INFECTIOUS AGENTS AS TRIGGER OF AUTOIMMUNE DISEASES

The prototype of autoimmune disease of infectious origin is rheumatic fever. It is caused by an anti-streptococcal immune response that cross-reacts with cardiac myosin (7). Another well-documented example is the GBS occurring in the course of *Campylobacter jejuni* infection and is mediated by anti-bacterial lipopolysaccharide antibodies that cross-react with human gangliosides (8). Similarly, antibodies directed against the Tax protein of the human T-lymphotropic virus type 1 (HTLV-1) and cross-reacting with the heterogeneous nuclear ribonucleoprotein-A1 (hnRNP-A1) self-antigen were demonstrated in HTLV-1-associated myelopathy/tropical spastic paraparesis (9). Although cross-reactivity between viral peptides and self-antigens was documented in type I diabetes and MS and despite circumstantial observations linking the overexpression of these diseases to previous viral infections, a clear-cut relation between the onset of organ-specific autoimmunity and viral infection has not been firmly established except for type 1 diabetes in the context of congenital rubella (10–12). The role of viruses is also suspected in systemic autoimmune diseases, especially SLE. However, such a role has only been clearly demonstrated in mixed cryoglobulinemia, a disease associated with hepatitis C (13).

It has also been proposed that some long-term complications of infections might be of autoimmune origin. This is the case for reactive arthritis consecutive to infection with intracellular bacteria, including *Chlamydia*, *Salmonella*, *Shigella*, *Borrelia*, and *Yersinia* spp. In these diseases, there is evidence of a persistent pathogenic immune response involving T lymphocytes, but whether such T-cell responses are directed against cross-reactive self-antigens or maintained by persistent bacterial antigens is still an open question (14,15). In Lyme arthritis, the identification of an immunodominant epitope of the outer surface protein A of *Borrelia burgdorferi* (Osp A) displaying significant homology with human LFA-1, an adhesion molecule of the β2 integrin family, provided convincing evidence for an autoimmune mechanism (16). Indeed, cross-reactive T-cell responses to OspA and LFA-1 were observed in blood and synovial fluid of patients with antibiotic-resistant chronic Lyme arthritis (16).

The role of infections as etiological agents of human autoimmune disease has been demonstrated in only few instances. However, their involvement in the exacerbation of a preexisting autoimmune disorder is rather well established. For example, in MS, epidemiological data strongly suggest that relapses of the disease can be triggered by both bacterial and viral infections (17,18). Several vaccine-preventable infections are well known to negatively influence the course of defined autoimmune diseases. Vaccination in such cases is highly recommended (e.g., influenza vaccination in patients with MS) (19) since no exacerbation has been recorded following the use of any of the current vaccines.

MECHANISMS OF AUTOIMMUNITY INDUCED BY INFECTIOUS AGENTS

It is generally assumed that activation and clonal expansion of autoreactive T lymphocytes represent critical steps in the pathogenesis of autoimmune diseases. Infections might be responsible for these key events through several nonmutually exclusive mechanisms including molecular mimicry, enhanced presentation of self-antigens, bystander activation, and impaired T-cell regulation (15).

Molecular Mimicry

The molecular mimicry hypothesis is based on sequence homologies between microbial peptides and self-antigen epitopes. At the T-cell level, this concept was initially established in an experimental model in which immunization with a hepatitis B (HB) virus polymerase peptide containing a six amino acid sequence of rabbit myelin basic protein (MBP) elicited an anti-MBP T-cell response leading to autoimmune encephalomyelitis (EAE) (20). The demonstration that a viral infection in itself can lead to autoimmune pathology caused by molecular mimicry was established in a murine model of herpes simplex keratitis in which pathogenic autoreactive T-cell clones were shown to cross-react with a peptide from the UL6 protein of the herpes simplex virus (21). Indeed, a single amino acid mutation in the UL6 T-cell epitope was sufficient to limit the capacity of the mutant virus to induce autoimmune corneal lesions (22). Conclusive evidence that a viral infection can induce pathogenic autoreactive T cells was also provided in a model of Theiler's murine encephalomyelitis virus encoding a mimicking peptide (23). Molecular mimicry at the level of epitopes recognized by $CD8^+$ T lymphocytes may also be involved in autoimmunity. This was shown in a model of inflammatory bowel disease induced in immunodeficient mice by $CD8^+$ T-cell clones directed against mycobacterial heat shock protein hsp60, which cross-react with hsp60 self-antigen (24).

B-cell epitope mimicry also occurs. Functional mimicry of host proteins may be quite widespread, as it may allow pathogens not only to evade an immune response but also to use cellular receptors as port of entry. Such functional mimicry of human glycosphingolipids by lipopolysaccharides (LPS) from several *Neisseria* sp. and from *Haemophilus influenzae* may have evolved to serve this function (25). Structural homology with autoimmune implications has been identified. A tetrasaccharide of the LPS core of the gastrointestinal pathogen *Campylobacter jejuni* can induce antibodies to human gangliosides and may be causally implicated in the autoimmune GBS (26). It is also well known that Lewis-like polysaccharide antigens from certain *Helicobacter pylori* strains induce antibodies that cross-react with gastric mucosa antigens and appear to contribute to atrophic gastritis in man (27).

Enhanced Presentation of Self-Antigens

Infection can promote processing and presentation of self-antigens by several mechanisms. First, cellular damages locally induced by viral or bacterial infection can result in the release of sequestered self-antigens that stimulate autoreactive T cells. This was clearly demonstrated in autoimmune diabetes induced by coxsackievirus B4 infection in mice (28). Second, the local inflammatory reaction elicited in tissues by microbial products can trigger dendritic cell maturation, which represents a key step in the induction phase of immune responses. Microbial products that engage toll-like receptors on dendritic cells can induce the upregulation of membrane expression of major histocompatibility complex (MHC) and costimulatory molecules and the secretion of cytokines, particularly interleukin (IL)-12, which promote T-cell activation (29). Third, a T-cell response directed toward a single self-peptide can ''spread'' to other self-epitopes during an inflammatory reaction. This process of ''epitope spreading'' has been well documented in murine models of encephalomyelitis (15).