

Pathophysiology of PsA Under the Microscope

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STOCKHOLM — Researchers are beginning to shed light on the pathophysiology of psoriatic arthritis, with recent findings focusing on the role of bone formation factors such as vascular endothelial growth factor and nuclear factor-kappa B ligand.

Psoriatic arthritis appears to have a different vascular and immunologic profile than rheumatoid arthritis, Dr. Christopher T. Ritchlin said at an international conference on psoriasis and psoriatic arthritis.

Spondyloarthritic tissue (including psoriatic tissue) is more vascular and has more neutrophil infiltration than normal tissue. This tissue also has infiltration of CD163-positive macrophages. "These are infrequent findings in rheumatoid arthritis," said Dr. Ritchlin of the clinical immunology research center at the University of Rochester (N.Y.). These findings seem to correlate with swollen joint count. In addition, no cyclic citrullinated peptide was found, which is a characteristic finding in rheumatoid arthritis.

Psoriatic arthritis tissue has been shown to contain greater levels of vascular endothelial growth factor (VEGF) than does rheumatoid arthritis tissue. VEGF is particularly interesting in PsA because it is involved in the stimulation of osteoclastogenesis, thereby enhancing bone formation.

Some patients with PsA have marked osteolysis in the distal digits of the feet and hands. To understand this process, Dr. Ritchlin and his colleagues looked at tissue samples of the bone/pannus junction from patients with PsA.

"We found very large, multinucleated osteoclasts at this junction," said Dr. Ritchlin. These osteoclasts were eroding deep pits into the bone. In addition, osteoclasts were found in greater numbers in patients with PsA than in those with RA; multinucleated osteoclasts were absent in patients with osteoarthritis.

Osteoclasts arise from CD14 monocytes. When CD14 monocytes are exposed to receptor activator of nuclear factor-kappa B ligand (RANKL)—which is expressed on synovial lining cells—and either macrophage colony stimulating factor (MCSF) or RANKL and VEGF, they differentiate into osteoclasts within a few days.

The researchers also found that RANKL is highly expressed in the synovial lining tissue of patients with PsA. In addition, staining of tissue from patients with PsA also showed that the expression of osteoprotegerin—which is an antagonist to RANKL, shutting down osteoclastogenesis—was limited to endothelial cells beneath the synovial lining.

Dr. Ritchlin and his colleagues hypothesized that osteoclast precursors move from subsynovial blood vessels toward RANKL-positive synovial lining tissue, where they convert to osteoclasts.

The researchers also hypothesized that CD14 monocytes in patients with PsA might already be committed to becoming

osteoclasts. To test this, the researchers collected peripheral blood mononuclear cells from psoriatic arthritis patients and left them in culture for 2 weeks.

The cultures were then stained for osteoclasts. Stained cells with three or more nuclei were counted as osteoclasts.

The researchers found numerous osteoclasts even in the absence of exogenous RANKL or MCSF. Very few such cells were found in cultures from healthy controls.

The researchers then treated the cultures with RANKL and MCSF. The osteoclasts from PsA patients increased in size, containing 30-40 nuclei. Fewer osteoclasts were seen in cultures from healthy controls and these were smaller (with fewer nuclei).

In another recent study, Dr. Ritchlin and his collaborators analyzed peripheral blood mononuclear cells from 19 patients with PsA, 46 healthy controls, and 48 patients with rheumatoid arthritis using gene

expression profiling. They found 257 genes that were underexpressed and 56 that were overexpressed in patients with PsA compared with healthy controls (Molec. Med., www.molmed.org/content/obp/10.2119_2006-00003.Gulko.pdf).

In particular, genes involved with mitogen-activated protein kinase pathways, ras protein, and B-cell function were expressed at reduced levels in patients with PsA, which supports dysregulation of the immune system. ■



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