Inhibiting cancer-causing protein could prevent scleroderma fibrosis

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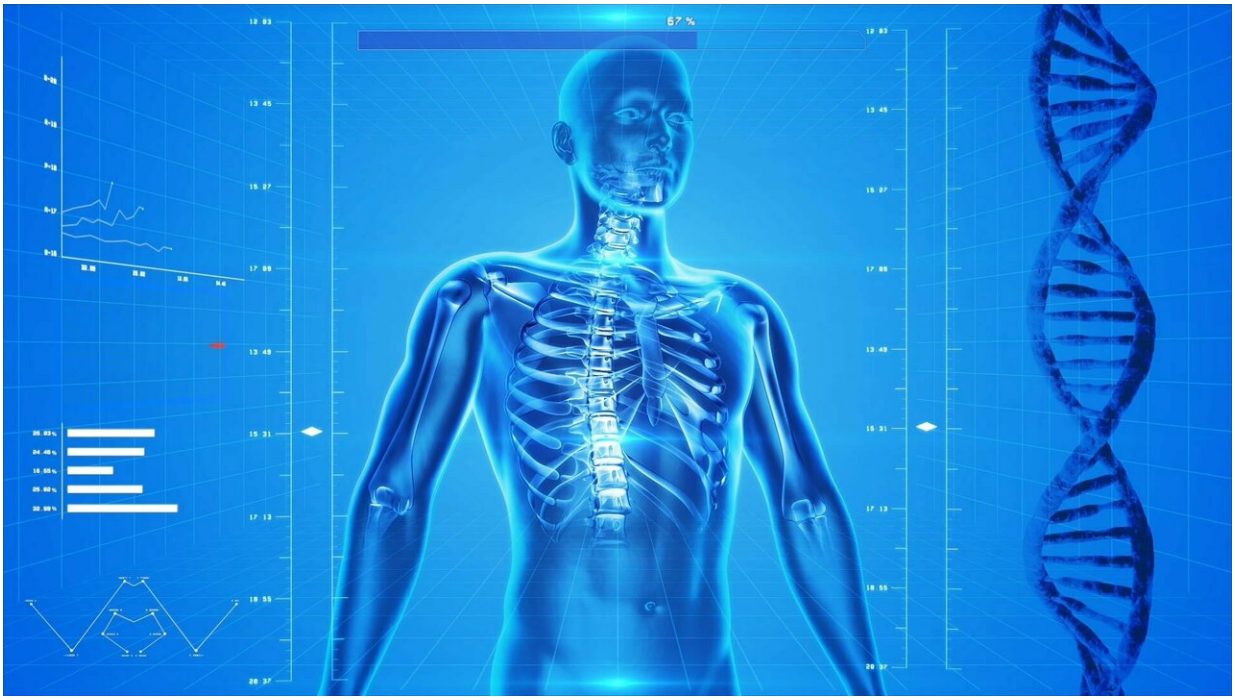

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A protein known to play a role in cancer may also be increasing fibrosis in scleroderma patients.

Scleroderma, a rare, chronic autoimmune disease, is marked by hardening of the skin and internal organs. Symptoms often include pain, stiffness, fatigue and breathing difficulties.

"The disease creates excessive fibroblast activation that ultimately results in tissue damage and organ failure," says Amr Sawalha, M.D., a professor in the Division of Rheumatology at the University of Michigan.

In a new study, published in *Proceedings of the National Academy of Sciences*, Sawalha and his team examined scleroderma at the molecular level to better understand the fibrosis process.

"We examined the molecule EZH2, which has been known to play a role in several types of cancer," Sawalha says. "This protein regulates gene expression, by affecting modifications that happen to DNA and other proteins attached to DNA, through a process called epigenetic regulation."

Sawalha and fellow researchers had previously identified a role for EZH2 in lupus, another autoimmune disease, flares.

"EZH2 is overexpressed in lupus T cells, which makes these white blood cells active in lupus patients," he says. "We then expanded our studies to scleroderma and specifically looked at the role of EZH2 in fibroblasts and endothelial cells in this disease."

Examining EZH2

The research team first isolated cells from scleroderma patients in collaboration with the Michigan Medicine Scleroderma Program. The program provides care for a large number of scleroderma patients at the University of Michigan. They then expanded their studies to animal models to further test findings identified in the human cells.

"Both increased fibrosis and abnormal blood vessel function, or defective angiogenesis, are major aspects of pathology in this

autoimmune disease," says Eliza Tsou, Ph.D., a research assistant professor at U-M and first author of the study. "We dissected the cells and found that increased levels of EZH2 were contributing to this disease process in scleroderma patients."

After identifying the molecule, the research team examined what happened in the cells when EZH2 was inhibited.

"When we suppressed EZH2, we found we could correct increased fibrosis and abnormal blood vessel function in scleroderma," Sawalha says.

Translating to the bedside

Because EZH2 is a molecule known to play a role in cancer patients, Sawalha says the ability to translate their laboratory work to patients may be easier.

"What is nice is that EZH2 inhibitors are already developed and in clinical trials in certain cancers," he says. "Therefore, our findings can be more readily translated to the bedside by repurposing already existing inhibitors for EZH2 to treat scleroderma."

As there are currently no effective treatment options for scleroderma, Sawalha notes that this type of research is important for future studies and trials.

"We will continue to research this disease at the molecular level and try to identify additional therapeutic targets for this patient population," he says.

More information: Pei-Suen Tsou et al, Inhibition of EZH2 prevents fibrosis and restores normal angiogenesis in scleroderma, *Proceedings of*

the National Academy of Sciences (2019). DOI: 10.1073/pnas.1813006116