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## Micro-RNA involvement in Progressive interstitial lung disease associated to systemic sclerosis

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**Objective:** Systemic sclerosis associated interstitial lung disease (SSc-ILD) is still one of the leading causes of mortality in SSc patients. We analyzed the micro-RNA (miRNA) gene expression of lung tissue and serum in prospective cohorts of patients with SSc-ILD and compared to controls.

**Methods:** RNA was isolated from lung tissue obtained by open lung biopsy in 12 SSc-ILD patients and from 5 control lungs. High-resolution computed tomography (HRCT) was performed at baseline and 2-3 years after treatment. miRNA and mRNA were analyzed by microarray and the resulting data analyzed by MirConnX network software. miRNA expression was correlated with mRNA expression and changes in the HRCT score (FibMax). Quantitative polymerase chain reaction (qPCR) was performed to confirm differential levels of miRNA.

**Results:** Lung miRNA microarray data distinguished patients with SSc-ILD from healthy controls with 185 miRNA differentially expressed ( $p < 0.05$ ,  $q < 0.25$ ). The MirConnX analysis in the lungs revealed 4 relevant upregulated miRNA in the complex mRNA-miRNA network: mir-182, mir-141, mir-155, and mir-195. Mir-21 was also found highly expressed in SSc-ILD lungs. mir-155 and mir-21 correlated strongly with altered lung mRNA expression such as CXCL13, SPP1, collagens and others. Several miRNAs were confirmed to be upregulated in the lungs of SSc-ILD by qPCR. Most importantly, both mir-155 and mir-21 correlated strongly with an image score of lung fibrosis (delta FibMax) with higher expression related to worsening disease.

**Conclusions:** miRNAs are dysregulated in lungs of SSc-ILD patients with mir-155 and mir-21 associated with progressive lung fibrosis. miRNAs show great potential as biomarkers for progressive SSc-ILD.

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## Targeting Nrf2 and AP-1 stress signaling in acute lung injury and repair

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Oxidative stress has been implicated in acute lung injury (ALI) and its severe form, acute respiratory distress syndrome (ARDS) both of which are clinical disorders with significant morbidity and mortality. Cellular stress related to oxygen supplementation (or hyperoxia) which is used as a therapy to maintain adequate tissue oxygenation in pre-term babies has been linked to the development of bronchopulmonary disease (BPD), a chronic lung disease with significant morbidity and mortality. Dr Reddy's lab research is focused primarily on understanding the exact mechanisms underlying defective lung tissue repair and persistent inflammation that are known to enhance susceptibility to bacterial/viral infection in ALI/ARDS patients leading to morbidity and often death in adults and neonates. We found that disruption of the Nrf2 transcription factor which is crucial for antioxidant gene expression impairs the resolution of oxidant (hyperoxia)-induced acute lung injury leading to defective lung tissue repair and persistent inflammation in both neonatal and adult mice. Importantly, our findings revealed that Nrf2 deficiency promotes susceptibility to bacterial infection after hyperoxic exposure ultimately leading to death of the host. We are using both genetic and pharmacologic approaches to elucidate the exact mechanisms by which Nrf2 and AP-1 signaling balance mediate the resolution of lung injury as a means of gaining insight into the development and perpetuation of ALI leading to infectious complications in neonates and adults. We are exploring how to pharmacologically amplify Nrf2-regulated signaling as a novel means to intervene and improve the outcomes of ALI and BPD using preclinical models and ex vivo samples.

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