A cytosolic surveillance mechanism activates the mitochondrial UPR

Sutandy, F.X.R., Gößner, I., Tascher, G. et al. *Nature* 618, 849–854 (2023).

Presenter: Hong-Chun Yen **Date/Time:** 2023/09/21, 16:10 -17:00

Commentator: Shih-Chieh, Lin, Ph.D. **Location:** 601 Classroom, Med College Building

Background: Maintenance of proteostasis is crucial for cellular functions. For decades, researchers have found that the Integrated Stress Response (ISR) reacts to multiple stresses in Eukaryotes. Research showed various mitochondrial pathologies were associated with mitochondrial stresses, indicating that mitochondria have been important in proteotoxic damage. To overcome proteotoxic stress, mitochondria are shown to activate another pathway instead of ISR. The Mitochondrial Unfolded Protein Response (UPR^{mt}), a retrograde mitochondria-nucleus transcriptional response, including mitochondria chaperones, *HSPD1*, *HSPE1* and *HSPA9*, and proteases, *LONP1*, acts as the safeguard in mitochondrial homeostasis. Different from canonical Unfolded Protein Responses (UPR) events presented in the cytosol, the previous studies showed the UPR^{mt} did not occur in IMS (Inner Membrane Space). The underlying mechanisms of the proteostasis communication between mitochondria and the nucleus remain unknown.

Objective: The authors asked what the molecular events are underlying the induction of the UPR^{mt} process.

Results: Cells within 3 hours of Gamitrinib-Triphenylphosphonium (GPTT) treatment, an inhibitor of HSP90, were performed in Time-resolved transcriptomic analysis. The results showed ISR-ATF4 axis was not required for UPR^{mt} induction. GO enrichment analysis showed ROS-related genes were transcriptionally upregulated in the GTPP situation. Directly induced ROS^{mt} in mitochondria showed ROS^{mt} is essential for UPR^{mt} signaling. Tracking ROS^{mt} with the H2O2 probe showed ROS^{mt} activates UPR^{mt} by diffusing into the cytosol. Next, by performing Multiplexed Redox Proteomics analysis, DNAJA1 (DnaJ heat shock protein family member A1) emerged as a target for UPR^{mt} activating oxidized by diffused ROS^{mt}. Quantitative Interaction Proteomics and Co-IP analysis revealed cytosolic HSP70 recruits to oxidized DNAJA1 in a ROS^{mt}-dependent manner. The author also confirmed mitochondrial protein precursor (c-mtProt) accumulated after GTPP treatment. By multiple biological methodologies, the author found HSF-1, an apex of mitochondrial stress-induced transcription factors, required oxidized DNAJA1 and c-mtProt to be released from the HSF-1/HSP70 complex for nuclear translocating. Finally, by pharmacological inhibition methodologies, the author confirmed that the ROS+ c-mtProt - DNAJA1-HSF1 axis showed to be the cytosolic surveillance for UPR^{mt} activation.

Conclusion: The author demonstrates that DNAJA1, HSP70, and HSF-1 act as cytosolic surveillance systems censoring mitochondrial ROS with c-mtProt to activate the UPR^{mt} process.

References:

1. Sutandy, F.X.R., Gößner, I., Tascher, G. et al. A cytosolic surveillance mechanism activates the mitochondrial UPR. Nature 618, 849–854 (2023). https://doi.org/10.1038/s41586-023-06142-0