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Review

The immune system as a self-centered network of lymphocytes

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ABSTRACT

This essay makes a brief historical and comparative review of selective and network theories of the immune system which is presented as a chemical sensory system with immune and non-immune functions. The ontogeny of immune networks is the result of both positive and negative selection of lymphocytes to self-epitopes that serve as a "template" for the recognition of foreign antigens. The development of immune networks progresses from single individual clones in early ontogeny into complex "information processing networks" in which lymphocytes are linked to inhibitory and stimulatory immune cells. The results of these regulatory interactions modulate immune responses and tolerance.

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1. Introduction

Paul Ehrlich [1] proposed the first theory to explain the mechanism of immunity. A few years before Behring and Kitasato [2] had discovered that rabbits immunized with diphtheria and tetanus toxoid would produce an antitoxin (antibodies). The origin of antibodies required a new theoretical framework and in his classical 1900 paper [1] Paul Ehrlich speculated that toxins acted by binding to cellular receptors in a 'lock-and-key" fashion. One of the physiological functions of these receptors when a toxin was not present was cellular nutrition. However, when the organism was challenged by an exogenous toxin, it would induce the cells to over produce and shed the excess receptors which would accumulate and neutralize the effects of the toxin on cells. In Ehrlich's views anti-toxins were the excess of shed cellular receptors. As these receptors had a function in the cells before the toxin was introduced, they pre-existed the toxin. Thus, one of the cornerstones of his theory was that for every antigen in nature, there should be a pre-existing cellular receptor in the organism. The antigen would select this pre-existing receptor and therefore, these where called "selective theories". One problem was that a selective theory left open the possibility that the organism would produce toxic 'autoantibodies" that could destroy its own tissues. Ehrlich suggested that animals were precluded of producing such damaging autoantibodies and called the concept "horror autotoxicus" [3], a mechanism that suggested a form of self non-self discrimination. Thus, since 1901 two cornerstones of selective theories are that first, for every recognized antigen there is a pre-existent antibody and second that the organism can discriminate between an exogenous and endogenous antigen.

Karl Landsteiner a strong opponent of the first selective theories, showed that organisms were able to produce toxic autoantibodies, casting doubt over the concept of horror autotoxicus [4]. Furthermore, he showed that immune responses could be produced against synthetic antigens or haptens that did not exist in nature [5]. Thus, how could the organism predict all the possible specificities "out there"? Both autoimmune diseases and responses to synthetic antigens shed doubts on the first selective theories and as alternatives, several "instructive theories" where proposed in which the antigen would serve as a template to generate the antibody [6,7]. The result was that the dispute between selective and instructive theories of adaptative immunity dominated the first half of the 20th century. This dispute was resolved with the general acceptance of modified selective theories of adaptative immunity [8,9]. Of particular interest is the "cellular" version of the origin of antibody formation, or the concept that each antibody represents a unique specificity and that each specific antibody is produced by a clone of antigen specific receptor bearing cells [8]. This phase marks the start of the "Clonal Theories" in immunity. As a theoretical framework, these theories refocus the field of immunology into the study of the cellular, ontogenetic and evolutive components that produce the immune specific receptors. Furthermore, there is a need to explain in biological terms how the tremendous diversity of pre-existing receptors is generated and this will be the main interest in immunology for the next 30 years. These theories will also spark new ideas based on the clonality model and some of the products of this phase include the positive selection model for T cell development [10] and modern

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danger theories [11]. The clonal theories are supported by a large set of data and have driven important research enquiries. However, these theories still analyze the immune system as "collections" of individual cells that recognize the antigen independently of one another.

In the introduction of his classical paper on the network theory of the immune system [12] Jerne suggested that the period between 1970 and 1990 would be dedicated to the study of multicellular networks. First generation network theories have fallen in disfavor mainly due to their low predictive power over the ability of an organism to discriminate self from non-self and regulate the immune response to a pathogen. Since then, we have learned much about the cellular composition and the interactions of each individual components of the immune system. Immunology has matured to a point where network theories can be revisited. The next generation of immune theories will incorporate multicellular regulatory interactions between immune cells and other tissues in the organism.

2. Clones vs networks

In clonal theories [8], each clone of cells from the adaptative arm of the immune system express a unique receptor which recognizes a limited number of epitopes. During development clones that recognize antigens with high affinity are killed in the process of negative selection, giving origin to the process of self non-self discrimination. For clonal theories this is the main mechanism by which tolerance is generated. In contrast to clonal theories, networks suggest that the immune system is analogous to a "chemical" based nervous system [12]. While the brain receives physical stimuli, the immune system receives chemical stimuli from the environment. Like in the nervous system, in an integrated immune system the networks of immune cells form both stimulatory and inhibitory interactions. In network theories every clone of cells in the adaptative immune system is interconnected and work in unison with the innate immune system and the tissues they are located. Thus, the tissues produce signals that influence the innate as well as the adaptative immune system. These in turn produce positive and negative regulatory signals to stimulate or repress groups of cells in the network.

In contrast to clonal selection theories, immune networks require the adaptative immune system to be autoreactive. Immune networks incorporate clonal selection which is required because the mechanism for the generation of the antigen-specific receptors in the immune repertoire is random. This results in a collection of clones that either have no functional antigen-specific receptor or express receptors that are not adapted to the organism they developed. Clonal selection assures that every cell has a functional epitope specific receptor and that these cells recognize self-epitopes only within a certain range of affinities. High affinity receptors are either eliminated by negative selection or generate suppressor cells. Thus, the immune system is tailored to the organism it is contained, like a glove fitting a hand. This function is essential for the development of a functional immune system. In an immune network, individual clones, even though autoreactive, do not cause autoimmunity on their own.

3. Colonization of the organism by the immune system

As described above the process of positive and negative "clonal selection" tailors the immune system to the organism. Since this process is very similar to a functioning ecosystem we can call it "colonization" of the organism by the immune system. Colonization means that survival of lymphocytes is dependent on recognition of self-epitopes. Thus, both the B and T cell repertoires undergo positive and negative selection [13,14] and while it is still open to debate how much of B cell positive selection is ligand-dependent [13] data suggest that at least B1 cells and neonatal B cells are positively selected by autoantigens [15,16]. In contrast, T cells are positively selected to recognize peptides presented by MHC molecules with low affinity in the thymus [17–19] and require continuous engagement of the TCR with low affinity peptide/MHC complexes in the periphery for survival [20,21]. Thus, in the periphery, ligand-dependent positive selection of B cells would require recognition of antigens and idiotopes present in other B cells, while T cells would require survival signals from self-peptide/MHC complexes. The requirement for continuous stimulation of BCR and TCR by self-epitopes presented by the organs where the cells are homing will result in a differential distribution of B and T cell specificities in the organism since each organ has its own specific self-epitopes. In agreement with this idea, Tregs present differential distribution of the TCR repertoire in different organs [22,23]. Thus, as immune cells slowly colonize the organism, local self-epitopes provide survival signals for local populations of lymphocytes which should be tailored for each organ in the organism and both TCR and BCR repertoires should be partially organ specific. Nowhere is this so well demonstrated as in γδ T cells which express specific Vγ gene combinations depending on the tissues they are expressed [24].

4. Self-epitope repertoire, tolerance and immunity

The positive and negative selection of immune receptors by self-epitopes drives the "colonization step" that integrates the immune system to the organism. The origin of the concept of self-recognition by immune receptors is as old as immunology. It is a consequence of the non-immune function of receptors in the original selective theory of Ehrlich [1]. He proposed that physiological ligands, like toxins interact in a lock-and-key fashion with the cellular receptor and in this way toxins interfere with the natural function of the ligand. A simplified version of this concept is that in nature most antigens belong to two classes: the first is toxins or molecules from pathogens that can interact with self-molecules, the second are self molecules that have suffered modifications by chemical reactions or genetic mutations. The recognition of self provides the immune system with templates that form both positive and negative "internal images" [12] of self-epitopes. When modifications of self-epitopes are chemically induced or generated by mutations they are alterations of the internal templates of self-epitopes already recognized by the immune system. These should be recognized with affinities and efficacies that are different from those of the original self template. Some clones would recognize the new modified template with lower affinity, others, with much higher affinity thus promoting an effector immune response. Such a system would assure that even immune repertoires with limited receptor diversity will have a template to recognize "altered self" or exogenous proteins that interact with self proteins. Furthermore, the use of an internal negative image of the self as a template to identify "non-self" components makes evolutionary sense. The genomes of mammals share many common metabolic, replicative, structural and genetic translation pathways with other eukaryotes, bacteria and archaea [25]. Because the proteins presented in these organisms are similar but not identical to ours, their proteins and peptides will serve as modified versions of our own internal templates. Thus, it is not surprising that we find in the thymus self-peptide-MHC class I complexes that are weakly similar to the cognate T cell epitope identified by many T cell clones [26,27]. This type of analysis is feasible for MHC class I molecules since these have closed ends that limit the size of presented peptides to 9–10 amino acids in length [28]. This allows for easy detection of self-peptides

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