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Mitochondria – endoplasmic reticulum crosstalk as therapeutic target against aging, cancer and diabetes

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Mitochondria are not only the master of cellular energy metabolism, they are also involved in multiple important processes including signal transduction, biosynthesis and gene expression. Noteworthy, mitochondria are also crucially involved in most pathological processes leading to cell dysfunctions and, ultimately, cell death. The reason of such ubiquitous involvement of mitochondria in cellular physiology and pathology is particularly achieved by intense interaction of the organelle with virtually all other cellular compartments. Very recently the endoplasmic reticulum (ER) – mitochondria axis received enormous attention. This interorganelle interface is organized in, so called, mitochondria-associated membranes (MAMs), the site where the exchange of substrates, products and ions takes place. Particular the latter one, namely Ca^{2+}, appears to be the most important regulator of such inter-organellar communication and recent studies revealed abnormal inter-organellar Ca^{2+} transfer as hallmark in many diseases like Alzheimer, diabetes mellitus, cancer and aging. Applying state-of-the-art techniques such like super-resolution fluorescence microscopy (Gottschalk et al. Pflügers Arch [in press], 2018), single Ca^{2+} channels recordings in the inner mitochondrial membrane (Bondarenko et al. Pflügers Arch. 467: 2509-25018, 2015), NMR or the design of genetically encoded biosensors (Eroglu et al. Nat. Commun. 7: 10623, 2016; Bischof et al. Nat. Commun. 8:1422, 2017; www.ngfi.eu), we discovered a posttranslational arginine metylation of the main regulator of the mitochondrial Ca^{2+} uptake, MICU1 (Madreiter-Sokolowski et al. Nat. Commun. 7:12897, 2016) that engages UCP2 as crucial facilitator for mitochondrial Ca^{2+} uptake (Trenker et al. Nat. Cell. Biol. 9: 445-452, 2007) under distinct pathological conditions. Accordingly, we are now able to envisage the specific changes in the ER – mitochondria axis in e.g. aging and cancer (Madreiter-Sokolowski et al Cell. Physiol. Biochem. 39: 1404-1420, 2016; Oncotarget 8: 80278-80285, 2017; Genes [in press], 2018). Based on this work, we are currently successfully testing potential leading compounds that are uniquely designed to counteract (so far) endothelial cell aging- or cancer-specific settings of the ER – mitochondria interface. Latest findings reveal a excellent specificity of these compounds that exclusively hits senescent or cancer cells and highlight the great potential of such strategies and compounds on either aging-associated vascular/endothelial dysfunction or cancer growth.