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Autoimmunity: an infection-related risk?

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Our first encounter with microbial flora at birth begins the development of our genetically distinct immune system, which develops through recognition of microbes that stimulate innate immune cells and their toll-like receptors and the adaptive immune response of B and T cells. These initial responses that develop as a result of recognition of microbes and pathogens during the early years of life may set the course for future immune responses [1,2]. Microbial colonization and infection with microbes and pathogens induces protective immune responses both at the mucosa [3,4] and in the blood and tissues [5,6]. It is evident that these microbial influences are important in development of the immune system including T-helper cell subsets and autoimmunity. Thus, individual unique immune genes such as the histocompatibility leukocyte antigens (HLAs) and environmental exposures combine to deliver immune responses that protect us against infections but also can make us susceptible to autoimmune diseases such as those described in this issue. Even in twins with comparable genetic makeup, there is little concordance in the case of infectious related autoimmune diseases such as rheumatic fever [7] or Sjogren's syndrome as discussed by Igoe and Scofield [8] in this issue.

The group A streptococcus has in the past been an excellent example of a single infectious agent, which can cause rheumatic fever with neurologic and cardiac autoimmune sequelae following infection [9]. However, the group of reviews in this issue point out how difficult it is to determine a single etiologic agent as the cause of many reportable autoimmune diseases such as systemic lupus erythematosus and Sjogren's syndrome [8], multiple sclerosis [10], and autoimmune myocarditis [11]. Multiple neurologic and neuropsychiatric disorders, which are associated with multiple infectious agents including schizophrenia, obsessive compulsive and autism spectrum disorders, bipolar disorder, encephalitic and chronic fatigue syndromes, and posttraumatic stress disorders are addressed in this issue by Hornig [12]. Neuropsychiatric illness most distressing for families is pediatric autoimmune neurologic disorder associated with streptococci and pediatric acute neuropsychiatric syndrome, which is associated with multiple infectious agents. In this issue, Hornig [12] describes both pathogenic and commensal microorganisms, which can induce autoantibodies that bind to

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Conflicts of interest

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the brain and alter behavior in animal models. Treatments such as antibiotics or immunotherapeutics are under investigation to improve outcomes in neuropsychiatric diseases [13,14]. Immune responses to a variety of microbes sharing a similar antigenic epitope or repeated infections with the same infectious pathogen provide a chronic antigen stimulus that may break immune tolerance and lead to enhanced responses against the microbe due to an adjuvant effect of microbial or environmental components. Hornig [12] discusses the affects of both commensal or pathogenic microbes on innate immune and inflammatory molecules that may disrupt brain development or open the blood–brain barrier to allow molecules to enter the brain that would otherwise be excluded. Both the innate and adaptive immune responses required to bring about changes in the brain in neuropsychiatric diseases are described in the article by Hornig [12]. She states ‘the veil is about to be lifted in these diseases’ so that we can understand the role of the immune system and its response to the multiple infectious agents and the ‘microbiome’ present in the intestinal flora [12].

In the article by Igoe and Scofield [8], the development of Sjogren’s syndrome is associated with a type I interferon signature due to multiple viral infections including Epstein–Barr virus (EBV), hepatitis C virus (HCV), and human T lymphocyte virus-1. They describe how HCV infection itself produces a ‘sicca-like’ syndrome in human disease [8]. In Sjogren’s syndrome, both genetic predisposition and environmental factors such as viral infections of the salivary glands and a predisposing cofactor dioxin have been shown to increase the risk of Sjogren’s syndrome [8]. As described in their review, the aryl hydrocarbon receptor, the prototypical exogenous ligand for dioxin, has a pronounced impact on dendritic cells, T-regulatory cells, B cells, and Th17 cells. EBV can be reactivated by dioxin and may be related to the immune responses triggered in salivary glands in Sjogren’s syndrome [8].

A common theme throughout autoimmune diseases and postinfectious sequelae such as myocarditis as described by Reddy *et al.* [11] is a process called molecular mimicry whereby antibodies and T-cell receptors recognize both microbe and self-antigen. Although molecular mimicry may be thought of as a phenomenon, it is a normal process of the immune system providing protection against multiple microbes, but when it is directed at both microbe and self-antigens, it may be detrimental. Most of the time, we benefit from cross-reactive antibodies and T cells that recognize multiple antigens.

The most well studied molecular mimicry in a human disease is that of streptococcal-induced rheumatic fever [9].

Studies of multiple sclerosis and virus infections are described in this issue by Cusick *et al.* [10], where interactions between viruses promote and exacerbate multiple sclerosis. Studies by Fujiami and colleagues suggest the very novel hypothesis that in addition to molecular mimicry that there are T cells, which express dual receptors for self-antigens and microbial antigens [10]. CD8⁺ T cells are generated in response to viral infections, and some T cells express dual receptors and may play a role in the disease pathogenesis and exacerbations by viral infections [10]. It was described that in multiple sclerosis, CD8⁺ T cells clonally outnumber the CD4⁺ T cell subset and are a reflection of the viral infections associated with multiple sclerosis. Viral interactions are discussed, which may promote or advance disease pathogenesis [10].

As antibodies and T cells work together to eliminate pathogens, T-cell and B-cell tolerance mechanisms work to prevent autoimmune disease. T cells that react too strongly with self are deleted in the thymus and B cells producing autoantibodies are clonally deleted or receptor edited to prevent autoimmune B or T cells from proliferating and reacting with self-antigens. Clones of B and T cells that escape central and peripheral tolerance and provide recognition of a number of infectious agents for protection can become harmful if they display high enough avidity to become cytotoxic or lead to inflammatory responses causing autoimmune disease. In the article about myocarditis by Huber and colleagues [11], they describe the importance of T regulatory cells in the prevention of autoimmune coxsackieviral-induced myocarditis in animal models. T regulatory cells are important in controlling and preventing autoimmune disease [15]. New findings indicate that γ -interferon is essential for maintaining inflammation, whereas interleukin-17 is necessary for progression of myocarditis to dilated cardiomyopathy in animal models of myocarditis [11]. Natural killer T (NKT) cells are discussed by Huber and colleagues [11] as a key regulator of viral clearance and maintenance of T regulatory cells in suppression of myocarditis and inflammatory heart disease. Studies of NKT cells described in myocarditis mouse models indicate that the NKT cell also may regulate antigen presentation by promoting polarization toward a protective anti-inflammatory phenotype [11].

To summarize, Table 1 suggests some of the various factors described in this issue: PUT THE Shortened LIST HERE which may be related to the pathogenesis of autoimmune diseases as a result of infections. Once infections trigger or exacerbate the autoimmune disease manifestations, there may be other factors such as chronic antigen stimulation and presentation as well as cytokine polarizing conditions, which will control proinflammatory dendritic cell and T helper cell responses that may maintain autoimmune disease once the infection has initially induced it.

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Table 1

Factors related to infection induced autoimmune diseases

Molecular mimicry between microbe and self-antigen in myocarditis
Viral-induced dual receptor CD8 ⁺ T cells in multiple sclerosis
NKT cells regulating viral clearance and T regulatory cells in myocarditis
Viral interactions in Sjogren’s syndrome and multiple sclerosis
Environmental cofactors such as dioxin effects on aryl hydrocarbon receptor and reactivation of EBV in Sjogren’s syndrome
Cytokine polarizing conditions and IL-17 in the progression of myocarditis
Autoantibodies and innate responses to multiple infections in neuropsychiatric disease
Adjuvant effects of microbes and the presence of the intestinal microbiome
HLA associations with disease

EBV, Epstein–Barr virus; HLA, histocompatibility leukocyte antigen; IL, interleukin; NKT, natural killer T.

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