Researchers identify mechanism underlying COPD disease persistence after smoking cessation

July 27 2011

Cigarette smoke exposure fundamentally alters airway tissue from people with chronic obstructive pulmonary disease (COPD) at the cellular level, laying the groundwork for airway thickening and even precipitating precancerous changes in cell proliferation that may be self-perpetuating long after cigarette smoke exposure ends, according to Australian researchers.

"We have demonstrated for the first time that the extracellular matrix (ECM) produced by fibroblasts following stimulation with cigarette smoke extract is functionally different than non-exposed ECM, and that the cigarette smoke itself may prime the airways in such a way to create an environment whereby airway remodeling is encouraged," wrote lead researcher David Krimmer, a PhD student who is working with senior investigator Dr. Brian Oliver at the Woolcock Institute of Medical Research, of the University of Sydney in Australia.

The study appeared online in advance of final publication in the American Thoracic Society's *American Journal of Respiratory* Cell and Molecular Biology.

COPD is projected to be the third-leading cause of death worldwide by 2020, and is characterized by emphysematous destruction of the alveoli and thickening of the airway wall. The primary cause is chronic exposure to particulate matter, most often cigarette smoke. While the

cause of emphysematous destruction of the alveoli is likely due to a combination of the cytotoxic and proinflammatory activity of cigarette smoke, it is unknown whether cigarette smoke itself can cause thickening of the airway walls.

"We aimed to examine whether cigarette smoke extract alters the ECM deposited by primary human lung fibroblasts, and if smoke-induced ECM can alter proliferation and cytokine release," wrote Mr. Krimmer. "We also investigated whether the release of pro-fibrotic cytokines from fibroblasts were increased by cigarette smoke exposure."

The researchers examined the response of human lung tissue from donors with and without COPD to cigarette smoke extract (CSE). They found that CSE exposure induced a significant increase in fibronectin deposition from the tissue of donors with COPD over the tissue of individuals without COPD. Similarly, they found that CSE upregulated the expression of perlecan—an ECM protein that is associated with tumor growth and angiogenesis—in COPD lung tissue. These findings demonstrate that cigarette smoke has the capacity to directly induce fibrotic changes. "As such, this will change the way researchers think about the etiology of fibrosis in COPD," said Mr. Krimmer.

Interestingly, the increase in fibronectin deposition was attenuated by an inhibitor of NF-κB (a protein complex that controls the transcription of DNA) in the COPD tissue.

The researchers also found that CSE exposure caused the COPD tissue to express a significantly greater amount of IL-8, a marker of inflammation, than non-COPD tissue.

Perhaps the most striking finding of the study was that the CSE-induced ECM caused fibroblasts to proliferate. "We have known for a long time that development of fibrosis is irreversible in people with COPD. Our

findings suggest that cigarette smoking alters the composition of the lung in such a way that fibrosis becomes self-perpetuating," explained Mr. Krimmer. "Cigarette smoking is obviously bad for everyone; however, in light of our findings, cigarette smoking is likely to be especially dangerous in people with pre-existing COPD."

"Together these findings paint a picture of how ECM may itself perpetuate the disease process of COPD long after patients have quit smoking," said Mr. Krimmer. "It is our hope that further research on how and why this occurs will result in viable therapeutic targets for reducing the detrimental airway changes underlying COPD."

"[Overall] this study has demonstrated that human lung fibroblasts obtained from donors with COPD are more responsive to CSE and produce pro-fibrotic cytokines more readily than non-COPD donors," said Mr. Krimmer. "We have also shown that CSE directly activates the NF-κB pathway, and have demonstrated that the ECM produced by lung fibroblasts following CSE exposure is functionally altered and has pro-proliferative characteristics."

Provided by American Thoracic Society