Lupus Pathogenesis May Involve Epstein-Barr Virus

BY NANCY WALSH
New Brunswick

New York — Evidence is mounting that implicates the Epstein-Barr virus (EBV) as the trigger that sets off the autoimmunity production central to the pathogenesis of systemic lupus erythematosus, according to Dr. Robert 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 suggested in 1966, but the technical means of proving a connection was lacking, and the idea was set aside.

The EBV hypothesis was resurrected during the 1980s. 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 outcome seen at a rheumatology meeting sponsored by New York University,” Harley said.

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 antigen, which otherwise is considered specific to 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 O k h a o m a a Health Sciences Center, Alabama.

An alteration in humoral response to the same EBV antigen makes the lupus seroconversion different from the EBV seroconversion seen in other autoimmune conditions. The disease being triggered by the virus is different from the disease triggered by the virus in other autoimmune conditions, according the Dr. Harley.

Despite its promise, serologic evidence of virus-reactive antibodies is not diagnostic of lupus. The non immune sera from healthy individuals can show the presence of antibodies against EBV. The presence of antibodies to EBV in non lupus patients is not specific for lupus, Dr. Harley said.

Several years ago, Dr. Harley and his colleagues had postulated that in lupus, antibodies to EBV would not only be present in greater amounts than in non lupus individuals, but they would also be specific for EBV antigens that were unique to lupus.

In his latest studies, Dr. Harley and his colleagues examined the sera of 117 lupus patients—46 patients from the New York locations and 71 patients from other centers across the country. The sera of 153 patients from the same geographic areas were used as controls.

Among the lupus sera, 99% were positive for EBV antibodies, whereas only 1% of the control sera were positive.

Moreover, the lupus sera lacked the antibodies to the Epstein-Barr nuclear antigen 1 (EBNA-1), which is the Epstein-Barr viral antigen that has been shown to be the target of EBV-specific autoreactive B cells present in the sera of some lupus patients with active disease.

The goal of the continuing studies is to determine whether the absence of antibodies to EBNA-1 among the lupus sera is due to a failure of the B cells targeted for autoreactivity to recognize EBNA-1 antigens, or to a failure of the B cells to respond to the EBNA-1 antigens that are recognized by lupus B cells.

The studies are also designed to determine whether the anti-EBV antibodies found in lupus sera are specific to epitopes on the EBV antigens that are unique to lupus or that are shared with other autoimmune conditions.

It is still not clear whether the presence of antibodies to EBV is a cause of lupus or a chance marker.

Further evidence has come from a 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 PPGMRPP that cross-reacts with a similar peptide, PPGPRP, 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 epistope spreading and, ultimately, clinical disease.

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

Dr. Harley’s group also is focusing on the genetics of artificial immunity, and the Arthritis and Immunology Research Program, which he heads, at the Oklahoma Medical Research Foundation in Oklahoma City maintains a registry and controls for com-plex lupus families that is available for academic work. The registry can be accessed at http://lupus.omrf.org.