Lupus Pathogenesis May Involve Epstein-Barr Virus

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NEW YORK — Evidence is mounting that implicates the Epstein-Barr virus as the trigger that sets off the autoantibody production central to the pathogenesis of systemic lupus erythematosus, according to Dr. John B. Harley.

It has long been assumed that an etiologic agent from the environment would be required to initiate the production of the antinuclear antibodies that begin to appear in lupus patients' sera long before clinical disease develops. An association of lupus with Epstein-Barr virus (EBV) was first noted more than 3 decades ago, but the technical means of proving a connection was lacking, and the idea was set aside.

The EBV hypothesis was resurrected during the 1990s, however. Because almost all adults are infected with the virus—a hindrance to finding an epidemiologic connection—Dr. Harley and his colleagues investigated a group of 117 children and adolescents with lupus. Among patients aged 4-19 years, an infection rate of approximately 70% would be expected, and indeed, that was what was found among 153 controls, he said.

Among the lupus patients, however, 99% had seroconverted against EBV. "This was an odds ratio of 50," Dr. Harley said at a rheumatology meeting sponsored by New York University.

Certain characteristics of the virus itself also lend credence to its etiologic probability. It infects B cells—B-cell dysregulation is prominent in lupus—and EBV itself can cause B-cell activation and autoantibody production. Among the antibodies that have been identified in patients with EBV-related mononucleosis are those targeting the Sm autoantigen, which otherwise is considered specific for lupus.

Infection is lifelong, providing continuous immune stimulation, and curiously, the virus also generates proteins that inhibit its own immune-mediated destruction, Dr. Harley said.

In lupus, it is the host response to the virus that is the crucial aberrant factor, rather than the virus itself, said Dr. Harley, professor of immunology and medicine, University of Oklahoma Health Sciences Center, Oklahoma City. An alteration in humoral response to Epstein-Barr nuclear antigen 1 (EBNA-1) appears to be involved, and in describing his findings in the pediatric cohort, Dr. Harley explained the altered response: "In the present study, lupus patients were shown to make higher concentrations of antibody against the fragments encompassing the amino and carboxyl ends of EBNA-1, while normal EBV-positive controls actually made higher levels of antibody against the middle fragment than did lupus patients" (Arthritis Rheum. 2006;54:360-8).

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Further evidence has come from molecular techniques including epitope mapping and peptide sequencing. The first anti-Sm autoantibodies that appear in lupus patients' sera bind to a structure known as PPPGMRPP that cross-reacts with a similar peptide, PPPGRRP, on EBNA-1, Dr. Harley explained. A similar capability has been identified with anti-Ro antibodies, and the generation of cross-reacting antibodies to Sm or Ro may be the "central and critical step that defines the onset of lupus-specific autoimmunity," he said. This critical step involving cross-reactive antibodies is then followed by epitope spreading and, ultimately, clinical disease.

Moreover, proof of the principle that a viral structure could generate autoimmunity was demonstrated by immunization of rabbits with the PPPGMRPP peptide. Following immunization, the animals went on to develop proteinuria, thrombocytopenia, elevated antinuclear antibody titers, and anti–double-stranded DNA antibodies (Nat. Med. 2005;11:85-9).

Dr. Harley's group also is focusing on the genetics of autoimmunity, and the Arthritis and Immunology Research Program, which he heads, at the Oklahoma Medical Research Foundation in Oklahoma City maintains a registry and repository of multiplex lupus families that is available for academic work. The registry can be accessed at http://lupus.omrf.org. ■