Decoding the Mechanistic Principles of Gene Regulation by Mitochondrial 3D Spatial Organization

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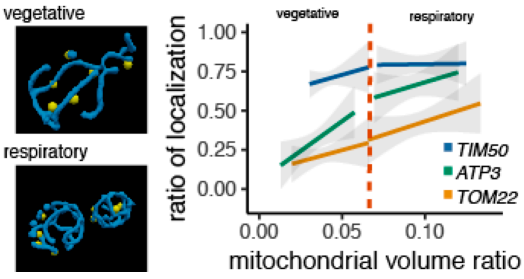
Mitochondria are key organelles within the cell involved in the production of ATP, serve as a hub for many biological reactions, and regulate many aspects of cellular activity such as cell senescence (aging), cancer and stressful conditions. Mitochondria are also very dynamic structures with fluctuating morphologic transitions in response to cellular and environmental perturbations. While there have been many studies investigating the pathways and conditions that alter mitochondrial morphology, the connection between these morphological changes and gene expression regulation is still a poorly explored question. How does changing mitochondrial morphology during aging, cancer, and stress impact gene regulation? How do mitochondria regulate mRNA localization and control translation in response to the metabolic needs of the cell?

We recently found that mitochondrial spatial organization can serve as a functional regulatory mechanism. Although nuclear-encoded mRNAs can be localized to the mitochondrial surface, the importance of this localization is unclear. As yeast switch to respiratory metabolism, there is an increase in the fraction of the cytoplasm that is mitochondrial. Our data point to this change in mitochondrial volume fraction increasing the localization of certain nuclear-encoded mRNAs to the surface of the mitochondria. Our single molecule visualization techniques combined with image processing and further stochastic modeling show that these mRNA movements can be described by the combination of the thermodynamics principles and mitochondrial geometrical information. Traditional biochemical techniques and RNA-seq based ribosome-profiling analysis show that mitochondrial mRNA localization is necessary and sufficient to increase protein production to levels required during respiratory growth. Furthermore, we find that ribosome stalling impacts mRNA sensitivity to mitochondrial volume fraction and counterintuitively leads to enhanced protein synthesis by increasing mRNA localization to mitochondria. This points to a mechanism by which cells are able to use translation elongation and the geometric constraints of the cell to fine-tune organelle-specific gene expression through mRNA localization.



Mitochondrial volume fraction and binding affinity regulates mRNA localization. Each mRNA species (colored lines) shows distinctive correlative patterns between localization and mitochondrial volume fraction upon respiratory condition change according to its unique binding affinity.

However, it remains unclear how eukaryotic cells coordinate mitochondrial morphology and protein production. Fragmented mitochondrial morphology is a hallmark of the dysfunction of mitochondrial activity and is observed in disease phenotypes. I will introduce our preliminary results suggesting that mitochondrial morphology affects mRNA localization and this results in heterogeneity of protein composition in each mitochondrial fragment. We propose this mechanism is a way to regulate the quality of mitochondrial fragments and accelerate the degradation of nonfunctional mitochondrial fragments. I will further discuss general principles that underlie the control of gene expression through mitochondrial morphological change during fluctuating environmental conditions across species.