Researchers Probe Lupus Causes, Treatments

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Washington, DC—Sometimes called the “great imitator” because its symptoms vary so widely that it is often mistaken for other conditions, the autoimmune disease systemic lupus erythematosus puzzles and frustrates those seeking diagnostics and treatments for the disorder. But now, these efforts may be helped by research presented at the annual conference of the American College of Rheumatology and the Association of Rheumatology Health Professionals that is beginning to reveal some of the variables affecting disease onset, severity, and remission.

“Not only will we understand [lupus] better from this research, but it should lead ultimately to some kind of preventive strategy of overt disease,” said Bevra Hahn, MD, of the University of California Los Angeles Medical Center.

In systemic lupus, which typically develops (without a known cause) in individuals in their 20s and 30s, antibodies produced by the patient’s immune system that target DNA, RNA, and associated proteins affect the skin, joints, kidneys, lungs, nervous system, and other organs of the body. It occurs 10 times more frequently among females than males and affects blacks more than whites. About 4000 white males, 41,000 white females, 31,000 black males, and 163,000 black females in the United States have the disease, according to the most recent prevalence data (http://www.rheumatology.org/publications/Prevalence98.asp?aud=prs).

AWAKENED X CHROMOSOME

Why lupus occurs more frequently in women than in men is unknown. “While estrogen contributes to the predisposition, other observations, such as young girls getting lupus more frequently than young boys, indicate that other factors contribute,” said Qianjin Lu, MD, PhD, of the Second Xiangya Hospital of Central South University, in Changsha, China. Recent research by Lu and his collaborators points to the “awakening” of a woman’s inactive X chromosome as a potential culprit.

In every somatic cell of a woman’s body, one of the 2 X chromosomes is randomly silenced. This phenomenon, which ensures that men and women have the same number of active genes, is a result of the attachment of methyl groups to DNA. Lu and colleagues hypothesized that one or more genes on the X chromosomes may be involved in lupus, and if the silenced genes on the inactive X chromosome become demethylated and active, their overexpression may predispose women to the disease.

CD40 ligand, a molecule that plays a role in inflammatory processes and antibody production, is overexpressed on T cells of women with lupus, contributing to autoantibody production. Because the gene coding for CD40 ligand is located on the X chromosome, Lu’s research team examined T cells from women with lupus and unaffected controls. In 8 women with lupus, only 25% of the DNA sequence that regulates expression of this gene was methylated compared with 42% in 5 healthy women; the lower the amount of methylation, the higher the level of disease activity.

The researchers also examined stimulated T cells from 6 men and 5 women with lupus matched for disease activity and from unaffected male and female controls. They found that expression of CD40 ligand increased 1.29-fold in the women with lupus compared with unaffected women but only 1.05-fold in the men compared with unaffected men, indicating that this molecule is overexpressed uniquely in women with lupus.

The unsilencing of the CD40 ligand gene on the normally inactive X chromosome “makes women with lupus express twice as much of the encoded protein as men can,” said Lu. This finding “suggests that other genes on the X chromosome may also be overexpressed in women with lupus, also potentially contributing to the disease process.”

“Here is a brand new, really brilliant idea on how being XX predisposes you to lupus,” said Hahn. Because other conditions such as rheumatoid arthritis and aging are also associated with DNA demethylation, the extra X chromosome in women could play a role in other conditions as well, Lu added.

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ANTIMICROBIAL LINK

Other research has uncovered details of the possible link of systemic lupus to the body’s innate immune response against microbial infections.


As the Yaa gene is expressed predominantly in B cells in affected mice, the defect is likely to be involved in the excessive activation of B cells, said first author Prapaporn Pisitkun, MD, a visiting fellow working at a National Institute of Allergy and Infectious Diseases laboratory in Rockville, Md. Microarray studies of gene expression revealed that 4 genes on the X chromosome are overexpressed in B cells of Yaa mice compared with cells in normal mice. Pisitkun and colleagues found that the Y chromosome of Yaa males have X chromosome DNA that includes a gene encoding the RNA-binding toll-like receptor 7 (TLR7).

TLR7 is part of a family of receptors that triggers innate immune reactions in humans and other animals to counter microbial infections. Duplication of the TLR7 gene makes Yaa B cells increase expression of TLR7 protein and become more responsive to the molecules that bind to them. The study’s results support the emerging concept that lupus arises at least in part due to errors made by TLRs in discriminating between self and microbes (Goodnow C. *Science.* 2006;312:1606-1608).

Differences in expression of TLRs or the molecules that interact with them may account for differences in autoimmunity in patients with lupus. Scientists are now looking for molecules in the signaling pathways linked to these receptors because therapies that target such molecules may have therapeutic potential. In that vein, recent studies indicate that the risk of developing lupus may be increased in individuals with certain variants in the gene that encodes a protein with a crucial role in the TLR-induced expression of molecules that contribute to inflammation (Sigurdsson S et al. *Am J Hum Genet.* 2005;76:528-537; Graham RR et al. *Nat Genet.* 2006;38:550-555).

B CELL DEPLETION THERAPY

Recent studies assessing potential therapies for lupus have suggested that depleting B cells from the body may reduce disease severity and even prolong remission. “B cell depletion is rapidly expanding in the treatment of several autoimmune diseases,” said Jennifer Anolik, MD, PhD, of the University of Rochester Medical Center, in Rochester, NY. “However, it is important to bear in mind a number of caveats of this therapy.”

While rituximab (an antibody that is directed against the CD20 antigen, causing B cell depletion) is often used for the treatment of non-Hodgkin lymphoma, little is known about the B cells that subsequently reconstitute the immune system’s arsenal or the therapy’s impact on immune function and immunological tolerance. In addition, clinical responses are heterogeneous, treatment response is unpredictable, and the mechanisms by which autoimmunity is ameliorated in patients with lupus following B cell depletion are unknown, said Anolik.

To better understand some of these unknowns, Anolik and colleagues evaluated the returning B cells after rituximab therapy in 10 patients with lupus and 11 patients with non-Hodgkin lymphoma. “Regardless of disease type, patients reconstitute their B cell pool with B cells that are functionally immature or in transition developmentally between immature and fully mature cells,” said Anolik.

However, in lupus patients, this reconstitution process seems more variable than in patients with diseases such as lymphoma and rheumatoid arthritis. Patients with lupus who experienced prolonged clinical remission had elevated numbers of immature B cells and a scarcity of mature memory B cells for several years after treatment. They also lacked antibodies against nuclear proteins and RNA.

The findings indicate that the characteristics of patients’ B cell depletion and reconstitution may have implications for immune competence as well as the quality and duration of treatment response. Immune tolerance may be restored in patients who experience B cell reconstitution with immature B cells, while B cell reconstitution dominated by mature memory B cells may indicate the need for retreatment, said Anolik.

“The possibility of ‘resetting the immune system’ and fundamentally altering the autoimmune disease process with this therapy is exciting,” said Anolik. However, an expansion of immature B cells and a delay in memory B cell recovery suggests the need for careful monitoring of antibody responses and for a better understanding of infectious risks and response to vaccination in rituximab-treated patients, the investigators noted.

EARLY, EFFECTIVE TREATMENT

Current treatment strategies for systemic lupus include nonsteroidal anti-inflammatory drugs, immunosuppressives, corticosteroids, and antimalarial agents, which act at a nonspecific level to restrain overactive immune and inflammatory responses. As researchers continue to study the potential causes of systemic lupus, they hope to find ways to intervene before symptoms become severe.

Autoantibodies are present for an average of approximately 3 years before the first clinical symptoms arise, said Hahn. “This means that there are probably regulatory mechanisms that are able to keep the autoantibodies from causing disease that eventually get exhausted over time in some people who go on to develop the disease,” she explained. A growing number of scientists are working to develop ways to detect these autoantibodies at an early stage and to design targeted therapies that are more effective than current treatments.