Scientists shine new light on inflammatory diseases

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Investigators at Hospital for Special Surgery have identified a new mechanism involved in the pathogenesis of inflammatory diseases such as rheumatoid arthritis. The mechanism may also shed some light on why gene therapy experiments that use adenoviruses to deliver genes to humans have run into problems. The study will appear online on March 16 in the journal *Nature Immunology*.

Tumor necrosis factor (TNF) is known to play a role in several important inflammatory diseases including rheumatoid arthritis. While much is known about early signaling pathways activated by TNF, little is known about delayed and chronic TNF responses. In addition, cells called macrophages produce TNF, but little is known about the effects of TNF on the macrophages themselves.

In studies using human blood cells and mice, scientists examined the responses of macrophages during a two-day period after being stimulated with TNF. They found that macrophages secreted TNF and that then the TNF activated surface receptors on the macrophages themselves, spurring the cells into a low and sustained production of a protein called interferon-beta. This protein acted synergistically with TNF signals to induce 1) sustained expression of genes encoding inflammatory molecules and 2) delayed expression of genes encoding interferon-response molecules.

“The striking thing about many of these genes that came to our attention first was that there were these classic interferon response genes which
had previously not been associated with TNF,” said Lionel Ivashkiv, M.D., director of Basic Research at Hospital for Special Surgery, who led the study. “It suggests a new mechanism by which TNF can drive and sustain inflammation.”

Experiments also revealed that the so-called autocrine loop was dependant on so-called interferon-response factor 1. “This was the first implication that IRF1 was linked to TNF inflammatory pathways,” said Dr. Ivashkiv.

The researchers say that these findings could lead scientists to ways of preventing the bone destruction that is associated with some diseases. “There is the potential to control inflammation and also to control bone destruction. This interferon response is very effective at preventing the destruction of bones, which is one of the major issues with rheumatoid arthritis,” said Dr. Ivashkiv. “So, what it does is sets up the next series of studies, in animal models, to try to determine whether this induction of interferon is beneficial or not.”

The new research could also help explain how a patient involved in a University of Pennsylvania gene therapy experiment that used an adenovirus to deliver the gene died. Host response to adenoviral vectors is dependant on both IRF1 and TNF.

“What we have described is that TNF has both pathogenic affects—it helps to sustain some of these inflammatory chemokines, but it also has a potential protective effect, because some of these interferon responses limit the amount of cell proliferation and they can also help to limit inflammation.”

Source: Hospital for Special Surgery