Title

Targeting fibroblast durotaxis as novel anti-fibrotic therapy for IPF

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***QJM* Abstract**

Plenary Scientific Session 8

Invited Faculty Speaker

Prof. Kevin Brown, University of Colorado, USA

'Lessons Learned in Clinical Trials in Pulmonary Fibrosis'

Targeting fibroblast durotaxis as novel anti-fibrotic therapy for IPF

Dr. David Lagares (Pulmonary and Critical Care Division, Massachusetts General Hospital, Harvard Medical School, Boston, USA)
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Matrix stiffening in the lungs can contribute to fibrosis by inducing fibroblasts differentiation into activated myofibroblasts, the principal effector cells responsible matrix deposition in idiopathic pulmonary fibrosis (IPF). Recently, we identified a novel mechanism through which gradients of matrix stiffness produced in the injured lung drives the progression of lung fibrosis, by recruiting additional fibroblasts to sites of injury and incipient fibrosis through durotaxis – the migration of cells from regions of lower to higher stiffness. IPF lung fibroblasts demonstrate hyperdurotactic activities compared to control fibroblasts. Mechanistically, we have more recently found striking evidence implicating microtubule dynamics in durotaxing IPF fibroblasts. These cells showed prominent leading edge protrusions containing α-tubulin, which we hypothesize are involved in fibroblast mechanosensing of stiffness gradients. Our studies demonstrated that microtubule polarization in durotaxing cells is regulated at least in part by acetylation of α-tubulin on lysine (K)40, which contribute to the functional specialization of microtubules during directed fibroblast migration. Accordingly, both α-tubulin K40 acetylation and α-tubulin acetyltransferase-1 (αTAT-1), the sole enzyme responsible for α-tubulin K40 acetylation in mammals, were markedly elevated in IPF lung fibroblasts compared to healthy controls. Functionally, siRNA-mediated knockdown of αTAT-1 inhibited IPF fibroblast durotaxis without affecting chemotaxis. Immunofluorescence staining of lung sections from bleomycin and saline-challenged mice demonstrated that α-tubulin K40 acetylation was also augmented specifically in αSMA+ myofibroblasts in fibrosis. In vivo, αTAT-1-deficient mice were protected from bleomycin-induced lung fibrosis, indicating that targeting fibroblast durotaxis through αTAT-1 inhibition is a novel therapeutic target for the treatment of IPF.

'Assessment of Prognostic and predictive properties of blood biomarkers in pivotal clinical studies of Pirfenidone'

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Cabanski, C.R., DePianto, D.J., Ramalingam, T.R., Tew, G.W., Jia, G., Abbas, A.R., Peng, K., Ray, J., Palme, S., Dziadek, S., Ritter, M., Kirchgaessler, K., Ley, B., Wolters, P.J., Collard, H.R., Arron, J.R.

Background: Heterogeneity in rates of disease progression in IPF may reflect diversity in underlying pathobiology, and represents a major challenge in predicting clinical progression and/or treatment benefit for individual IPF patients. Systemic biomarkers related to distinct pathologies and molecular pathways, including epithelial injury, bronchiolization, lymphoid aggregates, macrophage polarization, and activity of TGFb, Hedgehog, and IL-13 pathways, may reflect aggregate disease burden across total lung tissue. Prior studies have implicated peripheral blood levels of several biomarkers as prognostic for overall survival time in IPF patients. However, biomarker findings have generally not been directly compared and replicated between cohorts nor have they been extensively evaluated in interventional trials. In this study, using the CAPACITY and ASCEND phase III clinical trial cohorts, we directly compared multiple disease relevant biomarkers in plasma to identify which may be prognostic for clinical outcome measures and/or predictive for benefit from pirfenidone.
Methods: The test cohort comprised subjects pooled from the CAPACITY 004 and 006 studies (n = 307). Levels of 14 plasma proteins were measured at baseline: BMP7, CCL13, CCL17, CCL18, CXCL13, CXCL14, COMP, DKK1, IL-13, MMP3, MMP7, osteopontin, periostin, and YKL40. Prognostic and predictive performance was assessed for absolute change in FVC % predicted over 12 months (ΔFVC) and a binary "Progressor" outcome, defined as ≥10% absolute decline in FVC % predicted or death within 12 months. Based on pre-defined statistical criteria, selected biomarkers were then evaluated for replication in subjects from the ASCEND trial (n = 464).
Results: Several baseline biomarkers were prognostic for progression outcomes in placebo arms of the CAPACITY cohort. However, despite similar demographics and baseline biomarker distributions between cohorts, only CCL18 was consistently prognostic for ΔFVC in both the CAPACITY ($p = 0.03$) and ASCEND ($p < 0.01$) cohorts. Pirfenidone treatment benefit was consistent regardless of baseline biomarker levels, including CCL18, indicating that no predictive biomarkers were identified.
Conclusions: Blood CCL18 levels represent activity of a key molecular pathway in IPF disease progression with potential to inform new target discovery and clinical trial design. Future validation of these findings in prospective studies is warranted.