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The role of infections in the development of autoimmune disease

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Abstract

Since the discovery of immunological tolerance, the role of genetic and environmental factors in the development of autoimmune diseases has been actively discussed. One such factor is an infection. Microorganisms are considered to be triggers of autoimmune diseases, but their role in disease development is not completely understood. Animal experiments conclusively demonstrate the effects of microorganisms and their antigens on autoimmune pathology. However, results of clinical studies performed on patients with autoimmune pathologies are rarely informative and often contradictory, because the pre-existing disease can mask the association between causative pathogens and autoimmune pathology, thus, making the interpretation of results difficult. This review summarizes key hypotheses, including hidden or cryptic antigens, antigen modification, presence of superantigens, epitope spectrum extension, molecular mimicry, adjuvant and non-specific effect, antigen complementarity, and idiotypic–anti-idiotypic interactions that have been proposed to explain the mechanism of autoimmune disease development due to infections. Additionally, the advantages and disadvantages of these hypotheses and their comparisons are discussed. In most cases, facts proving one hypothesis can be reconsidered in the favor of another one. A number of the early hypotheses need to be reviewed taking into account the modern understanding of innate and adaptive immunity. As additional data on the relationship between infection and autoimmunity is collected, new hypotheses can be developed integrating main claims of previous hypotheses and add new ones.

Keywords: infection, autoimmunity, autoimmune diseases, pathogenesis.

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At the core of the pathogenesis of autoimmune diseases are two triggers–the breakdown of immunological tolerance and the development of an immune response to intrinsic antigens. According to the clonal selection theory proposed by F. M. Burnet in 1957, in the process of ontogenesis, those clones of lymphocytes die, which carry an antigen-recognizing receptor capable of binding to autoimmune antigens (negative selection). It was later supplemented with hypotheses for the blockade of auto-reactive clones with the help of various mechanisms, as a result of which they almost completely lose the ability to activate, but produce a small number of autoantibodies [1]. Normally, the number of such cells is small and does not affect the body adversely; however, if under certain conditions the clone starts to multiply, an autoimmune disease develops [2].

It is believed that auto-reactivity is part of the normal physiological process of the body to maintain homeostasis. Autoantibodies are involved in the processes of apoptosis, regeneration, and elimination of cellular debris that occur after natural cell death or damage [3]. The fact that autoantibodies are present in small quantities in many healthy individuals indicates that their mere presence is not a sign of pathology. However, in genetically predisposed individuals, autoantibodies can lead to the onset of an autoimmune disease [4].

In addition to genetic factors, environmental factors, such as microorganisms and persistent organic pollutants are now believed to play a significant role in the development of autoimmune pathology [2, 5]. The relationship between infection and autoimmunity is actively discussed [6–9], especially for pathogens, such as hepatitis B and C viruses [10, 11], herpesviruses [12, 13], Coxsackie B viruses [14–16], and *Streptococcus pyogenes* [17, 18]. Additionally, pathogens, including human immunodeficiency virus [19] and *Helicobacter pylori* can also induce an autoimmune pathology [20].

The role of opportunistic pathogens in autoimmune disease development has been studied in detail [21]. Recent epidemiological studies investigated the relationship between infectious diseases and 29 autoimmune diseases over a period of 25 years [22]. It is believed that microorganisms either trigger the autoimmune response or enhance the pre-existing sub-threshold to a full-blown response [6–9, 23]. However, there is no consensus on how the

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infectious process leads to an autoimmune disease. Some of the well-known hypotheses are presented below.

Hidden or cryptic antigens: This is one of the oldest hypotheses. According to this hypothesis, during embryogenesis, a number of intrinsic antigens, such as those of the immunologically privileged organs, including thyroid follicles, testes, eyes, and brain are "sequestered" or "invisible" to lymphocytes for their selection in the thymus. As a result, potentially auto-reactive lymphocyte clones escape from being removed or inactivated [2]. Although the heart is not classified as an immunologically privileged organ, intracellular proteins, such as cardiac myosin, actin, and troponin are also "invisible" to the immune system [23]. Cell lysis or extracellular tissue damage due to microbial proteases results in the destruction of histochemical barriers, and the release of hidden antigens, which activates the corresponding auto-reactive clone, eventually resulting in autoimmune disease.

However, it remains unexplained why tissue damage leads to the production of autoantibodies in some cases and not in others, and why the association between the presence of autoantibodies and the development of autoimmune pathology is inconsistent. How does the autoantigen present itself in the immune system, what is the direct involvement of the pathogen in this process, and why autoimmune disease occurs only in a small percentage of infected people are some of the unanswered questions.

Epitope spread is considered as a component of a physiological response of the immune system to infection. Upon the first contact with the microorganism, a dominant antigen (epitope) is recognized by the immune system generating a specific T and B cell response. Upon the next contact, a second dominant epitope is recognized. With each subsequent contact with the same pathogen, newer epitopes are recognized, thus, expanding the spectrum of T-lymphocytes and antibodies.

This mechanism strengthens the adaptive immune response, allowing it to target the pathogen using different antibodies in the event that one of the antigens on the pathogen cell surface undergoes a mutation. However, the presence of a greater number of antibodies increases the risk of potential cross-reactivity of one of these antibodies to intrinsic or self-antigens, resulting in an autoimmune disease. This is especially true for persistent infections accompanied by prolonged tissue damage and release of self-antigens, which leads to the development of an immune response against a large number of intrinsic epitopes. Over time, either new epitopes of the same protein or other proteins are involved in the process [24].

This hypothesis is confirmed by a number of experimental models [25, 26]. Clinical manifestations of autoimmune diseases usually arise only when several kinds of autoantibodies are generated against the target organ.

Modification of antigens: By contrast to the previous hypotheses, the modified antigen theory proposes that pathogens can modify their own antigens to resemble autoantigens, causing the immune system to perceive itself as an alien. This induces the production of antibodies and cytotoxic lymphocytes that target both modified as well as true autoantigens, potentially resulting in autoimmune disease [27].

Recently, microorganisms have been shown to cause epigenomic changes in the host. For example, pathogenic bacteria can disrupt the methylation pattern of the host *Toll-like receptor 4* (*TLR4*) [28]. The consequence of DNA hypomethylation is an increase in the expression of many genes, including those encoding pro-inflammatory cytokines, growth factors of T cells, and adhesion molecules, which can facilitate the transformation of normal antigen-specific T-lymphocytes into auto-reactive cytotoxic cells. DNA methylation is highly reduced in CD^{4+} lymphocytes in rheumatoid arthritis and systemic lupus erythematosus patients [29, 30].

Molecular mimicry: In the 1960s, K. Damian suggested that microorganisms could escape immunological surveillance, as their cell surface proteins (antigens) are similar in structure to those of the host cells. It was later discovered that when the microorganisms mimic the host cellular proteins sufficiently, the antibodies and T-lymphocytes cross-react with the host cells, causing tissue damage, triggering an autoimmune response. Thus, a hypothesis was formulated that the presence of cross-reactivity between the microbial antigens and intrinsic antigens leads to a breakdown of immunological tolerance and induce an autoimmune disease [31].

The basis of this phenomenon is the presence of the T-cell antigen-recognizing receptor (TCRR) capable of recognizing both self and microbial epitopes [32]. Once the antigen-presenting cell (APC) presents the pathogen-like epitopes to the T-lymphocyte, an immune response develops, which results in damage to intrinsic tissues either directly via cell lysis or indirectly through the activation of tissue mac-

rophages by cytokines and chemokines. The intrinsic antigens released in it become available for the APCs, which present it to the cross-reacting T-lymphocytes. This supports an active immune response even after elimination of the pathogen and becomes the basis for the development of autoimmune pathology.

Subsequently, the mechanism of cross-reactivity started to be associated with the presence of T-lymphocytes that express two types of TCRRs, one of which recognizes microbial antigen while the other recognizes intrinsic antigen. Because the T-lymphocyte carrying the intrinsic antigen-specific TCRR has a low distribution density, it avoids negative selection. When the T-lymphocyte carrying the microbial antigen-specific TCRR interacts with the pathogen, its clonal expansion occurs, which is inevitably accompanied by activation of the auto-reactive receptor causing autoimmune disease [33].

Despite a vast number of experimental and clinical studies confirming the role of molecular mimicry in the development of autoimmune disease, this hypothesis has received severe criticism in recent decades [34, 35]. Although homology between amino acid sequences of pathogen epitopes and self-epitopes was considered as the basis of mimicry, protein conformation, which significantly affects protein function, was not considered. In addition, the phenomenon of molecular mimicry is much more common than autoimmune diseases. Moreover, animal models reveal that purified autoantigens mimicking pathogenic antigens cause autoimmune pathology only when administered together with inactivated pathogens or their toxins, such as Freund's adjuvant [31]. Thus, molecular mimicry does not support the development of autoimmune disease.

Anti-idiotype hypothesis: In 1974, N.K. Erne formulated the idiotype—anti-idiotypic interaction hypothesis, according to which, immunoglobulins and their receptors have determinants possessing antigenic properties, referred to as an "idiotype." Some lymphocytes are able to recognize idiotypic determinants and induce the synthesis of anti-idiotypic antibodies. As such, antibodies that cross-react to intrinsic immunoglobulins are found in the blood serum of both healthy and diseased individuals. The anti-idiotypic response develops simultaneously with a regular immune response against the antigen and plays an important role in its regulation, i.e., the stimulation or inhibition of antibody biosynthesis in a feedback loop [2].

One of the mechanisms used by microorganisms, especially viruses, to enter the host cell is by binding to its membrane receptor. Therefore, antibodies directed against the viral ligand that binds the host cell receptor also bind the host cell receptor to function as anti-idiotypic autoantibodies. Thus, anti-idiotypic autoantibodies target the pathogen, as well as the intrinsic cells and tissues that the pathogen attacks, resulting in an autoimmune disease. For example, antibodies to Coxsackie virus B3 act as idiotypic antibodies to actin while recognizing antibodies to cardio myosin as anti-idiotypic [36].

However, this hypothesis does not answer a number of questions. For most autoimmune diseases, a specific cellular receptor that serves as a target for anti-idiotypic antibodies has not been defined. It is unclear why different autoantibodies are produced in autoimmune diseases when the virus binds to only one type of a cellular receptor. Moreover, an experimental model of autoimmune myocarditis demonstrated that anti-idiotypic antibodies suppress inflammatory response, which is inconsistent with this hypothesis [37].

Presence of superantigens: In the classical development of immune response, an antigen is recognized by the APC, processed, and presented to the $CD4^+$ lymphocyte (T-helper) as a peptide together with the class II histocompatibility complex. This complex then binds to the TCRR, which activates the T-helper resulting in an adaptive immune response. Microorganisms usually possess superantigens that immediately activate a large number of T- and B-lymphocytes, irrespective of their antigen specificity. In this case, however, such an antigen is not absorbed by the APC, and instead binds non-specifically to the variable part of the TCRR β-chain outside its antigen-binding site. This cross-links molecules of the main histocompatibility complex represented on the APC membrane and the TCRR [38], leading to the development of autoimmune disease in one of several possible ways [39]:

(1) Direct activation of pre-existing auto-reactive T-lymphocytes;

(2) Activation of auto-reactive B-lymphocytes due to direct stimulation of the antigen recognizing the immunoglobulin receptor, followed by polyclonal activation and synthesis of autoantibodies; or

(3) Activation of macrophages with subsequent production of pro-inflammatory cytokines, superoxide anions, and other mediators of inflammation.

The role of superantigens in the pathogenesis of systemic lupus erythematosus [40] and pemphigus [41] has been described.

Adjuvant or non-specific (bystander) effect: According to this hypothesis, microorganisms activate the receptors of innate immunity cells and/or induce the formation of pro-inflammatory cytokines and T-cell growth factors, which in turn activate and expand the pre-existing auto-reactive lymphocyte clones, resulting in autoimmune disease [42]. This hypothesis partly resonates with the hypothesis of hidden or cryptic antigens. Both these hypotheses suggest that tissue damage and cell death, which inevitably occur during an inflammatory response to a pathogen result in the release of intrinsic antigens, thus, making them available for the immune cells, including the auto-reactive cells. However, the development of a pathological reaction to the intrinsic antigen depends on a second signal, which can arise due to non-specific activation of the APC in an inflammatory reaction. Thus, all cellular and humoral factors associated with a local inflammatory response to a pathogen promote the development of autoimmune reactions similar to the domino effect. This mechanism is most often associated with persistent viral infections, especially the human herpes virus type 4 [43].

This hypothesis explains the need for the introduction of adjuvants in experimental models of autoimmune diseases. Adjuvants, such as pertussin, stimulate TLR4, and inflammasomes [44], which in turn activate Th1 and Th17 lymphocytes that are highly important for the development of autoimmune pathology [45]. Perhaps the simultaneous activation of receptors of innate immunity and self-antigens by microorganisms induces a synergistic effect, leading to the breakdown of immunological tolerance and, consequently, the development of autoimmune pathology.

Antigenic complementarity: This hypothesis combines the main provisions of the hypotheses of molecular mimicry and idiotype–anti-idiotypic interactions. According to this hypothesis, a specific combination of microbial peptides triggers an autoimmune disease, if at least one of the peptides is similar to the intrinsic antigens. In response to the formation of primary antibodies directed against the peptides, anti-idiotypic antibodies are produced. As a result, the immune system ceases to distinguish between "intrinsic" and "foreign," resulting in the production of autoantibodies and development of autoimmune pathology [46].

This hypothesis, unlike the previous one, explains the adjuvant effect not by the action of non-specific inflammatory factors, but by the molecular complementarity between the antigen and the adjuvant. In the antigen–adjuvant pair, both molecules act as adjuvants to one another, which enhance the immune response for each component. Such hyperactivation leads to a complex deregulation of immune interactions, resulting in autoimmune disease. If the adjuvant is not complementary to the antigen, autoimmune disease does not develop, despite the development of an immune response.

Conclusion

None of the current hypotheses provides a comprehensive analysis for the etiopathogenesis of autoimmune disorders, and the role of infection in their development. Numerous experimental and clinical studies, and mathematical modeling, demonstrate that each hypothesis is at least partially viable. However, in most cases, data supporting one of the hypotheses can be revised in favor of the other. Although all hypotheses recognize the role of microorganisms as a trigger in the development of autoimmune pathology, the interaction between infection and target tissue is interpreted differently.

Some of the hypotheses (hidden antigens, bystander effect, and expansion of the spectrum of epitopes) focus on changes in the immune response due to microorganism-induced inflammation, while other hypotheses (molecular mimicry and antigenic complementarity) emphasize the antigen specificity of the pathogen and the host. The antigenic complementarity hypothesis recognizes the importance of a second, either non-specific or specific signal for the establishment of autoimmune disease.

Although many early hypotheses emphasize the role of adaptive immunity in disease development, the evidence supporting the fundamental role of innate immunity in the development of an adaptive immune response is unquestionable. Thus, these hypotheses need to be revised. With new data accumulating on the relationship between infection and autoimmunity, we can expect the emergence of new hypotheses that modify the basic postulates of the previous ones based on new data.

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