop his/her own immunological homunculus.

But Mother gives more than her antibodies; babies usually, probably always, receive a transfusion of maternal blood in the course of normal birth. The blood transfusion contains living T cells, B cells, monocytes, and antigens. Although the mechanism is

not clear, blood transfusions have a profound influence on immune reactivity; transfusions of white blood cells have been discovered to reduce the rejection of allografts[17]. Mother's milk too contains lymphocytes, antibodies and antigens. Indeed, congenital exposure to maternal HLA antigens that the individual has not inherited appears to influence susceptibility to autoimmune disease later in life (J.J. Van Rood, submitted). Thus, our immune system, like our mitochondrial DNA, is imprinted matrilineally.

Antigenic experience and receptor images

The somatically generated receptor repertoire records the antigenic experience of the individual and so expands and refines the threefold set of primary internal images: the germ-line image of context and infection, the thymic image of self, and Mother's image of the environment. These primary images constitute a reference point that defines the intentionality of the immune system: which antigens it should seek out and remember. Thus, clonal activation is determined decisively by the primary internal organization of the immune system. Clonal selection by itself does not organize the immune system; rather, it is the state of organization of the immune system which organizes clonal selection. I wish to comment on two organizational elements: immune regulatory networks in general and the immunological homunculus.

Immune networks

Like a brain or a computer, the power of the immune system to rank signals, make decisions, and deploy effector forces must come from its many connected elements, its networks. Jerne promoted the idea of regulatory networks in his anti-idiotypic theory[18], a theory advanced by the work of many others (for example, see Refs 19 and 20). V-region-connected networks such as Jerne's can generate cognitive attributes like recognition, learning and memory[21]. However, theories based entirely on V-region networks miss the images of context and infection which are the products of evolutionary experience and which precede V-region connectivity. Not only the V-regions of antigen receptors (idiotypes), but germ-line-encoded cytokines[22], adhesion molecules[23], cell trafficking patterns[4], and, possibly, superantigens[24] organize immune behavior. Because these elements influence one another, the immune system can be seen to be composed of many networks connected by a variety of ligands.

The immune system, like the brain[11], uses parallel processing. Any package of antigens (cells, microorganisms, viruses) interacting with the immune system is dealt with simultaneously along different network channels. The germ-line elements (complement, NK cells, APCs, and so on), the B cells, and the T cells each analyse different features of the antigenic entity and extract the special information they intend to see: the signals of infection, the native conformation of macromolecules, the motifs and structure of processed peptides. These parallel channels, along which information is processed, interconnect through the interactions of monocytes, T cells, B cells and their products. For example, a B-cell receptor may recognize an antigen molecule by reason of the molecule's conformation, but the B cell won't be activated to secrete IgG antibodies, unless a T cell confirms that it can recognize a peptide sequence of the molecule processed and presented by the B cell. For safety and reliability, immune decisions are made by committees, not by single cells. Obviously, which particular cells comprise the committee determines the outcome. Note that immunologists have learned to influence committee decisions by immunizing with carriers and adjuvants.

Immunological homunculus regulation of autoimmune disease

The immunological homunculus is an internal image of the self acquired by early recognition of self antigens, both in the thymus and in the periphery. The self image is, in fact, composed of the committees of T and B cells that deal with the dominant self antigens[25–27].

At the outset, one may ask why the immune system bothers making internal images of self. If the intention of the immune system is to fight infection and if self tolerance based on clonal deletion is so logical to immunologists[12,28,29], why has evolution been forced to accommodate natural autoimmunity? Some may claim that natural autoimmunity is a mistake, a leakiness in thymic clonal deletion and anergy. However, natural autoimmunity is a universal phenomenon that has persisted throughout evolutionary time, and so must serve some useful purpose. I propose that the selective pressure for organized natural autoimmunity has been exerted by the molecular conservation of the biosphere. Cellular life depends on the functions of certain critical, and therefore highly conserved, molecules. Since molecular structure is the raw material of antigens, our conserved molecular self cannot be totally different immunologically from the conserved molecules of our parasites. This means that the immune system is constantly bombarded by self-like foreign molecules (such as the 65 kDa heat shock protein: hsp65) which arrive with parasites in the context of infection[30]. Autoimmunization which cannot be avoided must be dealt with.

Happily, besides posing a problem, the conservation of critical molecules can provide an immunological opportunity. Conserved molecules shared by different invaders can serve as common antigens. For example, hsp65 is hyperexpressed during infection both by microbial cells and by host cells; it is a trustworthy sign of infection[30]. Indeed, the immune response to many infectious agents often focuses on the most highly conserved, self-like antigens of the invader[27,30]; the immune system is capable of using autoimmunity to an hsp molecule to help reject an invading microbe[31]. I propose that the immunological homunculus organizes and regulates autoimmunity naturally to hsp65 and to other conserved molecules so that autoimmunity can be used to fight infections, reject tumor cells, or repair tissue damage without paying the price of chronic, progressive autoimmune disease. Considering our enterprising parasites, I dare say that an immune system incapable of autoimmunity is an immune system

incapable of guardianship. Autoimmunity is not merely a burden and an opportunity, it is a necessity.

Natural autoimmunity is benign because the immunological dominance of the major self antigens comprising the homunculus is encoded by two committees of cells: naturally-autoimmune T and B cells and their anti-idiotypic regulatory cells[25–27]. Dominant self antigens, in short, are self antigens anticipated by committees. The advantage is that dominance is welded to regulation; activation of homunculus autoimmune cells, even in the context of infection and inflammation, automatically activates a regulatory network. The autoimmune reaction to homunculus autoantigens is thus controlled; it withdraws from the effector mode when it is not needed. Consider that disease is not caused merely by recognition of self, but by an aggressive effector response that may (or may not) result from such recognition[27].

Moreover, the immunological dominance of the self antigens encoded within the homunculus acts as a protective attractor: by automatically diverting to themselves the brunt of any autoimmune process that happens to visit the organ, the dominant autoantigens spare the need for active tolerance to the other, non-dominant self antigens. Hence tolerance to the non-dominant self antigens is a side effect of the dominance encoded by the homunculus. Each tissue may have one or more dominant guardian self antigens: myelin basic protein in the central nervous system, myosin in muscle, collagen type II in joints, hsp65 in inflammation in general. The few dominant antigens of each organ constitute an immunological signature of the organ. This signature is encoded in the interactions of the networks of autoreactive cells centered around the dominant antigens. The nervous system, too, uses a signature strategy to define the organs that belong to the body[32]. It is the signature that defines the healthy self. Sercarz and his associates have directed attention to the fact that the non-dominant 'cryptic' epitopes (a counterfeit signature?) can be dangerous when they are noticed[33]. The homunculus concept explains the curious fact that natural autoimmunity is limited to relatively few self antigens; these self antigens are selected for their contribution to fitness.

The structuring of natural autoimmunity, which is the homunculus, also explains why there are so few autoimmune diseases and why their choice of target antigens seems to be so uniform. The relatively rare development of a chronic, progressive, and destructive autoimmune disease results from defective regulation of dominant natural autoimmunity. For example, systemic lupus erythematosis can be unleashed by immunization of mice to an idiotype of an anti-DNA antibody administered with a strong bacterial adjuvant[34]. Likewise T-cell autoimmunity to hsp65 is naturally benign[35] but, when it fails to get toned down by regulatory cells, anti-hsp65 autoimmunity can cause type I diabetes in mice[36] or arthritis in rats[37]. If weak regulatory connections contribute to the transition of natural autoimmunity to autoimmune disease, then a rational therapy for autoimmune disease may involve strengthening homunculus regulatory cells by active

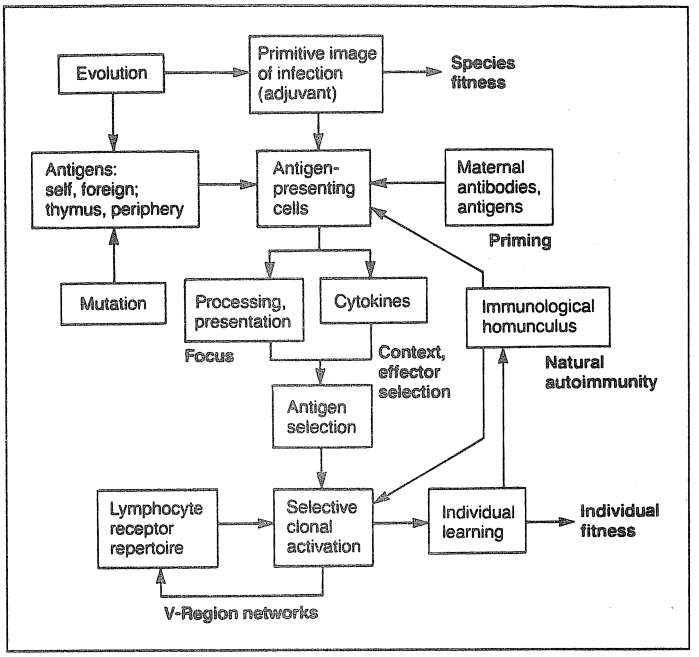

Fig. 2. *The cognitive paradigm. This paradigm proposes that clonal activation, which is tailored by the antigenic experience of each individual, is subject to the intervention of antigen selection, a process which expresses the evolutionary adaptations of the species. Antigens, self and foreign, are determined by evolution and by mutations. Evolution has also encoded, within the germ line, mechanisms of innate immunity that constitute a primitive image of infection. The agents of this primitive image include the APCs: macrophages, dendritic cells, endothelial cells, tissue cells and even B and T cells themselves. These cells ignore, destroy, or process and present certain epitopes and elaborate various cytokines. These activities provide focus, sense context and activate particular effector mechanisms. The outcome is the selection of certain antigens and molecular motifs as signals that function to activate selected clones. This form of antigen selection, in addition, is primed by maternal antibodies (an image of the infectious environment) and by maternal antigens. The immunological homunculus (an image of the key self antigens) is formed by contact with self antigens in the thymus and in the periphery. It includes T and B cells that recognize a limited number of dominant self antigens and the regulatory cells that interact with the autoimmune T and B cells. The homunculus is the expression of natural regulated autoimmunity; it influences the functioning of the APCs, the specificity of clonal activation, and the behavior of the regulatory networks, some of which are connected by V-region idiotypes. The output of the system is fitness, which profits from both foreign and self recognition.*

measures such as T-cell vaccination[38–41]. Indeed, endogenous T-cell vaccination may occur as the result of suffering a bout of an experimental autoimmune disease[8]. Perhaps much human autoimmunity, too, is self-curing and, therefore, undiagnosed.

Natural autoimmunity, the homunculus, promises to be a revealing field of inquiry. It remains to be discovered why the homunculus is composed of just certain self-antigens (the self signature), how the regulatory T and B cells get organized around the natural autoimmune T and B cells, how the regulatory cells control the effector state of the autoimmune cells, and if and how T-cell receptor restriction[42] fits into the homunculus. The immunological homunculus is not some 'little man' sitting outside of the system who rules autoimmunity; the homunculus is the characteristic organization of autoimmunity itself.

Epilogue

The evolutionary adaptations of the germ line, which defines the fitness of the species, culminate in suitable antigen selection by the apparatus of processing and presentation. The immune fitness of the individual is the outcome of selective clonal activation as it is constrained and guided by the process of antigen selection. Thus does the cognitive paradigm (Fig. 2) differ from the clonal selection paradigm (Fig. 1). Internal images allow the system to encode the essential fragments of the antigenic world to the system's specifications and utility; adaptation is fitting antigen selection and suitable response. Consider it this way: the cognitive paradigm is an immunologist's paradigm of the immune system's paradigm of the molecular world.

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