National research effort discovers relationship between inflammation, metabolism and scleroderma scarring

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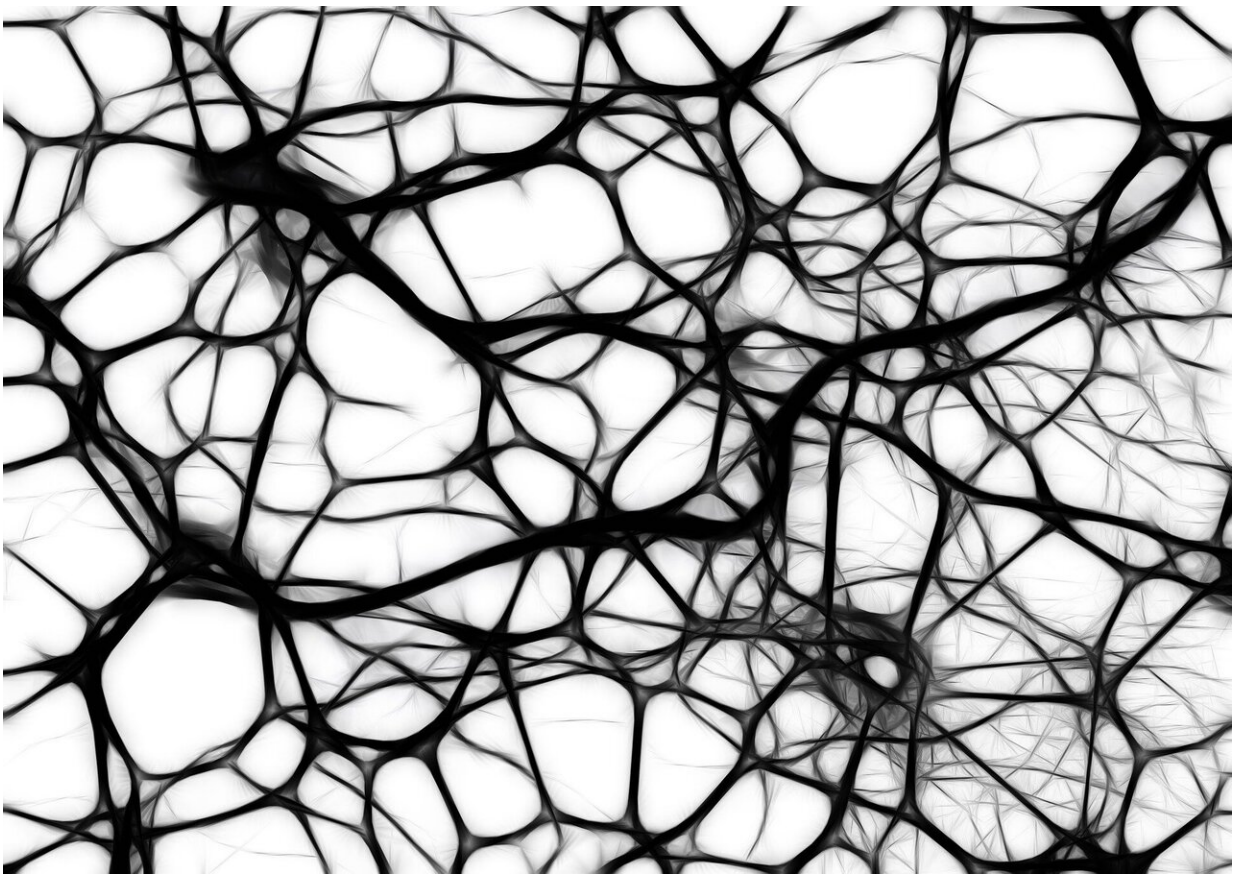

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Scleroderma, a chronic and currently incurable orphan disease where

tissue injury causes potentially lethal skin and lung scarring, remains poorly understood.

However, the defining characteristic of systemic sclerosis, the most serious form of scleroderma, is irreversible and progressive scarring that affects the skin and internal organs.

Published in *iScience*, Michigan Medicine's Scleroderma Program and the rheumatology and dermatology departments partnered with the Northwestern Scleroderma Program in Chicago and Mayo Clinic to investigate the causes of disabling scarring, using human patient samples, preclinical mouse models and explanted human skin.

"We found that scleroderma inflammation dramatically increases CD38, an enzyme that normally breaks down a metabolic nutrient, NAD+. When NAD+ levels decrease, tissue injury becomes chronic and progresses to scar formation rather than to healthy repair," says study author John Varga, M.D., division chief of rheumatology at Michigan Medicine.

According to the study, treatments that prevented NAD+ reduction in the mice, whether by boosting the levels of the nutrient genetically or pharmacologically, prevented scarring in the skin, lungs and abdominal wall.

"This is one of the first studies to find a relationship between CD38 and scleroderma, as well as the linking between inflammation and metabolism to skin and organ scarring," says study author Johann Gudjonsson, M.D. Ph.D., a dermatologist at Michigan Medicine.

Boosting NAD+ via the precursor nicotinamide riboside, a safe and inexpensive dietary supplement, prevented skin and other organ scarring, providing the researchers a previously undiscovered pathogenic role of

CD38 in scleroderma scarring.

"These results open the door to entirely novel treatments for fibrosis and scleroderma. Using precision medicine, these treatments could be selectively targeted to block CD38 in scleroderma patients who have elevated CD38," says study author Bo Shi, Ph.D., a research assistant professor of dermatology at Northwestern Medicine.

The research findings also create possibilities for restoring levels of NAD+ using pre-existing drugs, or well tolerated dietary supplements. Both of these therapeutic approaches are entirely novel strategies to halt scleroderma's most debilitating side effect.

Now, Varga looks forward to learning more about these testable approaches to treating scleroderma using safe, inexpensive agents in the Michigan Medicine Scleroderma Program, one of the preeminent integrated clinical and research programs for the diagnosis, prevention and cure of systemic sclerosis in the nation.

"We've defined a pathway that for the first time mechanistically links inflammation and metabolism to scarring in system sclerosis. These results provide a major advancement in unraveling the complexities of the disease, which is chronic, progressive and potentially deadly for many affected," says Varga.

"Now, we will look at designing and executing an early-stage 'proof of principle' clinical trial to assess the safety, tolerability and efficacy of such innovative treatments in patients."

More information: Bo Shi et al, Targeting CD38-dependent NAD+ metabolism to mitigate multiple organ fibrosis, *iScience* (2020). DOI: 10.1016/j.isci.2020.101902

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