Bioenergetics of Spindle Self-Organization

Spindle is an important subcellular structure that is responsible for the segregation of chromosomes during cell division. It is composed of filaments called microtubules and the associated proteins. Spindle is an intrinsic nonequilibrium structure. It is constantly undergoing self-organization characterized by the disassembling and reassembling of the microtubules and the moving and sliding of microtubules across each other driven by motor proteins. These nonequilibrium dynamics is critical in building and maintaining the structure of the spindle and generating forces to segregate chromosomes. To sustain this nonequilibrium state, spindle is constantly consuming energy, usually in the form of ATP and GTP. This energy is provided by cell metabolism. Defects in cell metabolism is known to induce chromosome segregation errors, leading to aneuploidy in cancer and infertility, but the mechanism remains unknown. One hypothesis is that chromosome segregation error is caused by defects in spindle self-organization induced by metabolic defects.

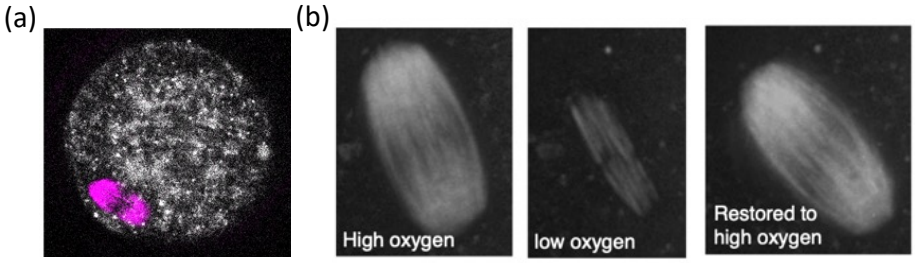

Figure: (a) Combined metabolic imaging of FAD in mitochondria (grey) and spindle (magenta) imaging in mouse oocytes. (b) Oxygen perturbation induces reversible disassembly and reassembly of meiotic spindle in mouse oocytes.

The goal of this project is to understand how metabolic potentials and fluxes impact spindle self-organization in meiotic and mitotic cells. Matured mouse oocyte is arrested in meiosis and maintains a steady-state meiotic spindle accompanied by steady-state metabolic activities for many hours, making itself an ideal system for perturbations to study the interplay between metabolism and spindle self-organization. Our preliminary results have revealed a remarkable response of spindle dynamics to oxygen perturbations: dropping oxygen level results in the shrinkage of the spindle, while recovery of oxygen level restores the spindle to its original size (Figure).

The candidate for this project will start by studying the mechanism underlying this spindle response and extend this study to systematically search for factors that connect metabolic activities with spindle dynamics. Integrating these findings, the candidate is expected to develop a quantitative theory for the bioenergetics of spindle self-organization. Techniques for this study include quantitative metabolic and spindle imaging, biophysical modeling of energy metabolism and spindle self-organization and biochemical perturbations. The success of this project will lead to a comprehensive understanding of what factors in metabolism influence spindle dynamics and by what mechanism, providing insights into how metabolic defects contribute to chromosome segregation errors.