



MITOCALCIUM - Mitochondrial calcium signaling: molecules, roles and pharmacological targeting

Mitochondrial Ca^{2+} homeostasis is an important component of the calcium-mediated cellular response to extracellular stimuli. It controls key organelle functions, such as aerobic metabolism and the induction of apoptotic cell death, and shapes the spatio-temporal pattern of the cytosolic $[\text{Ca}^{2+}]$ increase. While its physiological and pathological relevance is now fully appreciated, lack of molecular insight has severely limited mechanistic understanding and pharmacological targeting. We have now identified the long sought mitochondrial Ca^{2+} uniporter (MCU). This project stems from this ground-breaking result, and with a multidisciplinary approach investigates the biological role of MCU, tackling also its structure/function relationship and possible pharmacological exploitation. Specifically, the project will be divided in five major tasks

- i) The elucidation of the subcellular distribution of MCU and of the supramolecular organization of the mitochondrial Ca^{2+} influx machinery;
- ii) The clarification of the cross-talk with other signaling pathways, with major focus on regulatory mechanisms based on post-translational modifications (phosphorylation, acetylation, oxidation);
- iii) The development of suitable heterologous systems, in which wild-type MCU or mutants can be expressed; the purified protein (or the isolated mitochondria) will be utilized in electrophysiological studies to investigate the functional properties of the channel;
- iv) the elucidation of the protein structure, with the aim of developing specific inhibitors, based on molecular modelling and crystallization of the protein produced in the appropriate heterologous system;
- v) the generation of conditional and tissue-specific knockout models for investigating MCU function in vivo; the analysis of the phenotype, including the sensitivity to genetic or environmental causes of disease, will provide insight into the role of mitochondrial Ca^{2+} dysregulation in the pathogenesis and treatment of human disorders.

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Find out more: <https://cordis.europa.eu/project/id/294777>