ABSTRACT DR BRINTHA SELVARAJAH
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Position:	Clinical Training Fellow/ NIHR Clinical Lecture
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Presentation Title:	*'Metabolic Reprogramming in Idiopathic Pulmonary Fibrosis'*

ABSTRACT: (please keep your abstract within this page maximum 300 words)

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrotic interstitial lung disease of unknown aetiology. It conveys a poor median survival of 3.5 years, a prognosis worse than many cancers. The pathomechanisms that contribute to IPF are not fully elucidated and treatment options remain limited. Transforming growth factor-β (TGF-β) is a critical pro-fibrotic cytokine that drives fibroblast to myofibroblast differentiation resulting in excessive collagen deposition in the lung parenchyma. Subsequent distortion of the lung architecture leads to respiratory failure and ultimately death. Metabolic reprogramming underlies many diseases including cancer and akin to cancer, enhanced 18F-FDG-PET has been observed in IPF patients, suggesting altered glucose metabolism may also be a feature of IPF pathology. There is emerging evidence that alterations in the metabolism of myofibroblasts may be critical in fibroproliferative pathobiology.

We identify that TGF-β_1 increases the production of activating transcription factor 4 (ATF4), the transcriptional master regulator of amino acid metabolism, in order to supply glucose-derived glycine to meet the amino acid requirements associated with enhanced collagen production in response to myofibroblast differentiation. We further delineate the signaling pathways involved and show that TGF-β_1–induced ATF4 production was dependent on the cooperation between canonical TGF-β_1 signaling through Smad3 and activation of the mechanistic target of rapamycin complex 1 (mTORC1) and eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1) axis. ATF4 in turn promoted a transcriptional enhancement of the de novo serine-glycine biosynthetic pathway, as well as the glucose transporter 1 (GLUT1). Our findings suggest that targeting the TGF-β_1–mTORC1–ATF4 axis may represent a novel therapeutic strategy for interfering with myofibroblast function in fibrosis and potentially in other conditions, including cancer.