

Published in final edited form as:

Contact (Thousand Oaks). 2019 ; 2: . doi:10.1177/2515256419861227.

Mitochondrial–Endoplasmic Reticulum Interplay: A Lifelong On–Off Relationship?

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Abstract

This article comments recent publications that highlight an intriguing importance of specific settings in the interaction between the mitochondria and the endoplasmic reticulum to ensure cell-specific functions like the responsiveness to elevated glucose in pancreatic β -cells. Hence, alterations of the mitochondria–endoplasmic reticulum communications under various pathological conditions like aging or cancer often come with enhanced Ca^{2+} transfer that, in turn, yields stimulation of basal mitochondrial activity to meet the increasing adenosine triphosphate demand of the very cell. Such observations identify mitochondria-associated membranes as potential target for new therapeutic strategies against aging or cancer.

Keywords

mitochondria-associated membranes; MAMs; IRE1 α ; Ca^{2+} transfer; aging; mitochondria–ER coupling

Contact sites between mitochondria and endoplasmic reticulum (ER), stabilized by so-called mitochondria-associated ER membranes (MAMs), are forming highly dynamic signaling hubs to enable locally restricted and protected transfer of lipids and Ca^{2+} within these cellular subdomains (Csordas, Weaver, and Hajnoczky, 2018). The intraorganellar Ca^{2+} signaling within the MAMs is subject of situation-initiated alterations of its protein content (Carreras-Sureda et al., 2019) and may also consist of self-regulatory features as ER-derived Ca^{2+} controls the mobility of cristae and, thus, might establish a certain structure for ion transfer (Gottschalk et al., 2018). Notably, imbalances in the well-controlled homeostasis

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

within these regions, induced by changes in the transporter toolkit or alterations in the tethering between mitochondria and ER, have been associated with all types of age-related dysfunction, including neurodegeneration (Paillusson et al., 2016), metabolic and cardiovascular diseases (Thoudam et al., 2016; Tubbs et al., 2018), as well as cancer (Kerkhofs et al., 2018).

In our recent publication (Madreiter-Sokolowski et al., 2019), we reported enhanced ER–mitochondrial tethering in aged, serially passaged porcine aortic endothelial cells (PAECs) in comparison to young, freshly isolated PAECs. Confocal microscopy revealed increased ER–mitochondrial interaction in senescent endothelial cells, resulting in enhanced mitochondrial Ca^{2+} uptake in response to ER Ca^{2+} depletion upon stimulation with inositol 1,4,5-trisphosphate generating agonists. Increased mitochondrial Ca^{2+} levels, in turn, triggered mitochondrial metabolism by boosting the activity of Ca^{2+} dependent dehydrogenases of the Krebs cycle. However, the risk for mitochondrial Ca^{2+} overload-induced apoptosis increased under these conditions while at the same time increased expression of ER stress markers was observed. Consistent with these findings, specific vulnerability of cancer cells to Resveratrol has already previously been linked to enhanced mitochondrial Ca^{2+} uptake caused by increased ER–mitochondrial linkage in cancer cells (Madreiter-Sokolowski et al., 2016).

Recently, the dependency of insulin signaling on functional ER–mitochondria interactions could be demonstrated in mice and humans (Tubbs et al., 2018). Consistent with this report, we could show (Klec et al., 2019) that an ER Ca^{2+} leak, triggered by glycogen synthase kinase 3 β -driven phosphorylation of presenilin-1, induces a metabolic preactivation of mitochondria by elevation of mitochondrial Ca^{2+} levels in insulin secreting pancreatic β -cells. Besides the physiological importance for insulin secretion of these findings, these data may further point to the crucial role of ER–mitochondrial interplay in age-related diseases (e.g., diabetes mellitus type 2, Alzheimer’s disease). The enhanced ER–mitochondrial interplay might be crucial for aged cells to compensate age-related cellular dysfunction or inefficiency as well as for cancer cells to meet the increased energy demand due to their high proliferation activity. Nevertheless, increased ER–mitochondrial contact might also evolve an Achilles’ heel for all these cells by inducing the risk for mitochondrial Ca^{2+} overload or excessive production of reactive oxygen species.

Altogether, these findings point out that contact stability between mitochondria and ER may be a double-edged sword and mitochondrial Ca^{2+} homeostasis to be a crucial determinant for the cell’s fate (Figure 1). Understanding dynamics and features of mitochondrial–ER contact sites, including occurrence frequency and intensity, structural flexibility, and different mitochondrial Ca^{2+} uptake routes and their fine-tuning mechanisms under physiological and pathological conditions or aging, might unveil potential drug targets. These might help to find novel treatment strategies against still incurable types of cancer or ways to prevent the development of age-related diseases, such as type 2 diabetes mellitus. Considering recent reports about biphasic changes of mitochondrial metabolism during aging (Baker and Peleg, 2017), the timing of potential medical interventions might be crucial and especially challenging to get identified.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The research of the authors is funded by Nikon Austria within the Nikon-Center of Excellence Graz, the Austrian Science Fund (FWF) with projects P28529-B27 and I3716-B27 to R. M. and the FWF Doctoral Program Metabolic and Cardiovascular Disease (DK-W1226). The Nikon Center of Excellence, Graz, is supported by the Austrian infrastructure program 2013/2014, Nikon Austria Inc., and BioTechMed, Graz.

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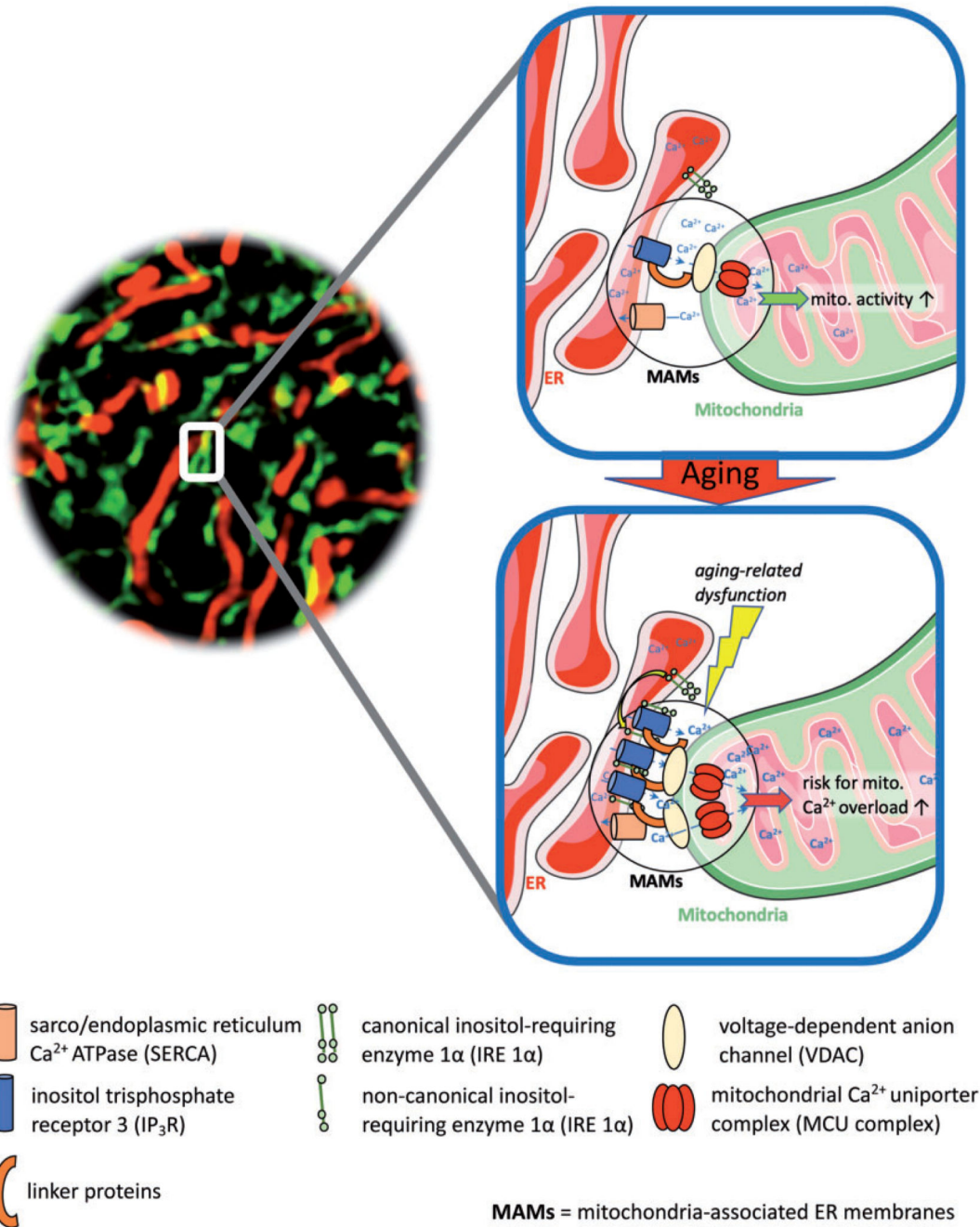


Figure 1.

Age-related changes in the assembly and function of proteins in regions of mitochondrial–ER contact sites. Aging-related cellular dysfunction is supposed to cause alterations in the protein assembly, among others trapping of IP₃R by IRE 1α within MAM regions, as well as in the ER–mitochondrial tethering, for example, by linker proteins. Thereby facilitated mitochondrial Ca²⁺ uptake via VDAC and the MCU complex might boost mitochondrial

activity and help to compensate age-related cellular inefficiency, but also brings the risk for mitochondrial Ca^{2+} overload-induced cell death.