

The significance of natural autoantibodies

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ABSTRACT

Autoimmune disease is a disorder that occurs because of autoimmunity. Natural autoantibodies (NAb) are an important component of the normal immune system, and B cells with these self specificities appear to be positively selected during development. There is autoimmunity without autoimmune disease. It is known that autoantibodies are formed in physiologic conditions, as well, and are directed against both self and non-self antigens without being necessarily harmful to the body. Natural autoantibodies are part of the immune texture and fulfill numerous roles. Natural autoantibodies perhaps also function to help in the clearance of senescent cells. Normal serum contains NAb of the IgG, IgM, and IgA isotypes. They may serve as future markers of autoimmune disorders.

Key words: natural autoantibodies, innate immune system, autoimmunity

Natural antibodies can be considered humoral factors of innate immunity, and their functional role in health and disease has been reexamined in recent years. The importance of natural antibodies reactive with self antigens (natural autoantibodies, NAb) has long been neglected, as tolerance to self was considered to be dependent on the deletion of autoreactive clones, rather than on peripheral control mechanisms. Thus, it is now well established that autoreactive antibodies B cells, and autoreactive T cells exist in healthy individuals (1).

- Reaction with antigens highly conserved throughout evolution (e.g. actin, histones)
- May be any of the 3 major isotypes (IgG, IgM, and IgA)
- Polyreactive, but with distinct fine specificities
- Constitute up to 20% of all immunoglobulins
- Have a physiologic role (e.g., participation in the general immunological homeostasis)
- React both with self and non-self antigens
- Are idiotypically interconnected

TABLE I. Characteristics of natural autoantibodies

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Natural autoantibodies exist independent of exposure to foreign antigens. It is not surprising that progress in this field is a direct reflection of the existing technology at the time of recognition of the autoimmune response.

The factors and the complex mechanisms that are involved in the development of pathological autoimmunity are incompletely understood. A relatively large fraction of serum immunoglobulins in healthy individuals binds to self-antigens, and a major subset of these autoantibodies has been labeled NAb. Most of these autoantibodies are IgM, bind to self-antigens with relatively low affinity, frequently cross-react with multiple different antigens (2).

The generation of NAb is not dependent on exogenous antigen stimuli but seems to be a profound element of the immune system. Natural antibodies exhibit a remarkably conserved repertoire that includes a broad specificity for self-antigens.

Although NAb that is detected in healthy individuals are similar to the autoimmune disease-associated autoantibodies in terms of V-gene usage, they tend to differ in their quantity and fine epitope specificity. Natural autoantibodies may evolve into genuine pathogenic autoantibodies (3).

Immunity is not only responsible for recognition and elimination of infectious particles, but also for removal of cellular waste, modified self structures and transformed cells. Natural antibodies can be considered humoral factors of innate immunity, and their functional role in health and disease has been reexamined in recent years. They are highly important during early life composing an elementary component of innate immune reactions (4).

Natural antibodies exhibit a remarkably conserved repertoire. For this reason, they are believed to be a product of natural selection and have been suggested to play an important role in "housekeeping" functions. Recent evidence has revealed an important function for these antibodies in the host response to consequences of oxidative stress.

Natural antibodies are found in healthy humans, apparently in the absence of immunization. Natural autoantibodies analysis could also enhance our understanding of the immune system (5).

The revolutionary techniques of modern molecular and cellular biology enhance almost

daily our knowledge about immunity and autoimmunity in men and experimental animals. Studies in both humans and mice suggest that a large portion of these autoantibodies are secreted by CD5⁺ B cells. The antibodies reactive with self or foreign molecules detectable in the absence of known immunization with the target antigen are termed natural antibodies. The repertoire of NAb might be used to study both B- and T-cell auto-reactivity, NAb might have a physiological role in body homeostasis. Indeed, natural autoimmunity performs several functions that include the scavenging of metabolic waste and senescent cells, a first line of protection against viral and bacterial infection, the control of autoimmune diseases (6).

Natural autoantibodies can recognize self-antigens that are also targeted during the progression of autoimmune disorders; these antigens include insulin, DNA, myelin basic protein and thyroglobulin among others.

Natural autoantibodies and disease-associated autoantibodies differ in their quantity and fine epitope specificity (7).

The detection of NAb in healthy individuals is in line with the idea of the immunological homunculus. Therefore, autoimmune disorders might simply arise as a consequence of the dysregulation of natural physiological autoimmunity. The mechanisms involved in the shift from physiological to pathological autoimmunity are unknown. IgM autoantibodies might also participate in immune regulation. However, in the last four decades there has been an avalanche of reports affirming the existence of NAb directed against diverse autoantigens. Furthermore, NAb have been shown to have physiologic roles.

The main characteristics of NAb include: a) reaction with both self and non-self antigens; b) are frequently of the IgM isotype, although other isotypes have been reported as well; and c) polyreactive, thus having the capability to react with different molecules.

Several functions have been attributed to NAb under physiological conditions: first line defense against infection, clearance of aging cells, anti-tumoral surveillance, anti-inflammatory activity, selection of immune repertoires and homeostasis of autoreactivity (8).

It has been proposed that NAb function primarily to control autoreactivity and immune homeostasis, in healthy individuals (9).

Natural antibodies are those present without deliberate antigenic challenge. Isohemagglutinins are IgM NAb to polysaccharide blood group antigens A and/or B. Individuals with blood type AB do not form isohemagglutinins, and children under 1 year of age generally do not either. In contrast to sensitization against the ABO blood groups, natural antibodies do not play a role in sensitization against the HLA alloantigens (10).

Other natural antibodies include heterophile antibodies (antibodies to sheep erythrocytes) and antibodies to streptolysin O, Escherichia coli and endotoxin. Nearly all normal individuals have antibodies at titers of at least 1:10 to some or all of these antigens because of their widespread distribution in food, inhaled particles and the respiratory flora.

Natural autoantibodies react with autoantigens that are also targeted in autoimmune disorders: as insulin, DNA, myelin basic protein and others (7,11).

Natural autoantibodies IgM have been shown to bind to multiple self-antigens during inflammation and tissue injury.

A striking phenomenon of immunity against malignant cells is that neither in animals nor in humans affinity-maturated tumor-specific IgG antibodies have been detected so far. All tumor-specific isolated antibodies were germ-line coded IgM NAb. From an evolutionary point of view, this makes sense because cancer cells are not infectious, so there is no need for memory (12).

The binding of NAb to antigens may contribute to their internalization by antigen-presenting cells. Of essential relevance for autoimmunity, is the role of NAb in participating in the selection of autoreactive B cells and in preventing the uncontrolled expansion of specific autoreactive clones, as well as the ability of NAb through V region-dependent complementary interactions to control autoreactivity under physiological conditions (13).

A role for NAb in immune surveillance against cancer, has been hypothesized. Thus, the binding of NAb to cell surface antigens on malignant cells enhances or retards tumor development (14).

Emerging evidence indicates that B cells also provide atheroprotective qualities. Atherosclerosis is now widely recognized as a chronic inflammatory disease that involves innate and

- Antikeratin antibodies enhance the elimination of keratin after keratinocyte death
- IgG NAb anti-band 3 protein participate in the elimination of senescent red blood cells
- IgM NAb increase resistance to tumors
- NAb may be cytotoxic
- NAb may inhibit interferon action by binding to the cell surface
- NAb may inhibit NK cell activity
- IgM NAb anti-IgG [F(ab)2] inhibits the binding of IgG to self-antigens
- NAb anti-idiotypic antibodies to pathogenic autoantibodies may have therapeutic potential
- Some NAb possess proteolytic activity on the vasoactive intestinal peptide
- IgM (but not IgG) NAb enhance phagocytosis of parasites
- Natural anti-trinitrophenyl autoantibodies protect against viral infection
- The levels of NAb increase during pathological states (e.g., autoimmune diseases)
- Titers of NAb increase following infections

TABLE II. Representative functions of natural autoantibodies

- The existence of various autoantibodies in healthy populations (e.g. first-degree relatives)
- Autoantibody activity of monoclonal gammopathies
- Hybridomas derived from normal subjects secrete autoantibodies.

TABLE III. Evidence for the existence of natural autoantibodies

- Anti-DNA
- Antihistones
- Lymphocytotoxic antibodies
- Anti-DNA idiotypes 16/6.3
- Antithyroid
- Anticentromere
- Antimitochondrial

TABLE IV. Natural autoantibodies found in healthy first-degree relatives of patients with autoimmune diseases

- Cord blood cells immortalized by Epstein-Barr virus
- Sera from healthy children
- Sera from healthy adults
- Aged population
- Patients with malignancies (solid tumor)

TABLE V. Natural autoantibodies in various conditions

adaptive immune responses. Both cellular and humoral components of the immune system have been implicated in atherogenesis. Recent evidence has revealed an important role of

natural antibodies in atherogenesis. The oxidation-specific epitopes are important and maybe immunodominant targets of natural antibodies, suggesting an important function for these antibodies in the host response to consequences of oxidative stress, for example, to the oxidative events that occur when cells undergo apoptosis. (15-17).

Future techniques as the use of protein microarrays and others may help us to better understand and utilize NAb for clinical practice. Many open questions remain to be solved by studies on men as well as animal models. □

CONCLUSION

Natural autoantibodies are found in the sera of healthy individuals, and they are polyreactive. Natural autoantibodies are a part of the immune system originating from B-1 and B-2 cells. Natural autoantibodies specific for the T-cell receptor are detected at low levels in the sera of healthy individuals.

The repertoire and reactivity pattern of NAb is remarkably conserved within each species and even between species.

Natural autoantibodies fulfill important and diverse immunological roles, providing very early innate immune protection, ensuring removal of possible autoantigens by scavenging dead or apoptotic cellular debris.

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