MedicalXpress

Researchers implicate well-known protein in fibrosis

November 20 2012

An international multi-disciplinary research team led by Northwestern Medicine scientists has uncovered a new role for the protein toll-like receptor 4 (TLR4) in the development of tissue fibrosis, or scarring.

This finding, recently reported in the American Journal of Pathology, has implications for the treatment of scleroderma, a condition for which there currently is no effective treatment.

TLR4 was previously implicated in inflammation, but its role in tissue fibrosis was unknown. Fibrosis is a hallmark of scleroderma and contributes to a range of common diseases including pulmonary fibrosis, kidney fibrosis, liver cirrhosis and radiation-induced scarring.

"We found that when the gene for TLR4 was mutated in mice, the mice became resistant to experimental scleroderma," said the study's first author Swati Bhattacharyya, research assistant professor of rheumatology at Northwestern University Feinberg School of Medicine. "Moreover, scleroderma patients showed abnormal TLR4 levels in fibrotic skin and lung tissue. This tells us we have found a therapeutic target."

Scleroderma is a chronic autoimmune disease which causes progressive tightening of the skin and can lead to serious internal organ damage and, in some cases, death. Scleroderma affects an estimated 300,000 people in the U.S., most frequently young-to-middle-aged women. Its cause and pathogenesis are unknown.

"The Northwestern research team continues to make fundamental discoveries that enhance our scientific understanding of scleroderma," said co-author John Varga, M.D., the John and Nancy Hughes Distinguished Professor of Rheumatology and professor of dermatology at Feinberg. "Careful dissection of the role of individual proteins in this disease enables us to make real progress toward novel treatments."

Researchers from Northwestern, Boston University, the University of Pittsburgh and the University Medical Center Nijmegen, Netherlands contributed to the study, which relied on tissue samples from human scleroderma patients and mouse models.

Agents that block TLR4 are already being developed for inflammation and sepsis in humans. Effective TLR4 inhibitor drugs may blunt and even possibly reverse the fibrosis in scleroderma, says Bhattacharyya. However, earlier attempts to develop therapeutics that block TLR4 have met with failure due to toxicity.

"These results, while significant, are preliminary. We now know that TLR4 plays a role in scleroderma, but much research remains to be done to develop safe and effective drugs to inhibit this pathway," she says.

The investigators are currently studying additional mouse models to better understand the role of TLR4 in fibrosis and are developing novel small molecules to selectively block TLR4 as a potential therapy.

Provided by Northwestern University