Mitochondrial Calcium Uptake in Health and Disease

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Mitochondria are the masters of cellular energy metabolism and are crucially involved in almost every metabolic and signal transduction pathway. Accordingly it is not surprising that mitochondrial dysfunction have been identified as hallmark in the pathogenesis of many server diseases like cancers, neurodegenerative and metabolic diseases, and aging. However, while the organelle's radical production was considered as the most dangerous development of this very organelle, recent research considers the role and engagement of mitochondria and its interaction with the endoplasmic reticulum as key phenomenon of cellular adaptation and pathogenesis. Considering the previous approaches of mitochondria research, three revolutionary discoveries pioneered the current understanding of mitochondria function in health and disease: *first*, utilizing new technologies that allowed us to monitor individual mitochondria, researchers realized that individual mitochondria often come with different missions/functions in one given cell. *Second*, while mitochondria research mostly built on experiments performed in isolated mitochondria, scientists acknowledged that this organelle is highly interacting with its own microenvironment and actively "reads" and selects its neighborhood, thus, studies on isolated mitochondria might come with a great limitations. *Third*, based on the outstanding observation of Otto Warburg how described a cancer specific metabolic status, mitochondria and its functional interaction with the endoplasmic reticulum have been discovered as the Hub of metabolic adaptations and changes promoting aging and causing/facilitating diseases while elevated radical production obviously attend such changes. Notably, mitochondrial calcium homeostasis appears to be the key regulator of the emerging functions of mitochondria in health and diseases. Noteworthy, the

mechanism of mitochondrial calcium uptake is far from being just a single protein that establishes a calcium permeable pore but is established by a very dynamic multi-protein complex that is under the control of cytosolic/intermembrane and matrix calcium, and posttranslational modifiers that alter the composition of this complex significantly.

This talk will give an overview on our most recent studies on the engagement of UCP2/3 in the regulation of mitochondrial calcium uptake, its posttranslational regulation, and so far unresolved features of mitochondrial dynamics. Finally, the engagement of mitochondria in the switch of cancer metabolism will be newly envisaged.