Early Evidence Backs Role of TNF Blockers in SpA

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BOSTON — Findings from a recent study provide preliminary evidence that toll-like receptors may play a key role in the response of spondyloarthropathy to treatment with tumor necrosis factor–blocking agents.

Belgian researchers Leen De Rycke, M.D., and colleagues from Ghent (Belgium) University Hospital found increased expression of toll-like receptor (TLR) 2 and TLR4 in the synovium and peripheral blood monocytes of patients with spondyloarthropathy (SpA). Anti-TNF-α drugs successfully suppressed both TLRs, according to their findings, which were presented as a poster at the annual meeting of the Federation of Clinical Immunology Societies.

Dr. De Rycke and colleagues enrolled a small cohort of patients with SpA and rheumatoid arthritis (RA) prior to receiving treatment with TNF-α inhibitors. At baseline and during the 12-week course of therapy, they analyzed synovial biopsies from 18 patients and flow cytometry of peripheral blood monocytes from 38 patients and 9 healthy controls. Findings prior to treatment demonstrated that despite increased expression of both TLRs in RA patients, expression of TLR2 and TLR4 was significantly higher in patients with SpA.

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After treatment, there was a "profound effect" of infliximab on monocyte TLR4 expression among SpA patients, and to a lesser extent the same was true in RA patients. In addition, monocyte TLR expression in SpA was below the normal level of healthy controls and TNF-α production was impaired.

Both infliximab and etanercept downregulated synovial TLR expression, "suggesting a class effect of TNF-α blockers," the investigators wrote. No effects of treatment on symptoms or other clinical findings were reported.

The findings "emphasize a central role for innate immune-mediated inflammation in SpA and provide an additional clue for the efficacy ... of TNF-α blockade," the authors concluded.

The TNF-α blockade may be capable of deterring an exaggerated TLR response. "Spondyloarthropathy inflammation is characterized by increased TLR2 and TLR4 expression, which [is] sharply reduced by TNF-α blockade," noted Dr. De Rycke and associates. "The strongly reduced TLR surface expression may lead to a decrease in the local and systemic proinflammatory response to autoimmune triggers or microbial agents."

TLRs play an important part in the innate immune system. While T and B lymphocytes are still preparing an adaptive immune response that takes days to formulate, TLRs are activated within minutes to hours after threatening molecular patterns are detected (J. Pediatr. 2004;144:421-9).

The target of a particular TLR is narrow. TLR4, for example, recognizes organisms that cause gram-negative bacillary septic shock, tuberculosis, and respiratory syncytial virus. Its companion TLR2 goes after gram-positive organisms responsible for other conditions, such as leprosy, Chagas' disease, fungal sepsis, measles, and periodontal disease. Though a TLR's focus is narrow, its powers are broad. For example, in the inflammatory cascade it launches, TLR4 enlists heavyweight genes such as TNF-α, interleukin-1, IL-6, and IL-8.

But problems occur when this finely tuned mechanism goes awry. Emerging evidence suggests that mutations in the TLR genes are associated with increased risk for severe infections and certain diseases.

Faulty TLR4, for example, appears to increase the risk of septic shock (Nat. Genet. 2000;25:187-91). Individuals with mutations in TLR2 produce less TNF-α in response to several microbial infections, leading to outcomes that are sometimes lethal.

Previous work by Dr. Rycke and associates suggested that TLR2 and TLR4 might play a prominent role in SpA synovitis, and differentiate SpA from rheumatoid arthritis (Arthritis Res. Ther. 2005;7:R35969). ■