



Read a commentary by Paul W. Noble, MD, of Duke University School of Medicine, on the clinical implications of the publication by Larsson O, et al, (*PLoS ONE*. 2008;3(9):e3220.) entitled, **“Fibrotic Myofibroblasts Manifest Genome-Wide Derangements of Translational Control.”**

Idiopathic pulmonary fibrosis (IPF) is a fatal condition characterized by the inexorable progression of restrictive lung disease with impaired gas exchange. Respiratory failure typically occurs within five years of diagnosis. The pathologic hallmarks of IPF are the accumulation of fibroblasts and extracellular matrix in the interstices of the lung. One of the pathologic peculiarities of IPF is the development of fibroblastic foci (FF). These are focal collections of fibroblasts that exhibit properties of smooth muscle such as contractile function and expression of α -smooth muscle cell actin (ASMA). FF are believed to be similar to wound myofibroblasts. While they can occur in other forms of interstitial lung disease, FF are most prominent in the usual interstitial pneumonia pattern that is the pathologic signature of IPF. These foci are juxtaposed to alveolar epithelial cells and the relationship between these two cell types is of ongoing interest in the pathobiology of IPF. The origin of myofibroblasts and the molecular regulation of their effector functions, such as extracellular matrix production, are incompletely understood. For decades the leading hypothesis to explain the unremitting proliferation of fibroblasts in IPF was that alveolar macrophages were releasing growth factors such as platelet-derived growth factor (PDGF), insulin-like growth factor-1 (IGF-1), and transforming growth factor- β (TGF- β) that then

acted on fibroblasts to stimulate proliferation and extracellular matrix production.

In recent years this hypothesis has been challenged by the concept that IPF fibroblasts are defective in the tight regulation of proliferation associated with normal physiologic repair. Two of the proponents of this concept over that last decade have been Drs. Craig Henke and Peter Bitterman at the University of Minnesota. Their collaborations have provided important data in support of the concept that IPF fibroblasts have inherent properties resulting in a phenotype with properties often observed in cancer cells. The essential observation has been that whereas myofibroblasts in healing wounds contract their matrix and undergo programmed cell death (apoptosis) in a timely manner, myofibroblasts in IPF lesions persist. They have previously shown that IPF fibroblasts respond differently to polymerized collagen in vitro than normal fibroblasts.¹ Compared to control fibroblasts, IPF fibroblasts exposed to polymerized collagen have reduced activity of a key suppressor of proliferation (PTEN), resulting in activation of a pro-survival signal (Akt), decreased apoptosis and myofibroblast proliferation.

Larsson et al² have taken a systems biology approach by simultaneously examining gene

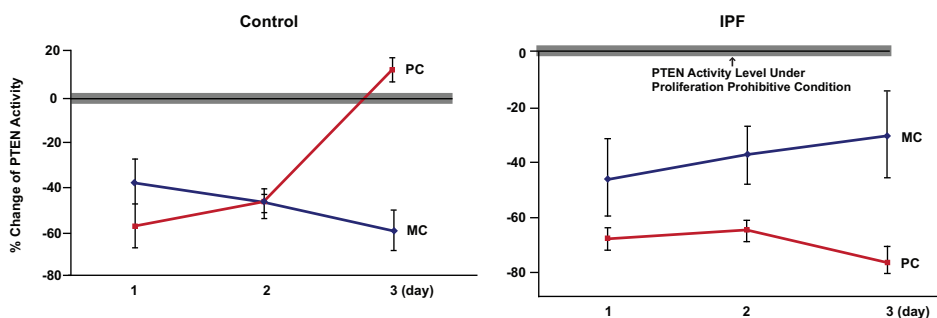
transcription and ribosome recruitment (a surrogate measure of protein expression). The rationale for this approach is that the deranged fibroblast phenotype may be related to altered transcription or translation of a subset of proteins. These selected proteins could be responsible for the cancer-like phenotype of the IPF fibroblast. The approach was to isolate fibroblasts from both normal lung tissue and IPF lung tissue. The 6 normal tissue samples were chosen from regions distant from lung cancer resection and the 6 IPF samples were either from VATS biopsy, autopsy or explants at the time of lung transplant. The fibroblasts were isolated from the lung tissue and cultured in vitro for 4 to 9 passages. The normal and IPF fibroblasts were then exposed to either “non-contractile” type I collagen gels or gels that were allowed to contract, an experimental condition designed to mimic the in vivo contractile properties of the myofibroblasts. Genome-wide transcriptional and translational profiling of these samples was then performed.

The interesting finding was that there was not a marked difference in the transcript abundance between normal and IPF fibroblasts under either collagen exposure. In contrast, there were much greater differences observed in translation. In non-contractile gels 1346 unique genes were identified that showed significantly different ribosome recruitment; 448 were found for fibroblasts cultured on the contractile substrate. The transcripts that were selectively recruited in IPF fibroblasts encode proteins whose functions are highly relevant to the pathobiology of IPF. These include proteins involved in regulating cell cycle function. In addition, pathways which have established roles in tissue fibrosis such as TGF- β and actin regulation were activated. The mTor pathway was also upregulated in IPF fibroblasts. This is an important growth-related pathway and represents a potential therapeutic target in IPF.

The source of myofibroblast accumulation in the IPF lung has been an area of active interest for years. The conventional concept is that myofibroblasts are largely derived from resident fibroblasts exposed to

FIGURE 1.

Regulation of PTEN is altered in IPF fibroblasts¹

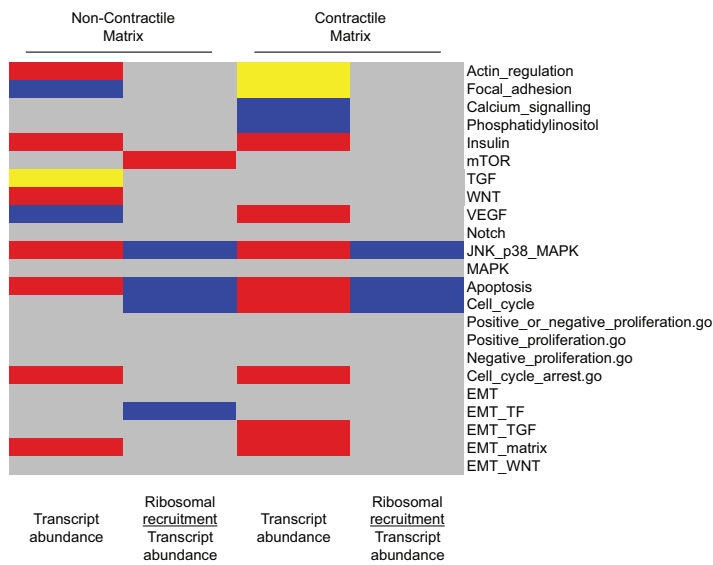


PTEN phosphatase assay showing the percent change in PTEN activity in control (n = 3) or IPF (n = 3) fibroblasts cultured on polymerized (PC) or monomeric collagen (MC) in growth factor-replete media compared with cells cultured under proliferation-prohibitive conditions.

continued



FIGURE 2.
Systems analysis of pathway activities and myofibroblast origin²



Pathways are shown in rows and conditions are shown in columns. A red box denotes that the pathway is activated in IPF compared with control myofibroblasts; blue boxes represent pathways that are activated in controls compared to IPF myofibroblasts. Yellow boxes signify a pathway that is activated both in IPF compared to controls and controls compared to IPF, and gray boxes represent pathways with no significant activity.

TGF- β . The authors analyzed transcription of subsets of genes known to be involved in the epithelial to mesenchymal transition. The results support an epithelial origin of some IPF myofibroblasts.

In summary, this important study provides new information on the role of fibroblasts/myofibroblasts in the pathobiology of IPF. These data provide further evidence in support of a central role for the fibroblast in the pathogenesis of IPF. While IPF fibroblasts are not truly cancer cells, they appear to share properties with tumor cells. This may provide a fruitful avenue for therapeutic intervention in the fibrotic process of IPF.

REFERENCES

1. Xia H, Diebold D, Nho R, et al. Pathological integrin signaling enhances proliferation of primary lung fibroblasts from patients with idiopathic pulmonary fibrosis. *J Exp Med.* 2008;205(7):1659-1672.
2. Larsson O, Diebold D, Fan D, et al. Fibrotic myofibroblasts manifest genome-wide derangements of translational control. *PLoS ONE.* 2008;3(9):e3220. Available at: <http://www.plosone.org/article/info:doi/10.1371/journal.pone.0003220>