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Lost in Translation: Endoplasmic Reticulum–Mitochondria Crosstalk in Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a devastating and progressive age-related disease characterized by the accumulation of scar tissue in the lung resulting in changes in the typical architecture of the distal parenchyma, leading to a fatal respiratory insufficiency. The aberrant activation and transdifferentiation of multiple cell types converge in the fibrotic lung's final phenotype, from the accumulation of differentiated fibroblasts into myofibroblasts to the appearance of apoptotic-resistant macrophages. Also, alterations of the alveolar epithelium underlie disease initiation and progression in IPF. The fragility and vulnerability to injury of type II alveolar epithelial cells (AECII) in IPF, with a reduced capacity to resolve cellular stress, have a pivotal role in trigging the events leading to the IPF pathobiology (1).

As a mechanism to cope with injury and to adapt to a new stress, cells can activate the unfolded protein response (UPR). This response originates in the endoplasmic reticulum (ER) and is known as the UPR^{ER}. A new mitochondrial stress signal dependent on the UPR also has been reported (2, 3). Two-pronged responses activate the expression of mitochondrial chaperones and mitochondrial import machinery (UPR^{mt}) while stimulating proteasome activity to limit the accumulation of mislocalized mitochondrial proteins in the cytosol where they can have a proteotoxic effect (UPR^{am} [unfolded protein response activated by mistargeting of proteins]). As the accumulation of unfolded proteins in the ER is the leading cause of ER stress (4), the UPR^{ER} upregulates cellular chaperone expression to enhance proper protein folding while simultaneously decreasing *de novo* protein synthesis and increasing degradation of any remaining unfolded aggregates. If the activation of the UPR is not enough to reverse the accumulation of unfolded proteins, it initiates a cascade of events leading to apoptosis or cell senescence. ER stress–triggered UPR^{ER} has been extensively studied in IPF (5), and it is considered a hallmark of alveolar epithelial injury and fragility. AECII cells in the IPF lung have a reduced capacity to resolve ER stress because of an impairment in autophagy (6). This progresses to the development of alterations in AECII function that result in impaired reepithelialization, a critical first step in the fibrotic cascade (1).

Mitochondria are tightly regulated organelles that are in constant communication with the intracellular environment. A double membrane physically separates them from the cytoplasm, so they are dependent on the translocation and import of proteins that have been synthesized in the cytosol. Mitochondria also possess their own translation machinery (mitochondrial DNA codes for 13 specific polypeptides), which needs to be protected from oxidation. Studies in model organisms *Caenorhabditis elegans* and *Drosophila* have revealed that upon the onset of mitochondrial stress, the nucleus activates an adaptive response (UPR^{mt}), which results in the transcriptional induction of genes promoting mitochondrial repair and recovery. However, if persistent, this stress will lead to irreparable mitochondrial dysfunction, a feature in age-related chronic lung diseases (7–9). In mammals, how UPR^{mt} is activated, executed, and integrated into the overall cellular stress response is still not fully understood. ATFS-1 (Stress activated transcription factor atfs-1) is the transcription factor acting as the master regulator of the UPR^{mt} activation in invertebrates. When ATFS-1 cannot be imported to the mitochondria as a consequence of mitochondrial stress or dysfunction, it is translocated to the nucleus where it activates UPR^{mt} and the expression of mitochondrial chaperones, proteases, and new import machinery to help restore mitochondrial homeostasis. Several studies postulate the possibility that ATF5, ATF4, and CHOP are the transcription factors controlling UPR^{mt} in mammals. The fact that these transcription factors are deeply linked to other stress responses such as UPR^{ER} or the integrated stress response highlights the complexity of the communication flow among ER, mitochondria, and nucleus.

The interconnection between ER stress and mitochondrial dysfunction is a critical factor in determining cellular fate and the decision to progress toward controlled cell death (apoptosis) or the initiation of a senescence program. Previous studies have shown that ER stress can directly control mitochondrial homeostasis through the integrated stress response transcription factor ATF3 (10). ATF3 transcriptionally regulates the mitochondrial kinase PINK1 (PTEN-induced putative kinase 1), and its upregulation provokes accumulation of depolarized mitochondria, increased production of mitochondrial reactive oxygen species, and loss of cell viability. AECII in IPF lungs show a high level of expression of ATF3 coupled with PINK1 deficiency. Concomitantly, these AECII exhibit higher susceptibility to apoptosis and, surprisingly, higher expression of senescence markers. Thus, the exact mechanisms by which all the stress responses are integrated and thereby control cellular fate is still an open question.

In this issue of the *Journal*, Jiang and colleagues (pp. 478–489) report that ATF4, but not ATF5, mediates UPR^{mt} in alveolar epithelial cells in response to specific mitochondrial stresses (11). Interestingly, after confirming that UPR^{ER} leads to UPR^{mt}, they show that UPR^{mt} does not activate UPR^{ER}, demonstrating how intricate and subtle these connections are. The authors elegantly describe the upregulation of ATF4 and UPR^{mt} markers in the lung of bleomycin-treated mice and AECII of IPF lungs. Also, they confirm a higher upregulation of proapoptotic and senescence

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makers in the alveolar epithelial cells of ATF4-overexpressing mice after bleomycin injury. The findings of Jiang and colleagues support the connection of UPR^{ER} and UPR^{mt} in alveolar epithelial cells and place ATF4 as a critical regulator of the mitochondrial stress response. This work opens a series of important questions, including what are the mechanisms by which cell aging can result in a disruption of the cross-talk between ER and mitochondria, and what are the factors that define the cellular progression to apoptosis versus cell senescence? Answers to these questions will give us a better understanding of the intracellular communication required for healthy cellular homeostasis. ■

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References

1. Selman M, Pardo A. The leading role of epithelial cells in the pathogenesis of idiopathic pulmonary fibrosis. *Cell Signal* 2020;66:109482.
2. Melber A, Haynes CM. UPR^{mt} regulation and output: a stress response mediated by mitochondrial-nuclear communication. *Cell Res* 2018;28: 281–295.
3. Callegari S, Dennerlein S. Sensing the stress: a role for the UPR^{mt} and UPR^{am} in the quality control of mitochondria. *Front Cell Dev Biol* 2018; 6:31.
4. Anderson NS, Haynes CM. Folding the mitochondrial UPR into the integrated stress response. *Trends Cell Biol* 2020;30:428–439.
5. Winters NI, Burman A, Kropski JA, Blackwell TS. Epithelial injury and dysfunction in the pathogenesis of idiopathic PulmonaryFibrosis. *Am J Med Sci* 2019;357:374–378.
6. Bueno M, Lai YC, Romero Y, Brands J, St Croix CM, Kamga C, *et al*. PINK1 deficiency impairs mitochondrial homeostasis and promotes lung fibrosis. *J Clin Invest* 2015;125:521–538.
7. Bueno M, Calyeca J, Rojas M, Mora AL. Mitochondria dysfunction and metabolic reprogramming as drivers of idiopathic pulmonary fibrosis. *Redox Biol* 2020;33:101509.
8. Mora AL, Bueno M, Rojas M. Mitochondria in the spotlight of aging and idiopathic pulmonary fibrosis. *J Clin Invest* 2017;127:405–414.
9. Rangarajan S, Bernard K, Thannickal VJ. Mitochondrial dysfunction in pulmonary fibrosis. *Ann Am Thorac Soc* 2017;14:S383–S388.
10. Bueno M, Brands J, Voltz L, Fiedler K, Mays B, St Croix C, *et al*. ATF3 represses PINK1 gene transcription in lung epithelial cells to control mitochondrial homeostasis. *Aging Cell* 2018;17:e12720.
11. Jiang D, Cui H, Xie N, Banerjee S, Liu RM, Dai H, *et al*. ATF4 mediates mitochondrial unfolded protein response in alveolar epithelial cells. *Am J Respir Cell Mol Biol* 2020;63:478–489.