

Review

Infections and autoimmune diseases

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Abstract

The high percentage of disease-discordant pairs of monozygotic twins demonstrates the central role of environmental factors in the etiology of autoimmune diseases. Efforts were first focussed on the search for triggering factors. The study of animal models has clearly shown that infections may trigger autoimmune diseases, as in the case of Coxsackie B4 virus in type I diabetes and the encephalomyocarditis virus in autoimmune myositis, two models in which viruses are thought to act by increasing immunogenicity of autoantigens secondary to local inflammation. The induction of a Guillain–Barré syndrome in rabbits after immunization with a peptide derived from *Campylobacter jejuni* is explained by mimicry between *C. jejuni* antigens and peripheral nerve axonal antigens. Other models involve chemical modification of autoantigens, as in the case of iodine-induced autoimmune thyroiditis. These mechanisms have so far only limited clinical counterparts (rheumatic fever, Guillain–Barré syndrome and drug-induced lupus or myasthenia gravis) but one may assume that unknown viruses may be at the origin of a number of chronic autoimmune diseases, such as type I diabetes and multiple sclerosis) as illustrated by the convergent data incriminating IFN- α in the pathophysiology of type I diabetes and systemic lupus erythematosus. Perhaps the difficulties met in identifying the etiologic viruses are due to the long lag time between the initial causal infection and onset of clinical disease. More surprisingly, infections may also protect from autoimmune diseases. Western countries are being confronted with a disturbing increase in the incidence of most immune disorders, including autoimmune and allergic diseases, inflammatory bowel diseases, and some lymphocyte malignancies. Converging epidemiological evidence indicates that this increase is linked to improvement of the socio-economic level of these countries, posing the question of the causal relationship and more precisely the nature of the link. Epidemiological and clinical data support the hygiene hypothesis according to which the decrease of infections observed over the last three decades is the main cause of the incessant increase in immune disorders. The hypothesis does not exclude an etiological role for specific pathogens in a given immune disorder as might notably be the case in inflammatory bowel diseases. Even in this setting, infections could still have a non-specific protective role. Independently of the need for confirmation by epidemiological prospective studies, the hygiene hypothesis still poses numerous questions concerning the nature of protective infectious agents, the timing of their involvement with regard to the natural history of immune diseases and, most importantly, the mechanisms of protection. Four orders of mechanisms are being explored. Antigenic competition is the first hypothesis (immune responses against pathogens compete with autoimmune and allergic responses). This is probably an important mechanism but its modalities are still elusive in spite of considerable experimental data. Its discussion in the context of homeostatic regulation of lymphocyte pools has shed new light on this hypothesis with possible competition for self MHC peptide recognition and interleukin-7. Another hypothesis deals with immunoregulation. Infectious agents stimulate a large variety of regulatory cells (Th2, CD25+, Tr1, NKT, ...) whose effects extend to other specificities than those which triggered their differentiation (bystander suppression). Infectious agents may also intervene through components which are not recognized as antigens but bind to specific receptors on cells of the immune system. Major attention has recently been drawn to Toll receptors (expressed on macrophages and possibly on regulatory T cells) and TIM proteins present on Th cells, which may express the function of the virus receptor (as in the case of the Hepatitis A virus and Tim-1). Experimental data will be presented to support each of these hypotheses. In any event, the final proof of principle will be derived from therapeutic trials where the immune disorders in question will be prevented or better cured by products derived from protective infectious agents. Numerous experimental data are already available in several models. Preliminary results have also been reported in atopic dermatitis using bacterial extracts and probiotics.

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1. Introduction

The role of environmental factors in the etiology of autoimmune diseases is clearly apparent when considering the disease concordance rate between monozygotic twins. More than 50 and sometimes 70 or 80% of monozygotic twins are discordant for major autoimmune diseases. Such discordance is particularly striking when considering the fact that twins share much the same environment, at least during childhood. Numerous investigations have been devoted to the search for environmental factors controlling the onset of autoimmune diseases. Efforts were initially focused on triggering factors. It was shown that some autoimmune diseases could be triggered by various drugs (e.g. α methyl dopa-induced autoimmune hemolytic anemia or β blocker-induced lupus). The role of iodine nutritional supplements was suspected from epidemiological studies in autoimmune thyroiditis [1] and corroborated in experimental animal models of the disease [2]. In fact, most studies have targeted infectious agents. As we shall see below, there are a number of examples where the etiological role of an infectious agent has indeed been demonstrated. It remains true, however, that in most cases, the infectious etiology has not been directly demonstrated even though several indirect arguments strongly suggest it. On the other hand, rather unexpectedly, it has become progressively apparent that infection could also protect against autoimmune diseases, according to the hygiene hypothesis initially formulated for allergic diseases.

The aim of this manuscript is to provide a brief review on the present knowledge of such putative contrasting effects of infectious agents in the etiology of autoimmune diseases. Such effects will be discussed independently of genetic factors, although obviously their expression closely depends on interactions between infections and genes predisposing to or protecting against autoimmune diseases.

2. The triggering role of infections

2.1. Introduction

Autoreactive B and T cells are present in all healthy subjects. Their repertoire is still ill-defined (and certainly skewed, as far as T cells are concerned) by intrathymic negative selection which eliminates autoreactive T cells presenting high affinity receptors for autoantigens expressed in the thymus. Peripheral physiological autoreactive T cells recognize a wide spectrum of major autoantigens distributed in all organs and known to be the target for a multitude of autoimmune diseases. Why, then, do these autoreactive cells not attack these organs and cause disease?

The double transgenic mouse model described by Ohashi and Zinkernagel [3] provides a good model to study this problem. These mice were obtained by hybridization of transgenic mice expressing large amounts of the lymphochoriomeningitis virus (LCMV) glycoprotein on the β cells of the islets of Langerhans and transgenic mice harboring a majority of CD8 T cells specific to the LCMV glycoprotein. These double

transgenic mice represent an extreme expression of the physiological autoreactivity paradox described above. Indeed, these mice have a large amount of a defined autoantigen on their β cells (the LCMV glycoprotein should be considered an autoantigen in such mice, since it is coded for in their genome and a majority of their CD8 T cells have high affinity receptors for such an autoantigen). Remarkably enough, these mice do not develop diabetes, except when they are infected by LCMV. One may assume that the infection induces major activation of glycoprotein-specific T cells that then acquire the capacity to lyse β cells and induce diabetes. This model provides an example of virus-induced autoimmune disease, even though it is of course a special case, inasmuch as the target viral protein is transgenically expressed on the β cells. It may be interesting to mention in this context that RIP-LCMV mice also become diabetic after LCMV infection in the absence of transgenic glycoprotein-specific TCRs [4]. The question is posed of the mechanisms by which dormant autoreactive T cells are activated in patients with autoimmune diseases in whom the viral protein is not an autoantigen since its expression only appears after the infection. Several mechanisms can be proposed to explain the modalities of the T cell activation which is necessary to break down the indifference described above.

2.2. Mechanisms

Three sets of mechanisms have been proposed.

2.2.1. Polyclonal lymphocyte activation

The first mechanism involves polyclonal B or T cell activation. The reality of the involvement of such mechanisms is elusive. It would imply, as far as autoreactive T cells are concerned, that one should find no or few somatic mutations in the autoantibody gene segment corresponding to complementarity-determining regions (CDR) since autoantigen-driven selection is not a primary event in this setting. This is in fact rarely the case, with the exception of some forms of systemic lupus erythematosus [5,6]. It is possible, however, that the major B and T cell activation which is observed in some diseases, notably viral and parasitic diseases, may explain some autoimmune states.

2.2.2. Antigen mimicry

The second mechanism is antigen mimicry. It has been noted that the protein sequence of a number of bacterial or viral proteins present a homology with autoantigen sequences [7,8]. There is a significant homology between the Cocksackie B4 virus protein and the glutamic acid decarboxylase sequence [9] and between the hepatitis B virus polymerase sequence and a segment of myelin-basic protein which has been incriminated in the pathogenesis of multiple sclerosis [10]. The list of such homologies is long. One must admit, however, that the consideration of such homologies often does not show definite evidence for a possible role for shared antigenic determinants between the infectious agent in question and the autoantigen. The bioinformatics-based search for homologies reveals the

existence of a large number of medium-length homologies, the relevance of which is elusive. For these reasons, it is important to collect more direct evidence on the responsibility of the shared epitope in question. Such evidence has only been obtained in a very limited number of diseases. We shall discuss here the two best-documented cases, namely rheumatic fever and Guillain–Barré syndrome.

Rheumatic fever is often associated with heart involvement, preceded by acute polyarthritis in a large percentage of cases. The disease is secondary to streptococcal infections. Epidemiological studies indicate that the onset of carditis usually appears after repeated streptococcal infections, some of which may have been clinically latent. Common antigenic determinants have been evidenced between streptococcal proteins and heart autoantigens [11], but their precise chemical nature has not yet been analyzed in depth. It is postulated that the strong hyper-immune response to these determinants, helped by the T cell response to unshared determinants, leads to the appearance of anti-heart autoimmunity. Heart-specific cross-reactive T cells were extracted from heart specimens of rheumatic fever patients obtained after surgery [12].

The case of Guillain–Barré syndrome is even more clear-cut. There is well-documented evidence of a temporal relationship between various infections or vaccinations and the onset of the syndrome, an acute polyradiculoneuritis. Particular attention has been drawn to intestinal infections by *Campylobacter jejuni*. Antibodies cross-reacting with *C. jejuni* and peripheral nerve gangliosides are detected in the serum of GBS patients [13]. Recently a strong homology was found between lipo-oligosaccharides present in *C. jejuni* and in ganglioside GM1. The etiological role of this lipo-oligosaccharide was strongly supported by the induction of clinically overt GBS in rabbits repeatedly immunized with the lipo-oligosaccharide [14].

2.2.3. Increased immunogenicity of organ autoantigens secondary to infection-mediated inflammation

A number of infectious agents induce localized inflammation of the target organ. This is notably the case for a wide spectrum of viruses. This information may be at the origin of an organ-specific autoimmune response which will enhance and perpetuate the inflammation. Two experimental models illustrate this mechanism. In Theiler's disease, the infection initially provokes a virus-specific encephalomyelitis associated with T cell reactivity to viral proteins [15]. However, within a few weeks, the virus-specific immune response is replaced by a bona fide autoimmune response, including myelin-basic protein (MBP)- and proteolipid protein (PLP)-specific T cell reactivity. It is this autoimmune response which is at the origin of the chronicity of the disease. Similarly, infection of mice with the Coxsackie B3 virus induces a long-term cardiomyositis which develops in two phases, the first viral, second autoimmune [16]. In these models, it is assumed that the initial virus-induced inflammation triggers overexpression of molecules participating in autoantigen recognition by T cells. These molecules include MHC molecules (class one and class two), costimulatory and adhesion molecules. It is interesting to

note that the blockade of the B7 CD28 costimulatory pathway inhibits the onset of the autoimmune phase of Theiler's disease [15]. The role of inflammation in triggering autoimmune disease is also supported by data obtained using the Coxsackie B4 (CB4) virus in non-obese diabetic (NOD) mice. CB4 has been incriminated in the etiology of human type 1 diabetes. It is an enterovirus with clear pancreatotropism. Infection with CB4 can induce diabetes in non-autoimmune-prone mouse strains and accelerate diabetes onset in diabetes-prone NOD mice. The fact that diabetes acceleration is also observed in BDC 2.5 transgenic NOD mice expressing an islet-specific TCR derived from a diabetogenic T cell clone suggests that the diabetogenic effect of the virus is mediated by inflammation, rather than by antigen-mimicry [17], which is very unlikely to be instrumental in mice showing a highly skewed T cell repertoire. It is tempting to believe that human counterparts of such experimental models explain some of the infection-associated autoimmune diseases. One has to admit, however, that no direct demonstration of such a mechanism has been made in human autoimmune diseases, possibly due to the difficulties met in identifying etiological viruses, as discussed below.

2.3. The search for etiological infectious agents

Major efforts have been devoted over the past few decades to the search for a definite etiological infectious agent in major autoimmune diseases. As discussed above, a very strong case was made for β hemolytic streptococci group A in rheumatic fever and *C. jejuni* in Guillain–Barré syndrome. Much more limited and controversial data have been reported in other autoimmune diseases which, interestingly, are usually chronic, at variance with the two cases just mentioned (RF and GBS) which are acute diseases. This relative failure, in spite of intensive research, is exemplified by the case of type 1 diabetes or multiple sclerosis. The situation of rheumatoid arthritis and systemic lupus erythematosus is even more complex.

2.3.1. The case of type 1 diabetes

Viruses have been considered major potential candidates for the etiology of T1D for several decades. The viral hypothesis was initially based on the temporal relationship between defined viral infections and the onset of overt diabetes [18]. This sequence was notably evoked for the Coxsackie B4 virus [19]. The argument is not very robust if one considers that T cell-mediated islet aggression probably begins many years before clinical onset in most patients and thus the incriminated infection. The infection could at most exacerbate the anti-islet response and accelerate disease onset. One should add that serological evidence (detection of antiviral antibodies in T1D patients) has always been elusive, as well as the episodic claims of virus isolation from pancreatic tissue [20]. The interest in enteroviruses has recently been renewed by a set of observations.

At the experimental level as well, there are rather limited data. The encephalomyocarditis virus has been reported to induce T1D in rodents [21], but the T1D is of the cytopathic type

in that case without much immunological involvement. The Coxsackie B4 virus can induce diabetes in mice with some features of autoimmune T1D [22], but it is not clear, as discussed above, whether disease pathogenesis involves a direct cytopathic effect or an immune β cell attack secondary to virus-induced inflammation.

Other interesting data have been derived from the RIP-*LCMV* transgenic mice described above. These mice develop T1D after *LCMV* infection according to a hit and run mechanism [4]. The viral infection stimulates the induction of *LCMV*gp-specific CD8 cytotoxic T lymphocytes which cause the disease, even though the virus is rapidly cleared through the action of such CTLs.

Collectively, these data are compatible with a viral etiology for T1D even though the diabetogenic virus is still unidentified. It might well be that the etiological infection takes place many years before clinical onset, questioning the role of pre-clinical infections and the disease's seasonal nature. This lag time would explain the difficulty in identifying the diabetogenic viruses, which in addition might not be unique.

Another very strong indirect indication for viruses in the etiology of T1D comes from the recent demonstration of an important role for interferon- α in the pathogenesis of autoimmune disease [23,24].

2.3.2. Possible explanations for unsuccessful identification of etiological infections

Several explanations may be proposed for the difficulties met in identifying etiological infections in human autoimmune diseases.

One may first hypothesize that the triggering infection takes place many years before the clinical onset of the autoimmune disease. It is possible that the triggering infection heals rapidly and that its virological and serological traces have disappeared by the time of clinical onset. There may still be antibodies to the pathogen, but their specificity to the autoimmune disease is doubtful, the more so since the infection in question may be relatively common in the general population. It is the genetic predisposition to react unfavorably to the infectious agent which causes the disease. Many healthy individuals are also infected by the pathogen, but they do not show any signs of autoimmunity. This hypothesis is well in keeping with the mechanisms discussed above, particularly the virus-mediated two phase disease, as in the cases of Theiler's disease and cardiomyositis. It is also illustrated by extensive studies performed in RIP-*LCMV* mice where infection with *LCMV* triggers diabetes according to such hit and run mechanisms [4].

Several viruses could cause a given autoimmune disease. Considering the inflammation-mediated mechanism discussed above, what counts is a tropism of the etiological virus for the target organ. It is conceivable that several viruses showing a tropism for the same organ could thus trigger an autoimmune response specific to the organ.

Lastly, it is fair to recognize that the methods presently used to incriminate a given infectious agent in a disease are difficult to interpret in the absence of a clear-cut temporal

relationship or disease prevention by vaccination. As mentioned above, the specificity of serological data is usually insufficient in the absence of IGM antibodies suggestive of a recent infection. Direct virus identification is complicated by the difficulties in getting relevant organ specimens and clinical epidemiology is confronted by the frequency of latent infections and the common lack of specificity in clinical signs.

2.4. Conclusions

Immunological studies performed in animal models of autoimmune diseases strongly suggest that infections represent the best candidates for the environmental factors triggering human autoimmune disease. Only limited data are available as yet which show strong indications in this direction. However, the bulk of indirect evidence, notably suggestive serological and virological data in some diseases, as well as the apparently important role of interferon- α in a number of autoimmune diseases, argue in favor of an etiological role for infections [23,24]. One may hope that the numerous studies in progress will provide the possibility of identifying some of the viruses or bacteria in question. This would be important for the understanding of disease pathogenesis. It might prove of crucial clinical interest by opening up major therapeutic perspectives including anti-infectious agents, chemicals and monoclonal antibodies and vaccination.

3. Protective effect of infections on autoimmune diseases

3.1. General introduction

Accumulating evidence from various sources suggests that the increase in autoimmune diseases observed in western countries is partly caused by a decline in infectious diseases and progress in hygiene. This notion, which was first developed for allergic diseases, applies to most, but not necessarily all, autoimmune diseases. It has recently been reviewed in several papers [25–27]. A summary of the main arguments will be presented here.

There is a concomitant decline in infections and increase in autoimmune diseases in western countries. The incidence of most autoimmune diseases has been steadily increasing over the last three decades in North America and Europe [25]. This trend has been particularly spectacular in type 1 diabetes, inflammatory bowel disease, and multiple sclerosis, though for the last disease, it seems a plateau has been reached. In the case of type 1 diabetes, the increased incidence is associated with a worrying decrease in age of onset with frequent involvement of very young children (less than 2–3 years old) [28]. This "epidemic" is not observed in less developed countries; within developed countries, it involves more northern than southern countries. Such a difference is not explained for the most part by genetic differences, since as shown for multiple sclerosis and type 1 diabetes, children from families having recently immigrated from low-incidence to high-incidence countries develop the disease with high incidence

[29,30]. This observation was notably made for type 1 diabetes in Pakistani families having immigrated to the UK.

At the same time, the incidence of major infectious diseases has decreased in developed countries, even though some serious infections have persisted and new ones have appeared, such as AIDS. Particular attention should be given in this context to gastrointestinal infections, which are very prominent in underdeveloped countries, and relatively rare today in western countries. This trend is clearly explained by the dramatic improvement in the quality of drinking water and food (cold chain) in western countries, particularly in young children.

The correlation of the decline in infections and the increase in autoimmune diseases is further suggested by the correlation which has been observed between socio-economic levels (including quality of sanitation), and the frequency of major autoimmune diseases, either when considering whole countries or individual patients [31]. It is interesting to note that the frequency of type 1 diabetes is higher in firstborns of multiplex families than in other children, which could be explained by a lower exposure of firstborns than siblings to infections [32].

3.2. Animal models

It has been proven in several animal models of autoimmune diseases that reduced exposure to infections increases risk of disease. It is sufficient to decontaminate NOD mice bred in conventional facilities to observe a major increase in diabetes frequency [25]. Conversely, deliberate infection of NOD mice with various bacteria, viruses, or parasites totally prevents diabetes onset if the infection is done at an early age. Similar data have been obtained for experimentally induced autoimmune diseases [25], as in the case of mycobacteria in experimental allergic encephalomyelitis [33]. It should be mentioned, however, that the protective role of infections is not a general rule, since some specific pathogen-free animals may develop autoimmune diseases, in particular conditions (transgenic T cell receptors or depletion of regulatory cells) and that infections may be required for the development of some autoimmune diseases, such as arthritis in the SKG mouse model [34] and inflammatory bowel disease [35]. It is interesting, though, that in the latter model, the disease is prevented by administration of non-pathogenic lactobacilli [36].

3.3. Underlying mechanisms

The mechanisms of the protective effect of infections on autoimmune diseases are most likely multifactorial. Most data are presently derived from animal models. Although autoimmune diseases are essentially TH1 diseases, while allergic diseases are TH2 diseases, it appears that the protective effect of infections on both types of disease is similar in each case. This is interesting, since it contradicts the notion initially put forth that infections exclusively protect against allergic diseases through stimulation of TH1 cells. In fact, there is a tendency toward increased incidence of concomitant

occurrence of allergic and autoimmune diseases in single individuals [37].

Three orders of mechanisms can be discussed which are neither mutually exclusive nor independent: competition, regulation, and stimulation of innate immunity.

3.3.1. Competition

We have long been aware of antigenic competition: immune responses to single antigens are usually stronger than the response to the antigen administered concomitantly with other antigens. Several mechanisms have been described to explain antigenic competition, including the pre-emption effect on macrophages, competition for cytokines or growth factors, and competition for peptide binding to MHC molecules. These mechanisms have been revisited in the context of the new concepts on lymphocyte homeostasis. It is now apparent that lymphocyte proliferation and survival depend on a number of homeostatic signals, including cytokines such as IL-7 and self-peptide MHC recognition. One may postulate that the strong immune responses that are elicited by infectious agents compete with immune responses against weaker antigens, such as autoantigens and allergens, for homeostatic signals [38]. This is supported by recent observations made in the NOD mouse showing that complete Freund's adjuvant has an anti-homeostatic effect [39].

3.3.2. Regulation

It has been shown in various models of immunoregulation that the suppressive effect induced by a defined antigen may extend to immune responses specific to other antigens (bystander suppression). It is thus conceivable that regulatory cells stimulated by infectious agents dampen autoimmune responses. This mechanism may of course include TH2 cells, although there is only limited data supporting it. Studies performed in our laboratory where NOD mice are protected from diabetes after administration of a Gram-positive bacterial extract have shown that TGF- β played an important role in conditions in which TH2 cytokines were not involved [40]. Additional studies showed that NKT cells could be involved inasmuch as CD1D^{-/-} NOD mice, which are devoid of NKT cells, show reduced protection by the bacterial extract as compared to wild-type mice.

3.3.3. Innate immunity

Toll-like receptors are thought to play an important role in the stimulation of autoimmune responses. This notion has recently been supported by studies performed in RIP-LCMV mice showing that virus-induced autoimmune diabetes depends on TLR3 stimulation and subsequent IFN- α production [41]. At the same time, it appears that TLR stimulation may prevent the onset of autoimmune disease. Thus administration of various TLR agonists (TLR2, 3, 4, and 9) in young NOD mice prevents diabetes onset ([42], N. Thiebmont, in preparation). In vitro and in vivo studies have revealed that this protection is associated with TLR-dependent production of IL-10 and TGF- β .

3.4. Conclusions

The increase in the incidence of major autoimmune diseases is probably multifactorial. The data discussed above show that an important factor relates to a decline in infections, or more generally, a decrease in the infectious environment, notably in the gut. This hypothesis requires confirmation and further documentation to answer the pending questions:

- (1) What is the evidence for a causal relationship between the decline of infections and increase of autoimmune and allergic diseases?
- (2) What are the components of hygiene improvement?
- (3) What are the mechanisms of the protective effect of infections on autoimmune and allergic diseases?
- (4) What are the diseases concerned by the hygiene hypothesis?
- (5) How does one explain that infections can either induce or protect from autoimmune diseases?
- (6) How can one prevent the undesirable effects of improved hygiene?

4. General conclusions

Infections are major players in the environmental factors which modulate the development of autoimmune diseases, both on the positive and negative sides. Underlying mechanisms are multiple and complex, probably different according to pathogens. It will be extremely interesting to correlate these mechanisms and more generally the infections in question with the polymorphism of genes predisposing to or protecting against the various autoimmune diseases. It is interesting to mention here the recently published association between the TLR2, TLR4, and TLR10 gene polymorphisms and asthma. This association might involve a wide spectrum of genes coding for various cytokines or receptors including virus receptors as suggested by asthma association with the hepatitis A virus receptor polymorphism. At the therapeutic level, these concepts should open up new perspectives either based on treatment or prevention of infections or immunostimulation attempting to safely reproduce the immunostimulatory effect of infections.

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