Causes found for stiff skin conditions

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By studying the genetics of a rare inherited disorder called stiff skin syndrome, researchers at the Johns Hopkins University School of Medicine have learned more about scleroderma, a condition affecting about one in 5,000 people that leads to hardening of the skin as well as other debilitating and often life-threatening problems. The findings, which appear this week in *Science Translational Medicine*, open doors to testing new treatments.

"Scleroderma is a common and often devastating condition yet its cause remains mysterious. My greatest hope is that this work will facilitate the development of new and better treatments," says Harry C. Dietz, M.D., the Victor A. McKusick Professor of Genetics and director of the Johns Hopkins William S. Smilow Center for Marfan Syndrome Research.

Also known as systemic sclerosis, scleroderma generally affects previously healthy young adults, causing scarring of skin and internal organs that can lead to heart and lung failure. "Most often individuals with scleroderma do not have other affected family members, precluding use of genetic techniques to map the underlying genes. Instead we turned to a rare but inherited form of isolated skin fibrosis called stiff skin syndrome, hoping to gain a foothold regarding cellular mechanisms that might prove relevant to both conditions," says Dietz.

A number of clues led Dietz and his team to strongly suspect a role for the connective tissue protein fibrillin-1 in these skin conditions. First, excess collagen is a hallmark feature of both stiff skin syndrome and scleroderma. While studying Marfan syndrome, a condition caused by a

deficiency of fibrillin-1, the researchers discovered that fibrillin-1 regulates the activity of TGFbeta, a molecule that induces cells to make more collagen. Second, other researchers have shown that duplication of a segment within the fibrillin-1 gene is associated with skin fibrosis in mice. And third, Dietz treated a patient at Johns Hopkins who had both stiff skin syndrome and eye problems associated with Marfan syndrome. "This seemed too much of a coincidence," he says.

So Dietz's team examined patients with stiff skin syndrome and found them to have excessive amounts of fibrillin-1 in the skin. The researchers then sequenced the fibrillin-1 gene in these same patients and found all the stiff skin syndrome mutations clustered in a single region of the fibrillin-1 protein known to interact with neighboring cells. Further examination showed that these mutations prevent fibrillin-1 from interacting with neighboring cells and lead to increased amounts and activity of TGFbeta, which causes excessive collagen outside cells.

The researchers then examined biopsies from patients with scleroderma and found all of the abnormalities seen in stiff skin syndrome. "It appears that fibriillin-1 helps to inform cells about the quality of their surroundings and also provides a mechanism — by concentrating TGFbeta — to induce extra cellular matrix production if the cell senses a deficiency," says Dietz. "A breakdown in signaling coupled with excessive fibrillin-1 and TGFbeta leads to a perfect storm for skin fibrosis in stiff skin syndrome."

While it remains unknown what triggers similar molecular events in scleroderma, these findings do suggest a number of potential treatment strategies, says Dietz.

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