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A conceptual model of the role of infectious agents in autoimmune diseases

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Abstract

The correlation between microbes and autoimmunity is well established, but many underlying mechanisms remain obscure. Thus, this paper attempts to elucidate the role of infectious agents (bacteria, viruses, etc.) in autoimmune diseases. To offer a concise framework for many relevant research findings, the following general conceptual model is proposed and discussed: autoimmune diseases arise from alterations in cells, tissues, or organs, caused by infectious agents. These alterations evolve with time, beginning as subtle, often undetectable changes. As the alterations become more severe, they can be identified by the immune system, which may subsequently attack the infected cells. This process allows for new explanations of relationships between triggers of autoimmunity and infectious agents, the time lag between infection and autoimmune response, the progressive nature of autoimmune diseases, and the role of virus persistence. It can also offer a new point of view on molecular mimicry and epitope spreading. The roles of genetic predisposition, sex, stress, dietary habits, the "hygiene hypothesis," and the healing effects of β-interferon also fit into this framework. In addition, the side effects of malignancy treatments using immune checkpoint inhibitors can also be explained. Adhering to the framework, it is concluded that treatments should aim to eliminate the cause of these evolving alterations, namely, the infectious agents. Presumably, they could be based on antibiotics and antiviral drugs. Future research directions are suggested for evaluating the proposed conceptual model.

Keywords: Autoimmune diseases; Infectious agents; Molecular mimicry; Epitope spreading; Hygiene hypothesis; Virus persistence; Immune checkpoint inhibitors; Resilience

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1. Introduction

Autoimmune diseases tend to evolve into a scourge, particularly in developed countries. At present, 80 – 120 diseases have been identified as autoimmune,[1] depending on the classification criteria.[2] A common feature of autoimmune diseases is the immune system's aberrant attack on the body's own cells, tissues, or organs, treating them as foreign. Despite this shared characteristic, different triggers and evolution courses have been identified, as described by Theofilopoulos *et al.*[3]

At a fundamental level, autoimmune diseases have been linked to various dysfunctions of the immune system, such as impaired tolerance,[4-6] hormonal dysregulation,[7] or

misdirection by infectious agents (bacteria, viruses, etc.), often in conjunction with environmental factors. Current mainstream treatments aimed at relieving symptoms are mainly based on immunosuppressive or immunomodulatory drugs.[8] Despite these advances, the precise mechanism and etiology of autoimmune diseases remain unclear.[9]

This paper is focused on the mechanism that underlies the autoimmune response. A general conceptual model and evidence supporting its plausibility are outlined and discussed. Moreover, several new explanations of autoimmune response features that can be derived from the model are presented and briefly discussed. Finally, research directions aimed at the development of new treatments for autoimmune diseases are proposed.

2. The proposed conceptual model

An outline of the proposed mechanism of autoimmune response is as follows: autoimmune diseases are due to alterations of the cells, tissues, or organs that are subsequently attacked by the immune system. These alterations are caused by infectious agents (bacteria, viruses, etc.) and evolve with time. Initially, they are small and often undetectable by the immune system. However, when they exceed a certain threshold, the affected cells are targeted and subsequently attacked by the immune system. It can be hypothesized that the targeted cells have a recognizable "imprint" of the pathogen. Autoimmune disease symptoms typically emerge when cumulative cell damage leads to detectable dysfunction, the nature of which depends on the specific disease. This time-dependent process is schematically presented in Figures 1 and 2, both of which depict time on the x-axis.

In Figure 1, the alteration degree is shown on the y-axis, the dark blue line represents the evolution of cell alteration with time, and the broken red line indicates the alteration's detection threshold. Similarly, in Figure 2, the cumulative tissue damage is shown on the y-axis, the dark blue line represents the evolution of damage with time, and the broken red line marks the onset of autoimmune disease symptoms.

2.1. Previous research correlating autoimmune diseases with infectious agents

The proposed model aligns with observations of many researchers, who have correlated autoimmune diseases with infectious agents, such as bacteria or viruses.[10-12] For example, Coxsackie enterovirus has been associated with type 1 diabetes[13] and Epstein–Barr virus with Guillain–Barré syndrome, multiple sclerosis, systemic lupus erythematosus (SLE), rheumatoid arthritis, and

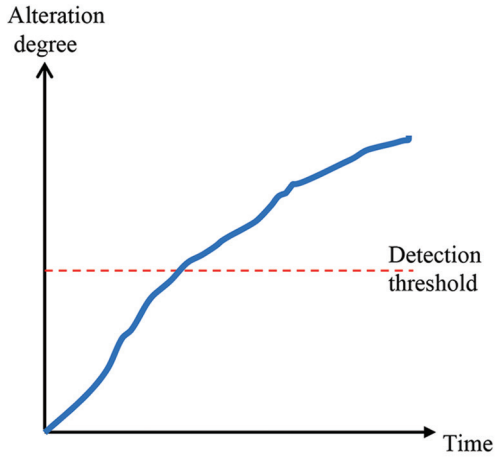

Figure 1. Evolution of cell alteration with time

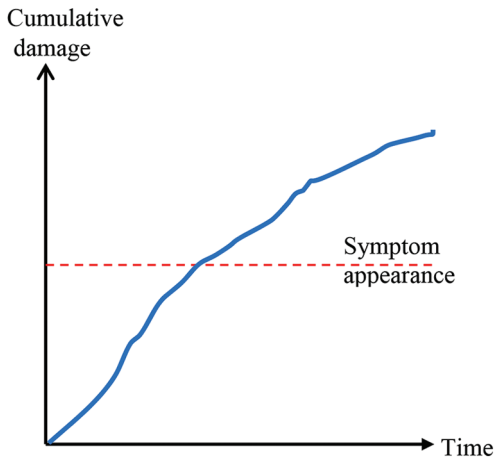

Figure 2. Evolution of cumulative tissue damage with time

other autoimmune diseases.[14] The severe acute respiratory syndrome coronavirus 2 virus has recently been considered a triggering factor of autoimmune diseases.[15] Moreover, vaccines have also been suspected of triggering such diseases.[16-18]

Regarding correlation with bacteria, a prominent, undisputable example is Sydenham chorea.[19] The attack of immune cells on the basal ganglia is triggered by infection with hemolytic streptococci. When diagnosed early, this disease can be successfully treated with a high dose of antibiotics, such as penicillin, to completely eliminate *Streptococcus*. This is followed by a lower long-term prophylaxis dose.[20] Recovery - and eventually cure - is manifested by the gradual elimination of movement disorders.

Another example is the pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. They are different from Sydenham chorea,[21]

and, as their name denotes, they are directly related to infections by gram-positive or spherical bacteria.

Moreover, inflammatory bowel diseases, comprising Crohn's disease and ulcerative colitis, have been related to gastrointestinal pathogens, such as *Campylobacter* species, *Salmonella* species, enterohepatic *Helicobacter* species, *Mycobacterium avium paratuberculosis*, *Clostridioides difficile*, and *Listeria monocytogenes*.[22] Notably, several gastrointestinal microbes and intestinal helminths have been inversely associated with the risk of inflammatory bowel diseases.[23]

Similarly, autoimmune thyroid diseases, namely, Graves's and Hashimoto's diseases, have been correlated with many types of infectious agents, such as hepatitis C virus, Coxsackie virus, *Yersinia enterocolitica*, *Borrelia burgdorferi*, *Helicobacter pylori*, and retroviruses.[24]

Other autoimmune diseases could also be induced or exacerbated by many different microbial infections, as summarized by Von Herrath *et al.*[25] Multiple sclerosis, for instance, has been related to viruses of the herpes[26] and the human endogenous retrovirus families, as well as protozoa and bacteria.[27] At the same time, Guillain-Barré syndrome has been associated mainly with *Campylobacter jejuni*, cytomegalovirus, Epstein-Barr virus, influenza A virus, *Mycoplasma pneumoniae*, and *Haemophilus influenzae*.[28] In addition, primary Sjögren's syndrome has been related to infections by viruses, such as Epstein–Barr[29] and hepatitis C.[30]

The correlations between common autoimmune diseases and specific pathogens are summarized in Table 1. The content should be considered as indicative, as a comprehensive review of all research relating autoimmune diseases to microbial infections is beyond the scope of this paper.

The role of Vitamin D in alleviating symptoms of inflammatory bowel diseases through "restoration" of intestinal microbiota and, eventually, of the gut barrier function,[31] is also indicative of the complex relationship between microbes and autoimmune diseases.

Moreover, another important correlation between pathogens and autoimmunity is found in the mechanism of bystander activation.[10,32,33] This phenomenon refers to the activation of T cells without antigen recognition, which is indirectly caused by the inflammatory environment generated during immune responses to pathogens. Bystander activation plays an important role in triggering or aggravating autoimmune diseases, such as multiple sclerosis, rheumatoid arthritis, type 1 diabetes, and autoimmune encephalomyelitis.

Autoimmunity has also been related to virus persistence.[33,34] The persistence of infectious agents plays a key role in the proposed conceptual model of autoimmune diseases, as it takes time for cellular alterations to accumulate to a detectable or recognizable extent.

Table 1. Correlations between common autoimmune diseases and specific pathogens

Autoimmune disease	Pathogens
Crohn's disease	*Campylobacter* species, *Salmonella* species, enterohepatic *Helicobacter* species, *Mycobacterium avium paratuberculosis, Clostridioides difficile*, and *Listeria monocytogenes*
Graves's disease	Hepatitis C virus, Coxsackie virus, *Yersinia enterocolitica, Borrelia burgdorferi, Helicobacter pylori,* and retroviruses
Guillain-Barré syndrome	*Campylobacter jejuni*, cytomegalovirus, Epstein-Barr virus, influenza A virus, *Mycoplasma pneumoniae*, and *Haemophilus influenzae*
Hashimoto's disease	Hepatitis C virus, Coxsackie virus, *Yersinia enterocolitica, Borrelia burgdorferi, Helicobacter pylori,* and retroviruses
Multiple sclerosis	Herpes, viruses of the human endogenous retrovirus family, protozoa, and bacteria
PANDAS	Gram-positive or spherical bacteria.
Rheumatoid arthritis	Epstein-Barr virus
Sjogren's syndrome	Epstein-Barr virus and hepatitis C virus
Sydenham chorea	Hemolytic streptococcus
Systemic lupus erythematosus	Epstein-Barr virus
Type 1 diabetes	Coxsackie enterovirus
Ulcerative colitis	*Campylobacter* species, *Salmonella* species, enterohepatic *Helicobacter* species, *Mycobacterium avium paratuberculosis, Clostridioides difficile*, and *Listeria monocytogenes*

Abbreviation: PANDAS: Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections.

3. Contribution of the proposed model to the understanding of autoimmunity

While the correlation of autoimmunity with infectious agents is well established, the mechanisms involved are not completely understood, and many relevant issues remain obscure.[35] The conceptual model proposed in this paper allows for new explanations of some important features of autoimmune diseases, which are outlined in the following paragraphs.

Progressive forms of autoimmune diseases can be explained in the following way: The patient's immune system targets specific cells (e.g., myelin in multiple

sclerosis) that already carry the pathogen's "imprint." Meanwhile, viruses or bacteria, which have not been eliminated, alter previously unaffected cells, which then become targets of the immune system.

Relapsing-remitting forms of autoimmune diseases in the proposed conceptual model can be understood as follows: the end of a relapsing phase occurs when the number of cells bearing a detectable pathogen's "imprint" falls below a threshold, which varies depending on the specific disease. The cessation of the inflammatory phase provides relief for the patients. Moreover, it may be accompanied by a certain degree of recovery, which depends on the resilience of the affected tissues, organs, or systems, particularly their regenerative capacity.

Nevertheless, the infectious agents have not been completely eliminated, and the "imprinting" process persists. During the remitting phase, this process remains undetected, while its rate might be lower than repair/regeneration. Symptoms reemerge when cumulative cellular damage, due to the attack of the immune system on altered cells, exceeds a certain threshold. New infections by pathogens may facilitate the onset of the subsequent relapsing phase by accelerating the "imprinting" process and/or by reactivating the patients' immune system.

Autoimmune diseases with good prognosis are considered cured when the immune system (naturally or with the support of antiviral drugs or antibiotics, as in Sydenham chorea) successfully eliminates the infectious agents, halting further cellular alteration. The degree of residual damage depends on the resilience of the affected system.

Notably, the role of resilience in general can be distinguished according to three types:

(i) Degree of damage from a given stress. In resilient systems, the damage does not completely inhibit the functioning of the stressed system.
(ii) Speed of recovery from damage that has occurred
(iii) The ability to substitute damaged parts with others that undertake the function of the damaged ones. This is particularly important in network structures, either biological or artificial. In most cases, a system that has recovered functionally is less resilient than before the damage.

Regarding the autoimmunity challenges discussed in this paper, the first and third types of resilience may contribute to the time lag between infection and detection of autoimmune response. Moreover, the second and third types contribute to patients' temporal recovery or permanent cure, in remitting-relapsing and good-prognosis autoimmune diseases, respectively.

Moreover, the role of molecular mimicry, which is considered "one of the leading mechanisms by which infectious or chemical agents may induce autoimmunity," as stated by Rojas *et al*.,[12(p100)] can be seen from a different point of view, in the framework of the proposed conceptual model. The basic idea is that autoimmune cells mistake self-cells as foreign, due to similarities between the host's protein structures and those of invading bacteria or viruses.[36] For instance, *Bacteroides fragilis*, a member of the normal human gut microbiota, encodes a protein similar to human ubiquitin and could trigger an autoimmune response.[37] There is an increase in evidence on the ability of bacteria to mimic human proteins and contribute to the onset of autoimmune diseases and their related clinical implications.[38] However, molecular mimicry may also have the "opposite" effect, allowing pathogens to evade the host's immune response.[39,40] This effect could be regarded as more predictable. The model, discussed in this paper, might offer the "missing link" between the two possible effects of molecular mimicry. During the first stage, the "invaders" avoid attacks by the immune system and can cause alterations to the host's cells. Subsequently, when the immune system can recognize them, it targets the "invaders" along with the cells with the pathogens' "imprint." This two-stage process can explain the time lag between infection and autoimmune response, as it takes some time for the infectious agents to affect a substantial number of cells to a degree detectable by the immune system. In the same framework, time-lag differences from disease to disease (and even from case to case for the same disease) can also be explained, as different infectious agents may be involved.

Another important issue, related to many autoimmune diseases, is epitope spreading.[41,42] As summarized by Cornaby *et al*.,[43] epitope spreading can be triggered by assorted viruses, bacterial infections, and stress. The occurrence can be justified in the conceptual model framework presented in this paper. As the alteration of infected cells evolves over time, it is reasonable to expect that the autoimmune response may target different epitopes within the same antigen, a phenomenon known as epitope spreading.

Finally, the role of the persistence of infectious agents is adequately explained, as their continued existence is essential for the continuation of the "imprinting" process.

4. The proposed model and other factors related to autoimmune responses

The roles of genetic predisposition, sex, dietary habits, stress, and lifestyle in developing autoimmune responses are well documented. These roles, together with the

"hygiene hypothesis" and the healing effects of interferon-β (IFN-β), fit well into the framework of the new approach to the mechanism of autoimmune diseases, as explained in the following paragraphs.

4.1. Genetic predisposition

The role of genetic factors in autoimmune diseases is indisputable.[5,44-46] Genetic predisposition to autoimmune diseases in general has been reported by Criswell *et al.*[47] and Li *et al.*[48] Criswell *et al.*[47] studied 265 multiplex families and found that at least two "core" autoimmune diseases were present in each of these families. Li *et al.*[48] analyzed the relationship between the polymorphisms of a particular gene and susceptibility to autoimmune diseases. In addition, the genetic susceptibility of specific organs to autoimmune diseases has been reported by Owen *et al.*[49]

The findings, which relate autoimmune diseases to genetic factors, fit well in the framework of the proposed model. If the problem lies with the attacked organ, it could be linked to its susceptibility to certain microbes, the "imprint" of which renders it a target of the immune system. This explains the existence of many autoimmune diseases, each affecting different systems of the patients. Moreover, the presence of more than one disease in multiplex families can be due to their members' infection by the same virus, resulting in different autoimmune diseases. Even if genetic predisposition is linked to features of the immune system, these features could relate to increased ability to recognize pathogens' imprints.

4.2. Sex

Women are generally more susceptible than men to many autoimmune diseases (such as SLE, thyroiditis, and rheumatoid arthritis), while they are more resistant to infections.[5,50] A similar difference is exhibited in vaccine responses: women generally develop higher antibody responses and may experience more adverse events than men.[51]

The link between resistance to infections and susceptibility to autoimmune diseases can be explained by the proposed model of the occurrence of autoimmune diseases. Women have a more efficient immune system, which eventually protects them better from infections. However, this efficacy makes it easier for the immune system to detect pathogens' imprints and, thus, attack self-cells, leading to more frequent occurrences of autoimmune responses. This explanation does not contradict findings relating sex-dependent differences with hormones (such as estrogens and progestins), genes on the X chromosome, or environmental factors. The only difference is that, in the framework of the proposed conceptual model, these factors can be considered as causes of differences between women and men, in terms of immune system efficiency (besides boosting or suppressing it directly).

It has been observed that during pregnancy, women are less susceptible to infections. As a result, fetuses are better protected. This reduction of susceptibility could be reasonably related to increased alertness of the immune system, which, in turn, could favor the appearance or exacerbation of autoimmune diseases. Nevertheless, this is not always the case. For instance, remission of rheumatoid arthritis during pregnancy has been extensively reported.[52] However, the causes are still unclear, and the proposed conceptual model does not offer an explanation, either.

4.3. Dietary habits

The correlation of diet with certain autoimmune diseases is statistically sound. Several explanations have been proposed in the literature, such as industrial food processing and food additive consumption. According to Lerner and Matthias,[53(p479)] "additives increase intestinal permeability by breaching the integrity of tight junction paracellular transfer. In fact, tight junction dysfunction is common in multiple autoimmune diseases." Moreover, micronutrient deficiency, such as Vitamin D hypovitaminosis, has been related to the onset and progression of autoimmune diseases[54] through impaired gut barrier function, due to deficient intestinal microbiota.[31] Diet has also been related to the onset of autoimmune diseases through molecular mimicry.[55]

Such observations fit very well in the framework of the proposed model: unhealthy or unbalanced diet habits render certain tissues more susceptible to infectious agents and facilitate their alteration, making them targets of the immune system.

4.4. Hygiene hypothesis

It is well-established that autoimmune diseases are much more widespread in developed countries than in developing ones.[56] The well-known "hygiene hypothesis"[57] directly correlates the decreasing incidence of infections in developed countries with the increase of autoimmune (and allergic) diseases.

This correlation, which is still an open research issue,[58] can be explained in the framework of the proposed mechanism of autoimmune diseases in the following way: in regions with poor hygienic conditions and limited access to medical treatment, many individuals succumb to diseases that rarely cause deaths in developed countries. However, in developed countries, some affected individuals, despite receiving treatment, are not completely cured. The infectious agents may not be completely eradicated and continue to leave their "imprint" on cells, organs, or systems, rendering them immune system targets.

4.5. Stress

It has been known for many years that stress (mainly chronic stress) can cause immunosuppression.[59] It may also increase the risk or exacerbation of autoimmune diseases,[7,59-62] which entail increased immune system activity. This apparent contradiction can be resolved in the framework of the proposed mechanism: in the first stage, stress-induced weakness of the immune system facilitates cell "imprinting" by pathogens. During the later stage, the immune system recognizes mounting alterations of the affected cells and attacks them. This two-stage process allows for a time lag between stress periods and exacerbations of autoimmune diseases.

4.6. Treatment of multiple sclerosis with IFNβ

IFNβ is mildly effective in treating the relapsing-remitting form of multiple sclerosis. However, the precise mechanisms through which IFNβ achieves its therapeutic effects are not fully understood.[63,64]

IFNs are known to stimulate cells infected by viruses to produce proteins that prevent virus replication within them, eventually hindering infections. The complex IFN contribution to combating cancer-associated viruses remains an active area of ongoing research.[65]

Given the undisputed antiviral properties of IFNs, irrespective of the exact mechanism, the therapeutic effect of IFNβ on multiple sclerosis can be reasonably related to its infection-stemming properties. This fits perfectly in the framework of the proposed model, which attributes the evolution of autoimmune diseases to residual infectious agents. As the disease has been related to different infectious agents, variations in the efficiency of their treatment with IFNβ could be attributed, at least partially, to the virus involved in each case.

5. Drug-induced autoimmunity

Some drugs have been linked to triggers of autoimmune diseases, such as SLE and rheumatoid arthritis.[5,66] The exact mechanism of drug-induced autoimmunity is still unknown. A case, which could reasonably be explained in the framework of the proposed conceptual model, is discussed in the following paragraph.

5.1. Treatment of malignancy

Some new treatments for malignancy have been related to autoimmunity. These treatments use immune checkpoint inhibitors (CPIs) to facilitate the patient's immune system to attack cancer cells. Side effects include a range of immune-related adverse events (IRAEs), from neurological effects[67,68] to rheumatological effects.[69] CPIs play an essential role in regulating immune responses.[70] Therefore, the appearance of such IRAEs could be expected, at least in the form of exacerbation of pre-existing autoimmune diseases. However, seemingly unrelated cells (tissues or organs) are also affected in certain instances. A possible explanation, closely related to the proposed model of autoimmune diseases, is that a similar, but distinct, process takes place in the second case. The underlying similarity is that the affected cells are not completely healthy. In the first case, the attacked cells bear the "imprint" of the pathogen, linked to a prior infection. In contrast, in the second case, they bear a slight cancerous alteration, which cannot be detected with current diagnostic means. The "boosted" immune system, on detecting alterations, even slight ones, attacks the affected cells, irrespective of the alteration's cause.

6. Conclusion

The proposed conceptual model, which attributes autoimmune diseases to progressive alteration of host cells caused by infectious agents, can explain many aspects of these diseases. If this model proves valid, halting the progression or even curing autoimmune diseases may be possible by developing new antibiotics or antiviral drugs. These drugs should aim to completely eliminate the infectious agents that cause cell alterations, rendering them immune system targets.

Halting the progress of an autoimmune disease does not result in the spontaneous restoration of damaged tissues. As mentioned in Section 3, the degree of residual damage depends on the resilience of each affected system. For this reason, it seems reasonable to combine antibiotics or antiviral therapies with immunomodulatory agents to reduce progressive damage until the underlying infectious cause is eliminated. Once the infectious agents are fully eradicated, continued use of immunomodulatory drugs may become unnecessary, or, at the very least, redundant.

7. Directions for further research

The following research directions would be very helpful to validate (or partially validate) the proposed conceptual model of the mechanism underlying autoimmune diseases, and to establish new treatment protocols, to the extent that the model proves accurate:

(i) Further statistical studies on the temporal correlation between the first manifestation or seizures of autoimmune diseases and infections from viruses or bacteria.
(ii) Clinical trials of existing and new antibiotics or antiviral drugs to stop the further progression of autoimmune diseases and eventually cure them.

(iii) Identify previously unknown infectious agents affecting organs or tissues commonly affected in autoimmune diseases.
(iv) Statistical studies on possible correlations between new malignancy treatments, eventually aiming at facilitating immune system response, and the appearance of IRAEs. In particular, if a relationship between cells (tissues or organs) affected by IRAEs and metastatic cancer expansions is detected, it could help understand the mechanism of this apparent disorientation of the immune system.

Research in this area could be pursued in parallel with research on the function of the immune system and the particular features of each autoimmune disease.

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Further disclosure

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