

REVIEW

The role of autoantibodies in health and disease

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Abstract

Serum of healthy individuals contains antibodies that react with self and non-self antigens, generated in absence of external antigen stimulation. These antibodies, called natural antibodies, are particularly IgM isotype, are considered natural autoantibodies (NAA), displaying a moderate affinity for self-antigens. Although incidence of NAA in healthy individuals is not reported, it is established that autoreactive antibodies and B-cells, as well as autoreactive T-cells, are present in healthy persons. The functional abilities of NAA are not clear but is well accepted that they may participate in a variety of activities, such as maintenance of immune homeostasis, regulation of the immune response, resistance to infections, transport and functional modulation of biologically active molecules. On the other hand, specific adaptive immune responses through high-affinity, class-switched IgG autoantibodies, which bind self-proteins, can cause tissue damage or malfunctions, inducing autoimmune diseases. The new technology that allows for more autoantibody screening may further enhance the clinical utility of autoantibody tests, making it possible to diagnose autoimmune disease in its early stages and to intervene before installing injuries. The aim of this review paper is to succinctly analyze the progress in the physiological role and regulatory significance of natural autoantibodies in health and disease.

Keywords: autoantibodies, physiological functions, autoimmune diseases, malignant diseases.

Introduction

The synthesis of antibodies is a vital way in which adaptive immune system works for the recognition and response to external threats. Some antibodies that are present in sera of healthy individuals, outside immunization with any antigen, and react with a variety of endogenous and exogenous antigens, are considered natural autoantibodies (NAA) [1]. Boyden first mentioned the term "natural autoantibodies", in 1963, after being identified autoreactive responses in sera of healthy persons [2].

The majority of NAA are particularly IgM isotype encoded by unmutated variable, diversity and joining [V(D)J] gene segments and display a moderate affinity for self-antigens. It is considered that NAA are present from birth, represent a substantial proportion of the normal antibodies, and contribute to the stimulation of primitive innate system [3–5]. Many works demonstrated that autoreactive B-cells, a substantial part of the B-cell repertoire, secrete NAA characterized by their broad reactivity directed against very well conserved public epitopes [6].

On the other hand, specific adaptive immune responses through high-affinity, class-switched IgG autoantibodies can cause tissue damage or malfunctions and induce autoimmune diseases, through binding to self-proteins [7–9].

IgM-NAA are produced by B-1 cells and intervene in defense against systemic bacterial and viral infections. B-1 cells are very efficient antigen presentation cells and may have an important role in the synthesis of pathogenic

autoantibodies reported in patients with autoimmune diseases, as rheumatoid arthritis, Sjögren's syndrome, primary antiphospholipid syndrome and systemic lupus [10, 11].

The trigger antigens for autoantibodies may be found in all cell types (e.g., chromatin) or be highly specific for a certain cell type in one organ of the body (e.g., thyroglobulin in cells of the thyroid gland). They can be represented by serum proteins, nucleic acids, carbohydrates, lipids, erythrocytes, cellular components, insulin [9].

The aim of our paper is to review the functional properties of NAA as well as the association of autoantibodies with some diseases pathogenesis, in order to enhance understanding of both natural autoimmunity and autoimmune disease mechanisms.

Natural autoantibodies in health (physiological functions)

The generation of NAA against self-antigens is a common phenomenon in humans; their low-affinity, potentially autoreactive cells persist to self-antigens is required for survival of T- and probably B-lymphocytes in the peripheral immune system. Because natural autoantibodies also recognize a wide variety of self-antigens, they have an important role in the development of the B-cell repertoire [6].

Principal characteristics of NAA are indicated in Table 1 [12].

Table 1 – Characteristics of autoreactive antibodies (Bellone, 2005)

Characteristics	Natural autoantibodies	Pathogenic autoantibodies
Serum titer	Low	High
Isotype	IgM>IgG>IgA	IgG>IgM>IgA
Antigen specificity	Low	High
V region	Germline	Somatic mutation

The functions of NAA are not clear but it is well accepted that they may participate in a different type of activities, such as maintenance of immune homeostasis, regulation of the immune response, resistance to infections, transport and functional modulation of biologically active molecules [13, 14].

The early immune repertoire is oriented to a prominent expression of spontaneously arising B-cell clones that produce autoantibodies of IgM isotype, which specifically recognized injured and senescent cells, often *via* oxidation-associated neo-determinants. Because NAA are poly-reactive, they have important regulatory activities and can occasionally serve as templates for autoimmunity [15, 16].

Chen *et al.* [17] have shown that IgM-NAA can enhance phagocytic clearance in apoptotic cells and block pathogenic IgG-immune complex-mediated inflammatory responses.

NAA may be implicated in the elimination of cell debris during inflammation; autoantibodies to inflammatory cytokines might protect against chronic inflammation [18].

Many authors sustain the role of natural antibodies in the regulation of the immune response and maintenance of immune homeostasis [19–21].

Clinical studies have suggested that anti-apoptotic cell (ac) IgM-NAA may modulate disease activity in some patients with autoimmune disease. There were shown that anti-ac NAA act in dendritic cells by inhibition of the mitogen-activated protein kinase (MAPK) transduction pathway. IgG-NAA, which have been found in several immunopathological states, are based on the same genetic elements as the antibodies oriented to exogenous antigens, and seem to be encoded by unmutated germ-line genes. NAA manifest various biological functions, both related and unrelated to the immune system. Avrameas [21] suggested that these antibodies, by interacting with a large number of self-constituents present in an organism, establish an extensive dynamic network that contributes to the general homeostasis of the organism. The adaptive immune system has elaborated specific pattern recognition proteins, providing a first line of host defense against pathogens. Some data indicate that these innate recognition proteins are also self-reactive and can initiate inflammation against self-tissues in a similar manner as with pathogens [22].

Scientific data from several reports support the idea that NAA contribute to the enhancement of primitive innate functions and are involved in the modulation of neurodegenerative disorders and malignancies, in ischemia reperfusion injury and atherosclerosis [23].

The repertoire of natural IgM antibodies are considered have been selected during immune evolution for their interventions to critical immunoregulatory properties. The clearance of dying cells is one of the most essential

functions of the immune system, important to prevent uncontrolled inflammation and autoimmunity [24].

Natural antibodies react with xenoantigens expressed by tissues between unrelated species and are capable to produce the immediate rejection of xenografts [25].

Experimental data from the literature indicates that natural antibodies with isotypes IgG and IgM classes against different self-antigens permanently present in the serum of healthy individuals have same specificity in the vast majority of healthy persons. Beneficial autoimmunity by IgM autoantibodies to proinflammatory mediators can diminish the effects of self-destructive immunity [25, 26].

There have been observed important deviations in the production and serum content of particular autoantibodies related to primary molecular changes, in different tissues and organs, accompanying many diseases. It seems that production and secretion of natural NAA are regulated directly by the quantity of respective antigens (by feedback principle) [26].

Many researchers have identified natural antibodies in the serum in the apparent absence of an antigenic stimulation; they were founded to neonates and germ-free animals [27]. The most important characteristic of NAA is their permanent presence in different compartments of the body (*e.g.*, blood stream, interstitial fluid, lymphatics). The content of IgG autoantibodies with defined specificities is nearly the same in capillary, venous or arterial blood. The broad antibacterial activity of the natural antibody repertoire is due to polyreactive antibodies. Delayed alteration from the optimal state induces reparative processes, which in turn recover molecular and functional homeostasis [28].

In situations where the pressure of modified antigenic is increased or the homeostatic status is altered, the body will acquire various diseases [27]. Due to their extensive reactivity for a wide variety of microbial compounds, NAA have a major role in the primary line of defense against infections [27]. It is generally accepted that the most important features of the immune system are to discriminate between self and non-self antigens and to elevate responses against non-self antigens. A general rationale of biologically active systems is that quantitative changes in different physiological parameters are directed to correct or compensate abnormal situation in the body.

The inflammation, a central mechanism of repair of injury and restoration of impaired is led and directed by autoantibodies. It is very important, from the medical point of view, to differentiate primary and secondary autoimmune processes. Primary autoimmune reactions, observed less often, are usually pathogenic in essence and may become a cause of autoimmune diseases but much more often, secondary transitory and physiological activation of natural autoimmunity, following primary and pathological molecular changes in organs, is directing to clearance of implicated cells [26, 28].

Because was observed that NAA have a weak reactivity toward a variety of self-antigens (DNA, nucleoproteins and phospholipids implicated in autoimmune disorders pathogenesis, is not clear whether these autoantibodies contribute to or protect from autoimmune diseases.

☐ Natural autoantibodies as protective immunoglobulins

The concept that autoimmunity is the cause of continued deterioration of the body has been challenged by a mass of events in which was demonstrated that autoimmunity provides protection in many cases [20].

The potential role of natural IgM autoantibodies as protectors to autoimmune and inflammatory diseases was shown in many works [29, 30]. Devitt & Marshall [29] considers that clearance of dying cells is one of the most important responsibilities of the immune system, which is required to prevent uncontrolled inflammation and autoimmunity. The authors shown that IgM-NAA recognizes apoptotic cells, enhance phagocytic clearance of dying cells and suppress innate response immune.

Natural autoantibodies, non-specific and with low-affinity binding to self-antigens may prevent autoreactive clones from reacting strong with self-antigens by masking their antigenic determinants. Humoral autoimmune protection is accomplished by protective autoantibodies, which play a role in preventing many autoimmune diseases, such as systemic lupus erythematosus (SLE). IgM anti-double-stranded (ds) DNA antibodies have a negative correlation with the severity of glomerulonephritis in SLE. The administration of IgM anti-ds DNA antibodies to mice with SLE prevented the development of lupus nephritis. Similarly, the presence of rheumatoid factor (RF) in SLE was suggested to be protective against the development of lupus nephritis. The autoimmunity against proinflammatory cytokines has also been communicated to play a role in the immunomodulation of autoimmune diseases (rheumatoid arthritis) [30, 31].

Pattern recognition receptors are activated by nuclear antigen associated IgG autoantibodies inducing cell death and tissue damage while IgM isotype autoantibodies to oxidation-associated neo-antigens can prevent these pathways. These IgM isotype autoantibodies are also reported to suppress crucial signaling pathways in the innate immune system, responsible for the control of inflammatory responses to Toll-like receptor agonists and disease-associated IgG autoantibodies. Natural autoantibodies, mainly of the IgM class and polyreactive, ensure early protection against germs, and play important roles in modulation of immune responses (innate and adaptive), conferring protection from many autoimmune and inflammatory injuries. Autoantibodies to oxidized low-density lipoprotein (OxLDL) are found within atherosclerotic lesions and in apparently healthy subjects, as well as patients with various manifestations of cardiovascular disease [30, 31]. Antiphospholipid antibodies (anti- β_2 -glycoprotein-I, anticardiolipin, and anti-OxLDL) are correlated with atherosclerosis and its effects in the general population [32, 33].

The protective role of autoimmunity is not limited to the cellular processes of the immune system, because the humoral process has also been identified to be implicated. For example, IgM autoantibodies were present at significantly higher levels in SLE patients with lower disease activity and with less severe organ damage with specificity for apoptotic cells. In lupus patients, higher levels of IgM antiphospholipid antibodies that bind to

β_2 -glycoprotein I (β_2 -GPI) and cardiolipin were correlated with less frequent renal disease manifestation [4].

The physiological class IgM of natural autoantibodies seems to modulate the severity or even prevent the onset of autoimmune disease [31, 34].

Knowledge on protective autoantibodies allows their use for therapeutic purposes. The protective autoantibodies may be utilized for the treatment of autoimmune diseases: *e.g.*, IgM anti-ds DNA might serve as useful treatments for SLE patients and anti-OxLDL antibodies for patients with atherosclerosis [33, 34].

☐ Autoantibodies as pathogenic antibodies

Boundaries between natural autoreactivity and pathological autoimmunity remains unclear. Autoimmune diseases are characterized by a sustained and persistent immune response against self-constituents and by a breakdown in tolerance. The common features of all autoimmune diseases are synthesis of autoantibodies, intervention of autoreactive T-lymphocytes and involvement of inflammation. The clearance of dying cells leads to post-apoptotic necrosis and release of several adjuvants that promote inflammation. The mechanisms of tissue damage in autoimmune diseases are essentially the same as those that operate in protective immunity and in hypersensitivity diseases. Autoantibodies against extracellular antigens cause inflammatory injury by mechanisms similar to type II and type III hypersensitivity reactions [5–8].

The antigenic molecular deviations from certain specialized populations of cells constitute the reason for quantitative changes in the serum content of autoantibodies with according specificity. Whether NAA, mainly IgM, provide a first line of defense against infections and contribute to the homeostasis of the immune system, autoantibodies of IgG isotype, with high avidity for the antigen, are responsible for pathological processes in connection with cell clearance, antigen-receptor signaling or cell effector functions [4, 14, 19].

Autoimmune diseases can be classified as organ-specific or not organ-specific, depending on whether the autoimmune response is directed against a particular tissue.

Autoantibodies, implicated in the pathogenesis of autoimmune mechanisms, are found at relatively high concentration in sera of patients and are the product of a T-helper cell-dependent activation of B-cells, which mature in conditions of prolonged contact with the antigen [22].

Several classes of autoantibodies with specificity for different types of autoimmune diseases have been described. For example, in SLE have been identified anti-ds DNA, anti-Sm and anti-ribosomal P autoantibodies; in scleroderma disease have been found anti-topoisomerase I (Scl-70) antibodies; in polymyositis and dermatomyositis have been identified anti-Jo-1 and Scl-70 antibodies [35].

In addition, autoantibodies with organ specificity have been found in organ-specific autoimmune diseases (*e.g.* in thyroiditis have been found thyroglobulin and thyroid peroxidase enzyme; in type 1 diabetes mellitus have been found insulin and glutamic acid decarboxylase autoantibodies; in primary biliary cirrhosis have been detected anti-mitochondrial autoantibodies) [15, 35].

The autoantibodies may announce status of disease or predict further clinical evolution of the disease [36].

The mechanisms for installation of autoimmune disease still remain disputable. An autoimmune response may be mediated humoral, cellular, or by both ways. Thus, CD4+ T-cells intervention is required for the synthesis of autoantibodies [12].

The principal autoimmune diseases mediated by antibodies are presented in Table 2.

Table 2 – The principal autoimmune diseases mediated by antibodies

Organ-specific autoimmune diseases	Systemic (not organ-specific) autoimmune diseases
<ul style="list-style-type: none"> ▪ autoimmune hemolytic anemia; ▪ autoimmune thrombocytopenia; ▪ autoimmune atrophic gastritis of pernicious anemia; ▪ myasthenia gravis; ▪ Goodpasture's syndrome. 	<ul style="list-style-type: none"> ▪ systemic lupus erythematosus.

In other autoimmune diseases are involved both T-lymphocytes and antibodies: organ-specific disease (type I diabetes mellitus, multiple sclerosis, Hashimoto's thyroiditis, Crohn's disease) and systemic diseases (rheumatoid arthritis, systemic sclerosis, Sjögren's syndrome) [37].

In organ-specific autoimmune diseases (such as myasthenia gravis or pemphigus), autoantibodies directly bind to and injure target organs. In some diseases, the autoimmune aggression results in the complete and irreversible loss of function of the targeted tissue (*e.g.*, Hashimoto's thyroiditis or insulin-dependent diabetes). The autoimmune reactions may cause persistent lesions inducing an overstimulation or inhibition of its function (*e.g.*, Graves-Basedow disease or myasthenia gravis). In other autoimmune conditions, the pathogenic events are multiple and produce destruction of several tissues (*e.g.*, SLE) [3, 15, 38].

IgG-NAA can be implicated in autoimmune diseases pathogenesis by several possibilities:

- autoantibodies can cause lesions by binding to self-tissues, activating the complement cascade and inducing hemolysis and/or removal of cells by phagocytic immune cells (in certain forms of hemolytic anemia autoantibodies bind to red blood cell surface antigens inducing hemolysis) [4, 14];
- autoantibodies can also interact with cell-surface receptors, producing modification of their functions (autoantibodies to the acetylcholine receptor block transmission at the neuromuscular junction resulting in myasthenia gravis; autoantibodies to the thyrotropin receptor block thyroid cell stimulation resulting in Graves' disease) [4, 14, 19];
- self-antigens, autoantibodies and complement can react to form immune complexes that deposit in tissues such as kidney, skin, vessels and joints (in lupus, rheumatoid arthritis, inflammatory heart disease, vasculitis and glomerulonephritis), causing local inflammation and tissue injury, engagement of FcγR activation of complement, internalization and activation of Toll-like receptors (*e.g.*, nucleic acid-recognizing autoantibodies form immune complexes with ribonucleoproteins, or deoxyribonucleoproteins in sera of patients with SLE and Sjögren's syndrome) [38, 39].

It is considered that autoantibodies alone are not able to produce autoimmune disease, without the intervention of triggering factors. Among the factors, considered triggers for autoimmune disease are infections, trauma and, in 50% of cases, psychological factors. It is also demonstrated that under the action of stress, a disorder in release of neuroendocrine hormones occurs, which in turn cause disturbances in cytokine synthesis [40–42].

The repertoires of natural self-reactive IgG antibodies in the sera of healthy individuals are stable throughout life but in autoimmune diseases are associated with severe generalized autoreactive perturbations. The intensity of IgG reactivity of toward self-epitopes is significantly higher in patients *versus* healthy individuals [3, 12, 22].

Many autoantibodies are useful biomarkers of disease. Because the immune system acts in normal state and in disease, autoantibodies may be used like effectors for medical practice as diagnostic and prognostic instruments. These antibodies can provide information about basic mechanisms of loss of tolerance and inflammation in patients with autoimmune diseases and are considered factors in classification of these disorders. In some autoimmune diseases, autoantibodies might be present before the appearance of clinical manifestations, manifest a great specificity and used as biomarkers offering a precision in diagnosis and appropriate therapeutic intervention [36, 40, 43].

☞ Autoantibodies in malignant diseases

The immune system has been shown to be involved in malignant disease and through the intervention of autoantibodies against tumor-associated antigens (TAAs).

Over the last several years, a broad number of human TAAs have been identified. TAAs can be largely classified into following categories: oncoviral antigens [tumorigenic transforming viruses: EBV (Epstein–Barr virus), HPV (human papillomavirus) E6/7]; mutated antigens [abnormal proteins that are expressed by cancer cells as a result of genetic alterations: p53, TGF-βRII (transforming growth factor-β receptor II)], overexpressed antigens (proteins that are overexpressed in cancer cells compared to normal cells: HER-2/neu, cyclin B1, etc.), post-translational alteration (alterations in protein glycosylation, ubiquitination, lipidation, methylation: MUC1, T-cell receptor, etc.), and cancer/testis antigens [tumor antigens that are also expressed by normal cells in testis and placenta: CAGE (cancer-associated antigen gene) family, SAGE (sarcoma antigen) family, etc.] [44–46].

The efforts to identify new TAA molecules and in-depth analysis of their role in tumor development and progression are important to find therapeutic strategies involving these tumor antigens. Several studies have shown that appreciable autoantibodies against certain TAAs are produced in cancer patients. These autoantibodies have been detected in the biological fluids of patients with various types of cancers and have been suggested to be useful as tumor markers and also suitable targets for therapy.

The activation of immune response to neoplastic diseases has been described as a pathophysiological phenomenon, called cancer immune surveillance, consisting in the antigen-specific recognition and destruction of own

cells that have become malignant [47]. This phenomenon was then described as a component of a more complex process of cancer-related immune response, called immune editing [48]. Recent development and use of research methods for exploring the immune system (*e.g.*, transgenic mouse models, monoclonal antibody technology, immunosuppressive capacity of neoplastic cells in the tumor microenvironment, etc.) enabled to study and to better understand the cancer immune surveillance and immune editing hypothesis.

An important finding that helped further clarification of these concepts was the demonstration that the immune system, apart from its ability to protect the organism against tumor development can also comprise the capacity to promote malignant growth, by selecting for tumor cells of lower immunogenicity [49, 50].

According to these theories, the immune editing process occurs in three phases: elimination, equilibrium, and escape. The autologous proteins of tumor cells, usually referred to as “tumor-associated antigens”, are considered to be altered in a manner that provide these proteins immunogenic, triggering the immune response in the elimination phase. The elimination phase also covers the induction of inflammatory signals that are responsible for enrolling the innate immune system by natural killer T-cells, the macrophages and the dendritic cells. During elimination phase, it is produced interferon- γ (IFN- γ) and chemokines (*e.g.*, CXCL10, CXCL9 and CXCL11) that induce tumor cell death. Surviving malignant cells from the elimination phase enter the equilibrium phase where cells undergo a selection and editing processes. However, malignant cells use complex mechanisms to escape from immune-mediated elimination. The final phase of the process refers to tumor cells that avoid from immune attack, begin to grow progressively to metastasis [51].

The capacity of cancer cells to evade immune destruction is thought to be caused by defects in antigen presentation or by expression of immunosuppressive factors by malignant cells.

Tumor microenvironment, or niche of a cancer cell, is the place around the mass of tumor cells, consisting of different cell types (immune cells, carcinoma associated fibroblasts, endothelial cells, etc.) and extracellular matrix. Tumor microenvironment may play a dual role, being involved in both tumor and host reaction to the activation of the immune system. Several types of carcinoma associated fibroblasts, such as mesenchymal stem cells (MSCs), produce immunoregulatory cytokines as TGF- β that block cytotoxic T-cells and natural killer T-cells, thus limiting the capacity of the immune system to eliminate cancer cells [52–57]. The role of MSCs in regulation of growth and immune response of the solid and liquid neoplasms, suggests their great potential in cancer therapy.

☐ Conclusions

Self-reactive immunity is essentially for defense of the body in normal state and disease. Natural autoantibodies, with IgM isotype, polyreactive, moderate intrinsic affinity but high avidity for self-antigens, and their associated B-cells, contribute to the enhancement of innate functions, prevent pathogenic processes and maintain or restore health status. Pathogenic autoantibodies, represented by IgG auto-

antibodies with high-affinity and high specificity, bind self-proteins and frequently cause autoimmune diseases. Studying autoantibodies is important in contemporaneous medicine, proving their efficiency in diagnosis and appropriate therapeutic intervention in autoimmune and malignant diseases.

Conflict of interests

The authors declare that they have no conflict of interests.

Acknowledgments

This paper was published under the frame of European Social Fund, Human Resources Development Operational Programme 2007–2013, Project No. POSDRU/159/1.5/S/136893.

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Received: October 3, 2015

Accepted: August 30, 2016