AMPK-mediated activation of MCU stimulates mitochondrial Ca^{2+} entry to promote mitotic progression

With the support by the National Natural Science Foundation of China, the research team directed by Prof. Pan Xin (潘欣)and Prof. Zhang XueMin (张学敏) at the State Key Laboratory of Toxicology and Medical Countermeasures, Institute of Pharmacology and Toxicology, National Center of Biomedical Analysis, recently reported that a mitochondrial Ca^{2+} transient is essential for mitotic progression, which was published as a cover story in *Nature Cell Biology* (2019, 21: 476—486).

How cells regulate and respond to energy demand is an important and unanswered question in biology. Mitosis represents one of the highest energy demanding processes a cell encounters. Since mitosis is a relatively rapid process, it necessarily requires an acute increase in ATP production. However, how mitotic cells sense this energy demand and signal to the energy generation machinery to produce enough energy for timely cell division remains poorly understood.

In this study, they unexpectedly observed a rapid mitochondrial calcium burst in mitotic cells, termed mitochondrial Ca^{2+} transient, which is mediated by the recently identified MCU. They show that the mitochondrial Ca^{2+} transient is a response to the acute energy stress observed during early mitosis. This is achieved by mitosis-specific MCU phosphorylation and activation by the energy sensor AMPK. MCU-mediated rapid calcium influx into the mitochondria boosts ATP production to restore the energy homeostasis. This acute energy generation mechanism is essential for proper spindle microtubule dynamics and spindle checkpoint inactivation which ensure timely chromosome segregation. Moreover, they show that MCU-deficient mice die during mid gestation with increased mitotic delay and apoptosis in their tissues. These findings demonstrate a novel mechanism by which cells sense acute energy needs to directly control MCU for rapid ATP production in mitosis.

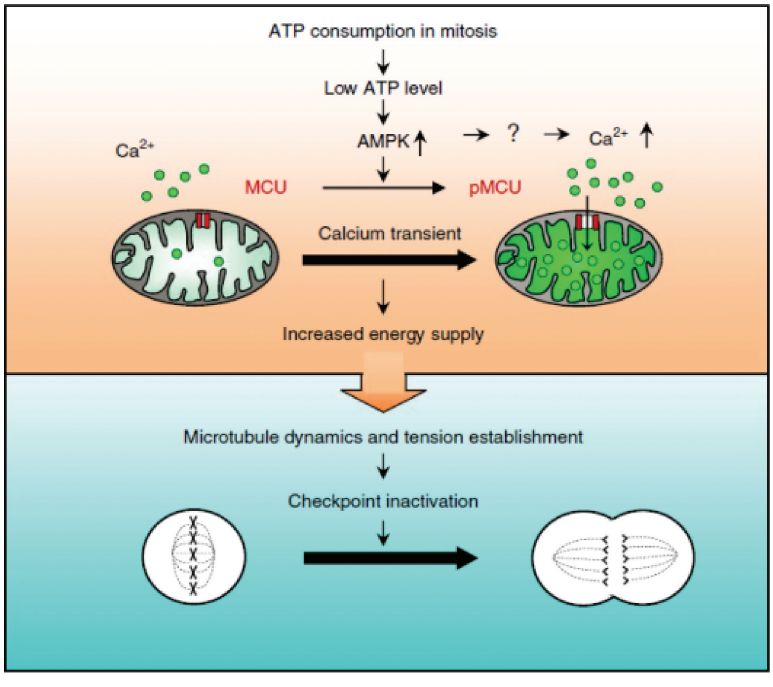

Figure Working model for AMPK-mediated MCU activation and mitochondrial Ca^{2+} transient in acute energy production for proper mitotic progression.

These findings reveal a mechanism of mitochondrial metabolic adaptation to acute cellular energy stress. This type of fast acting switch may be a general strategy for cells to timely sense energy demands to overcome the energetic stress during a number of diverse energy-consuming cellular processes.