How fibrosis develops in butterfly syndrome patients

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Children with a grave skin disorder known as butterfly syndrome develop severe and chronic blisters. Fibrosis, the thickening and scarring of connective tissues, is a major complication of the disease. Not only can fibrosis lead to club-like appendages where the skin grows over the fingers or toes, but Jefferson's Andrew South, Ph.D., an associate Professor in the department of Dermatology and Cutaneous Biology, has shown previously that fibrosis in butterfly syndrome patients also leads to an aggressive form of skin cancer that is often fatal. Now, Dr. South and colleagues have pinpointed how fibrosis develops in butterfly syndrome patients. The discovery points to a potential treatment for the debilitating complication.

The scientists suspected a protein called thrombospondin-1 (TSP1) might be involved in fibrosis. In previous research, Dr. South and colleagues discovered skin cells from butterfly syndrome patients have more TSP1 than skin cells from healthy individuals. In the new study, the researchers show TSP1 attaches to a protein that helps to hold layers of the skin together called collagen 7 (C7) in skin cells from healthy individuals. But C7 is missing in butterfly syndrome patients.

"We show for the first time in human cells that TSP1 binds to collagen 7 when it's there," says Dr. South, who published the results online January 23rd in the *Journal of Investigative Dermatology.* Since children with butterfly syndrome do not have much or any collagen 7, TSP1 instead is able to attach to a different molecule called transforming growth factor-β (TGFβ). TGFβ is a well-known signaling molecule that when activated

triggers a cascade of molecular signals that culminate in fibrosis.

"Our data points to that being the major driver of fibrosis in these patients," says Dr. South, who is also a researcher at the Sidney Kimmel Cancer Center—Jefferson Health.

The researchers went on to show a molecule that stops TSP1 from activating TGFβ reduces fibrosis in a tissue engineered model of the symptom. In addition to this potential therapy, the researchers are now sifting through nearly 1,500 FDA-approved molecules to look for other treatments.

"Now that we know one of the major activators of fibrosis is TSP1, we're looking to see whether it's possible to repurpose any of those drugs to treat fibrosis in butterfly syndrome patients," says Dr. South.

More information: Velina S. Atanasova et al, Thrombospondin-1 is a major activator of TGF-beta signaling in recessive dystrophic epidermolysis bullosa fibroblasts, *Journal of Investigative Dermatology* (2019). DOI: 10.1016/j.jid.2019.01.011

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