PULMONARY & CRITICAL CARE MEDICINE

The Division of Pulmonary and Critical Care Medicine is tackling an enigmatic clinical problem: pulmonary fibrosis, or scarring of the lungs. The damage affects the epithelial cells of the alveoli, the sac-like airways where oxygen and carbon dioxide are exchanged in order for us to breathe.

Idiopathic pulmonary fibrosis (IPF) is estimated to afflict 125,000 people in the United States, five million worldwide, and the incidence is rising. The disease is more common among men and people over 60 years old. Devastatingly, no effective treatment exists, and IPF is usually fatal. Fortunately, clinical clues are beginning to emerge that are helping physicians understand what causes the disease to progress and how to treat it.

A cadre of physician-scientists in the division is exploring many aspects of the disease—from the molecular level to animal models and, of course, human patients—in order to learn how IPF begins and progresses. Their goal is to identify strategies and targets for intervention that may one day lead to better diagnostic tests, treatments and ultimately a cure.

Pulmonary fibrosis represents an important arena for scientific and clinical inquiry into how an organ repairs itself in the face of injury, says Galen Toews, MD, division chief. The cellular and biochemical pathways involved in the scarring process seen in IPF, and which factors cause this process to go awry, are largely unknown.

Associate Professor, Victor Thannickal, MD, has identified one pathway involved in the scarring process. He and researchers in his laboratory have homed in on a family of enzymes, NADPH oxidases, or NOXes, which metabolize oxygen to generate reactive oxygen species (ROS). One of the homologs of this gene family, NOX4, activates progenitor cells in the lungs to produce myofibroblasts. Myofibroblasts play a role in tissue repair—as well as the scarring in IPF.

Dr. Thannickal’s lab has identified NOX4 in the lung tissues of patients with the disease, and in myofibroblasts isolated from diseased lungs.

Dr. Thannickal’s work may explain the overactive tissue repair process in some people. His findings support the notion of antagonistic pleiotropy, the idea that the same genes can have both a positive and negative effect. Perhaps the genes that encode for NOX enzymes are effective in normal tissue repair when we’re young, but lead to free radical injury and fibrosis as we age, which account for the higher incidence of IPF in older adults. Dr. Thannickal’s lab is developing compounds to inhibit NOX4. “We now have a way to target this pathway that could one day help our patients with IPF,” he says.

Kevin Flaherty, MD, associate professor, applies computer-aided analysis methods to computed tomography (CT) images to detect and quantify subtle changes in the disease. “These changes are very hard to detect with the naked eye,” he says. Better quantification methods of CT scan analysis mean physicians can more accurately define disease stages; they may also speed clinical trial evaluation, which could lead to faster drug development.

Associate Professor, Bethany Moore, PhD, focuses on the role of fibrocytes, cells that are derived from the bone marrow and have some characteristics of white blood cells. They also have the ability to differentiate into fibroblasts. Dr. Moore’s hypothesis is that in IPF, fibrocytes are recruited to the lung to help with repair. Once there, they may convert to fibroblasts, which produce collagen, and that leads to scarring. Preliminary research conducted at U-M indeed showed increased numbers of fibrocytes in the blood of IPF patients.

Now Dr. Moore’s laboratory is conducting a longitudinal study of nearly 400 IPF patients to verify those findings and see whether changes in fibrocyte levels correlate with disease progression and/or response to therapy. If they do, fibrocyte numbers may serve as a much needed biomarker to diagnose or stage the disease.

Together with Dr. Toews, Dr. Moore is investigating whether viral infection may trigger fibrotic lung disease or, if a patient already has IPF, whether a virus might trigger an acute exacerbation. Acute exacerbations, or a rapid, unexpected worsening of the disease, account for a significant number of IPF deaths. The team is using a mouse model of herpesvirus infection and has found that mice with fibrotic lung disease quickly worsen once exposed. In addition, exposure of the mice to herpesvirus infection first makes the mice more susceptible to fibrosis induction at a later time. In both situations, researchers have found that fibrocytes are among the cells that hurry to the lung. Dr. Moore now is taking a closer look at the signaling mechanisms and receptors that get fibrocytes to the lung in order to discover how to halt them.
**Fernando Martinez, MD** (below), is one of the most sought-after physicians who treat IPF. This year Dr. Martinez was appointed associate division chief for clinical research to continue his significant work designing and coordinating clinical trials at U-M and nationally. “The base of studies developed by Dr. Martinez is now a huge part of the division’s investigative portfolio as well as our training portfolio for fellows,” says Dr. Toews.

The appointment will allow Dr. Martinez “to continue to expand clinical research programs and ensure they’re tied closely to questions that have a direct impact on patients with IPF,” he says. That, he adds, “is what academic medicine is all about.”

Funding for the division’s work on idiopathic pulmonary fibrosis comes from NIH research project grants (R01s entitled, “Longitudinal Computer Analysis in IPF” and “Fibrocyte Phenotypes as Biomarkers in IPF Net Patients”) along with NIH clinical trial network funding (“Novel Therapeutic Approaches in IPF”). The Quest for Breath Foundation supports additional IPF research as well as patient support groups through the Martin Edward Galvin Fund for Idiopathic Pulmonary Fibrosis Research.

**Eric White, MD,** is defining the role of the extracellular matrix (ECM) in fibrosis. A dynamic complex of proteins and other substances that serve as a scaffolding or platform of sorts, the ECM also regulates the cells that bind to it by providing signals to influence cellular behavior. Fibroblasts produce the ECM, the main component of which is a protein called fibronectin. Dr. White has been looking more specifically at one form, long-known to play role in wound healing: EDA-containing fibronectin, or EDA cFN. He and his team hypothesized that EDA cFN is necessary in order for fibroblasts to be activated and for the scarring process to begin.

In experimental work published in the American Journal of Respiratory and Critical Care Medicine, Dr. White’s research group indeed found that mice deficient in EDA cFN could not develop fibrosis. He confirmed the role of EDA in humans by looking at lung tissue from IPF patients. Not surprisingly, he found elevated levels of EDA cFN as well as increased fibroblast cell activity in scarred areas. He continues to examine ways in which these cells and ECM proteins communicate in order to identify compounds that might interfere and prove therapeutic for patients.

**Right:** Transforming growth factor beta-treated human lung fibroblasts. The blue staining is DAPI to mark the nucleus. The green staining is FITC-labeling of alpha smooth muscle actin stress fibers (the hallmark of myofibroblasts). The red staining is focal adhesion kinase to mark focal adhesions.
Helping Women Breathe Easier: Clinical Programs in Women's Respiratory Health

One of a few physicians focusing on the interplay of gender and lung disease, MeiLan King Han, MD, heads a three-year-old clinic devoted to women with pulmonary disease. The Women’s Respiratory Clinic treats female patients with gender specific pulmonary disorders such as lung-related complications of pregnancy, in addition to lung diseases that, while not occurring exclusively in women, still have significant impact on women’s overall respiratory health.

Chronic obstructive pulmonary disease (COPD) is one such disease that is a major focus of the clinic. The prevalence of COPD, a progressive illness in which airway linings thicken and alveoli become less able to exchange gas, is on the rise in women. More women now die from COPD each year than men. Increased rates of smoking among women may be partially to blame, but other biological, physiologic, sociologic and environmental factors are likely at work—and yet to be teased apart.

Dr. Han helps women with COPD and other lung diseases join clinical trials which will help better understand the impact of the disease in women. For many years, COPD in women has not been actively studied. In fact, U-M is a member of the COPD Clinical Research Network, a consortium of COPD research centers funded by the NIH National Heart, Lung and Blood Institute.

The Lung Tissue Research Consortium, a four-center study, is amassing extensive clinical, radiological and biological data about IPF patients. Researchers now have access to information on the largest number of patients to date, a significant milestone since the disease is rare.

Population biologists and basic science researchers within the division also are heavily involved in a NIH 12-center clinical trial network, the IPFnet. Through this collaboration physicians and scientists together study the clinical presentation in patients, how the disease progresses, ways to characterize and stage it as well as ways to develop and test drugs to treat it.

MeiLan King Han, MD (below), studies the effects of gender on IPF. Unlike other lung diseases including chronic obstructive pulmonary disease, or COPD (see sidebar), women with IPF often survive longer than men—for reasons not yet understood.

In an article published in the European Respiratory Journal, Dr. Han found that hypoxemia during walking worsens more rapidly in male IPF patients than female patients, survival rates for men were also lower. One possible explanation may be relaxin, a pregnancy-related hormone that affects collagen turnover and may confer protection to women. This research will be the focus of Dr. Han’s recently funded National Institutes of Health (NIH) mentored career investigator award.

Investigators in the division are heavily involved in several large-scale clinical research initiatives supported by the NIH. The U-M is not only a leader in involving IPF patients in such studies, but physician-scientists play key roles in study design and protocol.

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