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Review

Naturally occurring B-cell autoreactivity: A critical overview

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Abstract

In over one century of research in immunology marked progress in the scientific knowledge and the implications derived from it has been made. At the same time several contradictory and seemingly opposing results have been obtained. The term autoimmunity is still conceived by many as a term directly related to an immunopathological state. However, strong evidence exist that not only the immune system is able to recognize self-constituents, but it appears also that this property is essential for homeostasis. Direct or indirect alterations of such self-recognition properties of the immune system may contribute to pathology. In this review, the most recent advances in the field of naturally occurring B-cell autoreactivity in health as well as in disease are presented and discussed.

Keywords: Natural autoantibodies; B-cells; Polyreactivity; Natural autoimmunity

1. Introduction

Immunology, as a scientific discipline, emerged at the end of the 19th and the beginning of the 20th century and has taken Chemistry as a prototype. Since then, however, enormous advances have been made not only in Chemistry but in the concept of biological implications as well. In this special issue we present a number of unique aspects that reveal the complexity of the living organism and the immune response [1–14].

Two principal concepts govern the immune system based on the idea that the exclusive role of the immune response is the protection of the organism from environmental pathogenic agents. Firstly, the defense is mediated by specific receptors for each pathogenic agent and secondly the immune system is educated not to recognize self antigens during ontogeny and acquires the self/non-self know how and tolerance to self-antigens. When for any reason this tolerance is broken, reaction with self-antigens occurs and an immunopathological state is induced.

Throughout the development of these concepts, a series of anthropomorphic perceptions have been introduced with the aim to interpret the results obtained and integrate them in a coherent and logical framework. The initial ''horror'' i.e. terror, fright, atrocity, panic (according to Roget's 21st Century Thesaurus Dictionary) and the subsequent ''tolerance'' i.e. open mindedness concession, altruism, clemency have been followed by many others like: ignorance, integrity, God, canonical, cardinal, danger, degeneracy, strange and so on. It is evident that these words denote feelings and behaviors peculiar to humans and one may wonder if the concepts reached are generally valid to all species.

In fact, the immense majority of species on earth are not able to induce a specific adaptive immune response. In spite of this, they resist infections, sometimes more effectively than humans, through so-called innate non-specific immunity. Therefore, it can be concluded that one of the two fundamental concepts raised, i.e. resistance to pathogenic agents mediated by immune recognition receptors of an extreme specificity, is only partially correct.

The second fundamental concept, i.e. the immune system is not able to react with constituents of its own organism ought to have been formulated differently. Indeed, it was well known already at the beginning of the last century that antibodies reacting with self-constituents, like spermatozoa, erythrocytes, polysaccharides and proteins, were present in the sera of normal humans and animals. However, since autoreactivity was in

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complete contradiction with accepted concepts, it has been marginalized and considered up until the end of the 1970s as background noise due to the possession by antibodies of glue-like properties. This picture has radically changed, however, in view of results obtained from a series of studies on natural autoantibodies (NAbs) performed during the past 30 years. During the last 10 years several reviews have appeared dealing with the various aspects of NAbs [15–30]. Earlier reviews on NAbs are given in four positional articles published [31–34].

Below, the results considered as the most representative and significant so far will be recalled briefly and completed while some others, reported recently, will also be presented. All results obtained are in accordance with and support the view that physiological autoimmunity plays a pivotal role in the functioning of the immune system.

2. Present knowledge on natural autoantibodies

2.1. Circulating NAbs

A series of studies have shown the presence of antibodies in the sera of normal humans and other higher vertebrates but also in those of very distant animal species like sharks. These antibodies react with the internal constituents of the organism and also with the external antigens of the environment. They recognize various intracellular and cell surface antigens as well as circulating macromolecules and haptens highly conserved during evolution.

In humans, mice and rats, these NAbs are of the IgM, IgG and IgA isotypes and are present not only in blood but also in other biological fluids, such as colostrum, saliva and cerebrospinal fluids [19,31–33]. In sera, high IgM titers are noted with autoantigens but not in plasma [35] while IgG and IgA titers with autoantigens are usually low. However, when IgM is isolated from plasma and IgG and IgA from sera, they show a considerable increase of their autoreactivities [31–35]. Similarly, it was found that in normal rats, non-immunoglobulin serum proteins prevent the binding of IgG to various glomerular autoantigens. By contrast, in rats with autoimmune glomerulonephritis, IgG in the serum show a strong binding to glomerular autoantigens, which, however, is inhibited by addition of sufficient amounts of non-immunoglobulin serum proteins [36]. These data suggest that binding of auto-antigens to the paratope of circulating NAbs often results in the masking of their antigen-binding reactivities.

When tested on a large panel of self and non-self-antigens, a proportion of human and murine NAbs are found to be mono-reactive like the antibodies obtained after experimental immunization. The great majority of antibodies found in normal sera, however, is polyreactive and, usually, recognizes a vast number of self and non-self-antigens. The extent of NAbs polyreactivity seems to be dependent on T-cells but the extremely limited number of studies carried out in this area are not conclusive [34].

The repertoires of NAbs from one individual to another differ but within one individual are stable with aging in children and adults [37,38]. Since IgM NAbs are present in newborn humans as well as in newborn, germ-free and antigen-free mice, it appears that their repertoires are largely independent of external antigenic contacts while those of IgG NAbs seem to necessitate the presence of external stimulations [39].

2.2. Cells producing NAbs

Studies with transgenic mouse lines have demonstrated that autoreactive B-cells producing NAbs are not deleted in the bone marrow but circulate and are positively selected by auto-antigens [40]. B-cells carrying polyreactive receptors and able to bind more than two antigens, were shown to be present in the newborn (50%) and the adult (20%) B-cell repertoire and to be widely distributed as well [41]. It is possible that the number of polyreactive B-cells noted may correspond to minimal values. Indeed, polyreactive B-cells and their secreted antibodies have a much higher probability of associating with self rather than non-self-antigens. Therefore, their auto-antigen-binding capacity might be masked and in order to reveal it, cells and antibodies should not only be isolated from their biological milieu, but further treated in order to dissociate possibly bound auto-antigen. Binding of auto-antigens to cell surface and circulating NAbs probably represents one of the important regulatory mechanisms designed to prevent induction of immunopathological states.

B-cell clones isolated from various healthy human lymphoid tissues and immortalized by Epstein–Barr virus infection and/or cell hybridization have been found to secrete IgM, IgG and IgA polyreactive monoclonal auto-antibodies. IgM and IgA predominate, but IgG are also found. In mice, B-cell clones obtained by cell hybridization from various lymphoid organs during fetal and adult life, almost exclusively secrete IgM polyreactive antibodies. However, polyreactive IgG NAbs are obtained from the spleen of mice following polyclonal stimulation and clones producing polyreactive IgA are obtained from mouse Payer's patches. It is possible that the B-cells which produce polyreactive IgM and, to a lesser degree, those producing polyreactive IgA are in a higher activation state than B-cells producing polyreactive IgG.

Although several studies have clearly shown that NAbs are produced by various B-cell subpopulations, including B1 and B2 cells [41], it is still often stated that NAbs are preferentially, if not exclusively, produced by peritoneal B1 CD5+ cells. This IgM producing B-cell subpopulation, however, responds very poorly to receptor-mediated activation and rarely undergoes affinity maturation [42] and therefore can't account for the high amounts of IgG NAbs found in the serum.

2.3. Structural and binding characteristics of NAbs

Polyreactive but also monoreactive NAbs are encoded by non-mutated germline genes. However, it was observed in several cases, that polyreactive IgG and IgA NAbs are encoded by mutated germline genes [20]. Polyreactive NAbs possess binding avidities ranging from 10^{-4} to 5×10^{-10} M with average values ranging from 10^{-6} to 5×10^{-7} M

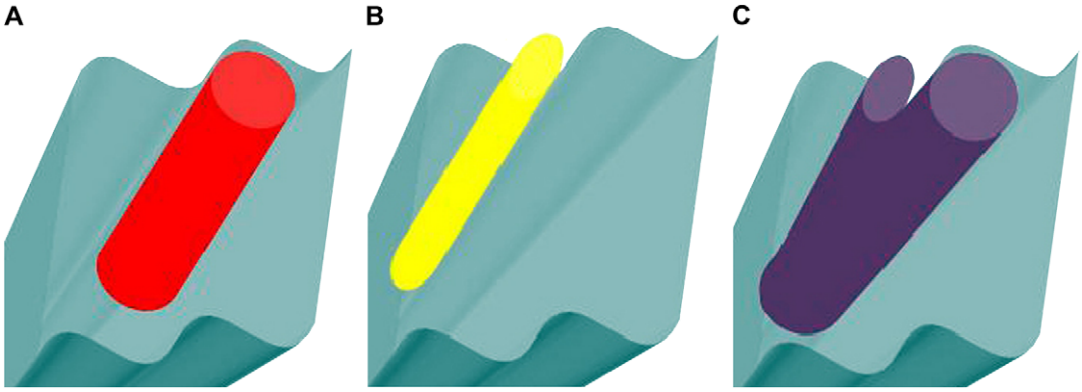

Fig. 1. Different epitopes bind to different sites of the same paratope (Refs. [24,44]).

whereas monoreactive NAbs possess binding affinities ranging from 10^{-8} to 5×10^{-11} M [16,25,26,31]. Polyreactive IgM was found to be generally more reactive with foreign (xenogeneic] proteins than with self or allogeneic proteins [43]. If so, it would appear that lymphocytes carrying IgM polyreactive NAbs, and possibly those carrying polyreactive IgG, could be preferentially recruited and activated by environmental rather than by self-antigens. Polyreactive NAbs usually exhibit relatively long H-CDR3 which often contain hydrophilic amino acids. Antigen binding capacities of polyreactive NAbs are much more sensitive to changes in temperature or treatment with dissociating agents. These results suggest that the paratope of polyreactive NAbs is more plastic than that of monoreactive antibodies [20,32]. Recently, it was shown that a given conformational state of the paratope of a polyreactive NAb can bind dissimilar epitopes at spatially different sites in the antigen-combining region [24,44,66] (Fig. 1). If so, a polyreactive NAb that has engaged all, or most, of its sites during association with an antigen, presenting its epitopes in the adequate spatial distribution, would in fact correspond to an antibody of an exquisite specificity recognizing a precise three-dimensional structure. However, the same antibody would be considered as "non-specific" because of its multiantigen-binding capacities, which are mediated by single or partial involvement of its distinct site present in the paratope. Thus, these recent results support the hypothesis already advanced that since each NAb exhibits a distinct polyreactivity profile that is unique, it might recognize closely related three-dimensional structures [33]. Furthermore, the observation that the amino acid residues within the sites of the paratope of the polyreactive antibody can undergo somatic mutations which are involved in the affinity maturation of the antibody are in accordance with the hypothesis previously raised, that is, some polyreactive NAbs producing cells may be precursors of monoreactive antibody producing cells [20,31,45].

2.4. Biological activities of NAbs

NAbs have been shown to express various biological functions, often contradictory and rather unexpected (Table 1). They contribute to the defense and elimination of bacteria, viruses and other pathogenic agents [26,46,47]. They also participate in the removal of apoptotic cells, as well as tumor and senescent cells [48,49], in the regulation of B and T-cells, cytokine action, inflammation, the presentation of antigens to T-cells, and in the development of autoimmune states [50–52]. Some are able to penetrate into living cells, to express enzymatic activities, and to promote remyelinization [22,27,29,53].

NAbs reacting with estrogen receptors express estrogenic activity, IgG NAbs by reacting with the opioid receptors show morphine like activity, IgG NAbs to thyrotropin receptors possess thyroid stimulating activity and those directed to high affinity IgE receptors trigger histamine release from basophils [54–57].

3. Physiological autoimmunity concept

The main conclusion from the studies on NAbs is that the normal immune repertoire is constituted, principally, and in most species exclusively, from polyreactive immune-receptors able to recognize self and non-self-antigens, but monoreactive receptors to exogenous and endogenous antigens are also present. In higher vertebrates, part of the DNA coding for the primordial polyreactive autoantibodies might have been rearranged in order to produce monoreactive antibodies,

Table 1
Indicative biological properties of naturally occurring autoantibodies and possible pathogenic effect in the case of inadequate or uncontrolled NAb network

Physiological effect	Uncontrolled or inadequate response-possible pathogenic result
Protection from	
• Bacteria	Sepsis
• Viruses	Chronic infection
• Other	
Anti-receptor antibodies	
• Anti-TSHR	Grave's disease
• Anti-opioid-R	Decreased pain threshold
Other homeostatic roles	
• Apoptotic-cell clearance	Autoimmune disease
• Anti-tumor activity	Disseminated cancer

possibly involved in more specialized functions of the organism, like those recognizing cytokines and viruses frequently found in normal sera [16,26]. Polyreactivity associated with autoreactivity is a highly conserved property of the immune system during evolution.

Autoreactivity associated with polyreactivity implies that B-cells and the antibodies they secrete establish multiple interactions, principally with the internal constituents of the organism but also with environmental constituents. An immense network is thus created. Regulatory processes involved in the functioning of the immune system derive from this vast, permanently modified and active network. Since such a network is associated with all the biological systems of the organism, it is probable that the immune system contributes also to the general homeostasis of the organism.

3.1. Functioning of the normal immune system

Internal and external weak stimuli arise continuously and maintain the NAb-producing cells in an active but unexcited state thereby maintaining the network. At higher than physiological levels of external stimulation, the network will be remodeled in order to integrate the new insults.

Strong external stimulations occur when infectious agents enter the organism. Infectious agents usually carry multi-similar epitopes and bind with higher avidity to polyreactive NAb producing cells than self-antigens which, normally, do not express such epitopes. Activation of these cells will occur, principally those carrying multimeric IgM and to a lesser degree those carrying IgG. NAbs will be produced in higher titers, they will bind to the infectious agent and, with the addition of complement, will facilitate its phagocytosis by macrophages and its elimination from the circulation.

Similar processes operate in internal, strong stimulations such as those encountered in inflammation. Cells in apoptosis bearing repetitive epitopes on their surface and debris of cells exposing repetitive antigenic structures will be eliminated following similar procedures.

On persistence of the infectious agent, polyreactive NAb producing cells will differentiate and divide allowing rearrangements and mutations of DNA. Cells secreting more and more specific antibodies will be selected because of the continuous presence of the pathogenic agent and finally a specific immune response will be achieved, although all intermediary stages will be present. Similar processes will occur with other sufficiently high external stimulations, such as those encountered when humans and animals are immunized with xenoantigens incorporated in adjuvants. It is obvious that, under these circumstances, B-cells carrying specific monoreactive NAbs as receptors directed against exogenous antigens, when present, will be activated and expanded clonally to give rise to increased amounts of the corresponding specific antibody.

These cascade events that modify the network and result in a continuous rise and fall of various stimuli are not sufficient to induce a specific immune response to self-antigens. They are not able to overcome a series of mechanisms that prevent the activation of lymphocytes by self-antigens and which include regulatory autoreactive T-cells, dendritic cells, blockage of B-cells by autoantigens as well as IgM and IgG Autoantibodies [21,22,27,29,30,58]. In special situations, however, like those encountered in newborn animals, when these regulatory mechanisms have not yet been fully established, immunization with endogenous antigens can result in a specific immune response to self-antigens [59].

3.2. Pathological states

In pathological situations, in which the immune system is not damaged and the network is functioning normally, weak alterations in the repertoire of NAbs can be noted. Indeed, titers and isotypes of NAbs were found to be altered in various non-immunopathological situations, namely: chronic hepatitis, hemophilia, leprosy, breast cancer, schizophrenia, Alzheimer's, autism, depressive disorder and epilepsy [32,60].

In autoimmune prone individuals, however, these cascade events can lead to the development of an immunopathological state, particularly after infections by pathogenic agents that have been found to induce high but distinct stimulations of cells producing NAbs [31,32]. Such stimulations usually profoundly alter the network, disturb B/T cell collaboration and facilitate the induction of an immunopathological state. In fact, it has been shown that infections by bacteria and viruses can lead to the establishment of autoimmune states in which NAbs participate [61–63].

Significant alterations in the repertoire and isotypes of NAbs have been reported to occur in various systemic and organ-specific autoimmune states in humans and experimental animal models, such as autoimmune hemolytic anemia, diabetes mellitus, autoimmune endocrinopathies, autoimmune hepatitis and primary biliary cirrhosis. In several other diseases, the NAb repertoire is not only altered but Nabs as well as the cells that produce them actively participate in the establishment of the pathological state, like in systemic lupus erythematosus, in rheumatoid arthritis, in chronic lymphocytic leukemia, in experimental autoimmune myasthenia gravis and in reperfusion injury.

In contrast to these results, however, which indicate participation of NAbs in the establishment of immunopathological states, others show that NAbs can interfere with and/or suppress the development of autoimmune diseases. The intravenous IgG (IVIG), which is used for the treatment of various autoimmune diseases, contain high amounts of IgG NAbs and their therapeutic effects mainly reflect the biological activities of these antibodies [15]. Polyreactive NAbs isolated from IVIG prevent the development of experimental autoimmune arthritis and encephalomyelitis in rats and reduce the occurrence of spontaneous diabetes mellitus in non-obese diabetic mice [51]. Similarly, polyreactive NAbs purified from the sera of parasite-infected mice, interfere with the development of the lupus syndrome in B/W mice [32]. Finally, not only polyclonal but also monoclonal NAbs can interfere with the development of autoimmune diseases [32–34,53]. Most recent results suggest that the depletion of peripheral B-cells through the use of monoclonal chimeric antibodies that target the

CD20 molecule has a beneficial effect in the activity and the progression of certain B-cell or autoantibody mediated diseases (i.e. systemic lupus erythematosus, rheumatoid arthritis, autoimmune thrombocytopenic purpura, etc.). Whether this therapeutic intervention affects and in which degree the NAbs network in such diseases remains to be studied [64,65].

These results strongly suggest that NAbs are involved in the progression of many immunopathological states in one way or another, and that their administration affects the development of these pathological processes. In this regard, it is plausible that susceptibility to autoimmune diseases may be related to an imperfect NAb network which is the consequence of a deficient library of NAb producing cells.

4. Conclusion

Certainly the classical notions on the functioning of the immune system represent a brilliant intellectual construction. They form the basis of the actual tremendous development of Immunology and present the immune system as unique, and hence very attractive to investigate. However, they do not take into consideration one of the basic rules, if not the fundamental rule, that governs functioning of the organism, i.e. self- recognition. Indeed, ligands that are synthesized by the organism react with receptors also synthesized by the organism. Positive and negative signals are emitted and maintain the homeostasis of the organism. The notion of physiological autoimmunity that emerges from the studies on NAbs follows this general rule while the classical notions stay away from it.

The existence of physiological autoimmunity allows the establishment of a dynamic homeostasis in which internal and external constituents are participating. Starting from this homeostasis and depending on the circumstances, the immune system can express different and often apparently contradictory aspects, such as producing polyreactive autoantibodies or antibodies strictly specific to antigens, eliminating from the organism damaged cells or causing inflammation, and inducing an immunopathological or, on the contrary, an immunoprophylactic state.

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