We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

5,500
Open access books available

136,000
International authors and editors

170M
Downloads

154
Countries delivered to

Our authors are among the

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS
BOOK CITATION INDEX
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Structure, Physiology, and Functions of Autoantibodies

Neval Yurttutan Uyar

Additional information is available at the end of the chapter

Abstract

Prevalence of autoimmune diseases is increasing. Antibodies are responsible for the humoral type of adaptive immune responses, glycoprotein structure and produced by B lymphocytes. Failure of Immunologic self-tolerance due to environmental and genetic factors may predipose the development of autoimmunity. Self-antigens are either tolerogenic or ignored. Central tolerance occurs at immature T and B lymphocytes in the thymus and bone marrow. Peripheral tolerance occurs at mature lymphocytes encounter self-antigens in peripheral tissues. Negative selection, regulatory T cells, anergy, activation-induced cell death, immune suppression, receptor editing are examples of important steps of immune tolerance. B lymphocytes that produce antibodies which bind self-antigen with medium/low affinity escape from anergy and those antibodies are called as natural autoantibodies but the other ones with high affinity are undergo anergy, The natural antibodies have play critical roles as; discrimination foreign from self, auto-multireactivity, regulate the immunomodulation, maintain tissue homeostasis. Natural autoantibodies work as the templates for the production of pathogenic autoantibodies which has high affinity, switch the class and diverse somatically under proper conditions. Pathogenic autoantibodies can protect or cause diseases via neutralization of self-antigens, opsonization, antibody-dependent cellular cytotoxicity, activation of the complement system, pro-inflammatory and anti-inflammatory effect.

Keywords: physiology, function, structure, autoantibody

1. Introduction

Autoimmune diseases have been increased for the past decades worldwide [1, 2].The prevalence of autoantibodies induced autoimmune diseases is over 2.5% [3].

Failure of immunologic tolerance may cause the development of autoimmune response and then autoimmune disease [4, 5].

The cause of autoimmune diseases is an association of genetic tendency and environmental factors cause alteration the immune regulatory genes by diver's mechanisms as epigenetics. In autoimmune diseases pathogenesis, both cellular (as in multiple sclerosis) and humoral (as in systemic lupus erythematosus (SLE)) type of the adaptive immune system takes a role. An autoimmune response does not inevitably signify the autoimmune disease [5, 6].

In most of autoimmune diseases, the autoantibodies could been found but not all. Even in some autoimmune diseases, the autoantibodies signify not autoimmune disease risk, but also the level of the autoantibodies signifies the severity. By autoantibodies, we can understand immunologic tolerance failure and pathogenesis mechanisms [7–15].

Autoantibodies are self-reactive antibodies. The self-antigens may be found in all cell types (e.g. chromatin, centromeres) and those autoimmune diseases is systemic or be highly specific for a specific cell type in one organ of the body (e.g. thyroglobulin in cells of the thyroid gland) and those autoimmune diseases is organ-specific. The self-antigens can be in proteins, nucleic acids, carbohydrates, lipids structure [16]. Immune tolerance is succeed by various mechanisms, occurred at both central and peripheral organs.

2. Autoantibody structure

An antibody molecule and also autoantibody are include of four polypeptide chains; composed of a pair of identical *heavy* (H) and *light* (L) chains. Molecular weight of light chain is 25 kDa and heavy chain is 50–70 kDa. The four chains joint together as a Y shaped. Each light chain is bound to one heavy chain, and the two heavy chains are bound to each other by disulfide bonds between two cysteine amino acid.

The antigen-binding site of chains that diverse at different antibody is called as the *variable* (V) regions and composed of amino acid N-terminal domains of the heavy and light chains. The part next to the V region is called the *constant* (C) region. A light chain is made up of one V and one C region, and a heavy chain has one V and three (at IgG, IgA) or four (at IgM, IgE) C regions. Each of them is 110 amino acids in length and fields into a characteristic three-dimensional shape called immunoglobulin (Ig). There are three hypervariable regions or CDRs at each variable region of the heavy chain (VH) and of the light chain (VL) which is just 6–10 amino acids in length. CDR3 is the greatest variability of three hypervariable region, at the junction of the V and C regions [4, 5] **Figure 1**.

Fab fragment (fragment antigen binding) is composed of a bonded whole light chain (with one V and one C region) and a heavy chain's V and first C region and recognizes the antigen. The Fc fragment (fragment crystalline) is the remaining region of heavy chain. Each antibody
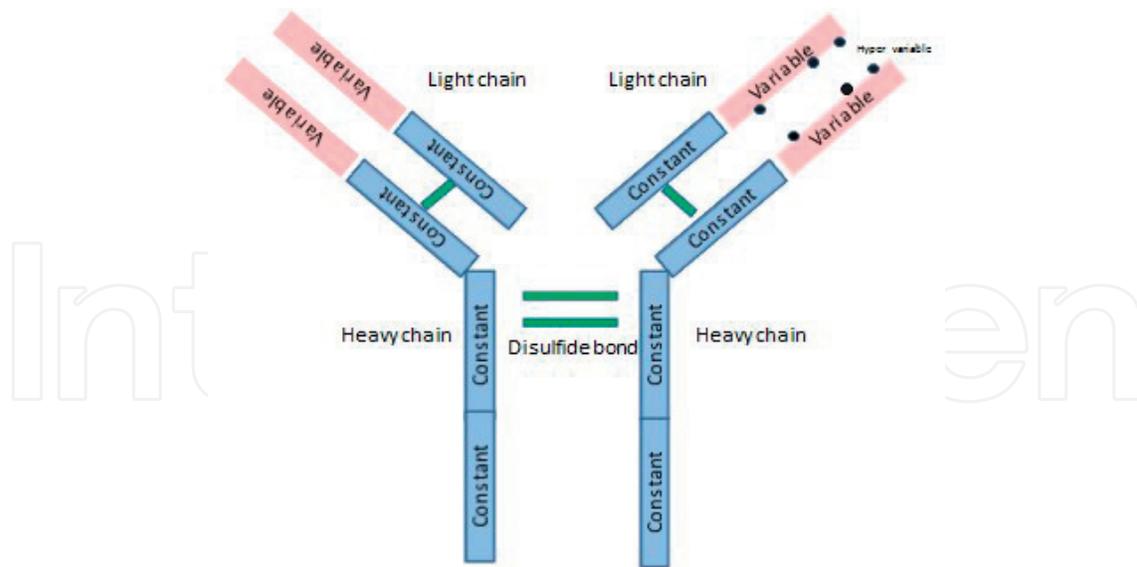
Figure 1. Structure of an antibody molecule (IgG).

contains two identical Fab fragments and one Fc fragment. The hinge region is located in the middle of the Fab and Fc regions and is very bending so helps the two Fab fragment getting closer to antigen far away. The C-Terminal end of the heavy chain of bound antibodies can terminate with or without anchoring in the cell membrane, but the C-Terminal end of the light chain terminates freely without attaching the cell membrane [4, 5].

There are two types of light chains according to C region, called κ and λ. Their functions are same. 60% of antibodies are κ chains and 40% are λ chains There are five types of heavy chains also according to C region, called μ, δ, γ, ε and α. Every combination of heavy chain and light chain is available. Antibodies are classified and entitled according to their heavy chains types (IgM, IgD, IgG, IgE and IgA) [4, 5].

There is five antibody isotypes with different functions and physical and biological properties, summarized in **Table 1**.

1. IgM: Heavy chain type is μ. It has pentamere structure with five Fc fragments where complement binds. The antigen+ pentamere antibody+ complement bound to five Fc complex starts strong complement activation and is removed by phagocytic cells or complement mediated lysis. So IgM plays critical role in neutralization but it has relatively low affinity and cannot penetrate into cells/tissues because of the pentamere structure. Half-life of IgG is approximately 10 days [4, 5].

2. IgG: Heavy chain type is γ. It has monomere structure and penetration rate is high e.g. penetare through the placenta There are four classes of IgG: G1, G2, G3 and G4. 65% of total IgG is G1. G1 and G3 activate complement system if the antigen is protein structure and the protein antigens are removed by phagocytic cells. G2 and G4 play role if the antigen is

Property	IgM	IgG	IgA	IgD	IgE
Heavy chain type	μ	γ	α	δ	E
% of total immunglobulin in serum	9	75	15	0.2	0.004
Structure	Monomer or pentamer	Monomer	Monomer or dimer	Monomer	Monomer
Molecular weight (×1000)	900	150	170 or 400	180	190
Complement fixation	++	++	—	—	—
Cross the placenta	—	++	—	—	—
Allergic response	—	—	—	—	++
Antigen receptor at B cell	++	—	—	+	—
Secretoral response	—	—	++	—	—

Table 1. Physical, biological properties and functions of immunoglobulins.

carbohydrate structure. Half-life of IgG is approximately 21 days. Since IgG has high affinity and high molar concentrations in plasma, it makes neutralization [4, 5, 17]. It also makes opsonization because of γ receptors of phagocytes. If N-terminal end is N-acetyl glucosamine, the IgG act as pro-inflammatory and if there is sialic acid then act as anti-inflammatory.

3. IgA: Heavy chain type is α. It has monomere or mostly dimere structure which consists of two basic units joined by a J chain. There are two classes of IgA: A1 and A2. IgA1 is in the serum while IgA2 is in secretions as; colostrum, salivary, eye tear, respiratory, digestion and genital and make neutralization of antigens at the mucosal sites. A2; secretory IgA (sIgA) is protected from lytic enzymes in the digestion tract by secretory component (SC) which is a part of the receptor and remains attached to the IgA-dimer [4, 5, 17].

4. IgD: Heavy chain type is δ. It has monomere structure. There are two classes of IgD: soluble and bound IgD. While function in immunology of soluble IgD is not known yet, IgD that bound on the cell membrane of newly produced B lymphocytes with IgM, activates of newly produced B lymphocytes by antigens [4, 5, 17].

5. IgE: Heavy chain type is ε. It has monomere structure. IgE plays role in parasitic infections and allergic reactions by binding to specific IgE receptors on mast cells and basophiles [4, 5].

3. Physiology of autoantibody

3.1. Physiology of antibody

Antibodies are responsible for the humoral type of adaptive immune responses, glycoprotein structure and produced by B lymphocytes.

Antigens can directly bind to antigen receptors of specific B lymphocytes. The type of reversible bond is non-covalent as; electrostatic attraction, hydrogen bonds, Van der Waals-, charge interactions and hydrophobic forces. Membrane–bound antibodies (IgM and IgD type) work

as antigen receptors of B lymphocytes (BLR) and can bind to antigens in proteins, lipids, carbohydrates and nucleic acids structures. T lymphocytes can react antigens just in protein structure. For an antigen-presenting cells (APC), there is not any necessity to present antigens to B lymphocytes. Epitopes antigens recognized by T cells are narrow linear peptides from 8 to 20 amino acids [4, 16, 17].

After binding of antigens to the receptors that are membrane- bound antibodies; IgM and IgD type, B lymphocyte become activated. The clonal expansion which means proliferation of antigen specific cells follows the activation of B lymphocytes and they differentiate into antibody-secreting effector cells. The specificity of the naïve B cell membrane-bound antibody receptors is same with the secreted free antibodies. During their differentiation period, some B cells may differentiate to produce antibodies with different heavy chain classes (or isotypes) called as heavy chain class (isotype) switching. After switching, different effector functions can be monitored. Repeated exposure to an antigen leads to the production of antibodies with increasing capacity to bind the antigen; called as affinity maturation [4, 18].

Antibodies responses are classified into two based on the requirement for T cell help; as T-independent or T-dependent

3.1.1. Antibody responses to T-independent antigens

If the structure of antigens is non-protein as polysaccharides, lipids, nucleic acids and others antibody responses evoke without the helper T cells participation. These non-protein antigens cannot bind to MHC molecules consequently cannot be detected by T cells.

For immunoglobulin receptor mediated signal transduction in B lymphocytes, the bringing together of two or more antigen molecules in an aggregate (cross-linking), or repeating epitopes of one antigen molecule is needed for antigen binding to membrane bound antibody of the B cell. Multivalent epitope (multiple identical epitopes) as in polysaccharide and lipid antigen can make cross-link many antigen receptors on a specific B cell consequently stimulate proliferation, differentiation and antibody production of B lymphocytes [4, 19].

3.1.2. Antibody responses to T-dependent antigens

Most soluble protein antigens cannot make cross-link because they do not contain multivalent epitope so cannot stimulate their proliferation and differentiation of B lymphocytes. Antigen-presenting cells process and helper T lymphocytes remember the protein [5].

Stimulations of two or more protein antigens lead at least three changes in B lymphocytes to improve the interaction of these B cells with helper T lymphocytes.

The changes are:

1. Increased expression of B7 co-stimulator,

2. Increased expression of cytokine receptor

3. Reduced expression of chemokine receptors.

The T cell activation by B cell requires antigen recognition and co-stimulation:

1. Antigen recognition: B lymphocytes work as antigen-presenting cells (APCs); B lymphocytes may bind, internalize and process the antigen protein, and present multiple different peptides of that protein to T lymphocyte.

2. Co-stimulation: The helper T cells are stimulated by B7 molecules as co-stimulator expressed by B cells.

CD40 ligand (CD40) and cytokines are expressed by CD4+ helper T lymphocytes after activation. CD40 ligand; a surface protein delivers the co-stimulatory signal in B cells and interacts with CD40 on the surface of B lymphocytes. Attachment of CD40 and cytokines stimulate B cell clonal expression and antibody production. Class switching and affinity maturation are also stimulated by helper T lymphocytes [4, 5, 19].

After B lymphocytes proliferation and differentiation into antibody-secreting plasma cells, the antibodies enter the blood through lymphoid follicle. Some plasma cells move to bone marrow, live at the bone marrow for months or years and continue to produce antibodies afterwards antigen is removed. These antibodies supply a rapid response when they meet with same antigen. The humoral immune response decreases physiologically by time because of programmed B cell death. But a small number of activated cells differentiate into memory cells, which "freeze" in a state for a very long time [4, 18, 19]. When the body encounter with the same antigen, the memory cells quickly change into antibody-secreting plasma cells and produce immunoglobulins. The two advantages of memory cells;

1. Shorter reaction day: instead of five or more days, it takes one or two.

2. B memory cells differentiate with class switch and somatic hypermutation so in case of reinfection, only memory cells with higher affinities and class switch are selected which are completely same with the B cell receptors of the original infection. Recurring antigen stimulation causes to helper T lymphocytes increase consecutively antibody increase with heavy chain class switching and affinity increase [17, 19].

3.2. Stimuli for generation of autoantibody

Failure of immunologic tolerance can cause the development of autoimmunity. With a genetic background, intolerance can be triggered by environmental factors as sunlight, drugs, chemicals, and infectious agents [5].

1. *Genetic factors*: Immunologic tolerance failure is multifactorial and genetic factors are just one of the cause. For example, the relative risk of having autoimmune disease is 5–50 times higher in siblings of affected individuals than in unrelated ones. Multiple genes; mostly MHC predispose to autoimmune disease and genetic predisposition is detected in many autoimmune diseases. For example, individual with HLA-DR4 gene can be suffered from rheumatoid arthritis but not everyone [5, 6].

2. *Environmental factors*: İnfections can cause the autoimmune diseases by activating self-reactive lymphocytes. The mechanism is like that an infection lead to a local immune response and activation of APCs. Activated APCs secretes co-stimulators - cytokines and

stimulate self-reactive T cells which react with self-antigens in the tissue [4]. Some peptide antigens of microbes are similar to self-antigens, so leads to cross-reactions; called as molecular mimicry [6]. For example; the antibodies against *Porphyromonas gingivalis*; a periodontal pathogen were increased before RA onset and had a relation with RA [20–23].

Microorganisms related autoimmune diseases are listed in **Table 2**.

Sun lights can trigger lupus diseases. Many drugs as procainamide, hydrocarbon pristine, hydralazine, chlorpromazine, methyldopa, quinidine, minocycline and nitrofurantoin can trigger autoimmunity or autoimmune disease through ANAs and ANCAs. Many chemical agents include heavy metals as mercury, gold, and cadmium, pesticides, herbicides, hydrazine can trigger autoimmunity [5].

In organ-specific autoimmune diseases, such as thyroiditis, type 1 diabetes mellitus and primary biliary cirrhosis, autoantibodies can be stimulated by infection of the target organ, through molecular mimicry [16, 24]. In systemic autoimmune diseases, such as systemic lupus, autoantibodies can be triggered by genetic factors. For example; a nuclear autoantibodies produced by antigenic drive from excessive release of death cells antigens and enhanced by intrinsic abnormalities in B or T cells [16, 24].

3.3. Production of autoantibody

3.3.1. Immunologic tolerance

The immune system can differentiate self from non-self [5]. Immunologic tolerance is lack of response to self-antigens that encounter with lymphocytes [6]. The recognition of self is a special set of immune events that all constituents of the organism take a role and may be interrupted by environmental and genetic factors [25–29]. There are three possible immune responses according to antigen type, after antigen encounter with the lymphocytes which has the receptors for a specific antigen;

1. Active immune response: Due to the active lymphocytes and antigen type is called immunogenic. For example, most of non-self-antigens

2. Tolerance: Due to inactive or killed lymphocytes and antigen type is called tolerogenic. For example, self-antigens

Microorganism	Related autoimmune diseases
Streptococcus pyogenes	Rheumatoid fever
Escherichia coli	Primary biliary cirrhosis
Shigella spp.	Reiter syndrome
Hepatitis B	Multiple sclerosis
Coxsackie B4	Type 1 diabetes mellitus
Cytomegalovirus	Scleroderma

Table 2. Infections related with autoimmune diseases.

3. Ignorance: The antigen cannot either stimulate immunity or induce tolerance. This situation is called as ignorance. For example, self-antigens [4, 5].

Immune tolerance is set of immune events, operating both at central immune organs and peripheral ones.

1. Central tolerance happens at immature T and B lymphocytes encounter self-antigens in the thymus and bone marrow.

2. Peripheral tolerance happens at mature lymphocytes encounter self-antigens in peripheral tissues [4, 5].

3.3.2. T lymphocyte tolerance

3.3.2.1. Central T lymphocyte tolerance

The immature T cells die by apoptosis, whenever encounter with self-high avidity protein antigens in the thymus. The immature lymphocytes in the thymus can recognize both self and non-self-antigens. If a self-antigen high in concentration and avidity meet with immature lymphocyte, lymphocytes receives signals that trigger apoptosis, finally dies. This is known as negative selection. Since the self-protein antigens are expressed mainly in thymus because of transcription factor responsible called AIRE (for autoimmune regulator), they are high in concentration [4, 19].

Some lymphocytes which escape from negative selection, mature to dangerous self-reactive T cells with CD4+ T and CD8+ T. They recognize self-antigens through class I and II MHC molecules [4, 18, 19].

And some other develop into regulatory T cells which regulate mostly suppress both naïve and memory T cell responses by a cell to cell contact and by down-regulating the expression of cytokines and co-stimulatory molecules on the antigen-presenting cells. Unfortunately this is not antigen specific reaction [4, 5, 18, 19].

3.3.2.2. Peripheral T lymphocytes tolerance

1. Anergy: Anergy is the functional inactivation of T lymphocytes occurs whenever level of the co-stimulators (second signals) is not enough for T cell activation. If level is enough, the co-stimulatory signal which is taken by CD80 and CD86; interaction of molecules expressed on the surface of APC or B cells, reacts with CD28 (or other receptors) on the T cell surface. If T cells with receptors for the self-antigens encounter with sufficient level of self-antigens (signal 1) but do not receive sufficient signal 2, they may induce long-lived T cell anergy [4, 5, 18, 19].

2. Deletion: Activation-induced cell death: Repeated activation of mature T lymphocytes by repeated encountering with the same antigen cause apoptosis and this is called deletion or activation-induced cell death [4, 18].

3. Immune suppression: Autoreactive mature T lymphocytes that encounter with self-antigen may develop into regulatory cells which suppress the self-reactive lymphocytes response [4, 18, 19].

3.3.2.3. B cell tolerance

If the self-antigens are in structure of polysaccharides, lipids and nucleic acids antigens, they must induce tolerance in B cell and prevent autoantibody production [4]. The B cell tolerance is a set of actions and finally ends with the depletion of or inactive autoreactive B cells. These processes occur at the every stage of B cell [30, 31].

3.4. Central B cell tolerance

When immature B cells encounter with self-antigens in the bone marrow, the B cells are killed and the process is called as negative selection [4].

When immature B cells recognize self-antigens in the bone marrow, they may activate their genes of antibodies and start to express a new light chain. These light chains bind to the previously produced Ig heavy chain to produce a new antigen receptor. This process is called receptor editing. The mechanisms of B cell tolerance are multifaceted and may involve receptor editing, controlled migration, and limited availability of BAFF, CD22, Siglec-G, miRNA, and follicular regulatory T cells [30–33].

3.4.1. Peripheral B cell tolerance

When mature B lymphocytes encounter with high concentration of self-antigens and B cells producing antibodies that bind with high affinity to self-antigens in peripheral lymphoid tissues, they become anergic; functionally inactivation. T cell-independent antigens can trigger strong signals in the B cell. If it is not strong, the B lymphocytes become anergic [30, 34, 35].

3.5. Role of natural autoantibody

Roles of self-reactive B cells are changing according to binding affinities to self-antigens. If self-reactive B cells produce antibodies with high affinity, they undergo elimination or anergy. But if self-reactive B cells produce antibodies with medium or low affinity, they may escape from anergy, even in non-autoimmune individuals [30, 34, 35].Therefore, a significant proportion of immunoglobulins in healthy individuals are made by these autoantibodies. Most of the medium/low affinity antibodies are multireactive and recognize both self and non-self-antigens [30, 35]. They are called as natural antibodies or natural autoantibodies [16, 17, 36]. Because of their multireactivity, the natural antibodies take an important role in the first part of defense against infections [16, 37] and natural autoantibodies in the development of the B cell repertoire [38].

Most of natural autoantibodies are IgM isotype, polyreactive with moderate and low affinity. Therefore, they bind to several unrelated antigens. Also there are natural mono-reactive antibodies [16, 36, 39, 40]. Natural autoantibodies are expressed mostly by CD5+ B1 cell which is

the most common B lymphocytes in the neonatal period and in marginal zone B cells [41, 42]. These B1 lymphocytes actively present antigens [43] and also play an important role in the pathogenic autoantibodies production of some autoimmune diseases, as rheumatoid arthritis, Sjögren syndrome, primary antiphospholipid syndrome and systemic lupus [44].

In the infantile periods as an evolutionary process, proteins participate mainly in the building and protection of the organism from non-self and self-antigens. During evolution period, these proteins are highly preserved as the autopolyreactive IgM natural autoantibodies (Nabs) produced mainly by B-1 CD5þ cells [25, 41] and also after class switch, polymeric and mono-meric IgG isotype antibodies are produced by mostly B2 cells [25, 45].

Natural antibodies take critical roles; such as:

1. Differentiation self from foreign

2. Recognition of self

3. At evolution period, autopolyreactivity

4. First line defense against non-self-antigens; bacterial and viral infections [46].

5. Regulate the immune system protect the system against tolerance breakdown and the autoimmune diseases.

6. Maintain tissue balance [47]: Up or down regulation of immunotolerance leads to suscep-tibility/ progressive or protective role in disease as chronic inflammatory disease [48], cancer [49], cardiovascular disease [50], and certain neurodegenerative conditions [33, 34].

7. Clearance of tissue and cell debris after degradation [51]; Most diseases is resulting the destruction of tissues/cells which leads to the continuous antigens release. Natural auto-antibody recognizes antigens in cell debris and can react with specific antigens of target tissues. In case of chronic inflammation, more natural autoantibody can be stimulated and some autoantigens can mutate to xenoantigens; after these mutations, more specific path-ogenic or protective antibodies can be produced [52].

During cell death, some multiple intracellular enzymes as nucleases and proteases are activated which cause the numerous cellular molecules cleavage; as a consequence, some hidden antigens are exposed and called as 'neoepitopes' or neodeterminants. Most of the neoepitopes are undergo to tolerance, but some undergo modification; as cleavage, phosphorylation and oxida-tion. The self-antigens released by dying cells can be changed by ultraviolet light, oxidation or cleavage by granzyme B [53] delivered by cytotoxic T cells and this change can lead to autoim-mune responses. In rheumatoid arthritis, cyclic citrullinated peptides autoantibodies (anti-CCP antibodies) are one of a neoepitope secondary to inflammation [54]. Citrulline is formed by deamination of the arginine amino acid during inflammation/oxidative stress or apoptosis.

3.6. Generation of pathogenic autoantibody

In specific autoimmune diseases, some of autoantibodies could be detected before beginning of the disease. For example; in SLE, rheumatoid arthritis, type I diabetes, limbic encephalitis and primary biliary cholangitis [55].

Changing from preclinical to clinical autoantibody has certain steps. In genetic predisposed individuals, autoantibodies are produced by autoreactive cells. These preclinical autoantibodies can stay for months or even years in these individuals. Under proper environmental conditions, the autoreactive cells would be activated and proliferated. Then, they produce large amounts of autoantibodies and inflammatory cytokines, which lead to tissue injury and the clinical symptoms are observed [6].

Natural autoantibodies can provide the templates for the higher-affinity and class-switched pathogenic autoantibodies, under appropriate conditions [16].

Production of pathogenic autoantibody:

1. Somatic hypermutation: Each antibody can bind at least 2 (IgG, IgD and IgE isotypes) – maximum 10 epitopes (IgM isotype) of an antigen, which has identical epitopes and are close enough. If the multiple antigen-antibody bind each other, the total strength of the bond is much greater than a single one. This is called the avidity of the interaction. The molar concentration of an antigen needed to occupy half the available antibody molecules in a solution is the dissociation constant (Kd) and used for expression of affinity. The lower the Kd means the higher the affinity. In a primary immune response, produced antibodies have a Kd in the range of 10^{-6}–10^{-9} M and after encountering with repeated antigens, the affinity can rises up to 10–11 M. This increase in antigen-binding strength is called affinity maturation or somatic hypermutation [4]. Mostly point mutations in the genes responsible for variable regions of antibody are detected [16]. They happen in the germinal centers of secondary follicles and AID enzyme that initiate them [17].

2. Class switching: The membrane bound IgM and IgD the antigen receptors of naïve B lymphocytes. After stimulation, the antigen specific clone B lymphocytes may proliferate and differentiate into antibody-secreting cells. Some of these B cells may secrete IgM, and some others may produce antibodies of other heavy chain classes. The change in Ig isotype production is called heavy chain class switching. The V regions remains same, specificity of B cells maintains [4].

The exons encoding the constant regions of all antibody classes on chromosome 14, are placed with μ (for IgM) nearest to variable region segments, followed by γ (IgG), α (IgA) and ε (IgE). By a successful VDJ rearrangement, first the nearest constant region which is μ is used, resulting in the production of IgM [17]. Unmutated or minimally mutated recombined VDJ gene sequences encode the multi and monoreactive natural IgM antibodies/autoantibodies [56]. AID deaminates cytidines in immunoglobulin VDJ and switch-region DNA, then ssDNA nicks, gaps or double-strand breaks are generated. Repair of these lesions involving error-prone translesion DNA polymerases are made by the B cell DNA and this results in insertions of point mutations or resolution of double-strand breaks, and hence, class-switch DNA recombination [57]. After class switch with the same variable region, these cells can express IgG if the exons encoding the γ constant region; IgA if it is α constant region; and IgE if it is ε constant region. T-lymphocytes and other cells release cytokines influence isotype of class switch [17].

Unmutated natural IgM autoantibodies expressed by B1 cells provide the 'templates' for the high-affinity and class-switched IgG and/or IgA autoantibodies which can cause autoimmune diseases [49, 58, 59]. Anti-DNA, anti-insulin and anti-IgG (RF) autoantibodies are pathogenic

high-affinity autoantibodies that undergo somatic hypermutation, class-switch DNA recombination and antigen driven clonal selection detected at systemic lupus, type 1 diabetes and rheumatoid arthritis patients [60]. Somatic hypermutation and class-switching [56, 60, 61] including the expression of activation-induced cytidine deaminase (AID) [62] are associated with the expansion of B-2 cells.

Class switch and somatic hypermutation are initiated by the same enzyme, AID, in the germinal centers of secondary follicles parallelly [17].

3. Somatic diversity: Somatic recombination: Antibodies are capable of binding a wide variety of antigen, since variable region of antibody molecules forms a flat surface field into different shapes. The epitopes or determinants are the parts of antigens that are recognized by antibodies based on sequence (linear determinants) or shape (conformational determinants). Some hidden antigen molecules are exposed after a physicochemical change, called as neodeterminants [4].

Diversity of antibodies is generated by the genetics arrangement of antibody production; unique molecular random generator. The variable region of an immunoglobulin is formed by both the heavy and the light chain which are carried on different chromosomes [5]. The variable portion of the heavy chain is encoded in separated gene segments of three types, V (variable; the number of gene segments is 65), D (diversity; 27) and J (joining; 6). A complete heavy chain variable region exon is randomly cobbled together by juxtaposing one V, one D and one J segment by a cut and paste process at the DNA level by an enzyme complex containing RAG-proteins (recombination activating gene) which excises intervening DNA, and normal DNA repair proteins directly rejoin the segments. Light chain genes have just V and J segments, not D [17]. In summary, the diversity of antigen binding is achieved by mostly V genes and their combination with different D and J genes. Different antibodies are produced by four different mechanisms as; randomly combining V-(D)-J segments, randomly combining heavy and light chain, imprecise joining and somatic hypermutation [4, 17]. Somatic diversity is performed during central B cell intolerance.

4. Genetic abnormalities: Some genetic alterations results clinical autoimmune disease but some alterations are influenced by environmental factors. For example; single gen knockout and overexpression lead to clinical autoimmune disease while most of the autoimmune disorders are polygenic. Three examples of spontaneous or induced genetic alterations lead to clinical diseases [16].

a. Abnormal survival of autoreactive lymphocytes: Mutations in Fas/CD95 causes over expression of the B cell stimulator BLyS; BAFF and the antiapoptotic regulator Bcl-2 which leads the abnormal survival of autoreactive lymphocytes. It causes an autoimmune lymphoproliferative syndrome/Canale Smith syndrome in humans [16, 63],

b. Defective removal of apoptotic cells: A group of proteins as Mer and serum opsonins (e.g., natural IgM antibodies, C1q, serum amyloid P component [SAP] and milk fat globulin epithelial growth factor-8 [MFGE8]) [64] take role in the removal of apoptotic cells. In Mer deficiency, macrophages take a proinflammatory signal not an anti-inflammatory one for ingestion of apoptotic cells. If there is a defective clearance of apoptotic cells in surface IgM, C1q, SAP and MFGE8, clearance of apoptotic cells leads to postapoptotic necrosis and/or through lack of engagement with specific inhibitory receptors on the phagocyte. In

MFG-E8 deficiency, apoptotic cells accumulate in germinal centers and in C1q-deficiency, apoptotic cells accumulate in the kidney. These deficiencies cause lupus-like diseases [16].

c. Breakdown in the regulation of B cell or T cell activation threshold: If threshold regulators of cbl-b, PD-1 and Zap-70 and the SLAM cluster in T cells, and Lyn and FcγRIIb in B cells change genetically, failure of peripheral immune system could happens. If lymphocytes are more easily activated, they produce more auto-antibodies as in systemic lupus. Mutations of Zap-70 lead to production of RFs as in rheumatoid arthritis [16, 65]. PD-1-deficiency causes lupus in C57BL/6 and myocarditis in BALB/c.

There is some signature autoantibodies cause autoimmune diseases as anti-endomysial antibodies (EMA), anti-gliadin antibodies (AGA). But there is not a specific antibody detected yet in several autoimmune diseases, as psoriasis [6].

Lymphocytes and APC are strongly activated by type I interferons (interferon-α and β) [66]. Patients with systemic lupus have elevated levels of interferon and autoantibodies as anti-DNA and Sm/RNP. By binding to chromatin which contains DNA or to Sm/RNP which contain small nuclear RNAs, they enter cells through the FcγR or B cell receptor. The intracellular Toll-like receptor is activated by nucleic acid which leads to production of interferon and activation of immune system. The protein antigen stimulates T cells, probably are responsible for the specificity of the immune response. These are called Toll hypothesis [67].

3.7. Systemic versus organ-specific autoimmune disease

Autoimmune disease can be classified as systemic or organ specific. Systemic autoimmune diseases (**Table 3**), involve multiple organs or tissues, whereas organ specific autoimmune

Disease	Organ(s) involved	Autoantibodies
Systemic lupus erythematosus	Joints, skin, nervous system, kidneys, blood cells, heart, lungs	Anti dsDNAb Anti Sm b Anti ribosomal P b Anti RNA helicase
Rheumatoid arthritis	Joints, blood, vessels, lungs	Anti citrullinated peptides b Rheumatoid factor
Sjögren's syndrome	Exocrine glands (salivary and lacrimal glands), kidneys, nerves	Anti Ro60 (SS-A) Anti Ro52 Anti La (SS-B)
Scleroderma	Skin, blood vessels, GI tract, lungs, kidneys	Anti topoisomerase I b Anti fi brillarin (U3 RNP) b Anti RNA polymerase I b Anti RNA polymerase III b
Polymyositis	Muscles, lungs	tRNA synthetases (Histidyl, alanyl, threonyl, glycyl, etc.) b Signal recognition particle b

Table 3. Some systemic autoimmune diseases.

Disease	Organ(s) involved	Autoantibodies
Hashimoto's thyroiditis	Thyroid	Thyroid peroxidase Thyroglobulin
Graves' disease	Thyroid	Thyroid-stimulating hormone receptor
Addison's disease	Adrenal glands	2I-hydroxylase
Type I diabetes	Pancreatic islet cells	Glutamic acid dehydrogenase, insulin islet cell antigens
Pemphigus vulgaris	Skin	Desmoglein 3
Bullous pemphigoid	Skin	230 kDa hemidesmosomal antigen
Vitiligo	Skin melanocytes	Unknown melanocyte antigens
Goodpasture's syndrome	Kidneys, lungs	Type VII collagen
Myasthenia gravis	Nervous system	Acetylcholine receptor
Multiple sclerosis	Nervous system	Unknown myelin antigens
Pernicious anemia	Gastric parietal cells	Parietal cell antigens, intrinsic factor
Primary biliary cirrhosis	Bile ducts	Dihydrolipoamide acyltransferase and other antigens b
Autoimmune hepatitis	Liver	Smooth muscle antigens (F-actin)

Table 4. Some organ-specific autoimmune diseases.

diseases (**Table 4**), involve a single organ or tissue. Almost all organs can be affected by either systemic or organ-specific autoimmune disease [5].

4. Function of autoantibodies; mechanism of protection and cause of diseases?

The antibodies' Fab regions bind to antigens and can block/stimulate the effects of them and the Fc regions can bind to many cells of immune system as phagocytes and complement and activate diverse effector mechanisms to eliminate these antigens; Fcγ-R (for IgG), Fcα-R (for IgA), Fcα/μ-R (for IgA and IgM), Fcε-R (for IgE). The effective binding of antigen-antibody occurs after recognization several IgG molecules. The affinity of the binding is too low with a single, free antibody. Bigger immune complexes by antigen and several Fc parts of antibodies causes to rapid internalization for phagocytosis and antigen clearance. Heavy chain class switching and affinity maturation enhance the protective functions of antibodies. There is an exception to this rule in mast cells and eosinophils, just binding a free (meaning non-antigen-complexed) IgE is enough because of their high-affinity Fc-ε-receptors [4, 17].

4.1. Some examples for the functions of antibodies and autoantibodies

1. Neutralization of foreign and self-antigens: Antibodies bind to block, or neutralize the activity of foreign or self-antigens [4].

2. Opsonization and phagocytosis: Complex of antibodies with foreign and self-antigens promote their ingestion by phagocytes (opsonization). When IgG1 and IgG3 isotype antibodies bind to a foreign or self-antigen, their Fc regions bind to a high affinity receptors called FcγRI (CD64), which are on neutrophils and macrophages. The binding of antibody Fc tails to FcγRI results in opsonization of antigenic molecules into a vesicle called a phagosome, where fuse with lysosomes and activates the neutrophil or phagocytes. The activated ones produces in their lysosomes, large amounts of reactive oxygen intermediates, nitric oxide, and proteolytic enzymes, all of them together destroy the ingested antigenic cells [4].

3. Antibody-dependent cellular cytotoxicity (ADCC): Natural killer (NK) cells produce an Fc receptor called FcγRIII, which binds to IgG antibodies. The activated NK cells discharge their granules, which contains proteins that kill the opsonized targets [4]

4. Activation of the complement system: Antigens without antibody, as part of innate immune response to infection, and antigens with antibody, as part of adaptive immunity can activate the complement system. The complement system takes role in the elimination of opsonized antigens [4]. Examples; activation of complement causes diseases at kidneys of systemic lupus and lupus nephritis patients, fetal loss associated with the antiphospholipid syndrome [68, 69], autoantibody administration into the transgenic K/BxN mouse of rheumatoid arthritis [70], in glucose-6-phosphate isomerase patient. In the NZB/W F1 murine model of immune-complex-mediated lupus nephritis, mice lacking the FcγRγ chain were protected from nephritis, indicating a critical role for FcγRs in tissue inflammation [71].

5. Mucosal immunity.

6. Pro-inflammatory and anti-inflammatory effect: natural polyautoreactive IgM antibodies can protect from autoimmune diseases [30]. Also IgG isotype autoantibodies has an anti-inflammatory capacities, according to their IgG subclass and the extent of glycosylation/ sialylation of the Fc glycan linked to Asn297 [71, 72]. These properties regulate the binding of antibody to a different Fc-receptors [72]. The receptors as FcγRI (CD64), FcγRIIIA (CD16a), and FcγRIIIB (CD16b) mediate activating signals, but also FcγRIIA and FcγRIIB (CD32) mediate inhibiting signals. Glycosylated/ sialylated different IgG isotypes antibodies bind to Fc-receptors for activating and inhibiting with different affinities [72]. According to glycosylation/sialylation patterns and IgG subclass determine, an autoantibody produces FcγR-mediated either pro- or anti-inflammatory functions [73]. So glycosylation of autoantibody can be an important regulator of autoimmune disorders [74]. While IgG isotypes produced with T cell-dependent reactions were poorly sialylated causes pro- inflammatory, a high degree of sialylation that mediates anti-inflammatory properties [75]. Activated B cells and plasma cells regulate both T cell differentiation into follicular helper T cells and cytokine profiles [76]. By stimulation of TLR, B lymphocytes produce different cytokines to dendritic cells [77]. Dendritic cells are the most important antigen-presenting cells to T cell. B cell also present the antigen to T cell and so promote the proliferation of activated T lymphocytes, the development of robust T effector responses, and normal T cell memory compartments [78]. TLR-signals in murine B cells promote IFN-γ production from T cells and control antibody isotype switching to IgG2 *in vivo* [77]. The cowork of activated B and T cells is crucial for the antibody responses and their outcome as pathogenic potential, that is, the antibody class and glycosylation/ sialylation pattern.

Testing of autoantibodies is diagnostic criteria in many diseases. But, also autoantibodies could be detected in healthy individuals [79]. Since isotype/subclass and glycosylation pattern is critical for the pathogenic potential of a particular antibody, it could be helpful for the diagnostic analysis. Pathogenic autoantibodies could be produced either by continuous formation of short-lived plasma cells or through the formation of long-lived plasma cells, or both [80]. Therapeutic treatment available nowadays could suppress B cell activation and short-lived plasma cell, while do nothing to long-lived plasma cells [81].

By contrast, mice with FcγRIIb knocked out spontaneously develop a lupus like disease [71]. Different isotypes antibodies have different affinities for the four FcγRs. IgG2a has higher affinity for FcγRIV, leading to inflammatory responses, whereas IgG1 selectively engages FcγRIIb, leading to inhibitory responses [30]. There is a similar relationships with human FcγRs and that the ability to protect or induce inflammation will change according to the isotype of the autoantibody and FcγR engaged.

7. Removal of cell debris: Natural autoantibodies takes role in the removal of cell debris during inflammation, and autoantibodies to inflammatory cytokines have protective functions against inflammation [82].

4.2. Mechanisms of autoimmune tissue injury

Immune responses can cause tissue injury and disorders called as hypersensitivity diseases. Hypersensitivity is a term of excessive or aberrant immune responses [4]. Tissue damage in autoimmune diseases can occur through several mechanisms, which are similar to three of the classical types of hypersensitivity reactions [5]:

1. Type II (caused by autoantibodies reactive with cell surface or matrix antigens):

Antibodies against cell and tissue may cause tissue and disease. IgM and IgG antibodies activate the phagocytosis of cells by binding to complement and Fc receptor- mediated leukocyte [4]. The reactions are caused by antibodies against self-protein antigens. Autoantibodies generated against cell surface antigens/extracellular matrix proteins may be cytotoxic (type IIA) or agonistic/antagonistic (type IIB). Autoantibodies to cell surface antigens may initiate cell destruction by complement- mediated lysis (cell destruction), phagocytosis, or antibody-dependent cell-mediated cytotoxicity (ADCC) [5]. At **Table 5**, some examples of antibody-mediated diseases are given.

Disease	Target antigen	Mechanism
Pemphigus vulgaris	Proteins in intercellular junction of epidermal cell	Antibody-mediated activation of proteinase, disruption of intercellular adhesion
Autoimmune hemolytic anemia	Erythrocytes membrane antigen	Opsonization and phagocytosis of erythrocytes
Myasthenia gravis	Acetylcholine receptor	Antibody inhibits acetylcholine binding

Table 5. Antibody-mediated diseases.

2. Type III (caused by immune complexes):

Autoantibodies can bind to circulating antigens and form immune complexes that deposit in vessels, tissues and cause tissue injury. Injury is mainly due to leukocyte recruitment and inflammation [4]. Autoantibodies can cause disease by forming immune complexes with the circulating antigens. Immune complex formation is a normal process to remove antigens and to phagocyte through Fc or complement receptors so are prevented their deposition. The efficiency of uptake of immune complexes by either Fc receptors or CR1 is proportional to the number of IgG molecules associated in the complex [5]. At **Table 6**, some examples of immune complex mediated diseases are given.

3. Type IV (delayed-type hypersensitivity, mediated by T cells):

T cell-mediated disease is caused by CD4 T lymphocytes or by killing of host cells by CD8 CTLs [4]. T cells recognize protein antigen-presenting cells in the context of class II major histocompatibility complex (MHC) molecules and produce the cytokines interferon γ (IFN-γ), interleukin 3 (IL-3), tumor necrosis factor (TNF) α, TNF-β, and granulocyte-macrophage colony-stimulating factor (GM-CSF). Elaboration of "TH1 (a subset of helper T cells) cytokines" leads to macrophage recruitment and activation, enhanced expression of adhesion molecules, and increased production of monocytes by the bone marrow [5]. At **Table 7**, some examples of T cell-mediated diseases are given.

Disease	Target antigen	Mechanism
Systemic lupus erythematosus	DNA, nucleoproteins	Complement and Fc region mediated
Polyarteritis nodosa	Hepatitis B surface antigen	Complement and Fc region mediated
Poststreptococcal glomerulonephritis	Streptococcal cell wall antigen	Complement and Fc region mediated

Table 6. Immune complex mediated diseases.

Disease	Target antigen	Mechanism
Rheumatoid arthritis	Antigen in joint synovium	T cell mediated
Type I diabetes mellitus	Islet cell antigen	T cell mediated

Table 7. T cell-mediated diseases.

Author details

Neval Yurttutan Uyar

Address all correspondence to: nevaluyar@gmail.com

Mehmet Ali Aydınlar Acibadem University, Istanbul, Turkey

References

[1] Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. The New England Journal of Medicine. 2002;**347**:911-920. DOI: 10.1056/NEJMra020100

[2] Vento S, Cainelli F. Autommune diseases in low and middle income countries: A neglected issue in global health. The Israel Medical Association Journal. 2016;**18**(1):54-55

[3] Eaton WW, Rose NR, Kalaydjian A, Pedersen MG, Mortensen PB. Epidemiology of auto-immune diseases in Denmark. Journal of Autoimmunity. 2007;**29**:1-9. DOI: 10.1016/j.jaut.2007.05.002

[4] Abbas AK, Lichtman AH. Basic Immunology–Functions and Disorders of Immune System. 2nd ed. Saunder; 2004. p 300. ISBN:0-7216-0241-X

[5] Zabriskie J.B. Essential Clinical Immunology. 2nd ed. Cambridge; 2009. p 362. ISBN-13 978-0-521-51681-5

[6] Ma W, Chang C, Gershwin ME, Lian Z. Development of autoantibodies precedes clinical manifestations ofautoimmune diseases: A comprehensive review. Journal of Autoimmunity. 2017;**83**:95-112. DOI: 10.1016/j.jaut.2017.07.003

[7] Cruz GI et al. A Child's HLA-DRB1 genotype increases maternal risk ofsystemic lupus erythematosus. Journal of Autoimmunity. 2016;**74**:201-207

[8] Ji J, Sundquist J, Sundquist K. Gender-specific incidence of autoimmune diseases from national registers. Journal of Autoimmunity. 2016;**69**:102-106

[9] Long H et al. The critical role of epigenetics in systemic lupus erythematosus and autoimmunity. Journal of Autoimmunity. 2016;**74**:118-138

[10] Teruel M, Alarcon-Riquelme ME. The genetic basis of systemic lupus erythematosus: What are the risk factors and what have we learned. Journal of Autoimmunity. 2016;**74**: 161-175

[11] Bao Y, Cao X. Epigenetic control of B cell development and B-cell-related immune disorders. Clinical Reviews in Allergy and Immunology. 2016;**50**(3):301-311

[12] Floreani A, Leung PS, Gershwin ME. Environmental basis of autoimmunity. Clinical Reviews in Allergy & Immunology. 2016;**50**(3):287-300

[13] Meroni PL, Penatti AE. Epigenetics and systemic lupus erythematosus: Unmet needs. Clinical Reviews in Allergy and Immunology. 2016;**50**(3):367-376

[14] Selmi C. Autoimmunity in 2015. Clinical Reviews in Allergy and Immunology. 2016;**51**(1): 110-119

[15] Wu HJ et al. Critical link between epigenetics and transcription factors in the induction of autoimmunity: A comprehensive review. Clinical Reviews in Allergy and Immunology. 2016;**50**(3):333-344

[16] Elkon K, Casali P. Nature and functions of autoantibodies. Nature Clinical Practice. Rheumatology. 2008 September;**4**(9):491-498. DOI: 10.1038/ncprheum0895

[17] Helmberg A. Immune system and immunology [Internet]. 2014. Available from: http://www.helmberg.at/immunology.htm

[18] Us A.D. Temel İmmunoloji ve Seroloji. 1st ed. Hipokrat Kitabevi. P367. ISBN:978-605-9160-39-1

[19] Levinson W. Review of Medical Microbiology and Immunology. 14th ed. Lange; 2013. p818. ISBN:978-0-07-184574-8

[20] Uhlig T, Hagen KB, Kvien TK. Current tobacco smoking, formal education, and the risk of rheumatoid arthritis. The Journal of Rheumatology. 1999;**26**(1):47-54

[21] Heliovaara M et al. Smoking and risk of rheumatoid arthritis. The Journal of Rheumatology. 1993;**20**(11):1830-1835

[22] Kharlamova N et al. Antibodies to *Porphyromonas gingivalis* indicate interaction between oral infection, smoking, and risk genes in rheumatoid arthritis etiology. Arthritis & Rhematology. 2016;**68**(3):604-613

[23] Johansson L et al. Concentration of antibodies against *Porphyromonas gingivalis* is increased before the onset of symptoms of rheumatoid arthritis. Arthritis Research & Therapy. 2016:18

[24] Kaklıkkaya N, Kaşifoğlu N, Sarıbaş Z, Şener B, Taşkınoğlu T, Yurttutan Uyar N. Klinik Örnekten Sonuç Raporuna Uygulama Rehberi. 2nd ed. Çağlayan offset; 2016. p152. ISBN: 978-605-84108-4-8

[25] Avrameas S, Selmi C. Natural autoantibodies in the physiology and pathophysiology of the immune system. Journal of Autoimmunity. 2013;**41**:46-49. DOI: 10.1016/j.jaut.2013.01.006

[26] Miller FW, Alfredsson L, Costenbader KH, Kamen DL, Nelson LM, Norris JM, et al. Epidemiology of environmental exposures and human autoimmune diseases: Findings from a National Institute of Environmental Health Sciences Expert Panel Workshop. Journal of Autoimmunity. 2012;**39**:259-271

[27] Selmi C, Leung PS, Sherr DH, Diaz M, Nyland JF, Monestier M, et al. Mechanisms of environmental influence on human autoimmunity: A National Institute Of Environmental Health Sciences Expert Panel Workshop. Journal of Autoimmunity. 2012;**39**:272-284

[28] Miller FW, Pollard KM, Parks CG, Germolec DR, Leung PS, Selmi C, et al. Criteria for environmentally associated autoimmune diseases. Journal of Autoimmunity. 2012;**39**:253-258

[29] Germolec D, Kono DH, Pfau JC, Pollard KM. Animal models used to examine the role of the environment in the development of autoimmune disease: Findings from an NIEHS expert panel workshop. Journal of Autoimmunity. 2012;**39**:285-293

[30] Ralf J, Ludwig RJ, Vanhoorelbeke K, Leypoldt F, Kaya Z, Bieber K, McLachlan SM, Komorowski L, Luo J, Cabral-Marques O, Hammers CM, Lindstrom JM, Lamprecht P, Fischer A, Riemekasten G, Tersteeg C, Sondermann P, Rapoport B, Wandinger KP, Probst C, Beidaq AE, Schmidt E, Verkman A, Manz RA, Nimmerjahn F. Mechanisms of autoantibody-induced pathology. Frontiers in Immunology. **8**:603. DOI: 10.3389/fimmu.2017.00603

[31] Pelanda R, Torres RM. Central B-cell tolerance: Where selection begins. Cold Spring Harbor Perspectives in Biology. 2012;**4**:a007146. DOI: 10.1101/cshperspect.a007146

[32] Gonzalez-Martin A, Adams BD, Lai M, Shepherd J, Salvador-Bernaldez M, Salvador JM, et al. The microRNA miR-148a functions as a critical regulator of B cell tolerance and autoimmunity. Nature Immunology. 2016;**17**:433-440. DOI: 10.1038/ni.3385

[33] Müller J, Nitschke L. The role of CD22 and Siglec-G in B-cell tolerance and autoimmune disease. Nature Reviews Rheumatology. 2014;**10**:422-428. DOI: 10.1038/ nrrheum.2014.54

[34] Tiller T, Tsuiji M, Yurasov S, Velinzon K, Nussenzweig MC, Wardemann H. Autoreactivity in human IgG+ memory B cells. Immunity. 2007;**26**:205-213. DOI: 10.1016/j.immuni.2007.01.009

[35] Wardemann H, Yurasov S, Schaefer A, Young JW, Meffre E, Nussenzweig MC. Predominant autoantibody production by early human B cell precursors. Science. 2003;**301**:1374-1377. DOI: 10.1126/science.1086907

[36] Avrameas S. Natural autoantibodies: From 'horror autotoxicus' to 'gnothi seauton'. Immunology Today. 1991;**12**:154-159

[37] Carroll MC. The lupus paradox. Nature Genetics. 1998;**19**:3-59. [PubMed: 9590274]

[38] Yurasov S, Nussenzweig MC. Regulation of autoreactive antibodies. Current Opinion in Rheumatology. 2007;**19**:421-426. [PubMed: 17762605]

[39] Spalter SH, Kaveri SV, Bonnin E, Mani JC, Cartron JP, Kazatchkine MD. Normal human serum contains natural antibodies reactive with autologous ABO blood group antigens. Blood. 1999;**93**:4418e24

[40] Ravindranath MH, Kaneku H, El-Awar N, Morales-Buenrostro LE, Terasaki PI. Antibodies to HLA-E in nonalloimmunized males: Pattern of HLA-Ia reactivity of anti-HLA-E-positive sera. Journal of Immunology. 2010;**185**:1935e48

[41] Baumgarth N. The double life of a B-1 cell: Self-reactivity selects for protective effector functions. Nature Reviews. Immunology. 2011;**11**:34e46

[42] Tiller T, Tsuiji M, Yurasov S, Velinzon K, Nussenzweig MC, Wardemann H. Autoreactivity in human IgGþ memory B cells. Immunity. 2007;**26**:205e13

[43] Tumas-Brundage KM, Notidis E, Heltemes L, Zhang X, Wysocki LJ, Manser T. Predominance of a novel splenic B cell population in mice expressing a transgene that encodes multireactive antibodies: Support for additional heterogeneity of the B cell compartment. International Immunology. 2001;**13**:475e84

[44] Roy B, Shukla S, Lyszkiewicz M, Krey M, Viegas N, Duber S, et al. Somatic hypermutation in peritoneal B1b cells. Molecular Immunology. 2009;**46**:1613e9

[45] Notkins AL. Polyreactivity of antibody molecules. Trends in Immunology. 2004;**25**:174-179

[46] Zhou ZH et al. The broad antibacterial activity of the natural antibody repertoire is due to polyreactive antibodies. Cell Host & Microbe. 2007;**1**:51-61

[47] Shoenfeld Y, Toubi E. Protective autoantibodies: Role in homeostasis, clinical importance, and therapeutic potential. Arthritis and Rheumatism. 2005;**52**:2599-2606

[48] Chen Y, Khanna S, Goodyear CS, Park YB, Raz E, Thiel S, et al. Regulation of dendritic cells and macrophages by an anti-apoptotic cell natural antibody that suppresses TLR responses and inhibits inflammatory arthritis. Journal of Immunology. 2009;**183**:1346-1359

[49] Toubi E, Shoenfeld Y. Protective autoimmunity in cancer (review). Oncology Reports. 2007;**17**:245-251

[50] de Faire U, Frostegard J. Natural antibodies against phosphorylcholine in cardiovascular disease. Annals of the New York Academy of Sciences. 2009;**1173**:292-300

[51] Grabar P. Some considerations of the problem of auto-antibody formation. Texas Reports on Biology and Medicine. 1965;**23**(Suppl. 1):278-284

[52] Zelenay S et al. Physiopathology of natural auto-antibodies: The case for regulation. Journal of Autoimmunity. 2007;**29**:229-235

[53] Casciola-Rosen L et al. Cleavage by granzyme B is strongly predictive of autoantigen status: Implications for initiation of autoimmunity. The Journal of Experimental Medicine. 1999;**190**:815-826. [PubMed: 10499920]

[54] Klareskog L et al. Genes, environment and immunity in the development of rheumatoid arthritis. Current Opinion in Immunology. 2006;**18**:867-875

[55] Arbuckle MR et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. The New England Journal of Medicine. 2003;**349**(16):1526-1533

[56] Harindranath N et al. Structure of the VH and VL segments of polyreactive and monoreactive human natural antibodies to HIV-1 and *Escherichia coli* β-galactosidase. International Immunology. 1993;**5**:1523-1533. [PubMed: 8312222]

[57] Diaz M, Casali P. Somatic immunoglobulin hypermutation. Current Opinion in Immunology. 2002;**14**:235-240. [PubMed: 11869898]

[58] Carroll MC, Prodeus AP. Linkages of innate and adaptive immunity. Current Opinion in Immunology. 1998;**10**:36-40. [PubMed: 9523108]

[59] Zhang M, Carroll MC. Natural antibody mediated innate autoimmune response. Molecular Immunology. 2007;**44**:103-110. [PubMed: 16876247]

[60] Mantovani L et al. Human rheumatoid B-1a (CD5+ B) cells make somatically hypermutated high affinity IgM rheumatoid factors. Journal of Immunology. 1993;**151**: 473-488. [PubMed: 7686945]

[61] Casali P, Schettino EW. Structure and function of natural antibodies. Current Topics in Microbiology and Immunology. 1996;**210**:167-179. [PubMed: 8565555]

[62] Honjo T et al. AID: How does it aid antibody diversity? Immunity 2004;**20**:659-668. [PubMed: 15189732]

[63] Straus SE et al. An inherited disorder of lymphocyte apoptosis: The autoimmune lymphoproliferative syndrome. Annals of Internal Medicine. 1999;**130**:591-601. [PubMed: 10189330]

[64] Peng Y et al. The role of IgM antibodies in the recognition and clearance of apoptotic cells. Molecular Immunology. 2005;**42**:781-787. [PubMed: 15829266]

[65] Sakaguchi N, et al. Altered thymic T-cell selection due to a mutation of the ZAP-70 gene causes autoimmune arthritis in mice. Nature. 2003;**426**:454-460. [PubMed: 14647385]

[66] Theofilopoulos AN, et al. Type I interferons (alpha/beta) in immunity and autoimmunity. Annual Review of Immunology. 2005;**23**:307-336. [PubMed: 15771573]

[67] Martin DA, Elkon KB. Autoantibodies make a U-turn: The toll hypothesis for autoantibody specificity. The Journal of Experimental Medicine. 2005;**202**:1465-1469. [PubMed: 16330812]

[68] Monach PA et al. The role of antibodies in mouse models of rheumatoid arthritis, and relevance to human disease. Advances in Immunology. 2004;**82**:217-248. [PubMed: 14975258]

[69] Baxendale HE, et al. Natural human antibodies to pneumococcus have distinctive molecular characteristics and protect against pneumococcal disease. Clinical and Experimental Immunology. 2008;**151**:51-60. [PubMed: 17983446]

[70] Clynes R, et al. Uncoupling of immune complex formation and kidney damage in autoimmune glomerulonephritis. Science. 1998;**279**:1052-1054. [PubMed: 9461440]

[71] Bolland S, Ravetch JV. Spontaneous autoimmune disease in Fc(gamma)RIIB-deficient mice results from strain-specific epistasis. Immunity. 2000;**13**:277-285. [PubMed: 10981970]

[72] Nimmerjahn F, Ravetch JV. Anti-inflammatory actions of intravenous immunoglobulin. Annual Review of Immunology. 2008;**26**:513-533. DOI: 10.1146/annurev. immunol.26. 021607.090232

[73] Anthony RM, Ravetch JV. A novel role for the IgG Fc glycan: The anti- inflammatory activity of sialylated IgG Fcs. Journal of Clinical Immunology. 2010;**30**(Suppl 1):S9-S14. DOI: 10.1007/s10875-010-9405-6

[74] Goulabchand R et al. Impact of autoantibody glycosylation in autoimmune diseases. Autoimmunity Reviews. 2014;**13**:742-750. DOI: 10.1016/j.autrev.2014.02.005

[75] Hess C et al. T cell-independent B cell activation induces immunosuppressive sialylated IgG antibodies. The Journal of Clinical Investigation. 2013;**123**:3788-3796. DOI:10.1172/JCI65938

[76] Fillatreau S, Gray D, Anderton SM. Not always the bad guys: B cells as regulators of autoimmune pathology. Nature Reviews. Immunology. 2008;**8**:391-397. DOI: 10.1038/nri2315

[77] Barr TA, Brown S, Ryan G, Zhao J, Gray D. TLR-mediated stimulation of APC: Distinct cytokine responses of B cells and dendritic cells. European Journal of Immunology. 2007;**37**:3040-3053. DOI: 10.1002/eji.200636483

[78] Crawford A et al. Primary T cell expansion and differentiation in vivo requires antigen presentation by B cells. Journal of Immunology. 2006;**176**:3498-3506. DOI: 10.4049/jimmunol.176.6.3498

[79] Nagele EP et al. Natural IgG autoantibodies are abundant and ubiquitous in human sera, and their number is influenced by age, gender, and disease. PLoS One. 2013;**8**:e60726. DOI: 10.1371/journal.pone.0060726

[80] Manz RA, Hauser AE, Hiepe F, Radbruch A. Maintenance of serum anti-body levels. Annual Review of Immunology. 2005;**23**:367-386. DOI: 10.1146/annurev. immunol.23.021704.115723

[81] Mumtaz IM, et al. Bone marrow of NZB/W mice is the major site for plasma cells resistant to dexamethasone and cyclophosphamide: Implications for the treatment of autoimmunity. Journal of Autoimmunology. 2012;**39**:180-188. Doi:10.1016/j.jaut.2012.05.010

[82] Wildbaum G, et al. Beneficial autoimmunity to proinflammatory mediators restrains the consequences of self-destructive immunity. Immunity. 2003;**19**:679-688. [PubMed: 14614855]