Metabolic Organization Through Glucose-Mediated Regulation of Mitochondrial Transport

Anamika Agrawal[1], Gulcin Pekkurnaz[2], and Elena F. Koslover[1]

***Short Abstract* — Metabolism in large eukaryotic cells can be enhanced by spatial localization of key enzymes to regions with the highest metabolic demands. In mammalian neurons, mitochondria have been shown to respond to glucose levels by halting active transport preferentially in high glucose regions. We use reaction-diffusion models to explore the physical limits on spatial organization of organelles through such regulated stopping of processive motion. Our results highlight that the effectivity of this regulatory mode is limited to a range of glucose concentrations, but that glucose-dependent mitochondrial halting provides a plausible mechanism for enhancing metabolic flux under hypoglycemic conditions.**

***Keywords* — intracellular transport; cytoplasmic organization; reaction-diffusion; metabolism**

I. Introduction

EXTENSIVE cells such as neurons often have spatially heterogeneous metabolic requirements. For instance, myelinated cells in the central nervous system tend to restrict glucose entry into the cell to narrow nodes of Ranvier that can be separated by hundreds of micrometers. The ability of mitochondria, the energetic powerhouses of the cell, to sense and respond to changing glucose levels is known to be critical to cellular health [1]. Recent experiments in cultured neurons have demonstrated that mitochondria can localize preferentially to subcellular regions with high glucose levels [2]. This localization is achieved through the glucose-dependent activation of *O*-GlcNAc transferase (OGT) and *O*-GlcNAc modification of Milton, an adaptor protein that links mitochondria to the molecular motors responsible for their long-range transport through the cell. Upon modification by OGT, Milton triggers a halting of the mitochondria, causing them to stop disproportionately in glucose-rich regions of the cell [2].

We leverage continuum physical models to investigate the efficiency of organelle localization by enhanced halting in response to a diffusive signal that is itself consumed by the organelles.

II. Results

We develop a simplified quantitative model for mitochondrial distribution in a long narrow cellular projection in the context of glucose-mediated halting of active transport. Our model postulates a fixed glucose concentration at localized regions corresponding to the nodes of Ranvier, combined with glucose diffusion and consumption through initial metabolism by hexokinase enzymes that are localized to mitochondria. The mitochondria are assumed to engage in bidirectional processive transport, initiating walks at a constant rate, and halting walks with a rate dependent on the local glucose levels. Steady-state glucose and mitochondrial distributions in this model are governed by just three dimensionless parameters: the glucose decay length scale (which quantifies the balance between diffusion and consumption) relative to the internode distance, the external glucose concentration relative to the Michaelis-Menten constant K_M for the utilization of glucose by hexokinase, and the equilibrium constant defining the balance between stopping and walking rates of mitochondria.

We demonstrate that efficient localization of mitochondria to the nodes requires intermediate external glucose concentrations. Overly high concentrations saturate hexokinase kinetics, resulting in high levels of glucose throughout the cell. Concentrations that are too low lead to insufficient stopping of the mitochondria, also allowing them to disperse throughout the domain. Quantitative analysis of our model indicates that external glucose concentrations must be below approximately 1mM to achieve mitochondrial accumulation at the glucose source. Comparison to physiological brain glucose (measured at 0.7-1.3mM depending on brain region [3]) implies that this spatial organization mechanism is expected to be significant under both physiologic and hypoglycemic conditions. Furthermore, we find that total glucose flux in a myelinated neuron under such conditions can be increased two-fold by the proposed mechanism of glucose-dependent tethering of mitochondria.

We additionally develop an analogous model for non-myelinated cells, incorporating spatially heterogeneous external glucose and limited glucose permeability into the cell via facilitated transport through glucose channels. This model is leveraged for quantitative comparison with experimental data on mitochondrial localization in cultured neurons exposed to a glucose gradient [2].

III. Conclusion

We outline the physical limits on spatial organization of organelles by regulated halting of active transport, highlighting the interplay between diffusion and decay of the signaling molecule and the organelle stopping rates. In particular, we demonstrate the potential for enhancing metabolic rate in myelinated neurons at low glucose conditions by glucose-dependent modification of the Milton adaptor protein.

Acknowledgements: This work was funded in part by the Chancellor's Research Excellence Scholarship, UCSD

[1]Department of Physics, UC San Diego. E-mail: ekoslover@ucsd.edu

[2]Division of Biological Sciences, Neurobiology Section, UC San Diego. E-mail: gpekkurnaz@ucsd.edu

References

[1] Nunnari J, Suomalainen A (2012). Mitochondria: in sickness and in health. *Cell* **148**, 1145–1159.

[2] Pekkurnaz, G, et al. (2014) Glucose regulates mitochondrial motility via Milton modification by O-GlcNAc transferase. *Cell*, ***158***, 54-68.

[3] McNay, EC., et al. (2001) Fluctuations in brain glucose concentration during behavioral testing: dissociations between brain areas and between brain and blood." *Neurobiol Learn Mem* 75.3, 325-337.