Intolerance to Maternal Cells May Trigger SLE

BY COLIN NELSON
Contributing Writer

BOSTON — Maternal cells that pass through the placenta to the fetus during pregnancy may trigger the chronic inflammatory response that marks systemic lupus erythematosus in children, according to the findings of a preliminary investigation presented as a poster at the annual meeting of the Federation of Clinical Immunology Societies.

Healthy children appear to have an intrinsic immunologic tolerance to these circulating maternal cells, but for reasons that remain unknown, children with systemic lupus erythematosus (SLE) may lack this tolerance, causing their immunologic systems to perceive their maternal cells as foreign and turn against them.

Mother and fetus exchange cells during pregnancy. Each may retain the cells of the other for decades—a situation known as either maternal microchimerism (maternal cells in the child) or fetal microchimerism (fetal cells in the mother). The arrangement is usually, but not always, benign.

Researchers have labored long over the contribution of fetal cells to maternal autoimmune disease. More recently, they've also begun to investigate the ways maternal cells may initiate or perpetuate autoimmune disease in the child.

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"Preliminary results suggest the hypothesis that immunological tolerance to maternal microchimerism is intrinsic to normal biology but may be lost in chronic inflammatory disease, leading to tissue-specific inflammation," Anne M. Stevens, M.D., and her colleagues wrote in a poster presentation.

In a study comparing heart sections from neonates who died of neonatal lupus syndrome-associated congenital heart block with sections from babies who died of other causes, Dr. Stevens and colleagues found that babies with neonatal lupus syndrome had maternal T cells in 15 of 15 sections of heart tissue. By contrast, maternal cells were present in only two of eight sections taken from the controls (Lancet 2003;362:1617-23).

Surprisingly, maternal cells had not only migrated to the heart but had differentiated into myocardial cells, as well. Maternal cells had also taken up residence as tissue-specific phenotypes in the liver, pancreas, and other organs.

What isn't clear at this point is whether the presence of maternal myocardial cells triggered an immunologic response that led to the fatal heart block—an assault akin to graft-versus-host disease—or if the neonate recruited the maternal cells to help repair an attack on the heart from some other source.

In a different investigation, Dr. Stevens and her colleagues enrolled 14 children with SLE and 24 healthy controls matched for age and sex. They measured the level of maternal DNA present in a blood sample from each child. To do this, they developed an assay that can detect human leukocyte antigen (HLA) alleles that are present in the mother but not inherent to the child.

To see whether lupus patients mount an immune response to maternal cells when exposed to maternal antigens, they stimulated T cells from all subjects with CD14+ macrophages donated by both the child's mother and an unrelated donor.

The results surprised the investigators once again.

Maternal DNA was apparent in comparable numbers of both SLE patients and controls. And healthy children responded to stimulation from an unrelated donor in a well-recognized pattern, "the way they would to any foreign HLA molecules," said Dr. Stevens. Some 14% of CD4+ leukocytes produced interferon-γ and 25% produced interleukin-4 (IL-4).

By contrast, only 2% produced interferon-γ and IL-4 in response to maternal cells, suggesting that "the control patient has tolerance to her mother," said Dr. Stevens.

Children with SLE also displayed a normal immunological response to cells from an unrelated donor. But their response to maternal cells was notably different from that of healthy controls: Some 20% of CD4+ leukocytes produced interferon-γ and 31% produced IL-4.

"The lupus patient has a normal response to an unrelated donor. And [the patient has] twice that response to her mother. So she's hyperactivated," said Dr. Stevens, a researcher at the Children's Hospital and Regional Medical Center, Seattle.

"Somehow the control patients had developed an immune tolerance to maternal antigens. Only 2% of their cells are actually responding to the mother's, which would explain why they can tolerate maternal microchimerism for decades."

These results are still preliminary, Dr. Stevens commented. "This has to be substantiated in many, many more people."

However, if additional evidence shores up her hypothesis, and maternal cells are shown to trigger an autoimmune response in SLE patients, clinicians might be able to halt the disease.

"Conceivably, we could target these maternal antigens or block the maternal HLA molecules and specifically stop this immune response. There are such a tiny number of cells involved that you would not be wiping out huge amounts of tissue. You'd be getting rid of the stimulus, and the rest of the body would be fine," Dr. Stevens said. ■

More Antibodies Implicated in SLE Nephritis

BY ROBERT FINN
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Individuals with systemic lupus erythematosus who go on to develop nephritis are more than five times as likely to have antibodies to lipoprotein lipase in their blood serum, according to findings from an investigation led by Morris Reichlin, M.D.

This suggests that the pathogenesis of lupus nephritis may involve cell-surface antigens that activate the complement system and promote vascular damage in the kidney and other organs when they are engaged by antibodies.

Other antibodies have previously been shown to be associated with systemic lupus nephritis, wrote Dr. Reichlin of the University of Oklahoma, in Oklahoma City.

These antibodies include anti-double-stranded DNA (anti-dsDNA), anti-ribosomal P protein (anti-P), anti-Ro/SSA, antihistones, anti-C_1q, and antinucleosomes. This is the first study to demonstrate an association between lupus nephritis and anti-lipoprotein lipase (anti-LPL).

According to the study, anti-LPL shows strong relationship to this SLE complication than any single specificity (Clin. Immunol. 2005;117:12-4).

In addition, Dr. Reichlin found that SLE patients with anti-LPL and anti-P antibodies were more than 17 times more likely to develop lupus nephritis than were those who had neither antibody. This result was highly significant, with a *P* value of .00002.

The study involved 35 patients with SLE who had developed nephritis that apparently had no other cause and 28 patients with SLE who had no evidence of nephritis.

Twenty-five (71.4%) of the patients with nephritis had anti-LPL antibodies in their serum compared with 9 (32%) of the patients without nephritis.

Twenty (57.1%) of the patients with nephritis had both anti-LPL and anti-P, compared with just two (7.1%) of the patients who as yet have no clinical evidence of nephritis.

"It will be of interest to follow those two patients to assess their outcomes," Dr. Reichlin wrote. ■