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From dysfunctional endoplasmic reticulum-mitochondria coupling to neurodegeneration

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ABSTRACT

Over the last years, contact sites between the endoplasmic reticulum (ER) and mitochondria have attracted great attention in the study of cell homeostasis and dysfunction, especially in the context of neurodegenerative disorders. This is largely due to the critical involvement of this subcellular compartment in a plethora of vital cellular functions: Ca^{2+} homeostasis, mitochondrial dynamics, transport, bioenergetics and turnover, ER stress, apoptotic signaling and inflammation. An increasing number of disease-associated proteins have been reported to physically associate with the ER-mitochondria interface, and cause structural and/or functional perturbations of this compartment. In the present review, we summarize current knowledge about the architecture and functions of the ER-mitochondria contact sites, and the consequences of their alteration in different neurodegenerative disorders. Special emphasis is placed on the caveats and difficulties in defining the nature and origin of the highlighted defects in ER-mitochondria communication, and their exact contribution to the neurodegenerative process.

1. Introduction

Neurodegeneration is a pathological condition due to the progressive and irreversible dysfunction and loss of neurons and synapses at selected areas of the nervous system. Depending on which region is affected, the clinical presentation and course of the pathology differs, explaining the vast spectrum of known neurodegenerative disorders: Alzheimer's disease (AD), Parkinson's disease (PD), fronto-temporal dementia (FTD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), hereditary spastic paraplegia (HSP), Charcot Marie Tooth (CMT). Common pathogenic mechanisms have been described for these diseases, including abnormal proteostasis, often associated with the formation of intracellular and/or extracellular protein inclusions, ER and oxidative stress, mitochondrial dysfunction, and neuroinflammation (Jellinger, 2010).

In the present review, we discuss the role of the ER-mitochondria interface in the maintenance of cellular homeostasis and summarize recent literature reporting defects in ER-mitochondria communication in different neurodegenerative disorders. We emphasize current limitations in studying this subcellular compartment and its regulators, and in defining its exact contribution to the process of neurodegeneration.

2. Multifaceted regulation of cellular physiology by the ER-mitochondria interface

2.1. Key moments in the study of ER-mitochondria contact sites

Sites of close apposition between the ER and mitochondria were initially observed on tissue electron micrographs in the late 50's (Copeland and Dalton, 1959). However, it is only in the 90's that we obtained insight into the biological significance of these contact sites. First, subcellular fractionation led to the isolation of a mitochondria-associated membrane fraction, referred to in subsequent studies as the MAM, containing the enzymatic activities involved in the biosynthesis of serine-containing phospholipids and lipid transfer between ER and mitochondria (Vance, 1990). Phosphatidylserine (PS) is produced at the ER by the PS synthase, and then shuttled into the inner mitochondrial (IM) membrane

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where it is converted by PS decarboxylase into phosphatidylethanolamine (PE). PE is then retranslocated to the ER and methylated into phosphatidylcholine (PC), the most abundant membrane lipid, by *N*-methyltransferase-2 (reviewed in (Vance, 2014), Fig. 1). In a similar manner, biosynthesis of the mitochondria-specific lipid cardiolipin (CL) and metabolism of cholesterol, the major component of lipid rafts, rely on enzymatic activities of both the ER and the mitochondrion, as well as shuttling of substrates between the two membranes.

Ca^{2+} imaging approaches revealed a second fundamental function of ER-mitochondria contacts: microdomains with high Ca^{2+} concentration form in the vicinity of mitochondria upon stimulation of ER Ca^{2+} release by 1,3,4 inositol triphosphate receptors (IP_3Rs), and play a central role in Ca^{2+} uptake into the mitochondrial matrix (Rizzuto et al., 1993, 1998). Further studies confirmed that Ca^{2+}-releasing channels of the ER (IP_3Rs, ryanodine receptors-RyRs) are enriched at contact sites (Garcia-Perez et al., 2008; Szabadkai et al., 2006). Upon stimulation, they transiently increase cytosolic Ca^{2+} concentration on the mitochondrial surface at levels compatible with efficient diffusion across voltage-dependent anion channels (VDACs) at the outer mitochondrial (OM) membrane (Rapizzi et al., 2002), and subsequent uptake by the low-affinity mitochondrial calcium uniporter (MCU), juxtaposed at the IM membrane ((Baughman et al., 2011; De Stefani et al., 2011), Fig. 1). The chaperone glucose-regulated protein 75 (GRP75) bridges IP_3R and VDAC at ER-mitochondria contact sites; this tripartite complex ensures the coupling of Ca^{2+} release from the ER with Ca^{2+} import into the mitochondrial matrix (Szabadkai et al., 2006), and most likely keeps ER and mitochondria at the appropriate distance for efficient Ca^{2+} diffusion (Csordas et al., 2006, 2010; Giacomello and Pellegrini, 2016).

Molecular chaperones at the ER, as well as the mitochondrial ATP synthase and the dehydrogenases that provide reducing equivalents to the respiratory chain, depend on Ca^{2+} concentration for efficient enzymatic activity. Hence, ER-to-mitochondria Ca^{2+} transfers are key determinants of ER folding capacity and mitochondrial metabolism (Cardenas et al., 2010; Simmen et al., 2010). Enhancement of these fluxes allows coping with an increased energy demand (Betz et al., 2013; Bravo et al., 2011), but an excess of these transfers initiates programmed cell death, as it will be discussed in the next section. The importance of mitochondrial Ca^{2+} uptake in cellular homeostasis is highlighted by the severity of the phenotypes associated with MCU dysfunction. In humans, mutations in the gene coding for the Ca^{2+}-sensitive MCU regulator MICU1 (mitochondrial calcium uptake 1) cause a multisystem disorder associated with myopathy and neurological symptoms

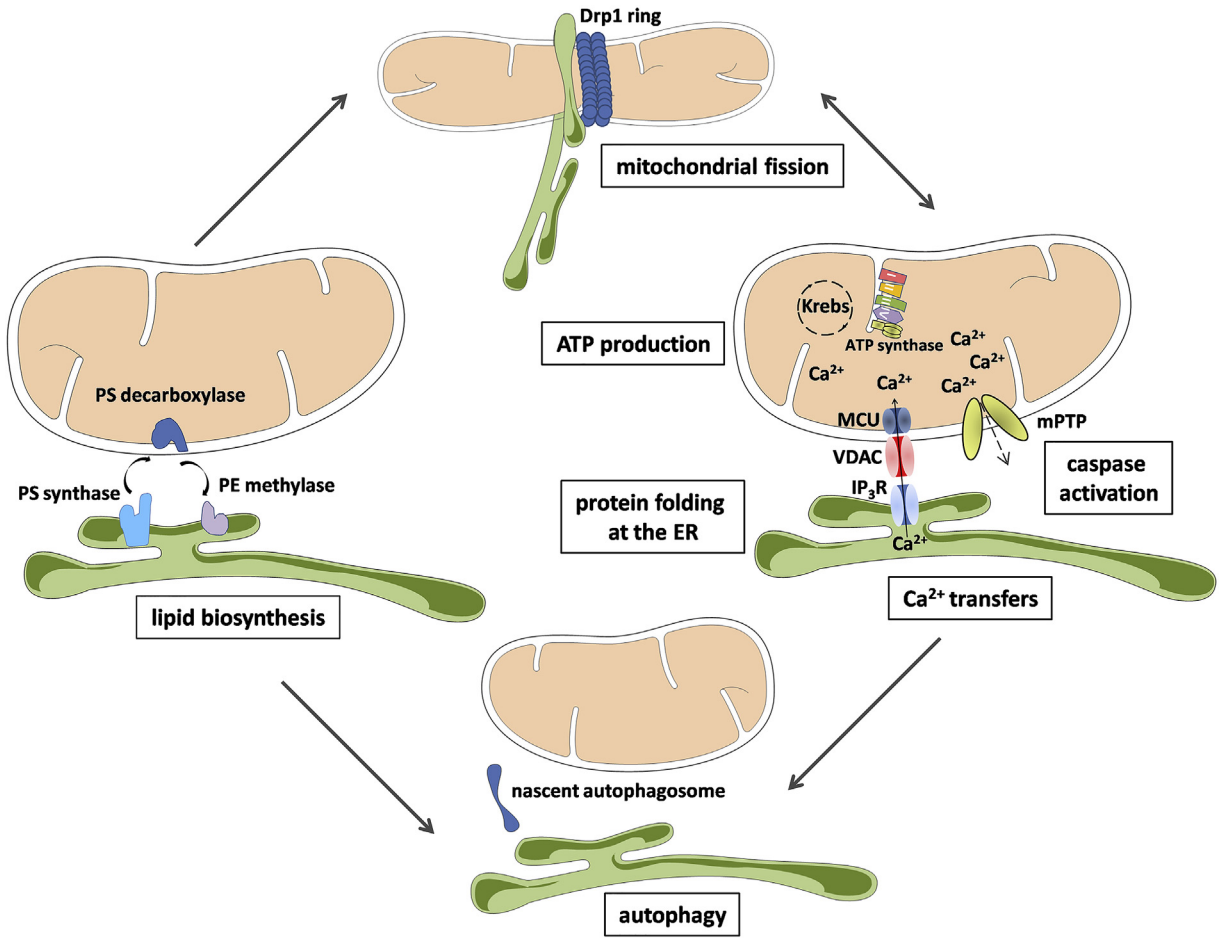

Fig. 1. Cross-talk between cellular metabolism, membrane dynamics and signaling at ER-mitochondria contacts. Contact sites between ER and mitochondria are crucial for phospholipid biosynthesis, mediated by ER (PS synthase and PE *N*-methyltransferase-2) and IM membrane-localized (PS decarboxylase) enzymes. They are also required for mitochondrial Ca^{2+} uptake, as they facilitate the coupling of IP_3R-mediated Ca^{2+} release from the ER to Ca^{2+} import into the matrix by VDACs and the MCU. Ca^{2+} in the mitochondrial matrix regulates the activity of several enzymes of the Krebs cycle and the ATP synthase, thus promoting ATP production. Mitochondrial Ca^{2+} overload, on the other hand, triggers mPTP opening, leading to caspase activation and apoptosis. ER-mitochondria contact sites are also involved in the constriction of mitochondria and Drp1 recruitment prior to mitochondrial fission, as well as in autophagosome formation. Cross-regulation between the different functions of the ER-mitochondria interface (illustrated by the arrows) is crucial to cellular homeostasis and adaptation to stress.