Table 6-8 Selected Non–HLA Genes Associated with Autoimmune Diseases

Putative Gene Involved	Diseases	Postulated Function of Encoded Protein and Role of Mutation/Polymorphism in Disease
Genes involved in immune regulation:		
PTPN22	RA, T1D, IBD	Protein tyrosine phosphatase, may affect signaling in lymphocytes and may alter negative selection or activation of self-reactive T cells
IL23R	IBD, PS, AS	Receptor for the T_H17-inducing cytokine IL-23; may alter differentiation of CD4+ T cells into pathogenic $T_H17$effector cells
CTLA4	T1D, RA	Inhibits T cell responses by terminating activation and promoting activity of regulatory T cells; may interfere with self-tolerance
IL2RA	MS, T1D	α chain of the receptor for IL-2, which is a growth and survival factor for activated and regulatory T cells; may affect development of effector cells and/or regulation of immune responses
Genes involved in immune responses to microbes:		
NOD2	IBD	Cytoplasmic sensor of bacteria expressed in Paneth and other intestinal epithelial cells; may control resistance to gut commensal bacteria
ATG16	IBD	Involved in autophagy; possible role in defense against microbes and maintenance of epithelial barrier function
IRF5, IFIH1	SLE	Role in type I interferon production; type I IFN is involved in the pathogenesis of SLE (see text)

AS, Ankylosing spondylitis; IBD, inflammatory bowel disease; MS, multiple sclerosis; PS, psoriasis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.
The probable linkage of these genes with various autoimmune diseases has been defined by genome-wide association studies (GWAS) and other methods for studying disease-associated polymorphisms.
Adapted from Zenewicz LA, Abraham C, Flavell RA, Cho JH: Unraveling the genetics of autoimmunity. Cell 2010;140:791.

variant is ineffective at sensing gut microbes, including commensal bacteria, resulting in entry of and chronic inflammatory responses against these normally well-tolerated organisms.

- Polymorphisms in the genes encoding the *IL-2 receptor (CD25)* and *IL-7 receptor* α chains are associated with multiple sclerosis and other autoimmune diseases. These cytokines may control the maintenance of regulatory T cells.

Many other polymorphisms have been described in particular autoimmune diseases, and we will mention some of these when we describe specific disorders. Although these genetic associations are beginning to reveal interesting clues about pathogenesis, the links between the genes, functions of their encoded proteins, and the diseases remain to be established.

We have previously mentioned that in mice and humans, gene knockouts and natural mutations affecting several individual genes result in autoimmunity. These genes include *AIRE*, *CTLA4*, *PD1*, *FAS*, *FASL*, and *IL2* and its receptor *CD25*. In addition, B cells express an Fc receptor that recognizes IgG antibodies bound to antigens and switches off further antibody production (a normal negative-feedback mechanism). Knockout of this receptor results in autoimmunity, presumably because the B cells can no longer be controlled. These examples provide valuable information about pathways of self-tolerance and immune regulation, but the diseases caused by these single gene mutations are rare and mutations in these genes are not the cause of most common autoimmune disorders.

Role of Infections

Autoimmune reactions may be triggered by infections. Two mechanisms have been postulated to explain the link between infections and autoimmunity (Fig. 6-23). First, infections may upregulate the expression of costimulators on APCs. If these cells are presenting self antigens, the result may be a breakdown of anergy and activation of T cells specific for the self antigens. Second, some microbes may express antigens that have the same amino acid sequences as self antigens. Immune responses against the microbial antigens may result in the activation of self-reactive lymphocytes. This phenomenon is called *molecular mimicry*. A clear example of such mimicry is rheumatic heart disease, in which antibodies against streptococcal proteins cross-react with myocardial proteins and cause myocarditis (Chapter 12). More subtle molecular mimicry may be involved in classic autoimmune diseases as well.

Microbes may induce other abnormalities that promote autoimmune reactions. Some viruses, such as Epstein-Barr virus (EBV) and HIV, cause polyclonal B-cell activation, which may result in production of autoantibodies. The tissue injury that is common in infections may release self antigens and structurally alter these antigens so that they are able to activate T cells that would not be tolerant to these new, modified antigens. Infections may induce the production of cytokines that recruit lymphocytes, including potentially self-reactive lymphocytes, to sites of self antigens.

Infections may protect against some autoimmune diseases. Although the role of infections in triggering autoimmunity has received a great deal of attention, recent epidemiologic studies suggest that the incidence of autoimmune diseases is increasing in developed countries as infections are better controlled. In some animal models (e.g., of type 1 diabetes) infections greatly reduce the incidence of disease. The underlying mechanisms are unclear; one possibility is that infections promote low-level IL-2 production, and this is essential for maintaining regulatory T cells.

Recently, there has been great interest in the idea that the normal gut and skin microbiome influences the development of autoimmunity. It is possible that different nonpathogenic microbes affect the relative proportions of effector and regulatory T cells, and shape the host response towards or away from aberrant activation. However, it is still not clear which microbes actually contribute to specific diseases in humans, or if the microbiome can be manipulated to prevent or treat these disorders.