Researchers learn how lung fibrosis begins and could be treated

June 27 2011

An invasive cell that leads to fibrosis of the lungs may be stopped by cutting off its supply of sugar, according to researchers at Duke University Medical Center.

Idiopathic pulmonary fibrosis (IPF), which affects about 100,000 people in the U.S. each year and leads to death within three years of diagnosis, has only one therapy in the U. S.: lung transplantation.

Duke researchers have found a possible new treatment by identifying a cell surface receptor on the invasive cells called myofibroblasts and an enzyme that produces a sugar the receptor recognizes.

Senior author Paul Noble, M.D., the Duke Division Chief of Pulmonary, Allergy, and Critical Care Medicine, and his team used a mouse model and later, human cells from IPF patients, to show that the invasive type of cell depends on both the enzyme that makes a sugar called hyaluronan and the cell receptor that recognizes hyaluronan, CD44.

"The animal model we used targeted excessive production of hyaluronan in the myofibroblasts," Noble said. "We found that these cells invaded and destroyed surrounding tissue matrix similar to the behavior of cancer cells during metastasis."

The study was published in the June 27 online edition of the Journal of Experimental Medicine.

The researchers reduced lung fibrosis in living mice by treating them with a blocking antibody against the CD44 receptor or stopping the production of the enzyme that produces hyaluronan. .

The invasiveness occurs when the myofibroblast produces excessive hyaluronan. Because the sugar is necessary for living (embryos without it don't develop), the sugar production cannot be completely blocked. Instead, the overproduction of the sugar must be stopped to keep the invasive cells from overtaking the spaces in the lung where vital gas exchange occurs.

The process of fibrosis in the lung is like a healing wound on skin, Noble said. The fibrotic cells clamp down, pull in the skin, and hold it together more tightly. In the lungs, this clamping down of small airways prevents essential respiration and leads to death due to irreversible loss of lung function.

An earlier paper Noble published in March in Science Translational Medicine showed that intracellular signaling proteins called beta-arrestins were necessary for fibroblasts to invade tissue. Mice with a targeted deletion in beta-arrestins didn't develop severe pulmonary fibrosis. He did this work with receptor-science pioneer Robert Lefkowitz, M.D., of Duke Departments of Medicine and Biochemistry.

The two studies, taken together, suggest several approaches to treating invasive fibrosis in the lungs, Noble said. They might specifically block hyaluronan production and the receptor for the sugar. Or they might block the invasion process by targeting beta-arrestins to prevent myofibroblasts from making contact with the matrix (noncellular part) of the lung.

Noble thinks looking at additional targets to block the invasion process might be the best approach of all. "If we can study human fibroblasts

and also the transgenic mouse as a model system, we could find more clues to stop the cells from invading," he said. "Several drugs are already approved that may have these properties that we need."

Provided by Duke University Medical Center