Hippo signaling pathway gives new insight into systemic sclerosis

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Credit: Jacob Dwyer, Justine Ross / Michigan Medicine

Systemic sclerosis causes the skin to tighten and harden resulting in a potentially fatal autoimmune condition that is associated with lung fibrosis and kidney disease.

University of Michigan Health researchers have studied the pathology of systemic sclerosis to understand better the disease and identify key

pathways in the disease process that can be targeted therapeutically. Now a research team led by University of Michigan Health's Dinesh Khanna, M.B.B.S., M.Sc., professor of rheumatology and Johann Gudjonsson, M.D., Ph.D., professor of dermatology, in collaboration with John Varga, M.D., professor and chief of rheumatology, has characterized the major cellular sources of fibrosis in the skin of patients with systemic sclerosis skin, identifying myofibroblasts and a subset of endothelial cells as the major contributors.

The work is published in the journal *Nature Communications*.

The research examined the Hippo signaling pathway, an evolutionarily conserved signaling pathway that plays a complex role in cellular function as a major pathway promoting fibrosis in systemic sclerosis. By directly targeting the Hippo signaling pathway, the research team demonstrated a reversal of the pro-fibrotic responses in both myofibroblasts and endothelial cells.

The discovery of this function of the Hippo signaling pathway in systemic sclerosis ties back to prior work that identified a regulator of this pathway as a key driver of sex biased immune responses, providing evidence that may help explain why systemic sclerosis is much more common in women than men.

The findings reported in this paper showed a marked effect from the drug verteporfin, which targets the Hippo signaling pathway, and rapid reversal of the pro-fibrotic phenotype in both myofibroblasts and endothelial cells.

"Verteporfin is approved for treatment of a subtype of macular degeneration suggesting that it could be repurposed towards treating systemic sclerosis," said Gudjonsson. "This work helps shift the focus towards a novel pathway that is a key driver of the major features

observed in systemic sclerosis and has the potential to be able to move quickly to testing in clinical trials."

Furthermore, the researchers believe the unique and comprehensive nature of the data generated in this project may become valuable to other investigators studying systemic sclerosis.

"This is something that Khanna and I aim to move towards creating a proof of concept trial in the near future for to test this theory and further advancements in systemic sclerosis treatment and care," said Gudjonsson.

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More information: Feiyang Ma et al, Systems-based identification of the Hippo pathway for promoting fibrotic mesenchymal differentiation in systemic sclerosis, *Nature Communications* (2024). DOI: 10.1038/s41467-023-44645-6

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