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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.

Keywords

Immunology; Self-peptides; Immune networks; T cells; B cells; Autoimmunity

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 were 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” were 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 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 $\gamma\delta$ T cells which express specific $V\gamma$ 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 (epitopes) with minimal similarity to the original epitope using bioinformatic tools. This is not easy in MHC class II antigens where the structure of the MHC is open, allowing for the binding of peptides of different lengths and with more than one anchor motif [28]. Nevertheless, positively selecting self-peptides with minimal similarity to the antigen were observed for MHC class II T cells as well [29]. Surprisingly, this similarity “imprint” of T cell specificity extends to mature T cells where all other cross-reactive epitopes for a given T cell clone are similar to the original epitope used to identify the original T cell reactivity [30]. In the periphery, the self-peptide MHC repertoire is expanded by the presentation of peripheral self-peptides produced by the processing and presentation of Ig framework epitopes [31] and from the somatic rearrangement and mutation of V genes on both B and T cells in the forms of CDR derived idiotypes [32]. Thus, the universe of potential self-epitopes generated by the diversification of the B and T cell receptors could be as large as the potential repertoire of foreign epitopes.

5. The immune system as a chemical sensory system

In an integrated immune system, one would expect recognition of self by the adaptative and innate immune mechanisms to be constant. Thus, like a chemical sensory system, the immune system registers all disturbances in the organism [12]. That means that besides the use of self to form a template for the recognition of non-self and altered-self, another function of positive selection towards recognition of self is to make the system able to detect disturbances in the tissues it is roaming. Disturbances should comprehend all quantitative and or qualitative alterations of self. This includes stimuli suggested by danger theories like damage associated molecular patterns (DAMPs) or pathogen associated molecular patterns (PAMPs) [11,33], metabolic changes in tissues, like the accumulation of early intermediates of the cholesterol biosynthetic pathway [34,35], traumatic events like wounds [36] and dietary epitopes [37–39], among others. Thus, disturbances can be defined more broadly than in previous models in which the main stimuli for the initiation of the immune response is tissue damage [40]. The immune system is constantly interacting with self even when the tissue is not damaged or attacked by a pathogen [20,21]. Subtle qualitative or quantitative changes in the self-epitope repertoire or pattern of protein expression are detected by the immune system and processed as information. Thus, many interactions of the immune system are with self antigens and do not promote any effector responses. However, these interactions could have physiological meaning. One is immunological, like recognition of mutated cells and tumors. Another is non immunological. As candidly suggested [40] all our technologies to study the immune system are biased towards effector immune responses and their regulation [40]. Thus, we measure the proliferation of T cell against antigens, the cytotoxic activity of antibodies, NK and T cells, autoimmune reactions and atopic reactions [40]. Fortunately, there are some clues of potential new functions of the immune system. In the normal development of hemi and holometabolous insects, phagocytosis by leukocytes removes dead cells and contributes to the tissue remodeling process that marks the transition of a larvae into the adult [41]. These contributions are not as clear in the normal physiology of mammals but TCR $\gamma\delta$ T cells seem to play an important role in wound healing [36] and chronic activation of TLRs by comensal microbes is required for the normal homeostasis of the intestinal epithelium [42]. While, these functions are mostly observed during experimental procedures that require wounding of the epithelial cells, it is tempting to speculate that these interactions with the immune system facilitate physiological self-renewal in steady state conditions.

6. Immune networks and immune cell populations

The parallel we want to drive between the immune system and the nervous system should also apply to populations of immune cells. An immune network allows for a large diversity of effector lineages beyond the classical Th1, Th2, Th9, Th17, Treg, etc. This is in agreement with new technologies that analyze individual cells in T cell populations, like single-cell deep sequencing [43] and time-of-flight based cytometry [44] that are revealing an amazing diversity of individual T cells with differential profiles of cytokine as well as master regulator transcription factors. The consequence of these studies could turn out in the near future to completely challenge our ideas about T cell lineages. It is certainly driving the development of new analytical tools to study the behavior of populations of lymphocytes,

instead of clones of lymphocytes. Thus, it should not surprise us if what we call lineages will turn out to be populations of T cells skewed towards producing one pattern of cytokines. Further, as we investigate more types of immune responses using these technologies, we will find more “skewed” populations besides the ones we classify as Th1, Th2, Th17 or T reg. The physiological meaning of this diversity of effector cells is not yet understood. However, limiting the diversity of T cells to a few lineages results in an artificial reduction of the potential diversity of effector cells and promotes the stereotype of a rigid immune system that has only a limited set of options when facing a challenge by a pathogen or tumor.

Networks propose that every cell of the immune system is involved on both positive and negative feedback loops. Thus, no single cell population is in fact only regulatory or effector. An effector cell that promotes one type of response inhibits another and a regulatory cell that inhibits one response promotes another. For example, the immune response to influenza virus infection in mice generates regulatory T cells, which are thought as immune suppressors per excellence. A model immune information processing network (IPN) with Tregs is presented in Fig. 1. In influenza infected mice, Tregs inhibit the development of Th1-like cells but stimulate the differentiation of follicular T helper cells (T_{FH}) which promote the production of high affinity antibodies that are specific for the influenza virus [45]. The formation of antigen-specific B cells can then form a positive feedback loop through antigen presentation by B cells, which are strong inducers of regulatory T cells [46] which in turn are strong promoters of T_{FH} [45]. In contrast, a negative feedback loop is generated by terminally differentiated B cells (plasma cells) that inhibit T_{FH} [47]. Further example where Tregs play a rather stimulatory role in immunity is in the promotion of a protective immune response and increased survival in mice infected with Herpesvirus-2 by accelerating the recruitment of NK and dendritic cells very early in the infection [48]. Other regulatory loops in the immune system are the regulation of IgG isotype subclass production by B cells. Here Th1 cells suppress the formation of Th2 cells and the production of IgG2a while promoting expression of the IgG2b isotype [49,50]. These studies suggest that every cell in the immune system has both repressive and stimulatory functions.

7. The ontogeny of the immune system: sensing thyself

The development of a functional immune system can occur in the absence of exogenous microbes and reduced stimulation by dietary antigens [51]. Germ-free animals have normal T cell numbers [51] although the expression of immunoglobulin isotypes is affected in the mesenteric lymphnodes [52]. Furthermore, the formation of cryptopatches, which are lymphoid aggregates in the intestine, are independent of the microbiota [53]. Germ-free animals can sustain a repertoire of activated B and T cells [54] and most types of Th effector populations like Th1, Th2, Tregs and in the absence of Tregs, Th17 cells [55,56]. This does not mean that microbes and dietary components do not play an important role in the functional maturation of the immune system as is well documented by an extensive literature. However, for the sake of our discussion, it does mean that a functional immune system can develop and maintain a considerable degree of endogenous activity in the absence of exogenous signals.

One stage during life that is relatively free of exogenous antigen is ontogeny. At birth the animal has a functional immune system ready to interact with the external microbiota or exogenous dietary components. The formation of interactions between immune cells during the ontogeny of the immune system has been well documented for the early B-cell repertoire as we will discuss in detail below. B cells produce antibodies and the interaction and connectivity of antibodies is easily tested. One possibility is that during early ontogeny there is relative independence of parts of the immune system, like the B and the T cell repertoires (Fig. 1). Each part develops separately and is tested for functionality and integrated with the other components as the animal ages (Fig. 1). Assuming a lack of exogenous stimulation, in the early stages of development, the neonatal immune system is skewed towards physiological recognition of self instead of classical immune effector functions. For example, during ontogeny in mice there is a hierarchy of APCs and neonatal macrophages [57–59] and dendritic cells [60] are not as efficient APCs as that of adult animals while neonatal B cells express adult levels of MHC class II antigens [59,61,62] and could be the main antigen presenting cells in early immune development.

This ordered pattern of development extends to the formation of the B and T cell repertoire. During development the acquisition of antigen specific B cell receptors is genetically determined [63]. The initial colonization of the organism by B cells is T independent and driven by neonatal CD5⁺/Ly-1⁺ B cells. These cells constitute significant proportion of neonatal B cell repertoire [64,65]. They are a self-replenishing population [66] of T-independent B cells [64,65] that have a negative regulatory function through the production of IL-10 [67]. Furthermore, the random mechanisms that generate the antibody diversity in the adult mouse are suppressed in neonatal mice. This includes the preferential expression of the proximal VH7183 family in pre-B and B cells of newborn mice [68–71] and the inhibition of N region nucleotides additions during Ig recombination [72,73]. Thus, the mouse B cell repertoire in early ontogeny has limited diversity and is rich in antibodies that are multispecific or autoreactive [74–76]. They are also organized in a functional idiotypic network of suppressive and stimulatory B-B cell interactions [77–79]. After birth, with all the environmental stimuli from diet and microbiota the neonatal pattern of the B cell repertoire is rapidly changed. Unless, animals are kept germ-free, in which case the expression of the proximal VH7183 gene family is still enriched in the B cell repertoire of adult mice [74], in animals developing in a conventional environment, the fetal pattern of VH gene expression starts changing at day 4 post-natal and culminates with the adult-like VH gene pattern at the seventh day after birth [69]. Thus, while a functional B cell repertoire is formed in an orderly fashion in the absence of external antigens, it quickly modifies itself to adapt to the stimuli from the exogenous environment after birth. In the adult, the CD5⁺/Ly-1⁺ B cells, which had a dominant role during ontogenesis, will specialize in the production of multireactive antibodies [80], IL-10 [81] most mouse serum IgM and IgM autoantibodies [65,82,83].

The pattern of development of the T cell repertoire is set by the intense selection of T cell specificities by peptide-MHC complexes during differentiation in the thymus [17,18]. However, it is not clear how much the fetal vs adult T cell repertoire differ from each other in the absence of external stimulation. Like in the B cell repertoire, the neonatal T cell repertoire has limited N-region diversity [84,85] and is slightly skewed towards the

expression of the most 3' proximal V α gene family [86]. That the neonatal and the adult T cell repertoires are different is suggested by the study of animal that have undergone neonatal thymectomy. In these animals, the adult T cell repertoire contains the TCR V β expression pattern more similar to that of the pre-thymectomy neonatal repertoire and that is different from the adult V β repertoire of euthymic animals [87,88]. Furthermore, the development of different T cell populations is also ordered and regulated, Tregs are detected at day 3 post-partum [89]. Thus, like the B-cell repertoire, the T cell repertoire has a temporally ordered development that is independent of exogenous stimulation. The studies on both the ontogeny of the B and T cell repertoire suggest that these repertoires develop in relative isolation in early ontogeny. This is why we can easily detect regulatory networks, for B and T cells. Latter, as the animal ages and the immune system matures, the two repertoires will coalesce and the main interactions will be between B:T cells, instead of T:T or B:B cells (Fig. 1).

8. On the reactivity to self and its regulation

All features of the immune system like development of lymphoid organs, formation of the adaptative B and T cell repertoires, differentiation of T helper effector populations, specially Tregs and Th2 cells occur in germ-free mice [55,56]. One could argue that an immune system developed in the absence of DAMPs or PAMPs would be quite safe from autoimmune disease. However, deletion of genes that regulate the negative selection of the T cell repertoire in the thymus like *Aire* [90] or genetic depletion of Tregs [55] result in severe autoimmune disease in germ-free animals. These findings suggest that just the endogenous activity of the germ-free immune repertoire even in the absence of DAMPs could cause autoimmune disease by being a DAMP itself and that active clonal deletion, anergy and regulatory mechanisms are required to keep this activity in check.

Autoimmune diseases can be quite instructive on the functions of the immune system. In the last 20 years Genome-wide Association Studies (GWAS) have uncovered a range of genes involved in different autoimmune diseases. The prime autoimmune disease association locus is the MHC which contains 224 loci, 40% of those related to immune functions, including the classical MHC antigens [91]. The association of the MHC was recently reanalyzed [92] and the authors confirmed the strong association of autoimmune diseases with classical MHC antigens and peptide presentation. The strongest cases for specific antigen presentation in autoimmune diseases so far have been found in rheumatoid arthritis [93], celiac disease, where the immunodominant T cell epitope in gluten has been identified [94] and HLA-B27 in ankylosing spondylitis. In the last case the association of HLA-B27 and ERAP1 which is an aminopeptidase responsible for trimming peptides that will be presented by HLA Class I antigens, accounts for almost 75% of all genetic signal detected in ankylosing spondylitis [95]. In contrast to the MHC, which is a universal susceptibility locus to autoimmune diseases, GWAS also identified non-MHC loci, some of these associated with several autoimmune diseases [96,97]. However, most of these genes are pleiotropic like interleukins, interleukin receptors, adaptors, kinases, phosphatases and others [96,97]. One good example is SH2B3/LNK, an adaptor that regulates the numbers of total T cells in the blood [98]. The common loss of function variant of SH2B3/LNK (R262W) that is associated with type 1 autoimmune diabetes and celiac disease induces an increase in total T cell,

specially CD4⁺ T helper cell numbers [98]. Another is PTPN22, which also has pleiotropic effects. In mouse T cells its absence results in a reduction of the threshold for T cell activation when recognizing self-peptides [99]. The pleiotropic nature of these genetic defects makes it difficult to pinpoint one particular function as the main culprit in the break of self-tolerance. Conversely, it also suggests that breaking tolerance may require the simultaneous action of several defective components in the immune system.

9. The structure of the immune network

Let's assume the immune system operates like an ecosystem. This means that in an antigen-free animal every immune cell population is "linked" first to the self-epitope it recognizes and then to the cell population that provides the cytokine milieu that promotes its expansion or contraction. Since the concentration of each self-peptide is limited, it means that every self-peptide can only sustain a limited number of T cells. A simplified model is the interaction between activated CD4⁺ T cells and CD4⁺CD25⁺ regulatory T cells. In antigen-free animals the activation of naïve CD4⁺ T cells would require recognition of self-peptides/MHC complexes. Thus, the number of activated T cells should be linked to the number of activating self-peptides. Activation leads CD4⁺ T cells to produce IL-2, a cytokine that is mainly but not exclusively produced by activated T cells [100]. IL-2 or signaling through the IL-2R α or IL-2R β receptor is necessary for CD4⁺CD25⁺ regulatory T cell function [101,102] and polymorphisms on the IL-2R α are also one of the main regulators of CD4⁺CD25⁺ T cell numbers in human blood [98]. The strict requirement for IL-2 links the numbers of CD4⁺CD25⁺ regulatory T cells to the numbers of activated T cells producing IL-2 [103] so that both the numbers of regulatory and activated T cells are linked to the concentration of stimulating self-peptides. Thus stimulating self-peptides are the limiting factor for both the numbers of Tregs and activated T cells. Once the stimulation by self-peptides reaches its limit, a negative feedback loop is formed in which the increase in CD4⁺CD25⁺ T cells caused by excess IL-2 inhibits activated CD4⁺ T cells and this reduces IL-2 production which results in reduction in Treg cell number. Thus, in a healthy animal, autoimmunity would be kept in check by the networks of T and B cells that are dependent on self-peptides and cytokines produced by other cells linked to them in stimulatory or inhibitory loops.

T cells are selected on a similar pool of public and private self-peptides and the TCR repertoire of both regulatory and non-regulatory T cells will have a considerable overlap [104–106] and recognize similar peptides, being they self [107] or non-self [105]. Thymus negative selection will constrain naïve T cells to recognize self-peptides with low affinity while regulatory T cells will recognize self-peptides with higher affinity [107]. Thus regulatory T cells have a more diverse repertoire and recognize self-peptides with higher affinity than naïve T cells [104,105]. This suggests that regulatory T cells would have competitive advantage over naïve T cells in terms of self-peptide/MHC complex recognition. Thus another effect of linking the number of CD4⁺CD25⁺ regulatory T cells to activated CD4⁺ T cells by their IL-2 requirement ensures that activated T cells are not always overrun by Tregs that recognize self-peptides with high affinity. The linking of an immune cell population to another is essential to build inhibitory and stimulatory branches into the network.

Expanding on this concept, the formation of links between T cells and other components of the immune system requires the recognition by T cells of public and private self-peptides presented on the MHC of other cellular lineages. For example, B cells will present Ig-framework self-peptides which are common to a B cell lineage (public) or peptides derived from CDR3 regions of immunoglobulins which are B cell clone specific (private self-peptides). Dendritic cells will have their own public and private self-peptide repertoire plus a repertoire derived from phagocytosed proteins [108]. The presence of some self-peptides like CLIP which is preferentially presented on mature DCs favors the development of Th2-like cells when presented in combination with antigen [108], effectively linking mature DCs with Th2 cells. Others like the conserved Ig-framework self-peptides will be presented by more than one APC, like B cells, DCs and macrophages and will favor the development of regulatory T cells in the thymus and when presented in combination with antigen promote the differentiation of regulatory T cells [109] which links Tregs to B cells.

These links between cells of the adaptive immune system and self-peptides and antigens presented by APCs are the basis of IPNs (Fig. 1). These networks are “fluid” because immune cells move in tissues and blood which contrasts with the nervous system where connections are mapped by physical interactions. The decision making process in IPNs depends on the weight of each inhibitory or stimulatory cell-cell interaction in the network. The presence of an antigen will induce the expansion of one cell population A and this will increase the weight of this cell population in the IPN. After removal of the antigen the stimulus for expansion of A is removed. Now inhibitory populations of cells linked to population A will bring the system back to equilibrium. This is very similar to the behavior of immune cells in Jerne's original network theory [12] only that IPNs are cellular networks.

10. Conclusions

A discussion of immune networks and their potential was presented. Forty years later, our knowledge of cellular lineages and their interactions in the immune response is greatly increased. The basic rules that will be part of a generalized network are: (1) That the immune system is built towards “self-recognition”; (2) cells of the immune system are negatively and positively selected towards self-epitopes/peptides; (3) recognition of self-epitopes is essential for lymphocyte survival; (4) T cells are “linked” to self-peptides and to the APCs that present the self-epitope; (5) all cells in the immune system are linked to one another and whether they are Tregs or Th1 cells they form both inhibitory and stimulatory interactions with other T cells and APCs.

Acknowledgments

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Fig. 1.

The formation of immune Information Processing Networks: The B and T cell repertoire are formed in relative isolation during fetal life (Top). The transition of one stage into another during repertoire development are indicated by blue arrows. This relative independence is visible in formation of the B repertoire and B cell idiotypic network by fetal and neonatal B cells around birth (Top right). Soon, after birth, both repertoires start to interact with each other (B:T cell interactions) and environmental factors, promoting the coalescence of the T:B repertoire (Middle panel). The neonatal idio-type anti-idio-type interactions of the early B cell repertoire are now diluted by T:B, stroma and APC cell interactions. This leads to a coalescence of APCs and the B and T cell repertoires with formation of IPNs (Bottom panel). A basic simplified immune IPN based on the studies of the response to influenza in mice presented in “Immune networks and immune cell populations” is shown here. Stimulatory interactions are presented by green arrows and inhibitory interactions by black blocking lines. Treg cells (TR) (red) are suppressive for Th1-like cells (Green) but stimulate the differentiation of T_{FH} (Blue) which promote the production of high affinity antigen specific antibodies. These antigen-specific B cells stimulate the formation of more regulatory T cells which stimulate more T_{FH}s. An inhibitory loop is promoted when B cells differentiate into plasma cells (P cells) which inhibit T_{FH} cells. Other potential regulatory loops are shown between TR and immature DCs (imDC) or mature DCs (mDC) and T cells.

Depicted in each cell population are “public” (triangles) and “private” (small dots) self-peptides in their MHC class I and Class II antigens and B cell epitopes (squares). The recognition of these self-peptides by T cells should promote the indexing of the T cell to the APC that presents the self-peptide. The figure presented here is not intended as an exact description of lymphoid tissue development but only as a guide to the formation of the repertoires and IPNs.