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Mitochondria and endoplasmic reticulum crosstalk in amyotrophic lateral sclerosis

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ABSTRACT

Physical and functional interactions between mitochondria and the endoplasmic reticulum (ER) are crucial for cell life. These two organelles are intimately connected and collaborate to essential processes, such as calcium homeostasis and phospholipid biosynthesis. The connections between mitochondria and endoplasmic reticulum occur through structures named mitochondria associated membranes (MAMs), which contain lipid rafts and a large number of proteins, many of which serve multiple functions at different cellular sites. Growing evidence strongly suggests that alterations of ER–mitochondria interactions are involved in neurodegenerative disorders, including amyotrophic lateral sclerosis (ALS), a devastating and rapidly fatal motor neuron disease. Mutations in proteins that participate in ER–mitochondria interactions and MAM functions are increasingly being associated with genetic forms of ALS and other neurodegenerative diseases. This evidence strongly suggests that, rather than considering the two organelles separately, a better understanding of the disease process can derive from studying the alterations in their crosstalk. In this review we discuss normal and pathological ER–mitochondria interactions and the evidence that link them to ALS.

Contents

1. Introduction

Cells depend on a compartmentalized system for biochemical processes and signaling responses to live and thrive. Mitochondria are double membrane organelles enclosing their own DNA (mitochondrial DNA) in the matrix. They are the main cellular energy producers through

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oxidative phosphorylation and the physical hubs for the majority of the enzymatic pathways of intermediate metabolism. The endoplasmic reticulum (ER) is a large membrane-bound network surrounding a single lumen that spreads throughout the cytoplasm. The ER is localized within reach of contact with all other membrane structures and organelles, including the nuclear envelope, plasma membrane, and mitochondria. The ER is particularly important for protein folding and intracellular calcium storage. Through physical and functional interactions, ER and mitochondria contribute to common crucial cellular processes, such as calcium homeostasis and lipid biosynthesis. Numerous lines of evidence suggest that dysfunction of these organelles participates in the pathogenesis of various neurodegenerative conditions, including amyotrophic lateral sclerosis (ALS). A large body of literature has addressed the involvement of ER and mitochondria individually. However, due to the emerging concept that these organelles are physically and functionally intertwined, it is logical to address ER–mitochondria interactions in discussing their roles in disease pathogenesis. This review article briefly describes established concepts supporting the involvement of mitochondria and ER in ALS, while delving deeper into emerging evidence for abnormal ER–mitochondria crosstalk in the context of ALS and discussing new perspectives in ER–mitochondria involvement in the pathogenesis of this disease.

2. Physiological mitochondria–ER interactions

Physical contacts between ER and mitochondria occur at specific sites called mitochondria associated membranes (MAMs). MAMs are specialized ER membranes tethered to mitochondria through a host of protein interactions. Many proteins have been identified in the MAMs (van Vliet et al., 2014). They can be broadly categorized into calcium signaling proteins, such as inositol 1,4,5-triphosphate (IP_3) receptor (IP_3R) and voltage dependent anion channel (VDAC), lipid metabolism, such as phosphatidylethanolamine N-methyltransferase 2 (PEMT2) and fatty acid-CoA ligase 4 (FACL4), autophagy related proteins, such as ATG15 and ATG4, and tethering proteins, such as mitofusin 2 (Mfn2).

Two fundamental mitochondria–ER functional interactions occurring at the MAMs are phospholipid biosynthesis and intracellular calcium handling. Enzymes involved in phospholipid biosynthesis are concentrated in MAMs, where they metabolize phospholipid intermediates both on the mitochondrial and the ER membranes (Vance, 2014). Phospholipid intermediates are shuttled back and forth between the two organelles during the biosynthetic process. For example, phosphatidylserine (PS) made in the ER is transferred to mitochondria to be converted to phosphatidylethanolamine (PE), and PE goes back to the ER to be incorporated into biological membranes.

MAMs are also involved in ER–mitochondria interactions through calcium transfer. The ER is a reservoir for intracellular calcium, able to store up to hundreds of micromolar calcium. Particularly in non-excitable cells, calcium signaling pathways are activated by hormones that act through G protein-coupled receptors and production of inositol 3-phosphate (IP_3), A puff of ER calcium released through IP_3R activates calcium-induced calcium release (ICICR) by ryanodine receptors (RyRs) to increase cytosolic calcium and trigger signals regulating a multiplicity of calcium-dependent systems. ICICR through RyRs is particularly important in muscle cells, where it activates myofibers contraction, but it has been proposed that it is also involved in neuronal plasticity (Barbara, 2002), suggesting a role for this receptor in intracellular signaling in neurons. Mitochondria actively take up calcium through the mitochondrial calcium uniporter (MCU). MCU activity is membrane potential dependent, and requires low micromolar calcium to initiate uptake (Baughman et al., 2011; De Stefani et al., 2011). Close apposition of ER and mitochondrial membranes at MAMs, where ER calcium is released through IP_3Rs and RyRs, allows for "hot spots" of calcium transfer from ER to mitochondria, because local calcium concentration is sufficient to trigger full MCU activity (Rizzuto et al., 1993, 2004). Calcium entry into mitochondria boosts oxidative phosphorylation, as the dehydrogenases of the Krebs cycle are stimulated by calcium (Cardenas et al., 2010; McCormack and Denton, 1980). On the other hand, excessive mitochondrial calcium accumulation can cause the opening of the mitochondrial permeability transition pore (MPTP), which has been associated with activation of cell death pathways (Rasola and Bernardi, 2011). It was demonstrated experimentally that altering the physical distance between the opposing membranes affect calcium flow from ER to mitochondria and cell viability (Csordas et al., 2006).

In addition to the interactions mentioned above, it was recently proposed that ER plays a critical role in the regulation of mitochondrial dynamics, especially organellar fission. ER-associated mitochondrial division (ERMD) is a process whereby the ER tubules wrap around mitochondria at the sites where division occurs (Friedman and Nunnari, 2014). This process is highly conserved throughout evolution and in yeast it depends on proteins of the ER (ER)–mitochondria encounter structure (ERMES) complex (Kornmann and Walter, 2010). This complex also regulates mtDNA nucleoid maintenance. Orthologs of ERMES components have not yet been identified in mammalian cells, but it is likely that MAM proteins serve analogous purposes. Furthermore, MAMs are involved in the process of mitophagy, as ER–mitochondria contacts are sites of phagophore membrane formation (Bockler and Westermann, 2014a,2014b).

3. Mitochondria–ER interactions in ALS

ALS is a debilitating disease with aggressively progressive muscle paralysis leading to death within few years of diagnosis. Paralysis is caused by a prominent degeneration of upper and lower motor neurons that communicate with muscle cells. There is an urgent need for effective therapies, because currently there are essentially no treatments available for ALS patients besides Riluzole, which prolongs life for a few months, at best. Familial ALS (fALS) patients with known genetic mutations are relatively rare, and over 90% of cases occur sporadically. Mutations in the gene encoding for the antioxidant superoxide dismutase 1 (SOD1) were discovered over 20 years ago in fALS patients (Rosen et al., 1993). Studies of SOD1 mutants have provided insight into the pathogenic mechanisms of ALS, but limited to a subset of approximately 10% of the familial cases. However, in the past 5 years, with the advancement of powerful sequencing tools, there has been a tremendous increase in the identification of genetic mutations responsible for fALS. Many mutations across more than 20 genes have been conclusively or putatively associated with ALS (Marangi and Traynor, 2015). Abnormalities found in genes such as TAR-DNA binding protein 43 (TDP43), fused in sarcoma (FUS), ubiquilin 2 (Ubqln2), vesicle associated membrane protein associated protein B (VAPB), and valosin containing protein (VCP), point to RNA metabolism and protein degradation as potential pathogenic pathways in ALS. However, several other genes, involved in completely different cellular pathways, point to a complex heterogeneity of fALS genetics. Furthermore, the same mutations can often cause different clinical phenotypes, even within the same family. Such clinical phenotypes can range from frontotemporal dementia to ALS or a combination of both, as in the case of the hexanucleotide expansion in the first intron of C9Orf72, a gene with still unknown function, which causes the most common form of fALS (DeJesus-Hernandez et al., 2011; Renton et al., 2011). Symptoms in these syndromic forms of fALS can also include myopathy, such as in the case of mutations in VAPB (Nishimura et al., 2004), VCP (Johnson et al., 2010), and the recently identified mitochondrial protein CHCHD10 (Ajroud-Driss et al., 2015; Bannwarth et al., 2014; Johnson et al., 2014a). Nevertheless, despite the apparent clinical variability in terms of associations of symptoms, widely different genetic causes of fALS appear to ultimately converge into common pathogenic pathways that result in motor neuron degeneration.

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