Physical mechanisms of regulating mitochondrial protein levels

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For living cells to maintain spatial organization and functional capacity, they must maintain protein levels in various cellular locations. This talk will focus on the physics of delivering proteins to and spreading proteins within mitochondria, an important organelle for cell metabolism. While mitochondria contain their own DNA copies that encode a small number of mitochondrial proteins, most mitochondrial proteins are encoded by DNA in the cell nucleus, and these proteins must be delivered to the mitochondria. Mitochondria, while frequently depicted as bean shaped, are often long tubes that branch and loop to form spatial networks that can span much of the cell volume. These mitochondrial networks undergo fusion and fission dynamics that rearrange the network structures. For certain genes, proteins can be delivered directly to mitochondria as the protein is synthesized by a ribosome on the mRNA, effectively tethering the mRNA to the mitochondria. I will describe how a combination of protein translation kinetics, which control whether an mRNA has proteins available to bind to the mitochondria, and diffusive search timescale mediated by cell geometry combine to regulate the localization of mRNA to mitochondria. We find that mRNA with longer durations of binding competence stick longer to the mitochondria but also are more likely to find the mitochondria before the mRNA is no longer able to bind. The stochastic delivery of proteins to mitochondria leads to differences in protein levels between mitochondria. I will explain how mRNA production and targeting control variation in mitochondrial protein levels, with a mitochondrial size-independent contribution to the variation level due to mRNA production and an increase in variation of certain gene levels for smaller mitochondria as smaller mitochondria have fewer independent delivery events. Mitochondrial fusion and fission dynamics allow proteins to diffusively spread through the organelle. Three-way junctions in the mitochondrial network are necessary for branches and loops. We find that three-way junction formation in the network structure leads to efficient spread with slower fusion and fission dynamics. Overall, mitochondrial networks dynamics, long-range transport, geometry, and diffusion combine to regulate protein levels in mitochondria.