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Infections and Autoimmunity—Good or Bad?[1]

Urs Christen; ... et. al

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BRIEF REVIEWS

Infections and Autoimmunity—Good or Bad?[1]

Urs Christen[2] and Matthias G. von Herrath

The relationship between infections and autoimmunity is complex. Current evidence indicates that microbes can initiate, enhance, or, conversely, abrogate autoimmunity. In this paper, we will review experimental examples illustrating mechanisms involved in these three scenarios. Microbial infections can act as environmental triggers inducing or promoting autoimmunity resulting in clinical manifestations of autoimmune disease in genetically predisposed individuals. However, increasing evidence suggests the opposite outcome, which is the prevention or amelioration of autoimmune processes following microbial encounters. These latter observations support conceptually the "hygiene hypothesis," suggesting that cleaner living conditions will lead to enhanced incidence of autoimmune disorders, asthma, and allergies. Because proof of concept in humans is difficult to obtain, we will discuss relevant animal model data in context with likely or proven human associations. Knowledge of mechanisms that underlie either positive or negative effects of infections on autoimmunity will facilitate exploration of molecular details for prospective clinical studies in the future. The Journal of Immunology,* 2005, 174: 7481–7486.

It is a generally accepted hypothesis that autoimmune diseases arise from an unfortunate combination of genetic susceptibility and environmental factors. Several genetic risk factors and protective elements that influence susceptibility for autoimmune disease have been identified (1–5). However, a considerable discordance in incidence of autoimmune disease comparing identical twins (6–8) suggests that, in many cases, additional factors, such as environmental modulators, could be involved (9). More recently, investigators at the Barbara Davis Center found that the concordance of autoantibodies among monozygotic twins from families at risk is close to 95%, yet disease penetrance is ~50% (P. Gottlieb, unpublished observations). This observation indicates that the environment would be a key modulator yet not necessarily an initiator of autoimmunity, unless a ubiquitous factor acts in concert with the genetic predisposition that can explain the development of autoantibodies to islet Ags in all cases.

Intuitively, infections by pathogens, such as viruses, bacteria, or parasites are prime candidates for enhancing autoimmune disease in susceptible individuals, because infections frequently induce strong inflammatory responses in various organs. There are several major pathways through which viruses and other pathogens can initiate or, more likely, modulate autoimmunity in an Ag-specific and/or Ag-nonspecific manner. However, some of these, as detailed in the following, can also act to ameliorate autoimmunity, which clearly illustrates the fine balance between positive vs negative effects caused by microbes (Figs. 1 and 2). Indeed, the latter scenario would fit well with the "hygiene hypothesis" that postulates a protective effect of infections against autoimmune disease (10).

1) Direct infection of target cells/organs can cause the release of sequestered autoantigens and enhance Ag presentation. However, some Ags might activate regulatory T cells and thus dampen rather than evoke aggressive responses (11, 12).

2) Chemokine gradients created following infection of selective sites or whole organs can attract a multitude of potentially autoaggressive lymphocytes to the site of infection. Conversely, viral infections in particular can attract potentially autoaggressive T cells away from an autoimmune process, if strong chemokine gradients caused by the infection exist at other sites (13).

3) Local inflammation might alter the repertoire of self-epitopes presented by APCs by changing the Ag degradation properties of the proteasome (14). If APCs are highly activated and fully matured, induction of Tregs might be unlikely under such conditions and autoimmunity will likely be worsened.

4) Presentation of pathogen epitopes with structural or sequential similarity to host (self) epitopes might specifically activate autoreactive lymphocytes, a concept termed molecular mimicry (15–20).

5) Intramolecular and intermolecular epitope spreading may occur from initial nonself epitopes (i.e., viral epitopes) to self (host) epitopes (21–23).

In the following, we will review evidence for pathogens that have been associated with autoimmune disorders and discuss examples of how such pathogens shape the autoimmune response of the host toward clinical disease or protection.

Known associations of human autoimmune diseases with microbial infections

Associations with infectious agents have been suggested for a multitude of autoimmune diseases, including type 1 diabetes

Immune Regulation Laboratory, La Jolla Institute for Allergy and Immunology, San Diego, CA 92121

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[2] Address correspondence and reprint requests to Dr. Urs Christen, Department of Developmental Immunology, La Jolla Institute for Allergy and Immunology, 10355 Science Center Drive, San Diego, CA 92121. E-mail address: christen@liai.org

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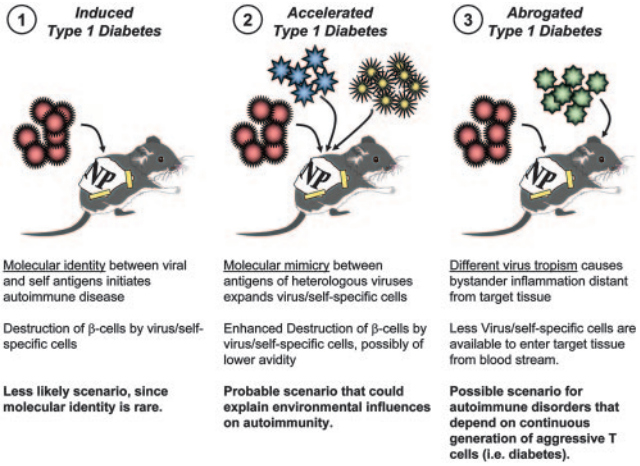

FIGURE 1. Induction, acceleration, and abrogation of autoimmunity in the RIP-LCMV-NP mouse model for T1D. 1) Diabetes is induced by LCMV infection of mice that express the identical viral NP specifically in the β cells of the pancreatic islets of Langerhans. 2) Diabetes cannot be induced by infection with a virus carrying epitopes that confer molecular mimicry with LCMV-NP. However, heterologous infection with viruses that share structural similarities can expand low avidity virus-specific T cells to high frequencies sufficient to accelerate the ongoing autoimmune destruction. 3) Diabetes can be abrogated by infection of mice with viruses that have a different tropism causing strong inflammation distant from the pancreatic target site.

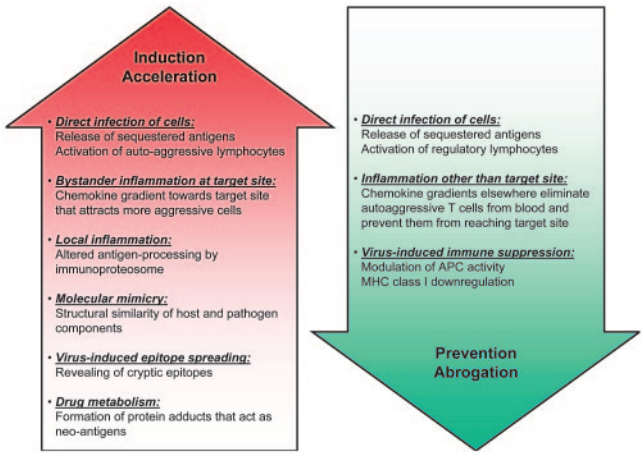

FIGURE 2. Summary of putative mechanisms involved in the initiation or abrogation of autoimmune disorders.

(T1D),[3] multiple sclerosis (MS), and ankylosing spondylitis (24). However, attempts to establish a direct epidemiological, statistically relevant association between microbial infections and various autoimmune disorders have been unsuccessful so far. In the following, we will discuss a few interesting scenarios. For example, hepatitic C virus has been suggested to be involved in the etiology a whole plethora of autoimmune disorders including myasthenia gravis (25), autoimmune hepatitis (26), cryoglobulinemic vasculitis (27), and rheumatoid diseases (28). EBV has been linked with chronic autoimmune diseases, like MS or systemic lupus erythematosus (SLE), because it readily infects (auto)reactive B lymphocytes (29). Evidence for EBV to act as an infectious precursor of SLE was recently demonstrated in mice that were immunized with either the initial autoantigenic epitope recognized in SLE patients or the cross-reactive EBV epitope EBNA-1 (30). Interestingly, both treatments caused clinical symptoms of SLE suggesting that molecular mimicry by EBV might be involved in the etiology of SLE (30). The occurrence of SLE has also been associated with parvovirus B-19 infection (31), and MS has been seen in individuals infected with human herpesvirus 6 (32, 33). Infections by coxsackievirus strains B3 and B4 have been proposed to play a role in the initiation of autoimmune myocarditis (34) and Sjögren's syndrome (35), respectively. Additional associations have been found in some cases for HSV type 1 (HSV-1) and autoimmune keratitis (16) and rotavirus infection and T1D (36, 37). Several viruses, including coxsackie B viruses (38) and rubella virus (39, 40), have been suggested to play a role in the pathogenesis of human T1D. One of the possibly strongest associations has been found between rotavirus infection in young infants and the first occurrence of islet autoantibodies (36). However, a recent study from Finland questioned such a possible association, because no difference in diabetes-associated autoantibody generation was found in susceptible children that either had or had not been infected with rotavirus (37).

This last example clearly documents how difficult it is to establish a direct epidemiological association between microbial infections and autoimmune disorders. Attempts have probably been unsuccessful so far because of multiple predicaments. First, patients suffering from autoimmune diseases and healthy individuals alike undergo multiple infections during their lifetime. Most are cleared by the time of disease diagnosis. Thus, virus infections can be considered as "hit and run" events that leave no precise footprints to document the patient's history of prior infections. Second, genetic factors, such as the MHC haplotype, are not only directly responsible for disease susceptibility, but will also influence the antiviral immune response profoundly. A third factor that adds to the complexity is that infections are less likely to directly initiate autoimmunity, but will rather accelerate a pre-existing autoimmune condition to progress to clinical disease. This implies that multiple sequential events could be necessary to precipitate disease and further complicates attempts to establish firm proof for the involvement of environmental factors. Fourth, the precise timing, location, and magnitude of inflammation and, for example, viral strain, might all play an important role. Indeed, recent studies have shown that modification of these parameters can switch a disease-enhancing viral infection to one that prevents diabetes (see Ref. 41 vs Ref. 42). As a last factor, one has to consider that certain infections might protect from autoimmunity rather than enhance it (13, 43). Thus, the entire infectious history of each patient might determine the overall immune status that results in autoimmune disease or not.

Among bacteria, infection with *Helicobacter pylori* has been associated with autoimmune gastritis (44, 45). Patients with group A *Streptococcus* infection were shown to have an increased risk of rheumatic heart disease (46), and *Streptococcus pyogenes*-induced acute rheumatic fever has been established as one of the best examples of postinfectious autoimmunity due to molecular mimicry between lysoganglioside of the host and *N*-acetyl-β-D-glucosamine, the dominant epitope of the group A streptococcal carbohydrate (47). Furthermore, new evidence suggests a

[3] Abbreviations used in this paper: T1D, type 1 diabetes; MS, multiple sclerosis; SLE, systemic lupus erythematosus; RIP, rat insulin promoter; LCMV, lymphocytic choriomeningitis virus; NP, nucleoprotein; TMEV, Theiler's murine encephalomyelitis virus; PDLN, pancreatic draining lymph node.

correlation between the xenobiotic-metabolizing bacterium *Novospingobium aromaticivorans* and primary biliary cirrhosis (48). In addition, the spirochete *Borrelia burgdorferi*, which is usually transmitted to the host by a tick bite, may induce chronic autoimmune diseases affecting multiple organs including the nervous system, cardiovascular system, joints, and muscles (49). Other microorganisms suggested to play role in autoimmune disorders include *Trypanosoma cruzi*, which was linked to chronic Chagas' cardiomyopathy (50) and the helminth worm *Schistosomas* (51).

Thus, in summary, although there have been many cases of reported positive and sometimes negative associations between pathogens and autoimmune disorders, clear proof for any given culprit has been difficult to establish. Therefore, it might be of benefit to have a closer look at the mechanisms that we know are playing a role in animal models. We might learn that common mechanisms rather than one single pathogen will govern the complex and multifaceted link between our environment and penetrance of autoimmune diseases.

Mechanistic lessons from animal models for autoimmune diseases

Many animal models have been generated to study the mechanisms of the autoimmune-mediated destruction process that leads to clinically overt autoimmune disease. Such animal models form a platform, where possible therapeutic treatments that target the termination or control of the autodestructive process can be evaluated. They can serve as very useful tools to understand the mechanisms that could underlie complex human autoimmune disorders and are well suited to establish proof-of-principle. Lastly, analysis of complex immune kinetics over time is possible, which can allow for more insight than testing of immune responses in humans, which is largely restricted to the blood and a few other accessible sites.

Initiation of autoimmune processes by infections

Taking all of the present evidence together, we believe that initiation of autoimmunity by microbial infections is less likely. Current evidence, at least for T1D, indicates that the genetic predisposition can almost entirely explain the generation of autoantibodies. Indeed, studies in animal models support the notion that it is difficult to break tolerance in an otherwise non-autoimmune-prone, naive individual. Recently, Ohashi's laboratory and our group have both demonstrated that cross-reactivity between viral and autoantigens cannot precipitate autoimmune disease in unprimed animals (19), unless systemic T cell activation thresholds are lowered, for example by the lack of Cbl-b (52). For example, to initiate a diabetogenic autoimmune response in naive animals, the rat insulin promoter (RIP)-lymphocytic choriomeningitis virus (LCMV) model uses a virus (LCMV) that shares an epitope that is identical with the targeted transgenic "self"-protein. Apparently, the strong antiviral immune response generates virus-specific lymphocytes sufficient in magnitude and affinity to target and destroy β cells bearing the identical (transgenic) self-component. We recently found that this is not that case if mice are infected with a virus that carries an epitope that is similar but not identical with the self-component, a scenario that might be more realistically and frequently in a human patient collective. Infection with Pichinde virus, which shares a similarity with the subdominant nucleoprotein $(NP)_{205–213}$ epitope of LCMV strain Armstrong that is normally used to induce T1D in the RIP-LCMV mouse, failed to induce disease (19). Thus, it is required that intrinsic mechanisms that normally protect us from autoimmunity are derailed. This, in our opinion, can be achieved genetically, for example through the autoimmune regulator (*AIRE*) gene (3, 53) or other immunogenetic mechanisms, for example those affecting the *TIM* (4, 54) or *CTLA4* loci (2). The emerging picture is that infectious events will much more likely affect disease penetrance in individuals that are genetically at risk.

Acceleration of ongoing established but "subclinical" autoimmune processes by infections

Recently, we reported that a realistic molecular mimicry situation between virus and host could accelerate an ongoing, already established autoimmune process leading to more rapid diabetes development (19). When LCMV-infected RIP-LCMV-NP mice received a secondary infection with Pichinde virus, the disease occurred much more rapidly (19). In this case, heterologous infection with two viruses, which shared a similar epitope, expanded a critical population of virus/self-specific lymphocytes to a magnitude sufficient to accelerate the destruction of the target tissue (islets of Langerhans). Our observations indicate that autoreactive lymphocytes that are per se incapable of inducing disease may become dangerous when encountering a "fertile field" of inflammation (24). Such a setting is provided in the presence of persistent infections because chronic inflammation may drive and expand cross-reactive lymphocytes as demonstrated recently in animals of HSV-1-induced herpes stromal keratitis (55) and in recombinant Theiler's murine encephalomyelitis virus (TMEV)-induced demyelination (56). Infection of mice with a HSV-1 mutant virus with a single amino acid change in the UL6 protein of HSV-1 affecting the putative mimicry epitope fails to induce herpes stromal keratitis. However, the mutant HSV-1 was able to induce disease in predisposed mice that received CD4 cells from wild-type virus-infected donors (55). In the TMEV model, recent data suggest that a molecular mimic of an encephalitogenic myelin proteolipid epitope when expressed by an engineered TMEV can both initiate CNS autoimmune disease and exacerbate a previously established disease (20).

In support of the concept that a local inflammation can act as a fertile field for Ag-driven autoimmune processes, several transgenic animal models that express inflammatory mediators such as cytokines and chemokines or MHC class I and costimulatory molecules have been created. Most of these underline the notion that inflammatory cytokines such as IFN-γ, TNF-α, IL-12, and IL-2 will enhance disease development, whereas certain factors such as IL-4 and TGF-β will dampen autoimmunity in most situations. This depends on the level and precise time when the cytokines are being expressed in relation to the autoimmune process (see Ref. 57 for review). In this paper, we will briefly review findings from a model established in our own laboratory that illustrates novel insight into the importance of trafficking of autoaggressive lymphocytes to the pancreatic islets. In our model, the local fertile field is provided in the pancreatic islets by specific expression of the Th1 cell attractant chemokine CXCL10 (IFN-inducible protein of 10 kDa), which leads to a spontaneous infiltration of islets by CD4 and CD8 T cells but

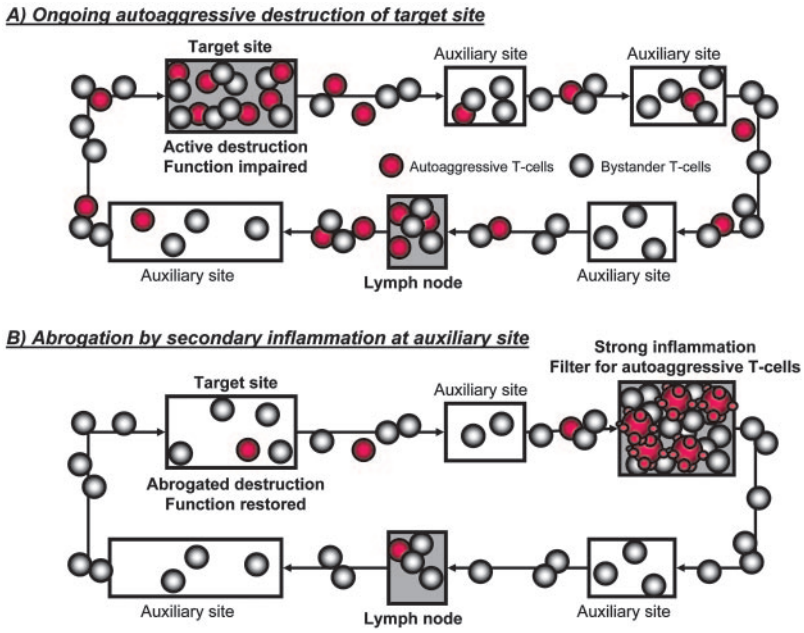

FIGURE 3. Strong inflammation may act as filters for autoaggressive T cells. *A*, Dynamic recirculation of both Ag-specific autoaggressive and unspecific bystander T cells between the target site of autoimmune destruction (i.e., pancreas in T1D), lymphoid organs, and auxiliary organs. Accumulation of autoaggressive T cells at the target site causes active destruction of target cells (i.e., β cells in T1D) and functional impairment (i.e., loss of insulin production in T1D). *B*, Strong inflammation at an auxiliary site, for example, by virus infection, might act as a filter for autoaggressive T cells that might be drawn toward the newly infected site along chemokine gradients. Once arrived at the inflamed site, they might die by hyperactivation-induced apoptosis. Such a permanent removal of autoaggressive T cells from the recirculating T cell pool would abrogate the ongoing autoimmune destruction at the target site and restore its metabolic functions.

no clinical diabetes.[4] However, when a strong antigenic stimulus was provided in RIP-LCMV mice following LCMV infection leading to activation of autoaggressive T lymphocytes, CXCL10 accelerated the autoimmune process.[4] Similar to the model that uses heterologous virus infections (see previous paragraph), disease acceleration was the result of a higher frequency of islet Ag-specific lymphocytes locally in the islets of Langerhans.[4] Another interesting result of this study was that bystander inflammation alone was not sufficient to induce disease, although the presence of large clusters of infiltrated cells in the islets did cause limited β cell impairment, indicating that islet Ag-specific lymphocytes have to be present to cause clinical disease. Similar enhancement of an established disease process has been described in NOD mice after coxsackie B virus infections (38, 42, 58). Thus, viral infections and other environmental modulators might directly affect disease penetrance in individuals with established autoimmune processes. This can occur through inflammation if the infection directly affects the target organ or, conversely, by directly augmenting autoreactive responses, for example, by molecular mimicry.

Abrogation of autoimmunity by infections

On the flip side, many experimental systems support the "hygiene hypothesis," which postulates that infection by viruses and inflammation will protect rather than induce/accelerate autoimmune diseases. For example, injection with coxsackieviruses can not only enhance (59) but also prevent disease in the NOD mouse (41). Furthermore, IFN-γ or TNF-α have protective effects in experimental autoimmune encephalomyelitis models or diabetes models when administered late during the disease process (for example, see Refs. 60 and 61). Mechanistically, several factors may play a role. First, inflammation caused by viruses, bacteria, and especially by parasites, such as helminthes, can shift the Th1-Th2 balance toward a more immunosuppressive state. In these situations, regulatory T cells might be induced or augmented. Indeed, recent studies have provided evidence for regulatory cells with specificity for pathogens to occur in *Leishmania major* (62), HSV (12), and Friend retrovirus (murine leukemia virus) infections (11). Second, inflammation might cause a massive hyperactivation of autoaggressive lymphocytes, which may lead to activation-induced cell death and diminish the systemic load of aggressive T cells. The concept that repeated encounter with strong antigenic stimuli will lead to contraction of an immune response is well established in viral infections, where the primary response undergoes a major contraction after Ag has been eliminated (63, 64). These considerations also imply that, to enhance autoimmunity, "just the right" type of stimulus is required: Pushing aggressive T cells too much will result in their rapid demise by apoptosis (13), whereas low-level stimuli such as those provided by molecular mimicry might expand dangerous T cell populations better by circumventing excessive apoptosis (13). Similarly, administration of mycobacterial preparations, such as bacille Calmette-Guérin, was demonstrated to prevent the onset and recurrence of T1D in NOD mice by inducing FasL- and TNFR55-dependent apoptosis of autoreactive T cells (65).

Third, infection at another location might keep autoaggressive cells from reaching the site of autoimmune destruction. It is this last possibility that may be responsible for the abrogation of T1D in NOD mice after LCMV infection that was initially observed more than a decade ago (66, 67). We recently demonstrated that infection of NOD and LCMV-immune RIP-LCMV mice with LCMV abrogated T1D. We proposed that this occurred because the "abrogative" virus grew predominantly in lymphoid organs and other sites rather than the pancreas or islets themselves (13). Infection with LCMV in these scenarios caused inflammation of the pancreatic draining lymph nodes (PDLN) characterized by extensive expression of the chemokine CXCL10. This resulted in accumulation of autoaggressive T cells in PDLN rather than the islets and lack of development of clinical disease (13). Interestingly, the protection from diabetes was permanent, possibly because many autoaggressive lymphocytes had been permanently deleted as indicated by an enhanced frequency of

[4] A. Rhode, M. Pauza, A. Barral, M. Oldstone, M. von Herrath, and U. Christen. Islet-specific expression of CXCL10 causes spontaneous infiltration and accelerates diabetes development. *Submitted for publication.*

islet-specific CD8 T cells undergoing apoptosis in the PDLN after LCMV infection (13). In a sense, sites of strong inflammation might therefore act as a filter for autoaggressive T cells eliminating them from the circulation and preventing them from reaching the pancreatic islets (this concept is illustrated in Fig. 3). Similar mechanisms might be at work in other scenarios, where infections protect from autoimmunity (41, 68).

Summary

It is apparent from the studies discussed in this article that microbial infections might enhance as well as protect from human autoimmune disorders. Direct proof for viruses to induce and/or accelerate autoimmunity in an individual patient is difficult to find because of a variety of reasons. Most problematic is the fact that the onset of clinical disease might be years to decades distant from the time of any environmental triggering event. Thus, at the time of disease diagnosis, no easily detectable traces of a causative pathogen(s) might remain in the host's system. It is even more challenging to demonstrate a protective effect of microbial infections, because, besides not being able to define the protective microbe(s), healthy individuals would not necessarily be routinely clinically evaluated. To date, the "hygiene hypothesis" is based mostly on retrospective epidemiological data showing that an increase in autoimmune diseases and allergies during the last decades is paralleled by a cleaner environment. In this context, a very interesting prospective study in a trial population of 317 students from Lambaréné, Gabon, was recently presented by Yazdanbakhsh's research group (69), which associated the lack of parasites with an increase in allergic asthma. These students, ~70% of whom were infected by intestinal helminthes, were treated with antihelminth drugs for 30 mo and were evaluated in 6-mo intervals for sensitivity to dust mites, total IgE levels, and helminth infection status. Interestingly, a significantly increased frequency of helminth-free students had allergic reactions against dust mites, indicating that helminthes might suppress allergic disorders (69). Naturally, this study generated a lot of interest and controversy (10). It is, for example remarkable that, although parasites, such as helminthes, had been eradicated in the United States by 1980, the incidence of asthma has been growing ever since (10). We think it is important that a multitude of factors are considered when attempting to correlate or provide proof for microbial infections to either enhance or abrogate autoimmune disorders. Over a lifetime, all of us are exposed to multiple infections that all influence immune reactivity and repertoire. In addition, other environmental factors, such as xenobiotics, have an impact on our immune system and have been associated with autoimmune disorders (for review, see Ref. 9). Thus, the likelihood for developing autoimmunity seems to be a complex integration of our individual history of exposure to environmental factors and the presence or absence of genetic risk factors.

Based on insights provided via animal models, we would propose for future epidemiological studies that the cumulative inflammatory history of each patient might be more important than a single infectious event. Along these lines, the precise type of inflammation and its occurrence in relation to an ongoing autoimmune process have to be documented precisely. We believe that, in the long run, such investigations will help us to distinguish between detrimental and beneficial inflammatory events, information that could be used to lower overall disease incidence.

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