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Nature and functions of autoantibodies

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SUMMARY

Antibodies that react with self-molecules occur in healthy individuals and are referred to as natural antibodies or autoantibodies. Natural autoantibodies are mainly IgM, are encoded by unmutated V(D)J genes and display a moderate affinity for self-antigens. They provide a first line of defense against infections, probably serve housekeeping functions and contribute to the homeostasis of the immune system. By contrast, high-affinity, somatically mutated IgG autoantibodies reflect a pathologic process whereby homeostatic pathways related to cell clearance, antigen-receptor signaling or cell effector functions are disturbed. In some autoimmune disorders, autoantibodies might be present before disease onset, show remarkable specificity and serve as biomarkers providing an opportunity for diagnosis and therapeutic intervention. In organ-specific autoimmune diseases, such as myasthenia gravis or pemphigus, autoantibodies directly bind to and injure target organs. In systemic autoimmune diseases, autoantibodies react with free molecules, such as phospholipids, as well as cell surface and nucleoprotein antigens, forming pathogenic antigen–antibody (immune) complexes. These autoantibodies injure tissues and organs through engagement of FcγR activation of complement as well as internalization and activation of Toll-like receptors. Activation of intracellular Toll-like receptors in plasmacytoid dendritic cells leads to the production of type I interferon, whereas engagement of intracellular Toll-like receptors on antigen-presenting cells stimulates cell activation and the production of other inflammatory cytokines. Thus, immune complexes might perpetuate a positive feedback loop amplifying inflammatory responses.

Keywords

apoptosis; autoantibody; class switching; interferon; somatic hypermutation

INTRODUCTION

Autoantibodies are antibodies that react with self-antigens. These antigens may be found in all cell types (e.g. chromatin, centromeres) or be highly specific for a specific cell type in one

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REVIEW CRITERIA
Published articles for inclusion in this Review were identified using PubMed from the extensive records of papers on organ-specific and systemic autoimmune diseases. The terms included in the search were “autoantibody”, “natural autoantibody”, “somatic hypermutation”, and “class switching”. All papers identified were English-language full text papers. The reference lists of identified articles were also searched manually for further papers.

Competing interests
The authors have declared no competing interests.

organ of the body (e.g. thyroglobulin in cells of the thyroid gland). They may comprise proteins, nucleic acids, carbohydrates, lipids or various combinations of these. In systemic lupus and related systemic auto-immune disorders, the dominant antigens are ribonucleoproteins (RNPs) or deoxyribonucleoproteins, for reasons that will be described later in this article. Many autoantibodies are useful biomarkers of disease. They can also inform us about basic mechanisms of loss of tolerance and inflammation in patients with autoimmune disorders.

Despite the physiological elimination (negative selection) or functional inactivation (anergy) of high-affinity, self-reactive T and B lymphocytes in the thymus and bone marrow, respectively, there is compelling evidence that low-affinity, potentially autoreactive cells persist and that low-affinity reactivity to self-antigens is required for survival of T and probably B lymphocytes in the peripheral immune system. Unsurprisingly, therefore, IgM and, occasionally, low titer IgG autoantibodies, for example rheumatoid factors (RFs), antibodies to single-stranded (ss)DNA and antinuclear antibodies, are detected in healthy individuals. As will be discussed later in this Review, the properties of these low-affinity, mainly unmutated IgM, autoantibodies differ fundamentally from those of high-affinity, somatically mutated IgG auto-antibodies in disease states, referred to in this Review as pathogenic autoantibodies. Here, we will discuss how these pathogenic autoantibodies occur, what accounts for their specificity, how they cause disease and whether they have value as biomarkers of specific diseases.

STIMULI FOR THE GENERATION OF AUTOANTIBODIES

The presence of autoantibodies highly specific for target organs in organ-specific autoimmune diseases, such as thyroiditis, type 1 diabetes mellitus and primary biliary cirrhosis, strongly suggest that autoantibodies are stimulated by inflammation in the target organ, although cross-reactivity with microbial antigens (molecular mimicry) cannot be excluded. Post-translationally modified self-antigens seemingly elicit autoantibodies that are highly specific and have prognostic value. In systemic auto-immune diseases, such as systemic lupus, the origin of autoantibodies is less clear because the antibodies are non-cell-type-specific and affect multiple target organs. As discussed later, genetic models indicate that autoantibodies to intracellular antigens can be stimulated by excessive antigenic drive from antigens released from dying cells as well as by enhanced responses associated with intrinsic abnormalities in B or T lymphocytes.

GENERATION OF PATHOGENIC AUTOANTIBODIES

Natural autoantibodies

Antibodies that bind to a variety of exogenous antigens, such as those on bacteria, viruses, and fungi, as well as self-antigens (e.g., nucleic acids, phospholipids, erythrocytes, serum proteins, cellular components, insulin or thyroglobulin) account for a significant proportion of immunoglobulins in healthy individuals.[1] Because they arise independently of known and/or deliberate immunization, they have been termed natural antibodies or autoantibodies. Because of their broad reactivity for a wide variety of microbial components, natural antibodies have a major role in the primary line of defense against infections.[2–5] Since they also recognize a variety of self-antigens, they have a role in the development of the B-cell repertoire and the homeostasis of the immune system.[6]

Most natural autoantibodies are IgM and polyreactive, that is, they bind to several unrelated antigens, generally with moderate intrinsic affinity, although natural mono-reactive antibodies also exist.[1,7,8] In spite of the low-to-moderate intrinsic affinity of their antigen-binding sites, owing to their decavalency natural IgM antibodies possess a high overall binding avidity, a feature that makes these antibodies particularly effective in binding antigens with a repetitive structure on the surface of cells, tissues, bacteria and viruses (Box 1). Natural autoantibodies

are produced mainly by ($CD5^+$) B-1 cells,[9] the predominant lymphocytes in the neonatal B-cell repertoire, and marginal zone B cells.[10–12] B-1 cells are highly effective in presenting antigen[13] and can have an important role in the production of pathogenic auto-antibodies in several autoimmune diseases, including rheumatoid arthritis, Sjögren's syndrome, primary antiphospholipid syndrome and systemic lupus.[14–18]

Somatic selection leads to high-affinity and class-switched autoantibodies

Selection of unmutated natural autoantibody templates through somatic hypermutation and class switching can result in the emergence of pathogenic autoantibodies. Somatic hypermutation inserts mainly point mutations in the genes of antibody variable regions, thereby providing the structural substrate for selection by antigen of higher affinity mutants and affinity maturation. Class switching substitutes the immunoglobulin constant region by recombination of upstream and downstream switch region DNA, thereby endowing an antibody with new and diverse biological effector functions. Polyreactive and monoreactive natural IgM antibodies and autoantibodies are encoded mainly by unmutated or minimally mutated recombined V(D)J gene sequences.[7,19] Owing to their ability to bind to self-antigens, unmutated natural IgM autoantibodies can mediate innate autoimmune responses and provide the 'templates' for the emergence of the high-affinity, somatically mutated and class-switched IgG and/or IgA autoantibodies characteristic of autoimmune conditions, particularly those associated with the expansion of B-1 cells.[3,20–23] Indeed, structure–function analysis of somatically mutated anti-DNA, anti-insulin and anti-IgG (RF) autoantibodies from patients with systemic lupus, type 1 diabetes and rheumatoid arthritis, respectively, have indicated that these pathogenic high-affinity autoantibodies emerge through a process of somatic hypermutation, class-switch DNA recombination and antigen-driven clonal selection.[24–30] This finding suggests that, at least in humans, B-1 precursors of natural antibody-producing lymphocytes possess, like B-2 cells, functional hypermutation and class-switch DNA recombination machineries,[1,7,8,16,19,25,27,28,31–35] including the expression of activation-induced cytidine deaminase (AID).[36,37] AID deaminates cytidines in immunoglobulin V(D)J and switch-region DNA, thereby initiating a cascade of events that lead to the generation of ssDNA nicks, gaps or double-strand breaks. Repair of these lesions by the B-cell DNA repair machinery, involving error-prone translesion DNA polymerases results in insertions of point mutations or resolution of double-strand breaks, and hence, class-switch DNA recombination.[37,38]

Although natural autoantibodies can, under appropriate conditions, provide the templates for the emergence of higher-affinity and class-switched pathogenic autoantibodies, their precise physiologic and pathogenic role remains to be defined.

Genetic abnormalities predisposing to autoantibody production

Production of pathogenic autoantibodies implies a substantial breach in tolerance to self-antigens. Genetic studies in humans have indicated that full-blown clinical autoimmune disease results from multiple genetic alterations that are likely to be influenced by environmental factors. Despite the polygenic nature of human auto-immune disorders, knockout and overexpression of single genes in mouse models have been particularly instructive in elucidating several key pathways that lead to autoimmunity associated with autoantibody production. We briefly highlight here spontaneous or induced genetic alterations in three general pathways that lead to systemic lupus or rheumatoid arthritis-like diseases in mice.

Abnormal survival of autoreactive lymphocytes

Alterations in molecules that promote the abnormal survival of autoreactive lymphocytes are well described. Examples of such alterations are mutations in Fas/CD95 that lead to the *lpr* phenotype in mice and autoimmune lymphoproliferative syndrome/Canale Smith syndrome in

humans,[39] overexpression of the B-cell stimulator BLyS (also known as BAFF) and overexpression of the antiapoptotic regulator Bcl-2.

Defective removal of apoptotic cells

Loss or deficiencies in the function of a number of proteins implicated in the removal of apoptotic cells have been reported to cause lupus-like diseases in mice. The proteins involved include receptors, such as Mer, as well as serum opsonins (e.g., natural IgM antibodies, C1q, serum amyloid P component [SAP] and milk fat globulin epithelial growth factor-8 [MFG-E8]), which coat dying cells.[40,41] The mechanisms involved differ. Mer deficiency results in macrophages receiving a proinflammatory rather than anti-inflammatory signal upon ingestion of apoptotic cells. Defective clearance of apoptotic cells in surface IgM, C1q, SAP and MFG-E8 knockout mice might predispose to lupus through slow clearance of apoptotic cells leading to postapoptotic necrosis and/or through lack of engagement with specific inhibitory receptors on the phagocyte. The sites at which defective apoptosis manifests differ; in C1q-deficient mice, apoptotic cells accumulate in the kidney, whereas in MFG-E8 knockout mice, apoptotic cells accumulate in germinal centers.

Breakdown in the regulation of B-cell or T-cell activation threshold

Genetic alterations have been reported in mice deficient in molecules that regulate the threshold of B-cell or T-cell activation, such as cbl-b, PD-1 and Zap-70 and the SLAM cluster in T cells, and Lyn and FcγRIIb in B cells. These genetic alterations lead to autoreactivity of lymphocytes in the peripheral immune system. In general, when lymphocytes are more easily activated, they are more likely to promote the production of auto-antibodies similar to the autoantibodies found in human systemic lupus. The predominance of lupus-type autoantibodies is probably explained by the exposure of immune cells to dying cells as part of normal cell turnover in the spleen and lymph nodes. Mutations in Zap-70, however, result in a disease very similar to human rheumatoid arthritis, including the production of RFs,[42] whereas expression of autoimmunity in PD-1-deficient mice differs, depending on the genetic background of the host: lupus in C57BL/6 and myocarditis in BALB/c mice.

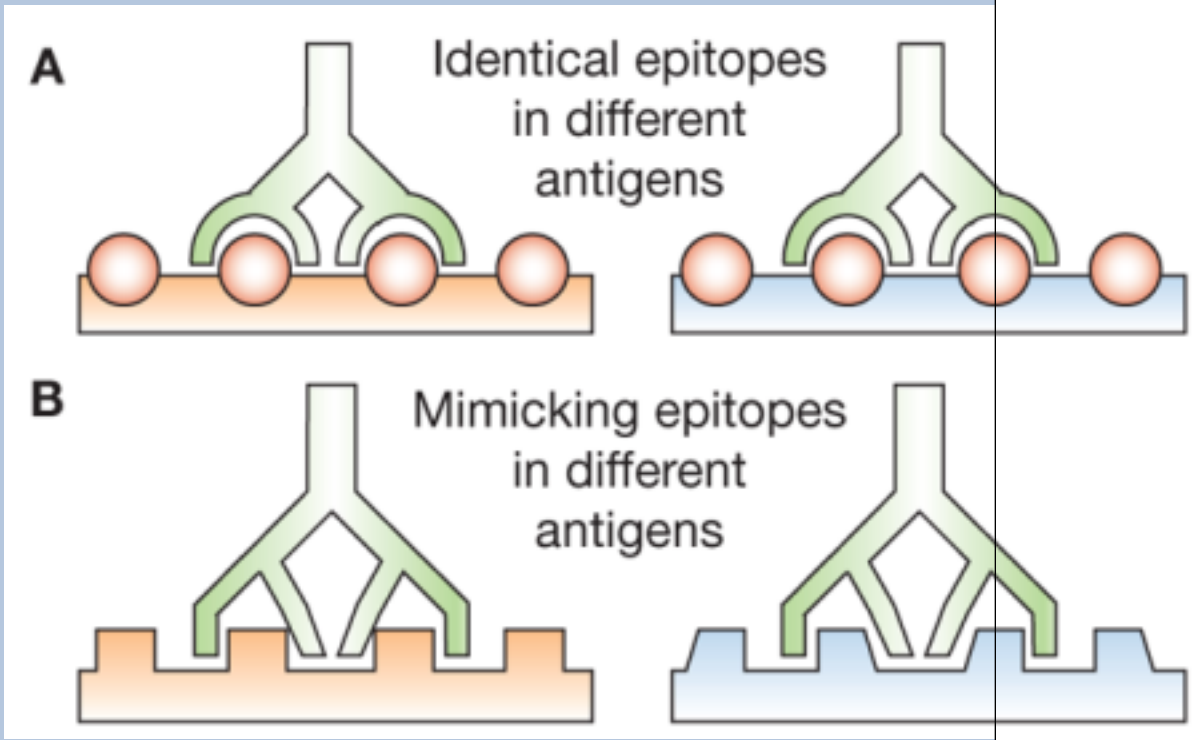
AUTOANTIBODY SPECIFICITY

Dying cells and cell debris serve as antigens

Apoptosis leads to the controlled activation of multiple intracellular nucleases and proteases, which, in turn, leads to the cleavage of numerous cellular molecules; one consequence of this autodigestion is the generation of ‘neoepitopes’. Some of these antigens undergo modification, including cleavage, phosphorylation and oxidation. Under normal conditions, these neoepitopes are also generated in the thymus and bone marrow, leading to tolerance. On the other hand, inflammatory changes in the peripheral immune system that might occur after exposure to ultraviolet light, oxidation or cleavage by granzyme B,[43] which is delivered by cytotoxic T cells, might qualitatively alter self-antigens released by dying cells and cause them to stimulate autoimmune responses. Autoantibodies to cyclic citrullinated peptides in rheumatoid arthritis (anti-CCP auto-antibodies) are an example of antibodies elicited by a neoepitope acquired secondary to inflammation.[44] Citrulline is formed by deamination of the amino acid arginine during inflammation/oxidative stress or apoptosis. Also, as discussed above, delayed clearance of dying cells leads to postapoptotic necrosis and release of several adjuvants that promote inflammation. Specific nucleoprotein antigens can become dominant in different systemic autoimmune disorders due to their abundance, stability, resistance to degradative enzymes and ability to stimulate Toll-like receptors, as discussed below.

Box 1 Antibody polyreactivity

Polyreactive natural monoclonal antibodies generated from healthy individuals bind to different antigens in a dose-saturable fashion and with different efficiencies.[18] Binding of these antibodies to a given antigen can be cross-inhibited by different antigens with variable efficiencies.[18] The ability of polyreactive natural antibodies to bind different antigens relies on two discrete types of antigen recognition, that is, recognition of (**A**) identical epitopes in the context of different antigens or (**B**) recognition of different epitopes in the context of different antigens.[15,18] Recognition of identical epitopes in the context of different antigens provides the correlate for classical immunological 'cross-reactivity'. It relies on structural features inherent to the antigens and it is at the basis of 'molecular mimicry'. Molecular mimicry can lead to autoimmune phenomena, such as those secondary to certain viral or bacterial infections.[60] However, recognition of identical epitopes in different antigenic contexts accounts for the observed polyreactivity of natural antibodies only in a few cases. Indeed, most natural polyreactive antibodies efficiently recognize antigens that are different in nature, such as proteins, nucleic acids, phospholipids and polysaccharides, and, therefore, are highly unlikely to share identical epitopes. This indicates that polyreactivity is a function of features inherent to the binding cleft of the antibody and not of structural features inherent to and shared by different antigens. The ability of anti-DNA autoantibodies to bind appropriately spaced phosphate residues in the context of a variety of polynucleotides and phospholipids exemplifies antibody reactivity for similar epitopes in the context of different antigens. As demonstrated by gene shuffling, recombination and targeted mutation experiments, the structural correlates for binding of different epitopes and antigens lie mainly in the complementarity-determining region 3 (CDR3) of the heavy chain of natural polyreactive autoantibodies.[5,19,27,28,33] The wide and mostly flat surface of CDR3 regions allows for the accommodation of ligands quite different in nature, but possessing some overall space-filling similarities.



Interferon-α and Toll-like receptors

Type I interferons (interferon-α and interferon-β) are potent activators of lymphocytes and antigen-presenting cells.[45] Patients with systemic lupus have increased levels of interferon in serum, but the reason was not always obvious. Serum from patients with systemic lupus or Sjögren's syndrome, when incubated with extracts of apoptotic or necrotic cells, stimulates the production of type I interferon, and this phenomenon is abrogated by exposure to nucleases. The molecular mechanisms that are responsible for interferon (and other cytokine) production have been clarified and possibly explain how autoantibodies against nucleoprotein antigens become self-perpetuating.[45] In brief, when anti-DNA autoantibodies that have bound to chromatin (which contains DNA) or those against Sm/RNP that have bound to Sm or RNP (which contain small nuclear RNAs) enter cells through the B-cell receptor or FcγR, the nucleic acid stimulates an intracellular Toll-like receptor (Figure 1), resulting in interferon production and immune activation. Although not yet proven, the presentation of peptides derived from the proteins stimulates T cells, probably accounting for the specificity of the immune response. These mechanisms, which have led to the so-called Toll hypothesis,[46,47] might apply to other systemic autoimmune diseases and could generate other cytokines as well.

HOW DO AUTOANTIBODIES CAUSE DISEASE?

Theoretically, autoantibodies might be neutral or have beneficial or harmful effects. For example, while autoantibodies to thyroglobulin might not make a critical contribution to thyroiditis, long-acting thyroid stimulators (i.e. autoantibodies to the TSH receptor) are responsible for thyrotoxicosis. Natural autoantibodies might be useful in the removal of cell debris during inflammation, and autoantibodies to inflammatory cytokines might protect against untoward inflammation.[48] In systemic auto-immune disorders, many autoantibodies seem to be directly injurious following deposition in tissue; they might also amplify inflammation and perpetuate autoantibody production by ferrying self-nucleoproteins into the cell and engaging Toll-like receptors, as discussed previously (Figure 1).

Some autoantibodies engage complement and/or FcγR effector pathways leading to inflammation. Antigen–antibody complexes are well known to cause vasculitis and glomerulonephritis.[49] Activation of complement has been consistently demonstrated in experimental models of immune-complex disease and in kidneys of patients with systemic lupus and lupus nephritis.[50] Other examples of autoantibody–complement-mediated injury include the passive transfer model of fetal loss associated with the antiphospholipid syndrome[51] and an unusual form of activation of the alternative complement pathway, induced by autoantibody administration into the transgenic K/BxN mouse as a model of rheumatoid arthritis.[52] Intriguingly, in the latter model, the alternative pathway of complement is activated by pathogenic auto-antibodies directed against the antigen glucose-6-phosphate isomerase. Complement activation predominantly causes inflammation by release of the anaphylotoxin C5a, resulting in attraction of neutrophils, and release of proteolytic enzymes and inflammatory cytokines.

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.[53] By contrast, mice with FcγRIIb knocked out spontaneously develop a lupus-like disease.[54] Antibodies of different isotypes have varying affinities for the four FcγRs. IgG_{2a} has higher affinity for FcγRIV, leading to inflammatory responses, whereas IgG_1 selectively engages FcγRIIb, inhibiting inflammatory responses.[55] It is likely that similar relationships will be found with human FcγRs and that the ability to protect from, or induce, inflammation will depend, in part, on the isotype of the autoantibody and FcγR engaged.

AUTOANTIBODIES IN DIAGNOSIS

Titers of some autoantibodies, such as RFs and those to ssDNA, are increased in infections and a variety of autoimmune disorders and are, therefore, of little help in the differential diagnosis of disease. By contrast, most of the autoantibodies found in systemic autoimmune diseases are not detected in chronic infections. A negative result for antinuclear antibody, when tested for by indirect immunofluorescence on HEp-2 cells, makes the diagnosis of systemic lupus or other systemic autoimmune disease unlikely, whereas a positive test with a titer greater than 1/160 strongly supports the diagnosis. Likewise, in contrast to the high sensitivity and low specificity of RFs for rheumatoid arthritis, the anti-CCP autoantibody generally has a sensitivity of 40–70%, but the specificity might be as high as 98%. About 90% of patients with undifferentiated arthritis and raised anti-CCP auto-antibody titers will develop rheumatoid arthritis within 3 years.[44]

Few autoantibodies can be used alone to diagnose an autoimmune disease, because individuals without overt clinical disease, particularly relatives of patients with autoimmune diseases, might have detectable titers. Furthermore, some autoantibodies, although highly specific, are present only in a minority of patients. For example, autoantibodies to Sm occur in only 3–30% of patients with systemic lupus. For these reasons, detection of autoantibodies is usually used to confirm a clinical diagnosis or to help to define a subset of patients within a diagnostic category.

For the majority of autoantibodies, variations in circulating titers have little prognostic value. Many biological variables, such as the class and subclass of the antibody, purity and homogeneity of the test autoantigen, epitope specificity of the antibody and variation between individuals in the effector phase of the inflammatory response, probably influence disease pathogenesis. Despite current limitations, some autoantibodies clearly have important clinical implications as early indicators of disease.[56] The presence of autoantibodies to Ro (SS-A) and La (SS-B) in pregnant women with or without a full-blown autoimmune disease conveys a substantially increased risk of the neonatal lupus syndrome.[57] Similarly, prospective studies of anticardiolipin autoantibodies in pregnant women have shown a significantly increased frequency of mid-trimester fetal loss in women with high levels of such autoantibodies. Measurement of certain autoantibodies is helpful in defining subsets of patients within a disease category. For example, patients with polymyositis and auto-antibodies to Jo-1 have a much higher frequency of lung interstitial fibrosis.[58] Various auto-antibodies, for example, to ribosomal P protein or NR2 glutamate receptor,[59] have been associated with central nervous system manifestations of systemic lupus. A cluster analysis approach has identified an association between various subsets of lupus patients and combinations of autoantibodies. Antigen arrays make multi-analyte and multivariate analysis of serum and other biological fluids possible. Thus, new opportunities to identify biomarkers for systemic lupus hold promise for more accurate diagnosis, assessment of disease activity and design of more specific therapies.

CONCLUSIONS

Autoantibodies with different qualities exist, and it is likely that low-affinity, but high-avidity polyreactive natural IgM autoantibodies have housekeeping roles. In general, high-affinity IgG autoantibodies that have undergone somatic hypermutation and class switching reflect a pathologic process. Far from being epiphenomena in systemic autoimmune diseases, these autoantibodies frequently cause tissue injury. This occurs not only by IgG Fc direct activation of effector pathways, but also by uptake and ingestion of immune complexes by cells, leading to activation of Toll-like receptor sensors of nucleic acids and release of inflammatory cytokines. The specificity of many auto-antibodies has great diagnostic utility and might also

have predictive value, such as with anti-CCP autoantibodies in rheumatoid arthritis. The specificity of autoantibodies in systemic auto-immunity also suggests an intimate relationship with disease pathogenesis—a story yet to unfold.

KEY POINTS

- Natural antibodies or autoantibodies, particularly IgM, that react with self-molecules occur in normal individuals and display a moderate affinity but high avidity for self-antigens
- High-affinity, somatically mutated, class-switched IgG autoantibodies reflect a pathologic process in which homeostatic pathways related to cell clearance, antigen-receptor signaling or cell effector functions are disturbed
- The mechanisms involved in immune- complex-mediated tissue injury include engagement of FcγRs and activation of complement, as well as internalization and activation of Toll-like receptors
- Autoantibodies might be detectable long before disease onset and serve as biomarkers enabling diagnosis and targeting of therapeutic intervention
- In organ-specific autoimmune diseases, autoantibodies directly injure target organs; in systemic autoimmune diseases, they can also bind to different self-molecules and cause disease through the formation of immune complexes
- Research is needed to clarify why certain antigens are targeted in different autoimmune diseases and how some antibodies activate, whereas others inhibit, immune responses

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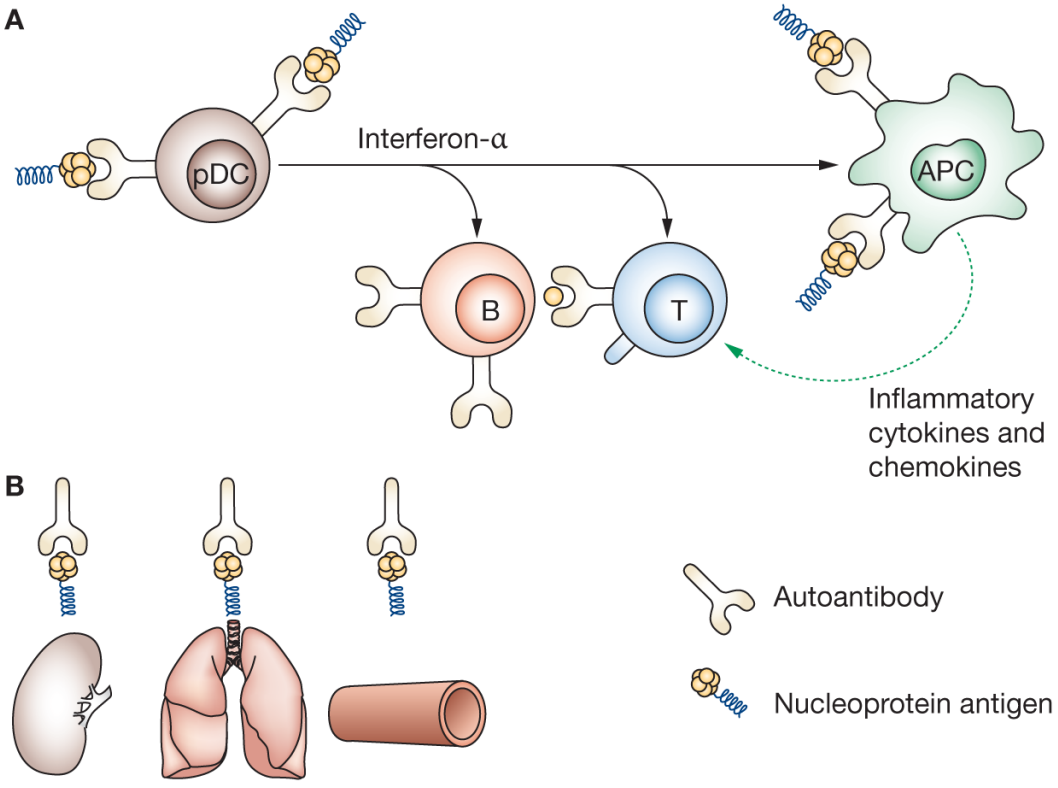

Figure 1.

Pathogenic autoantibodies cause inflammation and tissue injury. (**A**) Autoantibodies produced by B lymphocytes bind to self-antigens released by apoptotic or necrotic cells, forming antigen–antibody (immune) complexes. When antigens in the immune complexes contain nucleic acids and are endocytosed by pDCs, Toll-like receptors are activated and the pDCs secrete interferon-α. This cytokine activates B and T lymphocytes as well as APCs such as macrophages and dendritic cells. In addition, the immune complexes might be phagocytosed by APCs resulting in the release of other inflammatory cytokines (tumor necrosis factor-α, interleukin-6) and chemokines. (**B**) Immune complexes deposit in the vessels as well as the kidneys and lungs. The immune complexes activate inflammatory pathways through interaction with FcγRs and complement. Abbreviations: APC, antigen-presenting cell; pDC, plasmacytoid dendritic cell.