Metabolic flux partitioning and energetic costs in cells

Cells consume energy to drive a myriad of cellular processes to stay alive, to grow and proliferate. Cell metabolism provides free energy for these processes, usually in the form of ATP. Mitochondrial respiration is one of the major ATP production pathways. While the biochemical reactions and the associated molecular players have been extensively mapped out, how these pathways dynamically partition energy into different cellular processes remain largely unexplored[1]. Specifically, what are the energetic costs of fundamental cellular processes, such as biosynthesis, ion homeostasis, cell division, etc.? How do cells control and partition energy into these processes in response to changes in nutrient supply and energy demand? Addressing these questions will not only leads to a comprehensive quantification of the energy budget of a cell, but also provides the mechanistic basis to understand how metabolic defects impair cell functions in diseases.

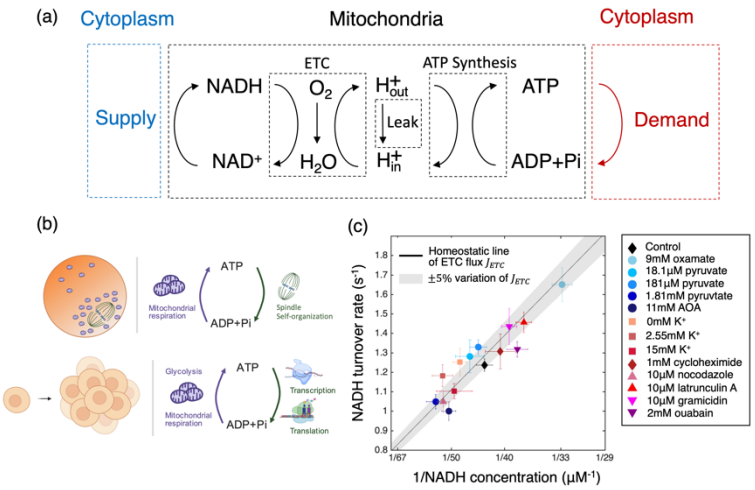

Figure: (a) Energy balance that relates the ATP consumption rate to ETC flux (equivalently OCR), ATP synthesis rate and proton leak. (b) Energy-consuming processes in cells. (c) homeostasis of ETC flux in mouse oocytes revealed by flux inference from fluorescence lifetime imaging of NADH: perturbing energy supply (blue) and demand (red) impact NADH redox reactions but do not impact ETC flux.

Our lab is developing metabolic imaging techniques to measure metabolic fluxes and metabolite concentrations in living cells with single cell and even subcellular resolution. Using this technique, we have discovered a striking phenomenon of flux homeostasis in mouse oocytes, where the oxygen consumption rate (OCR) of mitochondria, a proxy of energy production rate, remains constant despite of systematic perturbations in energy demand of the cell[2] (Figure). This is in stark contrast with conventional wisdom that OCR of mitochondria is controlled by energy demand. This observation begs the question of how mitochondrial OCR is controlled and how do cells balance a constant mitochondrial OCR with changing energy demand of the cell.

The candidate for this project will combine biophysical modeling with quantitative metabolic imaging and biochemical measurements to discover the mechanism of flux homeostasis and use this knowledge to understand how cells partition energy into different cellular processes and to map out the energetic costs in cells.

1. Yang, X., Heinemann M., Howard J., Huber G., Biswas S.I., Le Treut G., Lynch M., Montooth K. L., Needleman D. J., Pigolotti S., Rodenfels J., Ronceray P., Shankar S., Tavassoly I., Thutupalli S., Titov D.V., Wang J., and Foster P.J. (2021) Physical bioenergetics: Energy fluxes, budgets, and constraints in cells. *Proc Natl Acad Sci* 118 (26) e2026786118
2. Yang, X., Ha, G., and Needleman, D. J. (2021). A coarse-grained NADH redox model enables inference of subcellular metabolic fluxes from fluorescence lifetime imaging. eLife, 10:e73808.