hnRNPH1 maintains mitochondrial homeostasis by establishing NRF1/DRP1 retrograde signaling under mitochondrial stress

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Presenter: Chang-Chun WU **Date/Time**: 2025/10/02, 15:20-16:10

Commentator: Chi-Wu Chiang, Ph.D. **Location**: Rm. 601, Med College Building

Background: Mitochondria are central regulators of cellular homeostasis, coordinating energy production, calcium signaling, and metabolic adaptation. Dysfunctional mitochondria activate nuclear gene expression through retrograde signaling, a pathway well studied in yeast and worms but less understood in mammals. hnRNPH1, an RNA-binding protein best known for regulating mRNA splicing and highly expressed in cancers, has an unexplored role in mitochondrial retrograde signaling and cellular homeostasis.

Objective: This study aimed to determine whether hnRNPH1 mediates mitochondrial retrograde signaling under stress and to clarify how its interaction with DRP1 and NRF1 influences mitochondrial dynamics and cancer progression.

Results: Mitochondrial stress enhanced DRP1 activation and strengthened its interaction with hnRNPH1. Treatment of mitochondria uncoupler CCCP promoted hnRNPH1 translocation to mitochondria in a DRP1-dependent manner, where it facilitated DRP1 Ser616 phosphorylation, oligomerization, and fission. hnRNPH1 also accumulated in the nucleus in an AMPK-dependent manner and cooperated with NRF1 to activate DRP1 transcription independent of its splicing function. Loss of hnRNPH1 reduced mitochondrial membrane potential and mtDNA while elevating ROS, whereas its overexpression restored mitochondrial function and promoted mitophagy. Functionally, hnRNPH1 maintained mitochondrial quality by coordinating fission and retrograde signaling under stress. Importantly, elevated hnRNPH1 and DRP1 supported colorectal cancer cell growth and were upregulated in patient tumors, linking hnRNPH1 activation to cancer progression.

Conclusion: hnRNPH1 acts as a key mediator of mitochondrial retrograde signaling to maintain mitochondrial homeostasis under stress. By facilitating DRP1-dependent fission, mitophagy, and transcriptional reprogramming, hnRNPH1 supports mitochondrial quality control. Its upregulation in colorectal cancer links mitochondrial function to tumor progression, highlighting hnRNPH1 as a potential therapeutic target for intervention.