Mutual adaptive immune responses of B and T lymphocytes in autoimmune diseases

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Abstract
Classically, the immune mechanisms involved in the development of autoimmune diseases have led to their classification into two broad groups of diseases: one in which the pathological process is driven by T cells, and the other in which the humoral response is mediated by B lymphocytes by producing autoantibodies. are able to bind tissue autoantigens or contribute to the production of immune complexes. Given the progress made in deciphering the intimate mechanisms of the autoimmune reaction, it has been shown that T lymphocytes facilitate the adaptive immune responses of B lymphocytes, and B lymphocytes play a reciprocal role during CD4 + T cell activation in autoimmune diseases. The substantiation of a new type of diagnostic evaluation and therapeutic approach in autoimmune diseases starts from understanding the ultrastructural intimate mechanisms of occurrence and propagation of the autoimmune reaction, as well as from understanding the role of each component involved in this type of response. Most autoimmune diseases are caused by one or more immune system dysfunctions. In the case of many autoimmune diseases, the dysfunctions have a known and hereditary genetic determinism, through dominated or recessive autosomal mechanisms.

Key words: lymphocytes Th 17, B lymphocytes, cytokine BAFF, autoimmune diseases, genetic determinism.

Most autoimmune diseases are caused by one or more immune system dysfunctions. In the case of many autoimmune diseases, the dysfunctions have a genetic determinism known and inherited, through dominated or recessive autosomal mechanisms. There are also autoimmune diseases in which this is about a field with high genetic susceptibility, conventionally called so, due to insufficient knowledge of the intimate response mechanisms of the immune system, and also insufficient knowledge of the contributing factors as well as the promoting factors of the altered immune response.

Normally, the cells of the immune system act mainly on non-self structures of antigenic character, structures that do not belong to that organism and, physiologically, to a small extent on their own cells.

The autoimmune reaction defines an altered immune response of the body, in which the targets of the immune response molecules are represented by cells of self body structures, due to decreased tolerance towards them, followed by synthesis of autoantibodies or differentiation of autoreactive lymphocytes that no longer recognize the self, tolerance is completely lost and the immune response is focused against normal structures that become autoantigens or self-antigens.

Self-reactivity can be seen as a trigger for immune diseases, but there are not enough data to support this, but it is certain that self-reactivity is a factor amplifying the effects of pathological mechanisms of autoimmune diseases, mechanisms that will be well known deeper in the near future thanks to ultrastructural methods of study both *in vivo* and *in vitro*.

The main known mechanisms of the autoimmune reaction are:

- from the embryonic development, starting with the 4th week of intrauterine life, the induction of self-tolerance begins. Also from that moment, substances/ structures/ cells present in the body are not presented to lymphoid cells, do not recognize them physiologically, and these are called sequestered antigens. They escape lymphocyte control, because they are located either intracellularly or are bounded to anatomical barriers. For a

normal structural and functional organism, the sequestrated antigens will continue to be delimited by barriers and will never come into contact with the cells of the immune system. However, when a trauma, infectious process or surgery occurs, natural barriers are penetrated, destroying their integrity and releasing the sequestrated antigens. They become accessible to the cells of the immune system and this will cause an immune reaction. Among the autoimmune diseases triggered by these antigens there are certain demyelinating diseases of the central nervous system and Hashimoto's thyroiditis;

- As a result of the presence of known or unknown mutations takes place the proliferation of a lymphocyte clone with increased self-intolerance, followed by an altered suppressor T cell response and an abnormal T helper response, in particular Th17 which in turn causes a cascade of proinflammatory cytokines; T cells produced in this way are called autoreactive lymphocytes because they are unable to recognize structures as normal and consider them non-self structures.
- under the action of some physical, chemical, medicinal or biological factors (bacteria, viruses, fungi) the molecular conformation and the biochemical structure of the own proteins are altered, thus becoming autoantigens; this hypothesis is called the theory of the altered self.
- the structural similarity between exogenous antigens and own proteins is frequently encountered, some microbial agents have in their structure proteins identical to body own proteins; antibodies formed upon specific stimulation by the infectious agent target both the antigenic structures of the infectious agent and the own cells that are structurally similar to the structures of the infectious agent;
- polyclonal stimulation of B lymphocytes is produced in particular by Epstein-Barr virus, known to trigger infectious mononucleosis; this virus causes polyclonal activation of B lymphocytes that differentiate into plasma cells and begin to produce multiple sets of antibodies, some of which are autoantibodies.

Structural damage that occurs as a result of the autoimmune reaction is caused by cytotoxic autoantibodies, cytotoxic T lymphocytes, and immune complexes that trigger inflammatory and modulated cytokine repair processes.

In order to unify the opinions on the presence or absence of an autoimmune disease, the criteria for establishing its presence, known as the *Mackay* criteria, that define the presence of biochemical features that accompany the signs and symptoms specific to autoimmune disease:

- the presence of specific antibodies (autoantibodies);
- hyperglobulinemia due to overproduction of antibodies by activated plasma cells;
- interstitial storage of denatured immunoglobulins;
- proliferation of activated lymphocytes and plasma cells;
- good response of patients to corticosteroid therapy, cortisone being an immunosuppressant (1).

The substantiation of a new type of diagnostic evaluation and therapeutic approach in autoimmune diseases starts from understanding the ultrastructural intimate mechanisms of occurrence and propagation of the autoimmune reaction, as well as from understanding the role of each component involved in this type of response.

The major components involved in this type of response are B lymphocytes and the Th17 cell subset.

Classically, the immune mechanisms involved in the development of autoimmune diseases have led to their classification into two broad groups of diseases: one in which the pathological process is driven by T cells, and the other in which the humoral response is mediated by B lymphocytes by producing autoantibodies able to bind tissue autoantigens or contribute to the production of immune complexes. It is now recognized that T lymphocytes facilitate the adaptive immune responses of B lymphocytes, and B lymphocytes play a reciprocal role during the activation of CD4 + T cells in autoimmune diseases. For example, most autoantibodies present in autoimmune diseases are IgG-type, autoantibodies with somatic mutations, and this suggests that helper T cells drive the autoimmune response of B lymphocytes (2). B lymphocytes have been shown to be important mediators of autoimmune diseases described as mediated by T cells and includeing rheumatoid arthritis (RA), multiple sclerosis (MS) and type 1 diabetes (DZ1). In diseases in which autoimmune T cell clones determine the inflammatory process, autoantibody synthesis may be an important marker for the proliferation of autoantigen-specific B lymphocytes, lymphocytes that capture and present peptide autoantigens to the T cells.

B cells play a critical role in initiating and accelerating autoimmune diseases, especially those mediated by autoantibodies. In the peripheral lymphoid system, mature B cells are activated by self or foreign antigens and receive signals from helper T cells for differentiation into either memory B cells or antibody-producing plasma cells (3). Acquired evidence have revealed that epigenetic regulation modulates somatic hypermutations and recombinant DNA with class change during B cell activation and differentiation. Any abnormalities in these complex regulatory processes can contribute to aberrant antibody production, leading to autoimmune pathogenesis, e.g. in the case of systemic lupus erythematosus (SLE). Genome-wide association studies, have identified hundreds of gene polymorphisms, associated with the function and cell differentiation of B lymphocytes, which may increase the susceptibility to autoimmunity (4,5,6). Moreover, these epigenetic differences may occur under the action of environmental factors, such as infection, diet or medication (7). Therefore, the synergistic effects of epigenetic changes, induced both genetically and by environmental factors, may contribute to the etiopathogenesis of autoimmune diseases. Epigenetic changes mainly include DNA methylation / demethylation, histone modification, non-coding RNAs, nucleosome positioning, or heterochromatization that may ultimately determine gene expression (6) and therefore play important roles in various biological processes, such as would be cell growth, apoptosis, development, differentiation, immune response and aging. DNA methylation / demethylation, histone changes, and non-coding RNAs have been shown to help regulate T cell differentiation and cytokine production (8,9,10,11,12).

B cell tolerance is an essential mechanism for maintaining non-receptivity to thymus-independent autoantigens, such as lipids and polysaccharides. B cell tolerance is also important in preventing the development of antibody responses to protein antigens. Both central and peripheral mechanisms are involved in B cell tolerance. In central tolerance, immature B lymphocytes that recognize, with high affinity, autoantigens in the bone marrow are deleted or intervene by changing specificity in editing the receptors. This pathway is defined by the strength of BCR signaling: a strong BCR signal by binding with high affinity to an autoantigen, will erase or edit the receptor, while an intermediate binding affinity will allow B cells to survive and reach the periphery (13). Receptor editing is a major mechanism of central tolerance in B cells. Immature B cells in the bone marrow that encounter multivalent autoantigens return to the pre-B stage and continue to rearrange κ and, if necessary, λ light chain genes, and generates B cells that have a new light chain that are no longer

autoreactive. Immature B cells with light new chains that are no longer part of a self-reactive BCR migrate to the periphery because BT1 cells mature into newly generated IgM and IgD that express recirculating BT2 cells and then in mature recirculating B cells. If a mature B cell recognizes autoantigens in peripheral tissues without the specific response of helper T cells, this cell may be functionally inactivated by anergic mechanisms or killed by apoptosis. The AICDA enzyme is required for B cell tolerance in humans. This enzyme is required for CSR and somatic hypermutations. Patients with AICDA deficiency develop primary immunodeficiencies and autoimmune complications. Unique B cells from patients with AICDA deficiency have an abnormal Ig repertoire and high frequencies of autoreactive antibodies (14). Central tolerance mechanisms are crucial in the prevention of autoimmune diseases mediated by B lymphocytes, which opens new directions for research to discover molecules that restore the level of homeostatic tolerance. For example, the strong BCR signal, induced by high affinity binding to an autoantigen, will lead to deletion or editing of the high affinity receptor. If the BCR signaling potential is affected, for example, by overexpression of CD19 or PTPN22 polymorphisms (described in several autoimmune diseases), autoreactive B cells will not be deleted and may reach the periphery (15). These mechanisms lead to the growth of autoreactive B cells in the periphery and, consequently, to the possibility of developing autoimmune diseases. Thus, central tolerance decreases and consequently increases the risk of further development of an autoimmune disease, but additional factors (genetic, hormonal, environmental, etc.) control this evolution from autoimmunity to autoimmune disease.

B lymphocytes bind to an epitope specific to antigens through their BCR. After initial recognition, protein complexes and even proteins can be internalized and processed for antigen presentation. However, the protein may contain several epitopes in addition to the initially recognized epitope of BCR, which may fit into the binding grooves of MHCII molecules in cell B. Consequently, B cells may have not only the original epitope but also other epitopes. of the same protein or protein complex, and therefore trigger the specific differentiation of T cells (16). This phenomenon, known as epitope spread, allows autoantigens that were not the initial targets of autoreactive lymphocytes at the onset of autoimmunity to become antigens in later stages. This phenomenon is described in almost all immune diseases and is frequently associated with the evolution of the disease. Spread of the epitope can trigger clinically manifested autoimmune disease. The temporal progression of autoreactivity to autoimmune disease through the spread of the epitope occurs for example in childhood type 1 diabetes, insulin autoantibodies (IAA) being the first autoantibodies detected in the blood. Initially positive IAA children who develop later sequentially antibodies against other β cellular antigens, such as GAD and tyrosine-like proteins phosphatase-like proteins IA-2, usually progress to DZ1 (17). In contrast, children who remain positive only for IAA rarely develop the disease (18).

The main factor controlling the maturation, tolerance and malignancy of B cells, is the cytokine BAFF (activating factor of B cells belonging to the TNF family), discovered in 1999. The BAFF molecule plays a key role in B cell differentiation, survival and activation (19). BAFF, also known as B lymphocyte stimulator (BLyS), is a cytokine that prevents self-reactive B cell apoptosis. The BAFF family consists of two ligands, a proliferation-inducing ligand (APRIL) and BAFF and three membrane receptors, BCMA (B cell maturation antigen), TACI (transmembrane activator, calcium modulator and interaction ligand for cyclophilin) and BAFF-R (also known as BR3). Interactions between ligands and receptors vary: thus, BAFF interacts mainly with BR3, but can interact with

all three receptors, while APRIL can interact with TACI and BCMA, but not with BR3 (20). BAFF improves B cell survival, causes B cells to mature especially in the early stages of transition, and disrupts humoral tolerance by rescuing autoreactive B cells from apoptosis (21).

Another important class of B cells that has an effect on the development of autoimmunity is CD22. B cell responses are initiated by antigen binding to BCR and are altered by a wide repertoire of activating and inhibitory transmembrane co-receptors, expressed on the B cell surface (22, 23). In this context, the multifunctional BCR co-receptor, CD22, is interesting because it plays a critical role in establishing and modulating antigen receptor signaling thresholds for B cell activation (24). CD22, as part of the BCR complex, can modulate the intensity, quality, and duration of homeostatic and BCR-induced signals in an inhibitory or stimulatory capacity by ligand-dependent and independent mechanisms (25,26). The predominant effect of CD22 appears to be inhibitory (27). It occurs intracellularly during the late stage of B cell ontogenesis, but passes to the plasma membrane as B cells mature. CD22 is expressed at low levels in immature B cells and at higher levels in IgM +, IgD + mature B cells. However, it is absent on differentiated plasma cells. It is strongly expressed in follicular B cells, in the mantle and the marginal area, but is weakly present in germinal B cells (28). As mentioned above, in order for the immune system to function effectively, it is essential to mount an appropriate humoral response against potential pathogens, while avoiding autoimmunity and reactivity to autoantigens (29). Understanding CD22 function may therefore suggest methods for modulating humoral immunity and valuable help in discovering treatments for autoimmunity (30). Recent studies suggest the important role in defects and loss of CD22 functionality in the pathogenesis of autoimmune diseases, including systemic lupus erythematosus (SLE). *Epratuzumab* is a CD22 IgG1 antihuman monoclonal antibody that binds to the extracellular domain of CD22 and induces modest but significant intracellular phosphorylation. *Epratuzumab* reduces blood B cells by about 35-40% and has preferential effects on naive and transient B cells (31,32). *Epratuzumab* treatment has been used with moderate clinical success in systemic lupus erythematosus (SLE) and primary Sjögren's syndrome.

A functional subset of B cells, called regulatory B cells, has recently emerged as an important factor in maintaining immune tolerance. This subtype limits the excessive inflammatory response that occurs during the development of autoimmune diseases. The main regulatory function of B cells is mediated by the production of IL-10 which inhibits pro-inflammatory cytokines and supports the regular differentiation of T cells. Regulatory B cells were discovered in 2002 (33), when it was shown that B cells producing IL-10 may suppress inflammatory responses in experimental autoimmune encephalomyelitis, collagen-induced arthritis, and autoimmune colitis (34,35). Several B cell molecules can be targeted to treat autoimmune diseases.

The most studied target for B cell depletion in autoimmune disease is the CD20 antigen (differentiating antigen with human B cell restriction), a hydrophobic transmembrane protein with a molecular weight of approximately 35 kDa found on B cells, pre-B and mature B cells (36, 37) as well as in over 90% of B cells in non-Hodkin's lymphoma (38). Another therapeutic approach is to inhibit the effects of BAFF on B cells. This inhibition can be done by anti-BAFF or anti-BR3 monoclonal Abs, as well as by fusion proteins called BR3 or TACI. Selective BAFF blockers prevent BAFF from interacting with its receptors, leaving APRIL available to interact with TACI and BCMA. Drugs in this class include anti-BAFF antibodies (*Belimumab* or *Lymphostat B*) and a fusion protein consisting of human Ig Fc and the extracellular BR3 domain (*Briobacept*, for BAFF-R-Ig). Non-selective BAFF blockers eliminate both BAFF and APRIL interactions with all their

receptors. To date, there is only one drug in this class, which is human Ig Fc, fused to the extracellular TACI domain (*Atacicept*, TACI-Ig). Differences in the distribution of BAFF forms could indicate the potential of patients to respond to or resist BAFF antagonistic therapy. Treatment of B cells with TACI agonist antibody inhibits *in vitro* proliferation and activates a chimeric receptor containing intracellular and secondary TACI and secondarily induces apoptosis. These results also demonstrate that there is a critical level of TACI affinity in the regulation of B-cell homeostasis. The therapeutic effects of anti-BAFF therapy with *Belimumab* have been demonstrated in patients with systemic lupus erythematosus (SLE).

With the discovery of the Th17 cell subset and the biological functions of effector cytokines, the ability to understand the role of CD4 + T cells in adaptive immunity has increased. To understand the mechanisms of occurrence and propagation of the autoimmune reaction it is necessary to know the factors promoting Th17 cell differentiation, how IL-6, TGF-β, IL-23 and other factors control Th17 cells in various inflammatory conditions, as well as knowledge of in which the balance between the pathological and protective role of effector cytokines is maintained.

Helper 17 (Th17) T cells belong to a recently identified T-aid subset, in addition to the traditional Th1 and Th2 subset. These cells are characterized as preferred producers of interleukin-17A (IL-17A), IL-17F, IL-21 and IL-22. Th17 cells and their effector cytokines mediate defense mechanisms against various infections, especially infections with extracellular bacteria, and are involved in the pathogenesis of many autoimmune diseases. IL-17 and IL-22 receptors are widely expressed on various epithelial tissues. Th17 cell effector cytokines therefore mediate the crucial intersection between the immune system and tissues and play indispensable roles in tissue immunity.

IL-17A is the founding member of the cytokine family IL-17, which has five other members of the family, designated IL-17A to F. IL-17A is a disoduric-bound homodimeric glycoprotein consisting of 155 amino acids, which exerts part of its actions as a homodimer with a molecular weight of about 35 kDa (39). IL-17A homodimers are very effective in inducing the production of chemokines by epithelial cells and also have the greatest potency in inducing chemokine expression in epithelial cells, followed by IL-17A-F heterodimers, then IL-17F homodimers. Using neutralizing antibodies for these specific isoforms, it was shown that neutralizing IL-17A homodimers strongly blocked neutrophilic airway inflammation mediated by the adoptive transfer of ovalbumin-specific polarized Th17 cells and antigen-induced airway challenge. Thus, in this model of strategies blockage of airway inflammation targeting IL-17A and IL-17A to F, hetero-dimers could be most effective (39).

The initially described IL-17 receptor (IL-17RA) (40) is a type I transmembrane protein consisting of an extracellular domain of 293 amino acids, a transmembrane domain of 21 amino acids and a long cytoplasmic tail of 525 amino acids (41). IL-17RA receptor mRNA can be detected in epithelial cells, fibroblasts, B and T lymphocytes, myelomonocytic cells, and bone marrow stromal cells (42). IL-17RA protein is present on T lymphocytes in peripheral blood and vascular endothelial cells (43).

Both IL-17A and IL-17F induce the synthesis of granulopoietic factors (G-CSF and stem cell factor) and CXC chemokines: CXCL1, CXCL2, CXCL5 and CXCL8 in human epithelial cells (44,45). In addition to CXC and G-CSF chemokines, IL-17A can increase mRNA and mucin proteins, MUC5AC and MUC5B, in primary human bronchial epithelial cells in vitro. IL-17A also induces the expression of human beta-defensin-2 and CCL20 in lung epithelial cells. Although NF-

κB transcription factor has been implicated in IL-17R signaling before, the link between IL-17R and mitogen-activated protein kinase (MAPKs) and NF-κB activation has recently been elucidated. MAP kinases, especially p38 and extracellular signal regulated kinases (ERKs), are involved as mediators in the IL-17A-induced release of CXC chemokines in human bronchial epithelial cells *in vitro* (46). Moreover, CXCL8 production in human synoviocytes is also dependent on the NF-κB pathway and the PI-3 kinase-Akt pathway (47). Traf6 scaffold protein has been known for some time to be required for IL-17R signaling, but there are no Traf6 binding sites in the cytoplasmic domain of IL-17RA. Analysis of computerized databases showed that members of the IL-17R family contain SEFIR domains, which share homology with the Toll-IL-1R domains (48). NF-κB activator 1 (Act1), which is a critical adaptive protein for both TNF family activating factor (BAFF) and CD40 signaling, contains SEFIR and Traf6 binding sites. Indeed, Act1 binds to the cytoplasmic domain of IL-17RA and is a critical functional adapter for IL-17RA signaling (49) and the development of experimentally induced autoimmune encephalomyelitis and dextran-sodium-sulfate-induced colitis. TNF-alpha significantly synergizes with IL-17A and IL-17F in inducing the production of G-CSF, CXCL1 and CXCL8 in the epithelium, which is independent of the alteration of IL-17RA expression by TNF-alpha. In addition, IL-17A can also increase the production of CXCL1 and G-CSF by stabilizing mRNAs encoding these proteins (50), and the dominant effect of IL-17 is to stabilize mRNA for these molecules, rather than to alter transcription. Moreover, this effect is independent of TNF-α (51). Many elements about the IL-17 ligand and receptor signaling now come together; however, the precise mechanism of IL-17 synergy with TNF-α and IL-22 remains to be determined (52,53).

Another interleukin synthesized by Th17 cells is IL-21, an interleukin that performs critical functions in the development of Th17 cells. IL-21R is expressed on T cells, B cells, NK cells, dendritic cells (DC), macrophages and epithelial cells, indicating a wide range of actions for IL-21 (54,55,56). IL-21 is indispensable in regulating various immune responses. Both Th1 cytokine IFN-γ and Th2 cytokine IL-4 have important functions in promoting their own expression by Th1 and Th2 cells, respectively. Similarly, IL-21 functions in an autocrine loop to amplify the Th17 cell response and induce its own expression (57,58,59). IL-21, like IL-6, can promote the generation of Th17 cells over Treg cells. For both IL-21 and IL-6, this exchange appears to be mediated by STAT3 and RORγt. In addition, IL-21 has a number of more complex functions, beyond the regulation of Th17 cells. IL-21 can promote both humoral responses and cellular immunity, which are traditionally considered to be mediated by Th2 cytokines, such as IL-4, and Th1 cytokines, such as IFN-γ, respectively. First, IL-21 plays a critical role in B cell function. Second, IL-21 can also increase cellular immunity by promoting the functions of Th1 cells, CD8 + cells, and NK cells. IL-21 stimulates the production of IFN-γ in both Th1 and NK cells (60,61). Moreover, IL-21 synergizes with IL-15 in regulating the proliferation and activation of both naive and memory CD8 + T cells, and IL-21 also modulates the functional development of NK cells. In essence, IL-21 has clearly pleiotropic functions on various immune cells. However, its role on non-immune cells cannot be ignored. Recent studies have shown that IL-21 derived from T cells can act on intestinal fibroblasts and epithelial cells to synthesize matrix metalloproteinases (MMPs), which then mediate mucosal degradation (62).

IL-22 expression is also increased in many other autoimmune diseases. Interleukin 22 (IL-22) is also synthesized via Th17 cells. Increased serum IL-22 levels are present in both Crohn's disease (BC) and ulcerative colitis (63). In Crohn's disease, serum IL-22 correlates with disease activity.

IL-22 induces the synthesis of proinflammatory cytokines, as well as the proliferation and migration of several intestinal epithelial cell lines (63, 64). Elevated levels of IL-22 are also detected in the synovial tissues of patients with arthritis rheumatoid arthritis (RA), and IL-22 promotes the proliferation and production of chemokines by synovial fibroblasts (65). In addition to its proinflammatory role, IL-22 also induces tissue recovery and tissue wound healing responses, which suggests that it could prevent tissue damage in certain inflammatory conditions. This postulate was supported by studies conducted in the ConA-induced hepatitis model. IL-22 is substantially increased after ConA injection. IL-22 protects liver damage by improving the growth and survival of hepatocytes (66). In conclusion, IL-22 can exert both pathogenic and protective functions in autoimmune diseases, depending on the specific situations and target cells.

Th17 cells and their effector cytokines have both a pathological and protective role during inflammation. The balance of these functions is not well understood during the processes of many autoimmune and infectious diseases. The answers to these questions are important for the development of future therapeutic strategies for the treatment of various autoimmune and infectious diseases. Therapies that modulate the Th17 cell pathway for the treatment of autoimmune diseases are currently being tested in the clinic. For example, a p40 antibody has been tested in psoriasis and inflammatory bowel disease, as well as an IL-6R antibody in rheumatoid arthritis. Th17 cell effector cytokines, such as IL-17, IL-21 and IL-22, are potential future therapeutic targets. A challenge is to discover the balance between their beneficial and pathological roles, given the complicated functions of these cytokines in inflammation.

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