

Can infections protect against autoimmunity?

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Purpose of review

It has often been suggested that autoimmune diseases are initiated by certain infectious agents that mimic self-antigens or polyclonally activated autoreactive lymphocytes. An alternative, and not necessarily mutually exclusive, hypothesis that some infections might inhibit the onset of some autoimmune conditions has more recently been explored. In this review, the evidence suggesting that the current rise in the incidence of some autoimmune diseases is attributable to a decrease in the incidence of exposure to certain infections will be discussed.

Recent findings

Studies using animal models have shown that some infectious agents or products derived from them have the potential to inhibit the onset of autoimmunity. These studies have led to the suggestion that human autoimmune or allergic diseases might be alleviated by the use of microbial products. There are some data that would support such an observation.

Summary

The incidence of some autoimmune diseases has increased dramatically in recent years in the developed world. Many autoimmune diseases are governed by both genetic and environmental factors. Our immune system has coevolved with infectious agents. There have been marked changes in the exposure to certain infectious agents over the last 70 years. It has been proposed that certain infections of historical importance might inhibit the development of autoimmune disorder. This review highlights studies addressing the ways in which infectious agents might inhibit onset of autoimmunity, and how this might lead to the development of novel therapeutic approaches.

Keywords

autoimmunity, helminth, mycobacteria, type 1 diabetes

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Introduction

The incidence of some autoimmune diseases, as well as allergy, has risen dramatically in the developed world over the last 70 years. Most autoimmune diseases are governed by both genetic and environmental factors. As the rise in incidence of these disorders is faster than can be accounted for by genetic change, there has been considerable research into the role of environmental factors. Although it is clear that some autoimmune disorders may be initiated following an infectious insult, for others, it has proven difficult to identify an initiating infectious agent. Attention has, therefore, turned to the possibility that historically important infections may have inhibited the development of some autoimmune diseases [1]. In the context of allergy such a hypothesis was called ‘The Hygiene Hypothesis’ [2].

A role for environmental factors in the development of some autoimmune disorders

Apart from some single gene disorders such as immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome, autoimmune polyglandular endocrinopathy with candidiasis and ectodermal dysplasia (APECED) and autoimmune lymphoproliferative syndrome (ALPS) that lead to autoimmune disorder, the development of most autoimmune diseases is under complex genetic control. Studies of identical twins have shown that the concordance rate for development of autoimmune disease is around 40% in the case of type 1 diabetes (T1D), 30% for multiple sclerosis (MS) and around 24% for systemic lupus erythematosus (SLE) highlighting the additional involvement of environmental factors in the development of these autoimmune disorders. Much

research has been carried out not only to identify the genetic factors predisposing to the development of autoimmunity but also to determine which environmental factors are involved. There has been considerable interest in exploring the role of infection as a potential environmental factor leading to autoimmunity.

Epidemiological studies have demonstrated that autoimmune disorders such as MS, rheumatoid arthritis (RA), SLE often manifest themselves following microbial or viral infection [3], and streptococcal A infection is a well known trigger for rheumatic fever and rheumatic heart disease [4]. Bacterial and viral infections have also been associated with disease exacerbations in sufferers of autoimmune disorders [5,6]. A number of mechanisms for infection-induced autoimmunity have been postulated and reviewed [7], including molecular mimicry, polyclonal activation and bystander activation. Tissue destruction resulting from the immune response to infection could lead to the release of sequestered antigens and increase the presentation of autoantigens by dendritic cells or macrophages.

In the case of T1D, several infectious agents have been proposed as candidates for initiating autoimmune disorder. The reported seasonal onset of T1D [8] appeared to suggest that infection might play an initiating role in this autoimmune disorder. This appeared to be substantiated by the isolation of a virus from the pancreas of a diabetic individual, which in turn was able to induce diabetes in mice following transfer [9,10]. However, further understanding of the cause of T1D, particularly the observation of islet autoreactive immune responses several years prior to diabetes onset [11], and the failure to find evidence of a common viral insult has led to an alternative hypothesis. This hypothesis proposes that infection might historically have inhibited the development of autoimmune disease. This does not exclude the possibility that some autoimmune diseases and even some cases of T1D are initiated by a viral or bacterial infection.

Type 1 diabetes and immune regulation

There are some features of T1D that make this alternative hypothesis an attractive scenario. T1D is not a new disorder as there are records of its existence in ancient times. This T helper cell 1 (Th1)-mediated autoimmune disease is a disease of juvenile onset that was lethal before the 1920's when Banting and Best [12] discovered insulin.

Yet T1D, which is under polygenic control, is increasing dramatically in the developed world (in the UK, it is rising at an incidence rate of 4% per annum). This suggests that certain alleles have been retained in the population that can predispose to a potentially lethal disease. The retention of such alleles in a population,

or ones in linkage disequilibrium with them, is usually attributed to their having a historical selective advantage often against infectious agents. In the context of T1D, not only would such alleles have protected against potentially lethal infections and provided survival advantage but infection would also have inhibited the onset of T1D. Some of the evidence that infection might initiate or, in some cases, inhibit the development of autoimmunity will be presented. The mechanisms by which this might be achieved are reviewed in the following sections.

The healthy immune system is held in balanced equilibrium by continual surveillance and communication between the innate and adaptive arms of the immune system via cell-to-cell interactions and a range of chemical mediators such as cytokines and chemokines. If this system becomes imbalanced, the body may react against self-antigens or some exogenous antigens resulting in autoimmune or allergic disorders, respectively. Several cell types have been implicated in the control of auto-reactive responses including regulatory T cells (Tregs), dendritic cells and natural killer T (NKT) cells. Many studies have suggested that defects in immune regulation might lead to the development of autoimmunity. There is good evidence that both adaptive and naturally occurring Tregs (nTregs) are important in the control of autoimmune disease [13–15]. There are reports of a decrease in cell numbers and suppressive properties of Tregs associated with active bouts of rheumatoid diseases [16] and MS [17]. There have additionally been reports of reduced numbers of Tregs in patients with T1D [18] and in the nonobese diabetic (NOD) mouse model of this autoimmune disease [19]. However, others have suggested that there is no reduction in the numbers of Tregs [20], but that there may be a reduced functional activity of these Tregs [21,22,23[•]] that in the light of more recent publications may have been related to the resistance of the effector T cells to regulation [24^{••},25^{••}]. Another type of regulatory T cell, the NKT cell, has been implicated in regulating T1D as well as other autoimmune diseases. Reduced numbers of these cells have been associated with onset of diabetes in humans and in the NOD mouse model of T1D [26,27], whereas restoration of these cells can prevent diabetes onset [26]. α -galactosyl ceramide is known to be a ligand for murine CD1d-restricted NKT cells, and it has furthermore been shown that injection of this ligand into NOD mice expands the NKT cell population and prevents onset of T1D [28–30].

Infection can inhibit the onset of autoimmune diseases including type 1 diabetes

Over the last 70 years in the developed world, there have been enormous changes in our exposure to infectious agents. Marked improvement in living conditions and the

use of antibiotics together with vaccination strategies have ensured that we are no longer exposed to, or succumb to, agents that our ancestors encountered. Our ancestors would have been infected with a range of organisms from early childhood. Evidence for such infections can be found through the analyses of coprolites or prehistoric mummies such as the 'Ice Man' of the Otzal Alps or pre-Columbian mummies in Peru [31,32]. These studies have revealed the presence of a range of organisms to which these ancient people were exposed, including mycobacteria and parasites.

The hypothesis that infection with agents such as mycobacteria or helminth infections may inhibit onset of T1D can be tested with animal models of human T1D such as the NOD mouse. The NOD mouse spontaneously develops T1D and is widely used to analyse factors contributing to pancreatic β cell destruction [33].

Studies [1,34–38] in this model have shown that bacterial and helminth infections are able to prevent diabetes onset. Such effects of certain infections have been seen in experimental models of a range of human autoimmune diseases (Table 1) [39–55].

Interestingly, it has been shown that it is not always necessary to have an infectious disease, but that simple exposure to components of these organisms can inhibit

onset of autoimmune disorder. Soluble worm antigen (SWA) and soluble egg antigen (SEA) from *Schistosoma mansoni*, OM89 and OM85 from *Escherichia coli* and ES62 from *Acanthocheilonema viteae* have been demonstrated to have immunomodulatory activity in animal models of T1D, SLE and RA [37,50,56,57]. The timing of exposure to some of these agents is critical in determining outcome, in many cases early exposure being essential for the complete prevention of autoimmune disorder. On the strength of such observations, clinical trials have been initiated using infections with the pig whipworm *Trichurus suis* to treat inflammatory bowel disease with some reported success [44,45,58]. An additional clinical observation has provided some support for the proposition that helminth infection might alleviate autoimmune disorder. Correale and Farez [59] observed that patients suffering from MS had improved disability scores and fewer MRI incidents if they also had parasitic infections. Clinical trials have been initiated to test the hypothesis that parasitic infection ameliorates MS.

How might infections inhibit the development of autoimmune disorder?

Our immune systems have coevolved with infectious agents. Some of these infections utilize the host immune system and elicit responses to dampen down the host response and thus limit target tissue injury. The interactions of bacteria-derived, fungi-derived and parasite-derived molecules with toll-like receptors (TLRs) and C-type lectin receptors (CLRs) on cells of the innate and adaptive immune system enable them to modulate immune responses. Evidence is emerging from animal studies that exposure to infectious agents or products derived from them can inhibit the onset of autoimmune disorder through a range of mechanisms including reinforcing regulatory networks and also influencing trafficking of autoreactive T cells to sites of inflammation. In an animal model of MS, the trafficking of autoreactive cells has been shown to be affected by mycobacterial infection [60]. A comparable inhibition of trafficking of autoreactive T cells to the pancreas has been demonstrated in the NOD model of T1D following infection with *Salmonella typhimurium* and shown to be due to effects of infection on dendritic cells [55].

There are data demonstrating that the SEA of *Schistosoma mansoni* is able to influence activity of the dendritic cell to induce more interleukin-10 (IL-10) and reduce proinflammatory cytokine production, whereas SWA is a potent inducer of the NKT cells that have been shown to inhibit T1D [37]. Detailed study of the schistosome-specific phosphatidylserine has shown it to be capable of activating TLR2 on dendritic cells such that they gained the ability to induce the development of IL-10-producing Tregs [61]. In addition to direct effects on dendritic cells and NKT cells,

Table 1 Protective effect of pathogens on autoimmune disorders

Infectious agent disorder	References
Helminth	
<i>Schistosoma mansoni</i> type 1 diabetes (Infection, SEA, SWA or eggs)	[1,37]
Experimental colitis EAE	[39]
Induced Graves' disease	[40]
<i>Trichinella spiralis</i> (infection) EAE	[41]
Experimental colitis	[42]
Type 1 diabetes	[43]
<i>Trichuris suis</i> ulcerative colitis	[36]
Crohn's disease	[44]
<i>Heligmosomoides polygyrus</i> experimental colitis	[45]
Type 1 diabetes	[46]
<i>Acanthocheilonema viteae</i> collagen-induced arthritis ES-62	[36]
Bacterial	[47]
<i>Escherichia coli</i> rheumatoid arthritis (Extract OM 89) SLE	[48]
OM65 type 1 diabetes (Mixed bacterial cocktail)	[49]
<i>Mycobacteria avium</i> type 1 diabetes	[50]
<i>Mycobacterium bovis</i> -induced Graves' disease EAE	[35]
<i>Mycobacterium tuberculosis</i> EAE	[51]
HSP	[52]
<i>Bordetella pertussis</i> EAE	[53]
<i>Pseudomonas aeruginosa</i> type 1 diabetes	[54]
<i>Salmonella typhimurium</i> type 1 diabetes	[55]

EAE, experimental autoimmune encephalomyelitis; HSP, Henoch–Schönlein purpura; SEA, soluble egg antigen; SLE, systemic lupus erythematosus; SWA, soluble worm antigen.

helminths are known to induce a distinct subset of alternatively activated macrophages (aaMs), which secrete IL-10, IL-13 and transforming growth factor (TGF) that can inhibit Th1 cell proliferation and facilitate induction and recruitment of Th2 and Tregs [62]. OM-89, which has been shown to inhibit arthritis and SLE, has also been shown to induce IL-10 and inhibit proinflammatory cytokine production in RA patients [57]. Harnett and Harnett [56] have identified the phosphorylcholine moiety as the active component as the immunomodulator of ES-62 isolated from *A. viteae*. Phosphorylcholine has been demonstrated to bind to TLR4, modulating IL-12 and tumour necrosis factor (TNF) production and inducing Tregs. More recently, synthetic analogues of bacterial quorum-sensing molecules, *N*-(3-oxododecanoyl)-L-homoserine lactone (OdDHL) and 2-heptyl-3-hydroxy-4-quinolone (PQS), have been shown to have immunomodulatory activities, suppressing dendritic cell and T cell maturation [63]. OdDHL has also been shown to successfully inhibit diabetes onset in the NOD mouse model [54], and studies of the mechanism of action of OdDHL demonstrate its pleiotrophic nature. OdDHL has been demonstrated to freely enter mammalian cells and not via signalling through TLRs, as it is predominant in bacterial infections. More recently, it has been shown that OdDHL targets peroxisome proliferator-activated receptors (PPARs) inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and phosphorylation of mitogen-activated protein kinase (MAPK) p38 [64^{••},65[•]]. In the context of a Th1-mediated or Th17-mediated autoimmune disorder, the parasite-induced or bacteria-induced responses described above would inhibit autoimmune disorder. Recent research has focused on the isolation and characterization of immunomodulatory components and their targets [56,64^{••},66^{••},67] (Table 2). An understanding of the detailed mechanisms by which organisms mediate anti-inflammatory responses will lead to the identification of novel approaches for therapeutic intervention. It will also further enhance the understanding of the complex interplay between cells, their receptors and signalling pathways involved in autoimmunity.

Table 2 Immunomodulatory targets of bacterial and parasitic-derived molecules

Pathogen	Immunomodulatory target	Reference
<i>Schistosoma mansoni</i>		
Lysophosphatidylserine	TLR2	[42]
<i>Acanthocheilonema viteae</i>		
Phosphorylcholine	TLR4	[56]
<i>Trypanosoma cruzi</i>		
Glycoinositolphospholipid	TLR2/MΦs	[67]
<i>Pseudomonas aeruginosa</i>		
OdDHL	PPAR	[65 [•]]

OdDHL, *N*-(3-oxododecanoyl)-L-homoserine lactone; PPAR, peroxisome proliferator-activated receptor; TLR, toll-like receptor.

Conclusion

There has been longstanding interest in the role of infectious agents in the development of autoimmune diseases. Initial studies focused on the role infections might play in initiating autoimmune disorder. More recently, however, there has been increasing interest in the possibility that infection rather than precipitating autoimmunity might in some cases have historically prevented onset of autoimmunity.

There are data supporting this latter role for infection not just in the autoimmunity field but also in the allergy field. Infection may also play a role in some childhood leukaemias in which the epidemiology shares some parallels with autoimmune diseases such as T1D [68[•]]. The overarching mechanism by which infections might inhibit onset of autoimmunity, allergy or childhood leukaemia would be that some infections reinforce immune regulatory circuits preventing the emergence of deleterious cells.

Acknowledgement

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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This review serves to extensively summarize the range of helminthic infections and crude extracts that have been demonstrated to prevent autoimmune disorders in animal models. It also summarizes a range of isolated parasite products and their receptors, suggesting possible effects on the immunomodulatory process.

- 67 Ropert C, Ferreira LR, Campos MA, *et al.* Macrophage signaling by glycosylphosphatidylinositol-anchored mucin-like glycoproteins derived from *Trypanosoma cruzi* trypomastigotes. *Microbes Infect* 2002; 4:1015–1025.

- 68 Cooke A. Infection and autoimmunity. *Blood Cells Mol Dis* 2009; 42:105–107.

This study discusses the mechanisms by which infections may mediate the prevention of autoimmune disease and suggests parallels between the epidemiology of childhood leukaemias and autoimmune diseases such as T1D.