ATF4 Mediates Mitochondrial Unfolded Protein Response (UPR\text{mt}) in Alveolar Epithelial Cells

H. Cui\textsuperscript{1}, D. Jiang\textsuperscript{1}, N. Xie\textsuperscript{1}, S. Banerjee\textsuperscript{1}, R. Liu\textsuperscript{1}, H. Dai\textsuperscript{2}, V. J. Thannickal\textsuperscript{1}, G. Liu\textsuperscript{1}; \textsuperscript{1}\textit{Medicine, University of Alabama at Birmingham, Birmingham, AL, United States, \textsuperscript{2}\textit{Beijing Institute of Respiratory Medicine, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China.}

Mammalian cells are capable of adapting to and recovering from a variety of ER and mitochondrial stresses by activating a combination of signaling and transcriptional programs known as unfolded protein response (UPR). Alveolar epithelial cells frequently experience both ER and mitochondrial stresses in a range of lung disorders, such as idiopathic pulmonary fibrosis (IPF), acute lung injury (ALI) and chronic obstructive pulmonary disease (COPD). However, despite this apparent connection, such scenarios used to be perceived as independent mechanisms leading to these pathogeneses. Evidence is lacking if there is an interplay between these two phenomena in these cells. It is unknown if an integration of UPR\textsuperscript{ER} and UPR\textsuperscript{mt} exists in the stressed alveolar epithelial cells from these pathologies. In this study, we demonstrated that ATF4, but not ATF5, mediates UPR\textsuperscript{mt} in alveolar epithelial cells in response to various mitochondrial stressors. We found that UPR\textsuperscript{ER} led to UPR\textsuperscript{mt} and mitochondrial dysfunctions in an ATF4 dependent manner in these cells. In contrast, mitochondrial stresses did not induce UPR\textsuperscript{ER}. We found that alveolar epithelial ATF4 and UPR\textsuperscript{mt} were induced in the lungs of bleomycin treated aged mice and IPF patients. Finally, we found that inducible expression of ATF4 in mouse alveolar epithelial cells aggravated pulmonary UPR\textsuperscript{mt}, lung inflammation, body weight loss and death in response to bleomycin induced lung injury. In conclusion, our data demonstrate that ER stresses induce ATF4-dependent UPR\textsuperscript{mt} and mitochondrial dysfunctions, providing novel insight into mechanisms by which ER stresses contribute to the pathogenesis of various pulmonary diseases.

This abstract is funded by: NIH

\textit{Am J Respir Crit Care Med 2020;201:A2230}
\textit{Internet address: www.atsjournals.org}