

HIGHLIGHTED PAPERS BY JUNIOR INVESTIGATORS

Tensin 1 Is Essential for Myofibroblast Differentiation and Extracellular Matrix Formation

Pulmonary fibrosis is characterized by progressive extracellular matrix deposition orchestrated by myofibroblasts. Tensin 1 is a component of fibrillar adhesions that bind to extracellular fibronectin. Ksenija Bernau (a post-doctoral fellow) and Nathan Sandbo (an assistant professor of medicine at the University of Wisconsin–Madison) are first and senior authors, respectively, of a paper reporting that tensin 1 is up-regulated in the myofibroblasts of fibrotic lung. The authors found that tensin 1 is strongly up-regulated by transforming growth factor- β (TGF- β), but its expression is mediated downstream of the TGF- β receptor via signaling through the transcription factor megakaryoblastic leukemia-1, rather than Smad2/3. Small interfering RNA-mediated depletion of tensin 1 resulted in the loss of both focal adhesion and fibrillar adhesion formation along with focal adhesion kinase phosphorylation in response to TGF- β . Furthermore, cells depleted of tensin 1 did not undergo myofibroblast differentiation, nor were they able to assemble extracellular fibronectin matrix. Taken together, these results suggest that tensin 1 plays a key role in the maintenance of fibronectin-associated adhesive structures and signals in myofibroblasts. Targeting tensin 1 and its associated signaling may be a useful strategy for disrupting matrix formation during pulmonary fibrosis. See article by Bernau on page 465.

Mouse Genome-Wide Association Study of Preclinical Group II Pulmonary Hypertension Identifies *Egfr*

Pulmonary hypertension (PH) is a disease of the pulmonary vasculature that develops owing to a number of mechanisms. Although genes have been identified that contribute to the development of group 1 PH, the genetic predisposition to other PH disease groups remains poorly understood. A study by Neil Kelly and Josiah Radder (graduate students in the Medical Scientist Training Program at the University of Pittsburgh), with their colleagues, involved a strain survey of mice fed a high-fat diet as a model of PH secondary to left-sided heart disease (group 2 PH) and tested for genetic association with this phenotype. By looking at genes in chromosomal regions enriched with variants associated with maximum right ventricular pressure but not with left ventricular dysfunction and ranking them using a network-based approach, they identified *Egfr* as a candidate gene for group 2 PH. Protein and mRNA expression of EGFR were significantly higher in a PH-susceptible strain compared to a non-susceptible strain offering functional support for this candidate. These results suggest that *Egfr* and its inhibitors, which are already used clinically for other diseases, warrant further investigation in PH particularly as it relates to left-sided heart disease. See article by Kelly on page 488.

Glucose Transporter 1-Dependent Glycolysis Is Increased during Aging-Related Lung Fibrosis, and Phloretin Inhibits Lung Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a rapidly progressive, fatal fibrotic interstitial lung disease that is more prevalent in aging populations. Owing to the devastating, rapidly progressive nature of IPF and generally late diagnosis, therapeutic interventions are limited, and curative pharmacologic therapy has not been established. Recent studies have reported that IPF patients exhibit higher glycolytic activity in fibrotic areas, with positive retention index values being a strong predictor of earlier deterioration in pulmonary function and higher mortality. Work by Soo Jung Cho (a postdoctoral fellow working with Dr. Stout-Delgado and colleagues at Weill Cornell Medical College) examined the potential contribution of glucose transporter (GLUT) 1 to augmented glycolysis in fibrotic lung tissue. Using primary young and aged murine fibroblasts as well as the bleomycin murine model of experimental lung injury, the results of their study illustrate that increased GLUT1-dependent glycolysis contributed to enhanced fibrogenesis in aged lung. Pharmacological inhibition of GLUT1 by phloretin decreased fibrogenesis and suggested a role for GLUT1 mediating its profibrogenic effects through enhancement of noncanonical transforming growth factor- β signaling pathways. Taken together, results from their study may help support rational drug design and the development of therapies based on targeting GLUT1 and/or its upstream/downstream regulators. See article by Cho on page 521.

Inhibition of the $K_{Ca}3.1$ Channel Alleviates Established Pulmonary Fibrosis in a Large Animal Model

A study looking at the effect of inhibiting the $K_{Ca}3.1$ ion channel in a sheep model of pulmonary fibrosis (IPF) was carried out by Louise Organ and colleagues during her Ph.D. studies at the University of Melbourne, Parkeville, Victoria, Australia. The $K_{Ca}3.1$ ion channel has recently been shown to play a role in idiopathic pulmonary fibrosis pathogenesis. In this study, a specific inhibitor for the $K_{Ca}3.1$ ion channel, Senicapoc, was administered during early stages of fibrosis following bleomycin injury (2 weeks post injury) in a sheep model. Compared to vehicle-treated controls, Senicapoc-treated sheep had significantly less pathology and collagen production. Furthermore, treatment restored loss of lung function caused by bleomycin damage. They also show that Senicapoc targets fibroblasts, reducing wound-healing α -muscle actin expression and cell proliferation, both *in vivo* and *in vitro*. This study supports previous research conducted in human IPF-derived fibroblasts indicating that inhibiting $K_{Ca}3.1$ signaling may provide a novel therapeutic approach for IPF. See article by Organ on page 539.

NIH Corner

News from the National Heart, Lung, and Blood Institute Production Assistance for Cellular Therapies

The National Heart, Lung, and Blood Institute-sponsored Production Assistance for Cellular Therapies (PACT) program is designed to provide resources to the extramural research community to support the advancement of cellular therapy research. PACT will consider applications for cGMP/cGLP manufactured cellular products to be used to refine and optimize the preclinical assays and

models during the discovery phase as the candidate therapeutic moves through product life cycle. PACT also assists with the development of a formal manufacturing process of the clinical product under cGMP-compliant conditions.

The PACT program is interested in supporting research related to repair and regeneration of damaged/diseased tissues, organs, and biological systems and welcomes applications involving cardiovascular repair and disease, lung repair and disease, hematologic disease, and hematopoietic cell transplantation. Visit the PACT website at www.pactgroup.net for more information including how to apply online or contact Division of Lung Diseases staff at nhlbi_dld@nhlbi.nih.gov.