MedicalXpress

Study identifies novel role for a protein that could lead to new treatments for rheumatoid arthritis

May 22 2011

A new study by rheumatologists at Hospital for Special Surgery in New York has shown that a powerful pro-inflammatory protein, tumor necrosis factor (TNF), can also suppress aspects of inflammation. The researchers say the identification of the mechanism of how this occurs could potentially lead to new treatments for diseases such as rheumatoid arthritis. The study was published May 22 online in advance of publication in the journal *Nature Immunology*.

"Prior to this study, TNF has long been known as a potent pro-inflammatory cytokine, but if you look carefully through the literature, there are hints that it also has some suppressive functions, but nothing was known about the mechanisms," said Lionel Ivashkiv, M.D., associate chief scientific officer and physician in the Arthritis and Tissue Degeneration Program at Hospital for Special Surgery who led the study. "This is really the first mechanism showing how TNF can turn inflammation down."

Because many proteins have homeostatic functions, both driving and suppressing certain actions so a cell can maintain internal equilibrium, researchers thought TNF might not be an exception. "Most strong activators in the immune system trigger a feedback response to restrain the amount of inflammation," Dr. Ivashkiv said.

To find out, researchers designed experiments stimulating macrophages

with lipopolysaccharide (LPS), a prototypical inflammatory factor that stimulates receptors important in inflammation. In test tube studies, the researchers treated human monocytes and macrophages, cells that have a key role in inflammatory diseases, with TNF and then challenged these cells with LPS. They found that the TNF suppressed the inflammatory response of the macrophages and monocytes. They then gave mice low doses of TNF followed by high doses of LPS and found that the mice were protected from the effects of high dose LPS, which is usually lethal. They discovered that the mechanism by which TNF suppressed the inflammatory response involved a protein known as GSK3 (glycogen synthase kinase 3-alpha) and a gene known as TNFAIP3 that encodes the A20 protein. Experiments with a drug that can inhibit GSK3 as well as experiments with RNA interference of A20, which can block A20 gene function, helped identify the roles of this protein and gene.

The researchers say the findings could be used to develop potential therapies for diseases, such as rheumatoid arthritis. "We think it is relevant to rheumatoid arthritis, not only because the cells we are studying (the macrophages) are exactly the same cells that migrate into joints and make the inflammatory cytokines involved in rheumatoid arthritis, but because A20 is involved. TNFAIP3 is one of the best linked genes to rheumatoid arthritis," Dr. Ivashkiv said. "There are polymorphisms in the A20 gene that have been linked to RA pathogenesis."

The researchers hypothesize that patients who make less A20 are more susceptible to inflammation and thus rheumatoid arthritis. One approach to treating RA could be to increase A20 levels in patients who naturally make less A20 by manipulating GSK-3, since this study showed that GSK-3 influences A20. "The study sort of opens a line of investigation to understanding how A20 levels can be manipulated in patients with various diseases," Dr. Ivashkiv said.

The findings could be applied to other diseases besides arthritis. In conditions such as rheumatoid arthritis, you may want to boost A20, but in other settings such as cancer, where the macrophages are suppressed, you may want to inhibit A20 expression.

"What the study shows that is new is that TNF has suppressive functions in addition to its well-known activating functions," Dr. Ivashkiv said. "Before this study, people thought it might suppress adaptive immunity, but surprisingly we found that it actually suppresses a cell of the innate immune system, the macrophage, which is the same cell that makes it and, by doing that, it regulates its own production."

Provided by Hospital for Special Surgery