Key words documentation

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Abstract: Pulmonary fibrosis is progressive scarring of lung tissue occurring in systemic sclerosis (SSc) and interstitial pulmonary fibrosis (IPF), with limited treatment options. Pathophysiologically, excessive extracellular matrix (ECM) build up occurs, caused by persistently activated fibroblasts that differentiate into myofibroblasts. Since increased protein synthesis and cell proliferation require upregulation of metabolic pathways linked to the stimulation of mitochondrial biogenesis, the aim of this research was to examine metabolic perturbations and mitochondrial biogenesis in lung fibroblasts and subsequent effect on SSc and IPF pathogenesis. Bioinformatic analysis (gene set enrichment analysis and differential expression analysis) of two publicly accessible DNA microarray datasets produced lists of differentially expressed (DE) genes and enriched pathways. To determine possible functional interactions between the expressed proteins encoded by DE genes, STRING database was used. The results of SSc and IPF analysis showed perturbations in metabolic pathways expected in highly proliferative cells, such as increased glycolysis/gluconeogenesis, increased metabolism of purines, metabolism of pyrimidines and increased DNA replication. Furthermore, results showed perturbations of enzymes involved in all three stages of cell respiration (cytosolic glycolysis, mitochondrial citric acid cycle and oxidative phosphorylation).

In addition, dysregulation of genes associated with sphingolipid metabolism, with arginine and proline metabolism and with arachidonic acid metabolism was observed. Taken together, our results show profound metabolic changes, reflecting high energy demand of SSc and IPF fibroblasts. Lastly, although results show few DE genes in mitochondrial biogenesis, suggesting that this process is affected in both SSc and IPF, this pathway requires more specific examination for definitive conclusions.