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Gene Defect Produces Lupus-Like Disorder

Howard Hughes Medical Institute (HHMI) researchers have discovered a new type of genetic malfunction that causes an autoimmune disease in mice that resembles systemic lupus erythematosus in humans.

The findings suggest that abnormalities in a protein called Ro 60-kDa could cause the disease. The discovery also hints that the protein might normally play a protective role in the body by “hiding” defective complexes of RNA and protein, called ribonucleoproteins, from attack by the immune system.

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— **Sanda L. Wolin**

The research team, which included Sandra L. Wolin and Richard Flavell, both HHMI investigators at Yale University School of Medicine, published its findings June 3, 2003, in the online Early Edition of the *Proceedings of the National Academy of Sciences (PNAS)*.

According to Wolin, Ro has long been known to be an autoantigen in lupus patients. Autoantigens trigger the immune system to produce antibodies that attack the body's own components, resulting in autoimmune disease. Despite Ro's known role as an autoantigen, researchers have had a difficult time determining whether the autoantibodies directed against Ro and other autoantigens cause diseases like lupus. “Many rheumatologists think that the autoantibodies are an epiphenomenon—an interesting phenomenon but not directly related to the cause of lupus,” said Wolin.

The normal role of Ro was not well understood although it was known that the protein is normally found bound to small RNA molecules called Y RNAs, whose function remains somewhat mysterious. Wolin and her colleagues had begun to answer questions about Ro's function when their earlier experiments demonstrated that the Ro protein binds to small RNA molecules that are misfolded versions of those that help make up the cell's ribosomes, which are

its protein assembly lines.

To shed light on the function of Ro and its possible role in lupus, the researchers generated knockout mice that lacked the gene for the Ro protein. “Initially, we were disappointed because the knockout mice seemed fine,” said Wolin. “And then we noticed that a significant fraction of them were dying, while the wild-type mice were not.”

Closer study of the Ro-knockout mice revealed that they had kidney lesions similar to those observed in patients with lupus. Additional analyses revealed that the mice generated specific autoantibodies that were also similar to those found in lupus patients. And a third clue emerged from their studies: One strain of the knockout mice showed sensitivity to sunlight—a characteristic of human lupus patients that produce antibodies against the Ro protein.

Earlier studies by Wolin and her colleagues had already shown that the bacterium *Deinococcus radiodurans* —the world's most radiation-resistant organism—possesses the Ro protein complexed with an RNA that resembles a Y RNA. The group found that the Ro protein contributes to the resistance of the bacterium to irradiation with ultraviolet light. That finding suggested that the Ro/Y RNA complex plays a role in protecting against damage from ultraviolet radiation and could be compromised in lupus patients. Importantly, said Wolin, studies of the immune systems of the knockout mice indicated that they were normal, reducing the likelihood that a primary defect in the animals' immune systems was causing the lupus-like pathology.

While there are many other mouse models of lupus, said Wolin, “it is unprecedented that knocking out an intracellular RNA-binding protein would result in autoimmune disease.

“It's quite startling that if you knock out the Ro autoantigen in the mouse, you get an autoimmune disease that in many ways resembles systemic lupus,” she said. “Although it could be a coincidence, the fact that knocking out the gene produces a lupus-like disorder makes the Ro gene a candidate causative gene that is certainly worth looking at in patients,” said Wolin.

The scientists speculate in their *PNAS* article, “the Ro autoantigen may not be simply a passive target in the lupus immune response but, instead, may be important for the prevention of autoimmune disease.”

Wolin said the next steps are to explore the normal cellular function of Ro. If Ro is actively involved in a quality-control pathway, its malfunction might contribute to lupus by allowing defective ribonucleoproteins to be made by cells, she said. If this occurs, the defective ribonucleoproteins would be exposed to the immune system during the normal process of cell turnover. This could potentially trigger the immune system to produce autoantibodies.