Review

A Contribution to the Conceptual Model of Occurrence of Autoimmune Diseases

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A Contribution to the Conceptual Model of Occurrence of Autoimmune Diseases

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Abstract: In this paper, an attempt is made to shed additional light on the role of infectious agents (bacteria, viruses, etc.) in autoimmune diseases. While the correlation between them is well established, many points remain obscure. To offer a concise framework for many of the relevant research findings, the following conceptual model is discussed: autoimmune diseases are due to alterations of cells, tissues or organs, which are caused by infectious agents. These alterations evolve with time. Initially they are small and hardly detectable. As they become more severe, though, they are traced, and the infected cells are subsequently attacked by the immune system. The aforementioned process allows for new explanations of the relationship between triggers of autoimmunity and infectious agents, of the time lag between infection and autoimmune response and of the progressive nature of autoimmune diseases. It can also offer a new point of view of molecular mimicry and of epitope spreading. The roles of genetic predisposition, stress, diet habits and lifestyle fit in its framework, as well. Side effects of malignancy treatments using immune checkpoint inhibitors can also be explained. A conclusion of the aforementioned reasoning is that treatments should aim to completely eliminate the cause of these evolving alterations, namely the infectious agents. Presumably, they could be based on antibiotics and antiviral drugs. To check the validity of the proposed conceptual model, research directions are suggested in the last section of the paper.

Keywords: autoimmune diseases; infectious agents; molecular mimicry; epitope spreading; hygiene hypothesis; delayed autoimmune response; immune checkpoint inhibitors

1. Introduction

Autoimmune diseases tend to evolve into a scourge, in particular in developed countries. Up to now, at least 80 diseases have been identified as autoimmune. Their common feature is that the immune system of the patients attacks and damages cells, tissues or organs of their body as if they were foreign [1,2].

At a first level, autoimmune diseases are related to some malfunction of the immune system, e.g., impaired tolerance [3–5], dysregulation by hormones ,e.g., [6], or its deception by infectious agents (bacteria, viruses, etc.), combined with environmental factors; moreover, mainstream treatments, aiming at relieving symptoms, are mainly based on immunosuppressive or immunomodulatory drugs, e.g., [7]. The mechanism and aetiology of autoimmune diseases is still unclear, though (e.g., [8]).

In this paper, a model of the mechanism that underlies autoimmune response is outlined and discussed, together with evidence supporting its plausibility. Moreover, research directions, aiming at development of new treatments for autoimmune diseases are proposed.

2. The Proposed Model and Previous Research Supporting It

The outline of the proposed mechanism of autoimmune response follows: Autoimmune diseases are due to alterations of the cells, tissues or organs that are subsequently attacked by the immune

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system. These alterations are caused by infectious agents (bacteria, viruses, etc.) and evolve with time. Initially they are small and hardly detectable by the immune system. When they exceed a certain threshold, though, the affected cells are targeted and subsequently attacked by the immune system. It could be said that the cells attacked bear a recognizable "imprint" of the pathogen. Disease symptoms appear, when cumulative cell damage results in some detectable malfunction, which depends on the particular autoimmune disease.

This model is in line with observations of many researchers, who have correlated autoimmune diseases with infectious agents, such as bacteria or viruses, e.g., [9–11]. For example, Coxsackie enterovirus has been correlated with Type 1 Diabetes [12] and Epstein-Barr virus with Guillain-Barré syndrome, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis and other autoimmune diseases [13]. Quite recently, SARS CoV-2 virus has been considered as triggering factor of autoimmune diseases [14]. Even vaccines have been suspected of triggering autoimmune diseases [15–17].

Regarding correlation with bacteria, a prominent undisputable example is Sydenham's chorea, e.g., [18]. The attack of immune cells to the basal ganglia is set off by infection of the latter by hemolytic streptococcus. Even more important, this disease is successfully treated with a high dose of penicillin, when it is newly diagnosed, in order to eliminate streptococcus completely, followed by lower long-term prophylaxis dose [19]. Another example is offered by PANDAS, which are by definition associated with streptococcal throat infections [20].

Moreover, it has been proposed that one autoimmune disease could be induced or exacerbated by many different microbial or viral infections (e.g., [21]. Multiple sclerosis, for instance, has been related to viruses of the herpes (e.g., [22]) and the human endogenous retrovirus families, to protozoa and to bacteria [23], while Guillain-Barré syndrome has been associated mainly with Campylobacter jejuni, but also with cytomegalovirus (CMV), Epstein-Barr virus, influenza A virus, Mycoplasma pneumoniae, and Haemophilus influenzae [24].

An exhaustive list of works, correlating autoimmune diseases with viral or microbial infections, is beyond the scope of this paper.

3. Contribution of the Proposed Model to the Understanding of Autoimmunity

While the correlation of autoimmunity with infectious agents is well established, the proposed model allows for different explanations of some important features of autoimmune diseases. Their progressive nature, for instance, can be explained in the following way: The immune system attacks specific cells (e.g., myelin in multiple sclerosis) that bear already the pathogen's "imprint". Meanwhile, viruses or bacteria, which have not been eliminated completely, are altering previously unaffected cells, which are attacked in turn.

Relapsing-remitting forms of autoimmune diseases fit in the proposed conceptual model, as well: The end of a relapsing phase occurs when the number of cells, bearing a detectable pathogen's "imprint", falls below a threshold, which depends on the particular disease. The end of the inflammatory phase per se, is a cause of 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, and cells' regeneration rate.

Nevertheless, the infectious agents have not been eliminated completely and the "imprinting" process continuous. As long as the remitting phase lasts, this process remains undetected, while its rate might be lower than that of regeneration. Symptoms are noticed again, when cumulative cell damage, due to the attack of the immune system to altered cells, exceeds a certain threshold. New infections by pathogens may facilitate the onset of the subsequent relapsing phase, through accelerating the "imprinting" process and/or through alerting the patients' immune system.

Regarding cure of autoimmune diseases with good prognosis, it occurs when the immune system (naturally or with the support of antiviral drugs or antibiotics, as in Sydenham's chorea), manages to eliminate the infectious agents completely and, consequently, to stop further alteration of cells.

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Moreover, the role of molecular mimicry that is considered "one of the leading mechanisms by which infectious or chemical agents may induce autoimmunity" [11], can be seen from a somewhat different point of view. 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, e.g., [25]. For instance, Bacteroides fragilis, a member of the normal human gut microbiota, encodes a protein, which is very similar to human ubiquitin and could trigger autoimmune response [26]. Evidence on the ability of bacteria to mimic human proteins and to contribute to the onset of autoimmune diseases and on related clinical implications is mounting up, e.g., [27]. However, molecular mimicry may have also the "opposite" effect, namely allowing pathogens to evade host's immune response [28,29]. Actually, 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: At a first stage, the "invaders" avoid attacks of the immune system and are able to cause alterations of host's cells. Later on, when the immune system manages to recognize them, it attacks the cells with the pathogens' "imprint", as well. 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 be also explained, as different infectious agents may be involved.

Another important issue, related to many autoimmune diseases, is epitope spreading, e.g., [30,31]. As summarized by Cornaby et al. [32], it can be triggered by assorted viruses, bacterial infections, and stress. Its occurrence can be justified in the framework of the conceptual model, presented in this paper: As alteration of the infected cells evolves with time, it is reasonable that autoimmune response may target different epitopes within the same antigen, namely that epitope spreading will occur.

4. The Proposed Model and Other Factors Related to Autoimmune Responses

The roles of genetic predisposition, diet habits, stress and lifestyle in developing autoimmune responses are well documented. These roles, together with the "hygiene hypothesis", fit well in the framework of the new approach to the mechanism of autoimmune diseases, as it is explained in the following paragraphs.

4.1. Genetic Predisposition

The role of genetic predisposition looks indisputable, e.g., [4,33–35]. Genetic predisposition to autoimmune diseases in general has been reported, e.g., by Criswell et al [36], who studied 265 multiplex families and found out that at least two of "core" autoimmune diseases were present in each of these families, and by Li et al, [37], who analyzed the relationship between polymorphism of a particular gene and susceptibility to many autoimmune diseases. On the other hand, genetic susceptibility of particular organs to autoimmune diseases has been reported as well, e.g., [38].

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

4.2. Correlation with Diet

The correlation of diet with certain autoimmune diseases is statistically sound. A number of explanations has appeared in the literature, e.g., industrial food processing and food additive

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consumption [39]. According to these authors, "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, diet has been related to the onset of autoimmune diseases through molecular mimicry [40].

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

4.3. The Difference Between Developed and Developing Countries

It is well established that autoimmune diseases are much more widespread in developed countries than in developing ones, e.g., [41]. The well-known "hygiene hypothesis", e.g., [42], directly correlates the decreasing incidence of infections in developed countries with the increase of autoimmune (and allergic) diseases.

This correlation can be explained in the framework of the proposed mechanism of autoimmune diseases, in the following way: In areas where low hygienic conditions prevail and treatment means are lacking, many people die from diseases, which rarely cause deaths in developed countries. In the latter, though, some of those who are affected, and subsequently treated, are not completely cured; the infectious agents are not fully neutralized, but they continue to leave their "imprint" on cells, organs or systems, rendering them targets of the immune system.

4.4. The role of Stress

It has been known, since many years, that stress (mainly chronic stress) can cause immunosuppression, e.g., [43]. Nevertheless, it may also result in increased risk or exacerbations of autoimmune diseases, e.g., [6,43–46], which entail increased activity of the immune system. This apparent contradiction can be resolved in the framework of the proposed mechanism: At a first stage, stress-induced weakness of the immune system facilitates cell "imprinting" by pathogens. At a later stage, the immune system manages to recognize mounting alterations of the affected cells and attacks them. This two-stage process allows for time-lag between stress periods and exacerbations of autoimmune diseases.

5. Additional Indications Resulting From Disease Treatments

5.1. Treatment of Multiple Sclerosis with B-Interferon

Beta interferon (IFNβ) is mildly effective in treating the relapsing-remitting form of multiple sclerosis. The precise mechanisms through which IFNβ achieves its therapeutic effects are not fully understood [47,48].

Regarding interferons (IFNs), in general, it is known that they stimulate cells infected by viruses, to produce proteins that prevent virus replication within them; in this way, infections are eventually stemmed. The complex IFN contribution to combating cancer-associated viruses, in particular, is an issue of ongoing research, e.g., [49].

Given the undisputed antiviral properties of IFNs, and irrespective of the exact mechanism, the therapeutic effect of INFβ on multiple sclerosis can be reasonably related to its infection-stemming properties, namely it fits perfectly in the framework of the proposed model, which attributes the evolution of autoimmune diseases to residual infectious agents.

5.2. Treatment of Malignancy

Some new treatments of malignancy have been related to autoreactivity. These treatments use immune checkpoint inhibitors (CPIs) to facilitate the patient's immune system to attack successfully the cancer cells. Side-effects include a range of immune-related adverse events (IRAEs), from neurological [50,51] to rheumatological [52]. As CPIs play an essential role in regulating immune

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response, e.g., [53], the appearance of such IRAEs could be expected, at least in the form of exacerbation of pre-existing autoimmune diseases. Sometimes, though, seemingly unrelated cells (tissues or organs) are affected, as well. A possible explanation, in the framework of the proposed model, is that there are two similar, but distinct processes. The underlying similarity is that the affected cells are not completely healthy; the difference is that in the first case, they bear the pathogen's "imprint", while in the second they bear already a slight cancerous alteration, which cannot be detected with current diagnostic means. The loosely regulated immune system, upon detecting alterations, even slight ones, attacks the affected cells, irrespective of the alteration cause.

6. Main Conclusion—Directions for Further Research

The proposed conceptual model, which emphasizes the progressive alteration of host cells (from non-detectable by the immune system to severe) caused by infectious agents, can offer a coherent explanation of many aspects of autoimmune diseases. Provided that it is valid, the means to stop the progress, or even to cure autoimmune diseases, can be found in the development of new antibiotics or antiviral drugs. These drugs should aim at complete elimination of the infectious agents, which are responsible for the alteration of the cells, which are eventually attacked by the immune system. Research along this line could be followed in parallel with research on the function of the immune system and the particular features of each autoimmune disease.

The following research directions would be very helpful in order to check the validity (or partial validity) of the proposed model of the mechanism underlying autoimmune diseases and to establish new treatment protocols, insomuch as it is valid:

(a) Further statistical studies on the temporal correlation between first manifestation or seizures of autoimmune diseases and infections from viruses or bacteria.
(b) More statistical studies on possible correlations between new malignancy treatments, eventually aiming at facilitating immune system response, and appearance of IRAEs. Relationship between cells (tissues or organs) affected by IRAEs and metastatic cancer expansions could be revealing.
(c) Clinical trials of existing and new antibiotic or antiviral drugs to stop further progress of autoimmune diseases.
(d) Search for unknown infectious agents, affecting organs or tissues that may suffer from autoimmune diseases.

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