Dissecting subcellular metabolic gradients in mouse oocytes

Cell metabolism provides the energy and molecular building blocks to sustain life. Over one hundred years of research has provided tremendous knowledge about the molecules involved in metabolic pathways, however, how these pathways are organized in space and time is still poorly understood. It is increasingly clear that spatiotemporal control of metabolic activities is required to meet the dynamically changing energetic and biosynthetic demands of an organism during development. For example, as early as oocyte maturation, it has been observed that mitochondria interact with the spindle apparatus and actin to facilitate the migration and correct positioning of the meiotic spindle. Indeed, the correct spatial distribution of mitochondria is essential to this process. While the mechanics of the mitochondria-spindle-actin interactions have been studied, the metabolic aspects of this process remains unexplored. The spindle and actin networks are active structures that constantly consume ATP to maintain their structure and dynamics. In mouse oocytes, the energy is uniquely supplied by mitochondrial metabolism. Metabolic activities of the mitochondria are characterized by the metabolic flux through the electron transport chain (ETC flux), which is proportional to oxygen consumption rate (OCR). Due to a lack of measurement techniques, it has long been a mystery as to what the spatiotemporal patterns of the ETC flux or OCR during the maturation of oocytes look like. We have developed a unique quantitative technique to measure mitochondrial ETC flux with subcellular resolution[1]. Using this method, we have revealed the existence of subcellular gradients of mitochondrial ETC flux within mouse oocytes, where mitochondria closer to the meiotic spindle display lower ETC flux while mitochondria closer to the cell membrane display higher ETC flux (Figure 1). This represents the first measurement of metabolic flux gradients within a single cell and provides a starting point to study the mechanisms underlying the formation of these metabolic gradients. The proposed research aims to reveal how gradients of ETC fluxes are established in mouse oocytes as a result of the interaction among mitochondria, spindle and actin networks and how they influence oocyte maturation. This project will unite cell biology and metabolism by linking organelle dynamics with spatiotemporal control of metabolic activities.

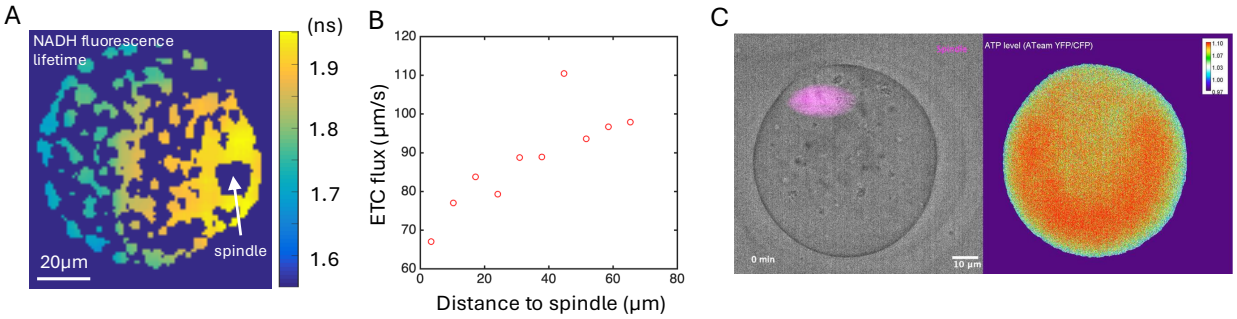

Figure 1 ***Spatial gradient of mitochondrial metabolism is associated with meiotic spindle.*** A. Spatial gradient of NADH fluorescence lifetime demonstrating heterogeneity of ETC flux associated with the spindle. B. NADH redox model reveals a lower ETC flux in mitochondria closer to the spindle compared to those further away. C. ATP level, measured by the FRET sensor ATeam, displays a lower ATP level towards the spindle, suggesting a potential ATP gradient as a result of the localized energy consumption of the spindle.

1. Yang X, Ha G and Needleman, DJ. A coarse-grained NADH redox model enables inference of subcellular metabolic fluxes from fluorescence lifetime imaging. doi:10.7554/eLife.73808