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Researchers identify likely causes, treatment strategies for systemic scleroderma

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Using mice, lab-grown cells and clues from a related disorder, Johns Hopkins researchers have greatly increased understanding of the causes of systemic sclerosis, showing that a critical culprit is a defect in the way certain cells communicate with their structural scaffolding. They say the new insights point the way toward potentially developing drugs for the disease, which affects approximately 100,000 people in the United States.

"Until now we've had little insight and no effective treatment strategies for systemic sclerosis, and many patients die within a year of diagnosis," says Hal Dietz, a professor in the Institute of Genetic Medicine and director of the Smilow Center for Marfan Syndrome Research at Johns Hopkins. "Our group created mouse models that allowed us to learn about the sequence of events that leads to the disease's symptoms, and we hope drugs can be developed that target one or more of these events." The Dietz team's results are described in the Oct. 10 issue of *Nature*.

Patients with systemic sclerosis, also known as systemic scleroderma, experience a sudden hardening, or fibrosis, of the skin. For some patients, this hardening occurs only in limited areas, but for others, it quickly spreads across the body and to organs such as the heart, intestines and kidneys. It is this fibrosis of the internal organs that is often fatal.

Systemic sclerosis rarely runs in families, Dietz says, making the gene for the disease, if it exists, very difficult to find. Without a known

genetic mutation, researchers had not been able to create a genetically altered mouse with which to study the condition. But Dietz's group was struck by the similarities between systemic sclerosis and a less severe, much rarer condition called stiff skin syndrome (SSS), which does run in families, and they suspected that learning more about SSS would also shed light on systemic sclerosis.

In a previous experiment , they pinpointed the genetic mutation responsible for SSS in a gene for a protein called fibrillin-1, which plays a role in other connective tissue disorders. In certain types of tissues, including skin, fibrillin-1 helps make up the scaffolding for cells. The specific changes in fibrillin-1 seen in SSS patients were predicted to impair the ability of cells to make contact with fibrillin-1 through bridging molecules called integrins.

In the current study, M.D./Ph.D. student Elizabeth Gerber created a line of mice with a genetic variant similar to that found in SSS patients. To test the group's hypothesis, Gerber also created a line of mice with a variant the team knew would prevent fibrillin-1 from interacting with integrin. As the team expected, both groups of mice developed patches of stiff skin, along with elevated levels of proteins and cells involved in the immune response—much like humans with SSS or systemic sclerosis. "It seemed we were right that the SSS mutation causes the condition by blocking fibrillin's interaction with integrin," Dietz says. "Something else we found was that both types of mice had high levels of integrin in their skin, which made us think their cells were trying to compensate for the lack of fibrillin-integrin interaction by making more and more integrin."

This still left open the question of what was ultimately causing fibrosis, however: Was it the integrin levels or the immune response? Dietz's group delved deeper into the question by creating mice that had both the SSS mutation and artificially low levels of integrin, and found that the

mice never developed fibrosis or an abnormal immune response. "They looked normal," Dietz says.

The team next tried waiting until mice with the SSS mutation had developed fibrosis, then treating them with a compound known to block a key molecule with known connections to both fibrosis and the immune response. This reversed the mice's skin fibrosis and immunologic abnormalities. The team also tested the compounds on lab-grown human skin cells with systemic sclerosis, with the same results. This raises the possibility that systemic sclerosis patients could eventually be treated with similar compounds in humans, Dietz says. A number of the compounds that proved effective in SSS mice and systemic sclerosis cells are currently being explored by drug companies for the treatment of other conditions, prominently including cancer.

The results raised another big question for the team: Which of the several types of skin cells were responsible for the runaway immune response and fibrosis? They traced the activity to so-called plasmacytoid dendritic cells, or pDCs, a cell type known to either tamp down or ramp up immune response, depending on the circumstances.

"Dietz's work gives scleroderma patients hope that we have gained fundamental insights into the process of fibrosis in scleroderma. In particular, I am confident that within a relatively short time, novel therapies can be tested in patients, and I am optimistic that such treatments will have a profound effect," says Luke Evnin, Ph.D., chairman of the board of directors of the Scleroderma Research Foundation and a scleroderma patient.

More information: Integrin-modulating therapy prevents fibrosis and autoimmunity in mouse models of scleroderma, DOI: 10.1038/nature12614

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