# The Role of Infections in the Pathogenesis of Autoimmune Diseases

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**Abstract**: The autoimmune diseases result from inappropriate responses of the immune system to self antigens. The etiology of autoimmune diseases remains largely unknown but candidate etiologic factors include genetic abnormalities and infections. Although there are considerable data supporting the role of infections in a variety of autoimmune diseases, this role has been unequivocally established in only a few autoimmune diseases. The difficulty in establishing the infectious etiology of autoimmune diseases stems from several factors such as the heterogeneity of clinical manifestations in individual autoimmune diseases and the time interval between infection and autoimmune disease. The data on this association derive from clinical observations, epidemiological studies and research using laboratory techniques, protein sequence database screening and animal models.

Infectious agents can cause autoimmune diseases by different mechanisms, which fall into two categories: antigen specific in which pathogen products or elements have a central role e.g. superantigens or epitope (molecular) mimicry, and antigen non-specific in which the pathogen provides the appropriate inflammatory setting for "bystander activation". The most important mechanisms are molecular mimicry and superantigens. As far as molecular mimicry is concerned the recent data on the degeneracy of T cell recognition have shifted the focus from searching for linear sequence homology to looking for similarity of antigenic surfaces. Special mention has to be made to retroviruses as they have some unique means of inducing autoimmunity.

**Keywords:** Autoimmune diseases, molecular mimicry, superantigens, retroviruses, infectious diseases,

## INTRODUCTION

Inappropriate responses of the immune system to self-antigens can lead to organ or tissue damage resulting to the clinical syndromes that we call autoimmmune diseases. One of the basic pathogenic mechanisms of autoimmune disease is a defect in immune tolerance, resulting in proliferation and activation of self reacting B and T cell clones [1,2]. Postulates for a disorder to be classified with the autoimmune diseases were originally set by Witebsky and they were the presence of autoantibodies or self-reacting lymphocytes, the identification of the self-antigen and the reproduction of the disease in experimental animals either after immunization or passive transfer of autoantibodies or self-reacting lymphocytes [3]. These criteria are still valid, however the need for additional postulates became obvious when it was found that the presence of self-reacting lymphocytes or autoantibodies is not equivalent to the presence of an autoimmune disease [4]. Self-reacting lymphocytes represent a subpopulation of the normal immune repertoire and only a small fraction of them are causing disease [5]. Similarly, autoantibodies are found in healthy individuals but they usually are of low affinity and rarely pathogenic. Consequently one must be careful to distinguish between autoimmunity, which is a physiologic phenomenon, and autoimmune diseases which are conditions of abnormal immune function [4].

Although our knowledge concerning the cellular and molecular mechanisms of the autoimmune diseases is quite detailed, their etiology remains obscure. We still do not know the factors which trigger the initiation of the anti-self response and this causes difficulty in the management of the autoimmune diseases. In this context several parameters have been studied as candidate etiologic factors. Among the most important of those are the genetic background of the patient (MHC alleles, mutations in cytokine genes or in molecules regulating apoptosis) and infections [6-8]. The hypothesis that infections can trigger or precipitate autoimmune diseases follows the fact that the primary role of the immune system is the defense and protection of the host from exogenous agents, usually infectious ones. For the development of protective immunity a large immune repertory is necessary. The size of the immune repertory is so large that it is inevitable that there would be autoreactive T or B cells. In other words protective immunity can lead to autoimmunity [9]. The association of infections and autoimmune diseases has long been recognized, and in fact the first human autoimmune disease described (paroxysmal cold haemoglobinuria) was considered a consequence of syphilis [10]. However the exact molecular and cellular mechanisms underlying this association have not been fully clarified. There is evidence of varying power for the involvement of infectious agents in the pathogenesis of several autoimmune diseases, but a clear pathogenic role has been established in only a few cases. Possible associations between infectious agents and autoimmune diseases or immune mediated disease are listed in Table 1.

Table 1: Possible Associations Between Autoimmune Diseases and Infectious Agents

| Disease | Infectious agent |
|---|---|
| Grave's disease | Y. enterocolitica |
| Type I diabetes mellitus | Coxsackie viruses, reovirus, mumps virus, rubella virus |
| Immune haemolytic anaemia | Epstein-Barr virus, Mycoplasmapneumoniae |
| Chaga's disease | Trypanosoma cruzi |
| Rheumatic fever | Group A Haemolytic streptococcus |
| Polyarteritis nodosa | Hepatitis B and C viruses, Human Immunodeficiency virus |
| Rheumatoid arthritis | Mycobacterium tuberculosis |
| Spondylarthropathies | Enterobacteriacae, Klebsiella sp. |
| Reactive arthritis | Enterobacteriacae, Chlamydia trachomatis |
| Systemic lupus erythematosus | Retroviruses |
| Crohn's disease | Mycobacterium paratuberculosis |
| Celiac disease | Adenoviruses |
| Psoriasis | Retroviruses, streptoccci |
| Henoch-Schoenlein purpura | b-haemolytic streptococcus |
| Kawasaki disease | Staphylococcus aureus, streptococci, Yersinia pseudotuberculosis |

The difficulties in defining the relation between infectious agents and autoimmune diseases stem from several factors [11]. Although systemic autoimmune diseases are classified as single entities, there is considerable heterogeneity in clinical manifestations and prognosis among patients classified under the same entity e.g. systemic lupus erythematosus. Therefore one may assume that this heterogeneity reflects differences in pathogenesis and, possibly, in etiology. Another important factor is the time interval between the infection and the presentation of the autoimmune disease which makes it difficult to associate epidemiologically an infection with a subsequent autoimmune disease. For example several years may pass between the infection with Trypanosoma cruzi and the presentation of the cardiomypathy of Chaga's disease [12]. The isolation of the infectious agent can be difficult or impossible, especially when the infection runs an asymptomatic or clinically insidious course. In this case

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1568-010X/05 $50.00+.00 

the infectious agent might not be present by the time the autoimmune disease is manifested. Similarly the isolation is dificult when the putative etiologic agents are newly described infectious agents such as Parvo virus B19, herpes simplex virus and various retroviruses. Difficulties may also arise from the fact that infections are sometimes accompanied by autoimmune manifestations (e.g. production of autoantibodies such as anticardiolipin antibodies in syphilis). However these manifestations do not usually have pathogenetic significance, that is, they do not fulfill the criteria for autoimmune disease. Finally the infectious agent may be a common one which causes disease only in susceptible (e.g. genetically) individuals.

## CRITERIA FOR THE ASSOCIATION BETWEEN INFECTIOUS AGENTS AND AUTOIMMNE DISEASES

At least two sets of criteria have been proposed in order to establish the infectious cause of an autoimmune disease, although they do not differ significantly [13,14].

At first the association between the infection and the autoimmune disease should be clearly established either showing a correlation or a causative association. Correlation can be documented by showing a temporal relationship between the infection and the autoimmune disease. To establish a causative association it is usually necessary to employ an animal model in which the specific infection precipitates a specific autoimmune disease.

When the association of the infectious agent and the autoimmune disease is established one should determine the mechanism of disease induction. This requires identifying the responsible microbial proteins and self-proteins or more specifically the responsible epitopes, establishing that these epitopes are relevant and cross-reactive, showing that the microbial and the self epitopes are required for the autoimmune disease induction and finally documenting that there are T cells which are cross-reactive to the microbial and self epitopes and they are required to induce the autoimmune disease.

The above criteria are stringent enough and when applied a definitive role of infectious agents can be established for only a few human autoimmune diseases e.g. Guillain-Barré syndrome, rheumatic fever, Lyme disease, reactive arthritis, ankylosing spondylitis, herpes simplex keratitis, Chaga's disease myocarditis and type I diabetes mellitus .

Data for the association between infectious agents and autoimmne diseases

The data for the above association are clinical, epidemiological and laboratory. The original data derived from clinical observations. It had been observed that certain infections were followed by particular autoimmune diseases in a relatively narrow time frame.

Rheumatic fever is a multisystemic disease which follows Group A streptococcal infections (usually pharyngitis) after a two to three weeks interval [15,16]. This association has been well established, as epidemics of streptococcal pharyngitis were followed by outbreaks of rheumatic fever. Rheumatic fever is now rare in the developed world because streptococcal pharyngitis is treated appropriately. This fact makes the association even more powerful as it suggests a causal association [15]. Reactive arthritis is an inflammatory arthritis accompanied by extra-articular manifestations which begins two to four weeks after either enteric infection by enterobacteriacea such as Salmonella, Shigella, Yersinia and Campylobacter or genital infection by *Clamydia trachomatis*. Relatively recently reactive arthritis has been noted to occur after respiratory infection by *Chlamydia pneumoniae* [17]. Lyme disease arthritis and poststreptococcal reactive arthritis can be considered as two special forms of reactive arthritis but they are usually classified as separate entities. Lyme disease is a multisystem infectious disease caused by *Borrellia burgdorferi* [18]. A few months after the acute phase of the disease, approximately 60% of untreated patients present a rheumatoid arthritis-like syndrome which is antibiotic resistant and it probably has an autoimmune basis [19]. Poststreptococcal reactive arthritis first described in 1959. It is a condition in which there is a poststreptococcal arthritis yet the Jones criteria for rheumatic fever are not fulfilled [20,21]. However some authors have suggested that it is a variant of acute rheumatic fever and it should be treated similarly [20]. Guillain-Barré syndrome is an acute inflammatory demyelinating polyneuropathy. In 50-75% of cases the syndrome occurs 10 days to 3 weeks after an infection, most often by *Campylobacter jejuni* [22,23]. The postinfectious nature of Guillain-Barré syndrome was recognized as early as 1892 by William Osler who used the term "acute postinfectious polyneuritis" [22]. The association was firmly established in the 1980's, when stool culture for *C. jejuni* became a routine [22].

The second set of data consists of epidemiological studies focusing on the relationship between the incidence of infection, immunity or exposure to an infectious agent with the incidence of autoimmune diseases in different groups of subjects. Some of these studies use the history of clinically apparent infection while others have used as criterion for exposure to the infectious agent the presence of antibodies against the infectious agent. An example of the former group is a study which examined the association of previous natural exposure or immunization against rubella, measles or mumps with the incidence of antipancreatic and antithyroid antibodies [24]. The latter group of studies is represented by studies which have found that the incidence of hepatitis B surface antigen was especially high in patients with vasculitis of the polyarteritis nodosa group [25,26]. In similar studies antibodies against hepatitis C virus have been detected in 70%-100% and viremia found in 86% of patients with mixed type II cryoglobulinemia [27,28]. Finally there are studies which have studied the presence of the infectious agent itself. This is the case with the Guilain-Barré syndrome in which *C. jejuni* was isolated in stool culture in 26% of patients but in only 2% of household controls [29].

The third set of data is the result of laboratory research. Usually in these studies the researchers have looked for evidence of immunity against the infectious agent or for its genetic material. For example chlamydial DNA has been isolated from the synovial fluid or from the synovial membrane of patients with reactive arthritis or Reiter's syndrome [30]. On the other hand although Borrelia-specific Th1 cells and antibodies have been found in synovial fluid, no DNA of *Borrelia burgdorferi* has been isolated from the synovial tissue or other tissues of patients with Lyme arthritis, suggesting an infectious trigger but a non-infectious mechanism for the arthritis [18,31,32].

The hypothesis that molecular mimicry is a possible mechanism linking infection and autoimmunity, has led several research teams to look for amino acid homology between the putative autoantigen and the implicated infectious agent [33]. At present protein sequence databases can be screened for amino acid homology with more than one infectious agents simultaneously. However there are several problems with this approach. As the size of the protein sequence databases increases the possibility of a short sequence homology increases too. Therefore some of the sequence homologies found in that way may be clinically irrelevant [34]. An analysis of the statistical significance of the sequence homology suggested that in order for a sequence homology not to represent a chance finding it should be seven or more amino acids long. In the same study it was calculated that for a 5 amino acid sequence up to 10 homologous sequences can be found in protein sequence databases [25].

With this technique amino acid sequence homology has been sought between infectious agents (viruses as well as bacteria) and myelin basic protein (MBP) which is a central nervous system antigen thought to be the autoantigen in multiple sclerosis. The amino acids of the MBP thought to be critical for binding of the peptide to the MHC and for recognition by the TCR were identified and the remaining amino acids were substituted resulting in 129 peptides containing the mimicry motifs. Only 8 of these peptides (7 viral and 1 bacterial) could activate T-cell clones from patients with multiple sclerosis. In only one of these 8 peptides the cross-reactivity with the MBP peptide could have been predicted on the basis of linear sequence homology [35,36]. This study underlines the fact that T cell recognition is more degenerate than we thought, creating an additional problem in assigning biological significance to a peptide linear sequence homology [33].

A last set of data on the role of infections in autoimmune disease pathogenesis comes from experimental models. Some of these models involve immunization of the animal with the putative cross-reactive peptide from the infectious agent. Immunization of BALB/c mice with peptides from *Chlamydia* species, bearing a sequence similarity with a peptide from the heavy chain of the $\alpha$ myosin of the mice (peptide M7A$\alpha$), results in inflammatory heart disease. T cells from these mice strongly recognize the myosin peptide and Chlamydia-specific T cells can induce myocarditis [37]. Another model, used for the study of herpetic keratitis, uses a mutant virus. Herpetic keratitis is an autoimmune disease of the cornea which is thought to be caused by T cells cross-reactive with a peptide from a herpes simplex virus (HSV-1) protein (UL6) and a corneal protein. A mutant HSV-1 lacking the *UL6* gene loses much of his ability to induce keratitis in mice [38]. Other models involve transgenic animals aberrantly expressing a protein of the infectious agent. Transgenic mice expressing proteins of the lymphocytic choriomeningitis (LCM) virus in oligodendrocytes have been used for the study of central nervous

system autoimmune diseases. When these mice are infected with the LCM virus, they initially develop a peripheral infection without central nervous system involvement. However, after the peripheral infection clears, the mice present chronic CNS inflammation which exacerbates with subsequent infections with other visuses, cross-reacting with the LCM virus [39].

## MECHANISMS OF INDUCTION OF AUTOIMMUNE DISEASES BY INFECTIOUS AGENTS

Infectious agents can cause autoimmune diseases by different mechanisms as shown in Table 2 [14,40]. Roughly these mechanism fall into two categories: antigen specific in which pathogen products or elements have a central role e.g. superantigens or epitope (molecular) mimicry, and antigen non-specific in which the pathogen provides the appropriate inflammatory setting and leads to various changes (e.g. enhanced processing and presentation of self-antigens, costimulatory signals, increased expression of MHC molecules) collectively known as "bystander activation" [13,14,41].

Table 2: Mechanisms of Induction of Autoimmune Disease by Infectious Agents

| |
|---|
| Molecular mimicry |
| Expression of modified, cryptic or new antigenic determinants |
| Superantigens |
| Increased processing and presentation of autoantigens |
| Cytokine release and immune activation |
| Lymphocyte activation |

These mechanisms lead to the activation of naïve autoreactive T cells, which are part of the normal T cell repertoire. However, it has to be reminded that the presence of autoreactive T cells is a necessary but not sufficient condition for the development of autoimmune diseases. Several other factors have to be present such as genetic susceptibility of the host, sufficient expansion of the autoreactive clone, the appropriate cytokine profile, access of the autoreactive cells to their targets and expression of MHC and costimulatory molecules by the antigen presenting cells of the target [36,42]. It is possible that for a given autoimmune disease more than one mechanisms operate simultaneously e.g. molecular mimicry and superantigens. Furthermore different mechanisms may operate in different stages of the disease. Some of these mechanisms have been extensively studied (e.g. molecular mimicry), while others (e.g. upregulation of MHC molecules expression, cytokine release) have not been studied as thoroughly.

### Molecular Mimicry

In the context of autoimmunity the term molecular mimicry denotes that peptide epitopes of an infectious agent have sequence homology with self-epitopes, therefore the foreign peptides can activate naïve autoreactive T cells specific for the corresponding self-epitopes.

On the part of the infectious agent molecular mimicry could be considered as an immune evasion mechanism. The presence in a pathogen of a molecule similar with a host antigen, could inhibit the immune response of the host against the pathogen because of the immune tolerance towards self-antigens [9]. Several strains of streptococci bear a capsule of hyduronic acid, which is a common constituent of mammal tissues. In this way these streptococci might be able to evade the immune response of the host [9].

In molecular mimicry the infectious agent bears an epitope which is similar to a host antigen, but different enough, so that the host raises an immune response against it. Subsequently the response could turn against the self-antigen because of cross-reactivity. Therefore molecular mimicry will initiate an autoimmune reaction but this is not by itself enough to cause autoimmune disease. As it has already been mentioned a number of other factors should contribute for the autoimmune disease development. In several cases of molecular mimicry the cross-reaction results in the production of autoantibodies only and not of self-reacting T lymphocytes and is therefore non-pathogenic.

Molecular mimicry is considered an important pathogenetic mechanism in rheumatic fever [43], in Guillain-Barre syndrome [44], in type I diabetes mellitus [45,46], in rheumatoid arthritis [47], in the spondylarthropathies [48], in multiple sclerosis [49], in Chagas' disease [50] and in herpes simplex keratitis [38].

Antibodies against a membrane antigen of beta-hemolytic streptococcus group A, the so-called type 5 protein M, have been detected in sera of patients with rheumatic fever [51]. These antibodies cross-react with myocardial tissue. There is close homology between regions of protein M and cardiac myosin [52]. However it has to be noted that although T cells responding both to an epitope of the protein M and to cardiac myosin epitopes have been isolated from patients with rheumatic heart disease, these T cells were also found in control donors [53]. Consequently it has not been unequivocally shown that there are pathogenic T lymphocytes reacting both with protein M and cardiac myosin in patients with rheumatic fever [34].

In patients with type I diabetes mellitus, sequence homology has been found between glutamic decarboxylase (GAD65), an enzyme found in pancreatic β cells, and the enzyme P2-C of Coxsakie B virus [54]. However although the cross-reactivity between these proteins has been documented in mice, it has not been clearly established in patients with diabetes mellitus [55,56].

In Chagas' disease a amino acid sequence hohology has been found between antigen B13 of T. Cruzi and the heavy chain of cardiac myosin. In Chagas' disease there are antibodies and T lymphocytes reacting both with B13 and cardiac myosin, firmly establishing the role of molecular mimicry in the pathogenesis of the disease [57].

A last but characteristic example of molecular mimicry is herpes simplex type I virus keratitis. A protein of the viral envelop (UL6) has structural homology with a protein of the human cornea. As a result herpes specific cytotoxic T lymphocytes destruct corneal tissue. Mice infected with mutant virus lacking UL6 develop keratitis much less frequently than mice infected with the wild-type virus [38].

Although the concept of molecular mimicry as an underlying mechanism of autoimmune diseases is a reasonable one, a complete sequence homology between a pathogen and human peptides has not yet been found [58]. Recent data have shown that the binding of peptides to the MHC is highly degenerate, i.e binding requires the presence of some critical amino acid residues usually the primary MHC contact residues. The remaining residues can be substituted with other amino acids. Indeed elution studies have shown that a single MHC class II molecule can bind hundreds of different peptides [59]. On the other hand the binding of the MHC-peptide complexes to the TCR could vary from very specific to degenerate [42] Additionally it has been found that even if all the critical peptides remain in place, changes in the non-critical peptides may affect the structure of the peptide and influence both the MHC binding and the TCR recognition [58]. It has been suggested that molecular mimicry concerning T cell epitopes is defined more by similar antigenic surfaces rather than sequence homology [60]. Therefore, taking into account the possible degeneracy in TCR recognition and the importance of the antigenic surface of the MHC-peptide comlex, the sequence similarity between foreign and self peptides might not be as important as we have been thinking.

Finally in most cases of molecular mimicry research has been focused on the immunodominant peptide of the autoimmune response. However in autoimmune diseases epitope spreading contributes significantly in the evolution of autoimmune diseases [49,61,62]. Consequently the search for mimic peptides should be extended, looking for the non-immunodominant peptides in an autoimmune disease [58].

### Superantigens

Superantigens are proteins produced by bacteria, mycoplasmae and virus-infected cells which can link T cell receptor with the V region of the β chain of MHC class II molecules, irrespective of the antigenic specificity of the T cell receptor [63]. This ability is only dependent on the expression of specific Vβ elements of the T cell receptor. As a result superantigens can activate a large number of T lymphocytes of differing antigenic specificities and they are potent immune stimulating molecules [63,64].

Superantigens can participate in the pathogenesis of autoimmune diseases in several ways [63-65].They can activate preexisting self reacting lymphocytes, which are normally anergic. By binding MHC class II of B cells with T cell receptor they can polyclonally activate self reacting B cells with the production of autoantibodies. T lymphocytes are activated by the antigen and they provide help to B cells, irrespective of their antigenic specificity. Another mechanism is the activation of antigen

presenting cells, such as macrophages, with cytokine production, and free radicals and other inflammatory mediators release. This activation can disturb the normal antigen presentation resulting in the presentation of self or cryptic antigens to self reacting T cells.

The largest part of the evidence concerning the role of superantigens in the pathogenesis of autoimmune diseases is indirect. The main finding consists of selective expansion of particular Vβ elements in the face of lack of clonality, which is expressed by extensive junctional diversity [65]. These findings must be accompanied by evidence of infection by a superantigen-producing pathogen, be it microbiological, serological, or isolation of genetic material of the pathogen. Substantial data exist for the role of superantigens in the pathogenesis of experimental allergic encephalomyelitis (EAE), an animal model of multiple sclerosis induce by immunization with myelin basic protein (MBP). It has been found that staphylococcal enterotoxin A and B (SEA and SEB), both potent superantigens, can induce relapse in mice having EAE in remission [66].

Another example of a possible pathogenetic role of superantigens is Kawasaki disease, a vasculitic disease involving the skin, lymph nodes, and the heart. Kawasaki disease is an immune mediated disease, although it has not been confirmed that it is an autoimmune one [67]. In patients with acute Kawasaki disease a selective expansion of Vβ2+ and Vβ8.1 T cells has been found, using molecular techniques as well as anti-TCR antibodies [68]. It is important to stress that in this study the levels of the Vβ2+ and Vβ8.1 T cells were significantly reduced during convalescence [69]. It is also noted that sequencing revealed extensive N-region junctional diversity in the TCRs of these patients. Furthermore, superantigen producing bacteria (St.aureus, streptococci) have been isolated from the 13/16 of patients with Kawasaki disease, adding further evidence in support of the role of superantigens in the pathogenesis of Kawasaki disease.

However the role of superantigens in the pathogenesis of autoimmune diseases is far from clear. In the same set of experiments we have previously mentioned, it was found that the effect of staphylococcal enterotoxins dependent on the timing of the administration and on the immune status of the host. The administration of SEA or SEB only, does not induce EAE in mice, but it can induce EAE in mice pre- immunized with MBP but which had not developed EAE [65]. On the other hand SEB treatment before MBP immunization inhibits the induction of EAE while pretreatment with SEA does not. Conversely post-immunization treatment with SEA in mice pretreated with SEB induces EAE and post-immunization administration of SEB reactivates EAE in mice pretreated with SEB [70]. These findings suggest that there is a complex network of factors in the pathogenesis of autoimmune diseases, in which the role of superantigens has not yet been elucidated but is definitely important.

### Cryptic, Modified or Novel Antigens

The shaping of the immune repertoire of T lymphocytes occurs in the thymus. During this process, which forms the basis of central tolerance, T lymphocytes reacting strongly against self antigens are eliminated. Except from this process of central tolerance there are also mechanism ensuring peripheral tolerance [71,72]. However there is a population of T lymphocytes which, although they are specific for particular self antigens, they have not been eliminated in the thymus and have escaped peripheral tolerance. This is because these self antigens, the so-called cryptic or subdominant antigens, have not been presented appropriately to induce tolerance [73]. Following tissue injury and cell death, as it happens in several infections, the cryptic antigens are exposed and become accessible to the self reacting T lymphocytes. The critical question is how the cryptic epitopes become immunogenic so that they can activate the self reacting lymphocytes and initiate and autoimmune response [33].

A similar mechanism may operate with non-cryptic antigens of the host which can be modified by tissue injury, cell death, oxidative stress and free radicals production which occur during infections. Under these conditions not only non-cryptic antigens are modified but novel antigens can be created as well. As it happens with the exposed cryptic antigens, the modified non-cryptic and the novel antigens are not recognized as self by the host, and they can possibly trigger autoimmunity [33].

### Other Mechanisms

So far we have discussed the so-called antigen specific mechanism of induction of autoimmune diseases by pathogens. A variety of other antigen nonspecific mechanisms contribute to this end, and they are collectively known as "bystander activation". These mechanisms include increased MHC class I or II molecules expression, enhanced processing and presentation of self antigens, cytokine release with immune activation, direct lymphocyte activation by lymphotropic viruses, and changes in the function of lymphocytes and macrophages [14,41,74]. These changes might happen during infections. All the above mechanisms are not primarily responsible and another mechanism e.g. molecular mimicry or superantigens is necessary for the induction of autoimmune disease. Probably the most important of these mechanisms is the enhanced processing and presentation of self antigens which supports the expansion or spreading of the immune response towards other than the original self peptides, a mechanism called "epitope spreading" [61,75]. The role of epitope spreading is illustrated by the model of Theiler's murine encephalomyelitis virus, a chronic demyelinating disease [76].

### The Role of Retroviruses

Retroviruses have a special role. Their basic property is the incorporation of their genome to the host genome, resulting in the expression of their proteins by the host cells for indefinite periods. Because of this the distinction between self and non-self by the host becomes problematic.

Although there is no direct evidence associating retroviral infections with autoimmune diseases, there are data from animal models as well as epidemiological studies supporting this association. Retroviral infections in sheep (maedi/visna virus) and goats (caprine arthritis encephalitis) present a clinical picture similar to that of systemic human autoimmune diseases such as rheumatoid arthritis and multiple sclerosis [40]. In mice strains susceptible to systemic lupus erythematosus (e.g. New Zealand Black) immune complexes containing retroviral antigens (gp70) and the respective antibodies have been isolated [77]. Additionally in another SLE susceptible mice strain (MLR/lpr) endogenous retroviral sequences have been isolated from their DNA [78].

In humans the data are fewer. Human T cell lymphotropic virus type I (HTLV-I) can present as chronic arthritis, in patients which are seropositive but who do not have the typical manifestations of this infection such as adult T cell leukemia or tropical spastic paraparesis [79]. Another example is AIDS where autoimmune mechanisms are important in its pathogenesis. The proteins gp120 and gp41 of the HIV present sequence homology with MHC class II (HLA-DR and HLA-DQ), thereby acting as "alloepitopes", initiating an immune response [80].

The exact mechanisms by which retroviruses can cause autoimmune disease are unknown but persisting antigenemia, molecular mimicry and superantigens of the virus have been implicated. These mechanisms are common to many types of viruses but there are two mechanisms which are used specifically by retroviruses [40,81]. The first is the *trans*-activation of genes of molecules involved in inflammatory reactions (e.g. IL-2, α subunit of IL-2 receptor, CM-CSF, TGF-β) from the *trans*-acting transcription activators of retroviral genes. These proteins upregulate the transcription of non viral genes and suppress the repress the expression of other genes. The second mechanism involves the inactivation or transcriptional activation of immune regulatory genes (the so called autogenes). These genes are thought to regulate the immune response and their dysregulated expression could lead to autoimmune disease [82].

## CONCLUSION

The relation between infections and autoimmune diseases is a hard to solve problem. We have presented data, from epidemiological, clinical and laboratory research, but the majority of these studies has not clearly shown the etiologic and pathogenetic role of infections in autoimmune diseases. The establishment of the role of infectious diseases could lead to novel therapeutic strategies for autoimmune diseases such as vaccination for the prevention of autoimmune diseases [83].

According to a suggested theory the evolutionary pressure from infections (e.g. tuberculosis) has shaped a resistant population, but at the same time it has created an immune environment in which the autoreactive Th1 cells are inadequately controlled, resulting in autoimmune disease tendency (autoimmune phenotype). The fundamental evidence of the supporters of this theory is the association of resistance to tuberculosis and autoimmune diseases. Populations with exposure and consequent resistance to tuberculosis show increased frequency of autoimmune diseases, while populations which have not been exposed to tuberculosis have a low incidence of autoimmune diseases [84].

After all there is a conundrum which has to be solved: infections are common while autoimmune diseases are infrequent.

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