Cell Calcium 62 (2017) 1–15

Contents lists available at ScienceDirect

Cell Calcium

journal homepage: www.elsevier.com/locate/ceca

The endoplasmic reticulum-mitochondria coupling in health and disease: Molecules, functions and significance

Riccardo Filadi [a], Pierre Theurey [a], Paola Pizzo [a,b,*]

[a] Department of Biomedical Sciences, University of Padova, Italy
[b] Neuroscience Institute, National Research Council (CNR), Padova, Italy

ARTICLE INFO

Article history:
Received 5 December 2016
Received in revised form 9 January 2017
Accepted 9 January 2017
Available online 12 January 2017

Keywords:
Calcium (Ca^{2+})
Mitochondria
Endoplasmic reticulum (ER)
Inter-organelle contacts
ER-mitochondria tethering
Mitochondria-Associated Membranes (MAMs)
Mitofusin 2

ABSTRACT

The close apposition between endoplasmic reticulum (ER) and mitochondria represents a key platform, capable to regulate different fundamental cellular pathways. Among these, Ca^{2+} signaling and lipid homeostasis have been demonstrated over the last years to be deeply modulated by ER-mitochondria cross-talk. Given its importance in cell life/death decisions, increasing evidence suggests that alterations of the ER-mitochondria axis could be responsible for the onset and progression of several diseases, including neurodegeneration, cancer and obesity. However, the molecular identity of the proteins controlling this inter-organelle apposition is still debated. In this review, we summarize the main cellular pathways controlled by ER-mitochondria appositions, focusing on the principal molecules reported to be involved in this interplay and on those diseases for which alterations in organelles communication have been reported.

Contents

* Corresponding author at: Department of Biomedical Sciences, University of Padova, Via U. Bassi 48, 35121 Padova, Italy.
E-mail address: paola.pizzo@unipd.it (P. Pizzo).

http://dx.doi.org/10.1016/j.ceca.2017.01.003
0143-4160/

1. Introduction

Inter-organelle communication represents an emerging aspect in cell biology: indeed, cellular organelles do not function as isolated structures but rather form dynamic interconnected networks which can be modulated according to cellular needs. In particular, the endoplasmic reticulum (ER)-mitochondria physical/functional coupling plays a central role in a variety of cell pathways and increasing evidence highlights its alteration in several diseases, including diabetes and obesity, cancer and neurodegenerative diseases, such as Alzheimer's Disease (AD), Parkinson's Disease (PD) and Amyotrophic Lateral Sclerosis (ALS).

Physical contacts between ER and mitochondria have been firstly observed by EM in the 50's in rat tissues [1] but such features have been considered for long time to be artifacts of fixation. More recent experiments in living cells expressing GFP variants within the two organelles [2] and electron micrograph images of quickly frozen samples [3] have demonstrated conclusively that such physical interactions between the two organelles indeed exist (Fig. 1A-B). Similar structures were then described in yeast and, recently, also in plants [4,5]. Their composition and thickness, however, are not constant and the distance between ER and the outer mitochondrial membrane (OMM) can be extremely variable, ranging from ~10 nm up to 80–100 nm [6]. Usually, at smooth ER-mitochondria contact sites the gap between the two opposing membranes is smaller (10–15 nm) than in the case of rough ER (typically 20–30 nm) [7], probably to allow ribosomes accommodation. Regions in which OMM and ER membranes proceed in parallel at larger distances (50–100 nm) have been also reported (see for instance [8]), and can be continuous to sites in which the two organelles are closer or, on the contrary, exist as separate, independent units. However, while in the case of the closer contacts (below ~30 nm) [7] electron-dense filamentous structures, proteinaceous in their nature, clearly protrude from the two opposing membranes (Fig. 1A), such structures have never been observed for the more distant organelles appositions. Thus, whether these latter are randomly occurring or tightly regulated, physiologically relevant events, is still unknown.

This contribution aims to update ER-mitochondria connections from multiple points of view: i) the molecules involved in the formation/modulation of ER-mitochondria inter-organelle structures; ii) the specific cellular functions dependent on ER-mitochondria coupling, especially those relying on their Ca^{2+} cross-talk; iii) the alterations of the ER-mitochondria platform described in different diseases and reported to be pathogenic.

2. Molecules: proteinaceous structures connecting the ER to mitochondria

2.1. Physical and functional tethers

The molecular identity of the structures mediating ER-mitochondria tethering is more defined in yeast, where two principal protein complexes are involved: the ER-mitochondria encounter structure (ERMES) and the ER membrane protein complex (EMC) (Fig. 2). Both structures were identified by genetic screens in *S. cerevisiae* mutant cells whose growth/lipid metabolism defects could be rescued by artificial ER-mitochondria tethers.

ERMES is formed by the cytosolic protein Mdm12, the ER membrane protein Mmm1 and the OMM proteins Mdm34 and Mdm10 [9]. In addition to the four core components, the mitochondrial Rho-like GTPase Gem1 represents a facultative regulatory subunit of the ERMES complex [10]. ERMES has been functionally implicated in ER-mitochondria lipid transport (though different groups failed to find defects in lipid metabolism in cells lacking the complex), as well as in several other cellular pathways, such as mitochondrial dynamics, inheritance, protein import, mitochondrial DNA (mtDNA) inheritance and mitophagy (see [11] for a recent review). Importantly, ERMES homologs have not been identified in mammals, while the mitochondrial proteins Miro1/2, involved in Ca^{2+}-dependent mitochondrial transport mediated by the kinesin adapter Milton [12], are the metazoan orthologue of Gem1.

The more recently identified tethering complex EMC contains in yeast six proteins, Emc1-6 [13] and is also required for phosphatidylserine (PS) import into mitochondria and assembly of multi-pass ER-membrane proteins [14]. Emc proteins interact with the mitochondrial protein Tom5 of the translocase of the outer membrane (TOM) complex, forming a tether between the two organelles [13]. EMC is a highly conserved protein complex, present in every major eukaryotic lineage, and in mammalian cells contains four additional proteins (Emc7–10) [15].

Recently, a proteomic analysis identified the ER transmembrane protein Ltc1/Lam6 as a potential additional tether in yeast, thanks to its interaction with the OMM proteins TOM70/71 [16]. Ltc1/Lam6 has also been observed to mediate the transfer of sterols between the two membranes.

Less clear is the molecular nature of the physical tether between the two organelles in metazoan cells. Several proteins have been demonstrated to modulate ER-mitochondria coupling: the majority of them appears to be located on either the OMM or specific ER membrane domains, called mitochondria-associated membranes (MAM) [17]. Despite the growing number of these proteins, the formal and univocal demonstration that the lack of a given molecule abolishes ER-mitochondria contacts has never been provided. Most likely, different and independent tethering complexes may exist and compensate one for the lack of the others, increasing the complexity of the analysis.

One multi-protein structure that strongly correlates with functional ER-mitochondria coupling is the IP3R-Grp75-VDAC complex (Fig. 2). In particular, it has been shown that ER resident inositol trisphosphates receptors, IP3Rs, (especially the MAM enriched IP3R3) physically interact with the cytosolic fraction of the mitochondrial chaperone Grp75 and the voltage-dependent anion channel 1 (VDAC1) of the OMM [18], functionally favoring mitochondrial Ca^{2+} uptake upon IP3-dependent ER Ca^{2+} release (see below). The role of such complex as a physical tether between the two organelles is however questionable, since DT40 cells knock-out (KO) for the three IP3R isoforms show, by EM analysis, unmodified ER-mitochondria physical association [7].

The molecular scaffold formed by the ER resident vesicle-associated membrane protein-associated protein B, VAPB, and the OMM protein tyrosine phosphatase-interacting protein-51, PTPIP51, has been also demonstrated to be involved in physical and functional ER-mitochondria tethering [19,20]. Genetic manipulation of these proteins are linked to variations in organelles juxtaposition and altered ER-mitochondria Ca^{2+} cross-talk. Interestingly, these functionalities are also affected by the expression of both VAPB mutants linked to Amyotrophic Lateral Sclerosis (ALS) [19] or the ALS-associated proteins TDP43 [20] and FUS [21], that disrupt the endogenous VAPB-PTPIP51 interaction, indicating a key role for the mitochondria-ER axis in ALS pathogenesis (see below).

In mammalian cells, the mitochondrial protein PTPIP51 has been recently reported to physically interact also with the ER-located oxysterol-binding protein (OSBP)-related proteins ORP5 and ORP8 [22] (see also below), two molecules previously shown to be important for cortical ER-plasma membrane contacts [23].

Another example of protein regulating ER-mitochondria juxtaposition is the phosphofurin acidic cluster sorting 2 protein, PACS-2, a cytosolic multifunctional sorting protein which controls organelles apposition in a B-cell receptor-associated protein 31, BAP31 (an ER cargo receptor), –dependent manner [24]. However, the role of PACS-2 on ER-mitochondria juxtaposition is not com-