Medical Xpress

Study sheds light on deadly lung disease

April 14 2008

Systemic sclerosis (SSc), also known as scleroderma, is characterized by the formation of fibrosis, or scar tissue, on internal organs as well as the skin. Beyond its disfiguring symptoms, SSc is associated with a high rate of deadly lung disease. Pulmonary fibrosis strikes at least one-third of SSc sufferers, and kills 30 percent within 10 years. Assessing and treating SSc remains challenging, despite recent clinical trials, due in part to an incomplete understanding of the origins and progression of this autoimmune disorder.

To add to the understanding of SSc, particularly as it relates to lung fibrosis, researchers with the Royal Free and University College Medical School and Royal Brompton Hospital in London conducted experiments on a novel mouse model of scleroderma. Their results, published in the April 2008 issue of *Arthritis & Rheumatism*, provide insight into extreme vulnerability to fibrosis associated with injury to alveolar epithelial cells (AECs)—cells that line the tiny air sacs in the lungs—aggravated by the expression of a major immune-system player, transforming growth factor alpha (TGF alpha).

Led by Dr. Christopher P. Denton, the researchers generated a transgenic mouse strain, which develops ubiquitous skin and sporadic lung scar tissue—characteristics similar to humans with SSc and pulmonary fibrosis. They then set out to test their hypothesis that these transgenic mice would be more susceptible than wild-type mice to lung disease. To induce minor lung injury, a single dose of either saline or the antibiotic bleomycin—a widely accepted model of SSc skin fibrosis—was administered surgically to populations of both transgenic

and wild-type mice. Representatives from each mouse strain were left untreated to serve as controls. After 3, 7, 10, 14, 21, 35, and 60 days, lung samples were dissected and preserved for biochemical, histological, and electron microscopic analysis.

Transgenic mice consistently demonstrated an exaggerated fibrosis-proliferation response to minor lung injury. The lungs from transgenic mice given normal, unbuffered saline demonstrated fibrotic traits similar to lungs from wild-type mice injected with fibrosis-inducing bleomycin, indicating a very low threshold for epithelial injury in the transgenic strain. Among other notable findings, electron microscopy revealed AEC abnormalities in the lungs of transgenic controls and bleomycin-affected wild-type mice; the lungs of transgenic mice given bleomycin showed severe epithelial damage.

The level of collagen was elevated in the lungs from transgenic mice after doses of either bleomycin or saline. After injury with bleomycin, the lungs of transgenic mice demonstrated increased density of the TGF alpha protein, implicated in the formation of fibrosis as well as tissue inflammation. Persistent fibrosis in transgenic mice injured with bleomycin was found independent of inflammation, but associated with impaired alveolar epithelial repair.

“These results suggest that in the context of fibroblast-specific perturbation of TGF alpha signaling, even minor epithelial injury induces significant fibrosis,” Dr. Denton concludes. “The model supports a central role for TGF alpha in determining fibrosis and demonstrates that lung fibroblasts may regulate the response of AECs to injury.”

Despite its limitations, including the fact that animal models with targeted genetic manipulations cannot fully represent all the facets and factors in the associated human disease process, this novel mouse study contributes to the understanding of the pathogenesis of systemic

sclerosis and pulmonary fibrosis. What's more, it provides a valuable reference point and motivation for future studies into anti-fibrotic therapies.

Source: Wiley