Primary Biliary Cirrhosis and E. coli-induced Pyelonephritis; Are Infectious Agents Related to the Pathogenesis of Primary Biliary Cirrhosis?

Key words: Primary Biliary Cirrhosis, infection, E. coli, pyelonephritis

Primary Biliary Cirrhosis (PBC) is considered as a model of organ-specific autoimmune disease based on the serological findings of anti-mitochondrial antibodies (AMA), infiltrates of T cells, and selective destruction of epithelial cells in the liver. Anti-mitochondrial antibodies are directed at the inner lipoyl domains of 2-oxo-dehydrogenase enzymes, particularly the E2 component of pyruvate dehydrogenase complex (PDC-E2) (1). Although the etiology of PBC is still unknown, numerous studies have implicated infectious agents as triggering events in the breakdown of self-tolerance.

Ohno and colleagues, in this issue of the Journal, report a patient diagnosed with E-coli-induced pyelonephritis and sepsis, and also exhibiting findings indicative of PBC including markedly increased hepatobiliary enzymes and elevated anti-mitochondrial antibodies (2). Interestingly, these abnormal laboratory data returned to normal after the infection was alleviated. The authors speculated that the infection of E-coli in this patient induced the production of antibodies against E-coli PDC and other components, and anti-mitochondrial antibody reactive to PDC in biliary epithelial cells was produced due to cross-reactivity.

There is no solid data supporting the role for microbial agents in the etiology of PBC (3). Nevertheless, molecular mimicry for an extrinsic protein of an infectious agent has long been suggested as a possible initiating event in PBC. PDC-E2, particularly its inner lipoyl domain with a lipoated lysine residue, is highly conserved between bacteria, yeast and mammals (4). AMA has been shown to react with both human and bacterial mitochondria (5). High prevalence of bacteruria with a high recurrence rate in females with PBC has been demonstrated (6). The reactivity of PBC sera with an extract of Mycobacterium gordonae, and the reactivity of antibodies to the M. gordonae 65 kDa heat-shock protein with the mitochondrial antigen in PBC has been demonstrated (7, 8). Recent data also suggest bacterial infection in the PBC liver by identifying the gene encoding either bacterial 16S ribosomal RNA or Helicobacter species (9, 10). Jones et al have also suggested the role of bacterial motif DNA as an adjuvant for the breakdown of tolerance to the PDC molecule in a murine experimental model (11).

Molecular mimicry between host autoantigens and unrelated exogenous proteins is one of the hypotheses used to explain how autoantibodies to self-proteins as well as autoreactive T cells arise, break tolerance, and lead to autoimmune disease. Evidence of molecular mimicry stems from reports showing mimicry epitopes from Borrelia burgdorferi in Lyme-arthritis and from Chlamidia pneumoniae in autoimmune inflammatory heart disease (12, 13). Moreover, evidence has been reported for the induction of autoimmune disease by viral infection through molecular mimicry in herpes stromal keratitis (14). Thus, it can be proposed that the autoimmune phenomena in PBC also result from both B cell and T cell epitopes of microbial proteins being mimicked by peptides.

Shimoda et al have demonstrated the presence of molecular mimicry at the CD4 T cell clonal level between human and E. coli PDC E2 (15). Molecular mimicry in PBC has also been analyzed at the CD8 T cell level. Alignment algorithms were used to search for amino acid homologues between PDC-E2159-167, the newly identified MHC class I restricted epitope, and microbial proteins (16). Agnostic effects of these homologous peptides on the PDC-E2 specific cytotoxic T lymphocytes (CTLs) were assessed. PDC-E2159-167-specific CTLs cross-react with a partially homologous peptide derived from Pseudomonas aeruginosa.

The mechanisms involved in the breakdown of self-tolerance is one of the most important issues in defining the basis of PBC. Breakdown of tolerance to PDC molecule at the B-cell level has been shown in a murine experimental model. In contrast, the breakdown of T-cell tolerance to PDC was difficult to achieve (17). It has also been demonstrated that AMA alone does not induce an immune response to the normal biliary cells. In the case presented in this Journal, the patient has elevated hepatobiliary enzyme as well as anti-mitochondrial antibodies (2). Some type of additional immunological dysregulation, derived from either a genetic or environmental factor, could be another trigger, which is still open to investigation.
References


