Oxidant-Mediated Transcription and Post-Translational Modification of PGC-1α Is Required for Fibrotic Repair

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RATIONALE: Idiopathic pulmonary fibrosis (IPF) is a progressive lung disease associated with mitochondrial oxidative stress. Mitochondrial reactive oxygen species (mtROS) are important for cell homeostasis by regulating mitochondrial dynamics, including mitochondrial biogenesis. Mitochondrial dynamics are necessary to support long-term cellular activities, such as lung remodeling, and often promote apoptosis resistance. Monocyte-derived macrophages contribute to the pathogenesis of IPF by increased recruitment to the lung and by generating mtROS.

METHODS: Lung macrophages were obtained by BAL from normal and IPF subjects. In vivo studies used WT and mice harboring a conditional deletion of peroxisome proliferator-activated receptor coactivator (PGC)-1α in monocyte-derived macrophages. Mice were exposed to saline or bleomycin and euthanized at 21 days. For time course studies, mice were harvested 0, 5, 10, 14, and 21 days after exposure. A small molecule mitochondrial division inhibitor or vehicle was administered daily to mice by i.p. beginning 10 days after exposure. Mitochondrial biogenesis was determined by flow cytometry, transmission electron microscopy, RT-PCR, and immunoblot analysis. The relationship between monocyte-derived macrophages and apoptosis resistance was evaluated by flow cytometry, TUNEL, and caspase-3 activity. To evaluate regulation of PGC-1α, constructs were generated by mutating the p38 MAPK and Akt phosphorylation sites on PGC-1α.

RESULTS: Here, we show that IPF BAL cells display increased mitochondrial biogenesis that is, in part, due to increased nuclear expression of PGC-1α. Bleomycin-exposed mice showed evidence of fibrosis 10 days after exposure, which correlated with enhanced mitochondrial biogenesis in isolated BAL cells. Contributing to the fibrotic phenotype, monocyte-derived macrophages from bleomycin-exposed mice were resistant to apoptosis, while residential macrophages showed increased apoptosis. Oxidant-mediated activation of the p38 MAPK regulated PGC-1α and promoted mitochondrial biogenesis in monocyte-derived macrophages. Demonstrating the importance of mitochondrial biogenesis, mice harboring a conditional deletion of PGC-1α in monocyte-derived macrophages (PGC-1α⁻/⁻/Csf1r⁺MerCreMer) or mice administered a chemical inhibitor of mitochondrial division showed reduced biogenesis and increased apoptosis in monocyte-derived macrophages, and these mice were protected from pulmonary fibrosis.

CONCLUSIONS: These observations suggest that PGC-1α maintains mitochondrial homeostasis in monocyte-derived macrophages to induce apoptosis resistance, which contributes to the pathogenesis of pulmonary fibrosis. Targeting PGC-1α and mitochondrial biogenesis in monocyte-derived macrophages may provide a novel therapeutic target to protect against the development and/or progression of pulmonary fibrosis.