Researchers foresee new therapies and diagnostics for deadly fibrotic diseases

January 9 2013

A team of scientists has developed a playbook for ending the devastating impact of fibrotic diseases of the liver, lung, kidney, and other organs, which are responsible for as many as 45 percent of all deaths in the industrialized world. Despite the prevalence of these illnesses, which are caused by buildup of scar tissue, there are no approved antifibrotic drugs on the market in the U.S. A top fibrosis expert from the Icahn School of Medicine at Mount Sinai and three other institutions have described drug targets and compounds they hope will prove broadly effective in an article, "Therapy for Fibrotic Diseases: Nearing the Starting Line," appearing in the January 9 issue of *Science Translational Medicine*.

Scientists and drug companies are taking important steps to address the unmet need for fibrosis treatments. Among other advances, researchers have discovered and started to validate biomarkers that will facilitate testing of new drugs in clinical trials, according to the article.

"The insights we have described lay the groundwork for a new understanding of treatment approaches and diagnostics," said Scott Friedman, MD, the Dean for Therapeutic Discovery at Mount Sinai and lead author of the article. Diseases such as pulmonary fibrosis, renal fibrosis and hepatic cirrhosis represent "a huge unmet medical need," said Dr. Friedman, who is also the Director of the Division of Liver Diseases and its Centers for Fibrosis Research and Alcohol Liver Disease. "New treatments that are already in clinical trials exemplify a range of strategies harnessed by several pharmaceutical and biotechnology companies."

In the past, the fibrosis field has suffered from a lack of communication among disease experts focused on individual organs, and scientists did not fully consider similarities in cellular dysfunction found in all fibrotic diseases. However, growing synergies across medical specialties have sharpened the perspective on how fibrotic diseases are triggered by injury to epithelial tissues—the layers of densely packed cells that line all the organs of the body.

Recent research has produced a more coherent, comprehensive view of how these tissue injuries provoke dysregulation of cell differentiation, signaling, and protein secretion, Dr. Friedman said. "Investigators across the field are putting aside organ-centric views and coming up with what we think are the overarching characteristics of fibrosis. Understanding how the disease develops can help us diagnose and treat it, regardless of where in the body the fibrotic tissue presents," said Dr. Friedman, who co-authored the review article with colleagues from the University of California, San Francisco, the University of Washington, Seattle and Biogen Idec, based in Cambridge, Mass.

Dr. Friedman estimated that hundreds of clinical trials are currently underway, testing dozens of antifibrotic drugs. Some of the most promising studies focus on blocking a pathway driven by a molecule known as TGFß, which was identified more than 20 years ago as a central mediator of fibrosis. While there have been concerns that inhibiting this pathway could also impair the healthy process of tumor suppression, authors of the article describe several promising experimental drugs, including a variety of humanized antibodies developed by Genzyme, Eli Lilly, and Biogen Idec.

Following a different strategy, Gilead Sciences is using antibodies to block an enzyme that promotes cross-links among proteins in scar tissue. Such cross-linking is thought to stiffen the scar and hamper normal tissue repair and scar resolution. A third approach, explored by

Genentech, Novartis, MedImmune and Sanofi, targets cytokines, or messenger chemicals, IL-4 and IL-13, which regulate fibrosis in several animal models.

"This is really the tip of the iceberg," said Dr. Friedman. "In all likelihood, a large number of clinical trials will follow, built, in part, on the lessons learned through these studies."

"We hope our publication will serve as a template, not just for investigators, but for drug companies that are starting to inch into this space," said Dr. Friedman, who was the first scientist to isolate and characterize the hepatic stellate cell, the key cell type responsible for scar production in liver. "Our intention was to capture the leading edge of the science and also to provide pointers for how to move the field forward."

Researchers in this area face a number of hurdles. One challenge, for example, involves developing an appropriate design for clinical trials in illnesses such as hepatic cirrhosis, which involves scarring of the liver over as much as 30 years. "If a trial lasts only one or two years in a disease that affects patients for decades, developing measurements that accurately reflect the disease is difficult," Dr. Friedman noted. "This really represents the current Achilles' heel in trial design, which could be overcome with better methods to detect improvements following therapy."

Provided by The Mount Sinai Hospital