Scientists identify agent that can block fibrosis of skin, lungs

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Researchers at the University of Pittsburgh School of Medicine have identified an agent that in lab tests protected the skin and lungs from fibrosis, a process that can ultimately end in organ failure and even death because the damaged tissue becomes scarred and can no longer function properly. The findings were published today in *Science Translational Medicine*.

There are no effective therapies for life-threatening illnesses such as idiopathic pulmonary fibrosis and systemic sclerosis, which cause progressive organ scarring and failure, said senior author Carol A. Feghali-Bostwick, Ph.D., associate professor, Division of Pulmonary, Allergy and Critical Care Medicine, and co-Director of the Scleroderma Center, Pitt School of Medicine.

"It's estimated that tissue fibrosis contributes to 45 percent of all deaths in developed countries because organ failure is the final common pathway for numerous diseases," she said. "Identifying a way to stop this process from happening could have enormous impact on mortality and quality of life."

The research team evaluated E4, a piece of protein or peptide derived from endostatin, a component of collagen known for its inhibition of new blood vessel growth. In lab tests, healthy human skin cells that were treated to become fibrotic remained normal when E4 was present. The skin and lungs of mice were protected from cell death and tissue scarring by a single injection of E4 administered five or eight days after they

were given the cancer drug bleomycin, which is known to induce fibrosis. The peptide also could reverse scarring that had already occurred, the researchers found.

In a unique approach, the investigators also tested E4 in human skin maintained in the laboratory to confirm it would be effective in treating fibrosis in a human tissue. E4 blocked new and ongoing fibrosis in human skin.

The agent might work by stalling the cross-linking of collagen needed to form thick scars, Dr. Feghali-Bostwick said. While the body naturally produces endostatin, it appears that it cannot make sufficient amounts to counteract fibrosis development in some diseases.

"This endostatin peptide passes two important hurdles that suggest it is a promising candidate drug for development for patients with idiopathic pulmonary fibrosis and systemic sclerosis" said Mark T. Gladwin, M.D., chief, Division of Pulmonary, Allergy and Critical Care Medicine at UPMC and Pitt. "It reverses established disease in animal models and it reverses fibrosis in the human skin fibrosis model."

In a case of serendipity, the researchers discovered E4 while exploring the process of fibrosis. Post-doctoral fellow and study co-author Yukie Yamaguchi, M.D., Ph.D., was conducting some experiments with proteins thought to facilitate the scarring process.

"Dr. Yamaguchi showed me the tests that showed endostatin wasn't working to increase fibrosis, but in fact shut it down," Dr. Feghali-Bostwick said. "It was the opposite of what we expected and I was very excited about our finding. As Louis Pasteur once said, 'chance favors the prepared mind.'"