Molecule known to slow inflammation linked to scleroderma, could be treatment target

January 31 2023, by Valerie Goodwin

Credit: Justine Ross and Jacob Dwyer / Michigan Medicine

A molecule that was until recently known as a brake on inflammation has now been implicated in fibrosis in scleroderma patients.

Scleroderma is an autoimmune disease that causes a buildup of scar tissue on organs. The disease can be fatal and there is currently no cure.

A study published in *Nature Communications* has found that scleroderma patients have reduced expression of A20 in their skin and lungs. The A20 molecule normally prevents formation of fibrosis, while altered A20 expression or function in scleroderma contributes to fibrosis.

The function of A20 has been studied in inflammatory conditions such as rheumatoid arthritis, inflammatory bowel disease, psoriasis, and lupus, but its role in scleroderma has gone unnoticed. The discovery of the A20 molecule's novel function explains why cells in people with scleroderma are hyperactivated.

"The A20 molecule has not been linked to scleroderma until now," said John Varga, MD., a senior author of the paper and professor of rheumatology at the University of Michigan Medical School. "This discovery is a building block for potential future scleroderma treatment."

This large multi-center study was conducted using cell as well as genetically engineered mice models. The mice lacking the A20 molecule developed advanced fibrosis.

"As A20 is downregulated in scleroderma, approaches to augment endogenous A20 expression or function might represent clinically viable therapeutic approaches for scleroderma and other intractable fibrosing conditions," said Swati Bhattacharyya, Ph.D., one of the paper's senior authors and a member in Varga's lab. "Interestingly, our preliminary data suggested that both adiponectin and small molecule adiponectin receptor agonist, AdipoRon, can induce A20 expression and exerted antifibrotic effects," she said.

Researchers plan to precisely define how A20 regulates fibrosis and how endogenous A20 levels can be boosted as an innovative treatment for fibrosis.

More information: Wenxia Wang et al, Fibroblast A20 governs fibrosis susceptibility and its repression by DREAM promotes fibrosis in multiple organs, *Nature Communications* (2022). DOI: 10.1038/s41467-022-33767-y