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Review

ER-to-mitochondria miscommunication and metabolic diseases

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ABSTRACT

Eukaryotic cells contain a variety of subcellular organelles, each of which performs unique tasks. Thus follows that in order to coordinate these different intracellular functions, a highly dynamic system of communication must exist between the various compartments. Direct endoplasmic reticulum (ER)–mitochondria communication is facilitated by the physical interaction of their membranes in dedicated structural domains known as mitochondria-associated membranes (MAMs), which facilitate calcium (Ca^{2+}) and lipid transfer between organelles and also act as platforms for signaling. Numerous studies have demonstrated the importance of MAM in ensuring correct function of both organelles, and recently MAMs have been implicated in the genesis of various human diseases. Here, we review the salient structural features of interorganellar communication via MAM and discuss the most common experimental techniques employed to assess functionality of these domains. Finally, we will highlight the contribution of MAM to a variety of cellular functions and consider the potential role of MAM in the genesis of metabolic diseases. In doing so, the importance for cell functions of maintaining appropriate communication between ER and mitochondria will be emphasized.

1. Introduction

Eukaryotic cells are characterized by a high degree of compartmentalization of biological and biochemical functions within specialized membrane-bound organelles [1–3]. These cellular compartments are often further partitioned into subdomains, thus providing a mechanism to segregate specific processes into different regions within the same organelle. Although this division is essential for separating potentially incompatible activities, regulated integration of cellular physiology depends upon effective cross-talk and functional coordination between multiple organelles [4–6]. Such inter-organelle communication is frequently achieved by direct physical contact between organellar membranes and the necessary interactions are often highly regulated as well as dynamic in time and space [4–7]. One of the best characterized such inter-organellar communication sites is the connection between the endoplasmic reticulum (ER) and mitochondria. The first evidence for the existence of sites of physical interaction between these membranes came from electron microscopy studies over 50 years ago [8]. Rather interestingly, ER–mitochondria contacts were only isolated some 30 years later, by means of subcellular fractionation using Percoll density gradients [9,10]. This early evidence for the existence of physical ER–mitochondria interactions led to the genesis of the term MAMs, standing for Mitochondria-associated ER membranes [11]. Ever since their discovery, the importance of these contact sites in organelle cross-talk has been confirmed using numerous approaches (Fig. 1) [4–6,12].

ER–mitochondria contact sites permit reciprocal regulation of function in both organelles, thereby impacting various cellular activities, including energy metabolism, Ca^{2+} handling [13], lipid homeostasis [9] as well as regulation of cell death and survival [4–7]. In this review, we highlight the role of a number of proteins important in regulating the ER–mitochondria interface, as well as key experimental approaches used to study these inter-organellar contact sites and their physiological function. We will also discuss how alterations in ER-to-mitochondria communication contribute to the pathogenesis of major metabolic diseases.

2. ER–mitochondria coupling

ER and mitochondria communicate through close physical juxtapositioning of the two membranes, with distances between the two

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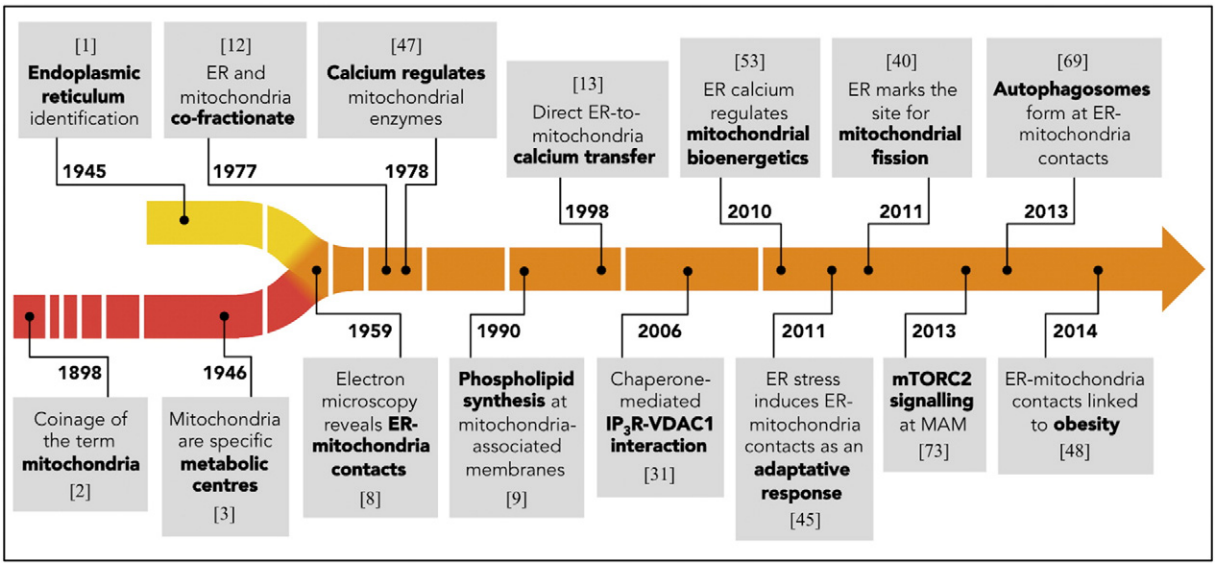

Fig. 1. ER–mitochondria contacts research timeline. Since the identification of ER–mitochondria contacts using electron microscopy, many aspects of their functional roles have been uncovered. Alterations in lipid metabolism, Ca^{2+} homeostasis and stress responses, as well as the development of metabolic diseases represent the perhaps best-characterized consequences attributed to cross-talk between both organelles.

ranging from 10 to 25 nm. Despite the close proximity of the two organelles, their membranes do not fuse, thus preserving their identity and functionality [4,5,14]. Domain-specific tethering structures help to establish and maintain the MAM, which can be either stable or transient [15]. At the molecular level, these tethering structures are composed of proteins and lipids, residing in the outer mitochondrial membrane

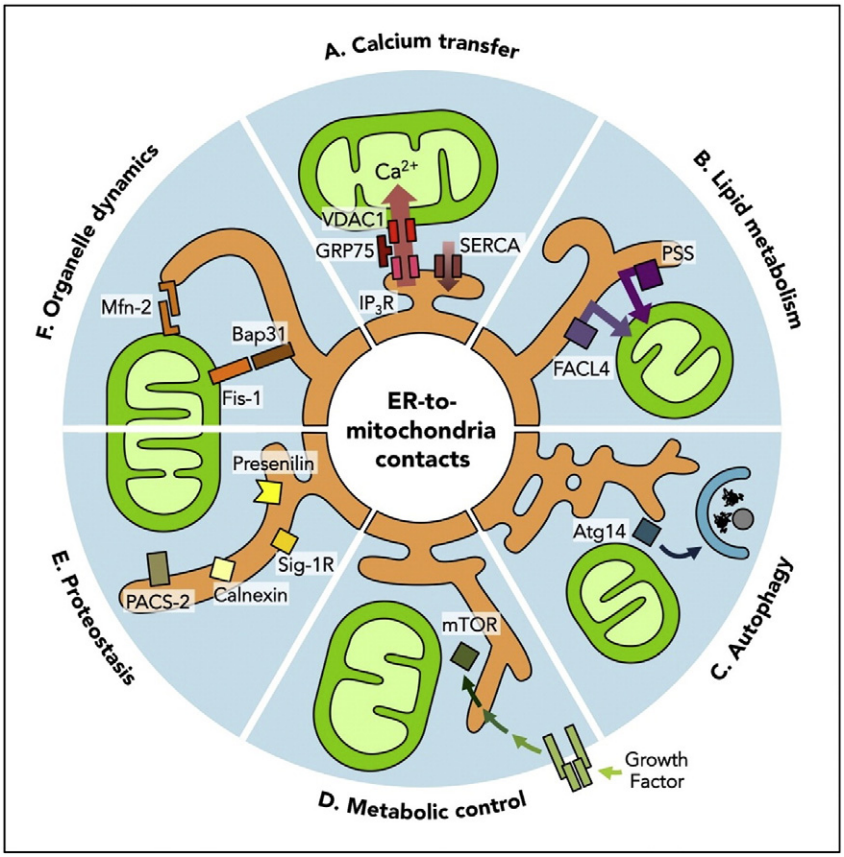

Fig. 2. ER–mitochondria contacts and cell physiology. A, Direct Ca^{2+} transfer occurs between ER and mitochondria via IP_3R and VDAC channels coupled to the cytoplasmic chaperone GRP75. The SERCA pump is also present at the ER–mitochondria interface. B, Crucial enzymes for lipid metabolism reside at the ER–mitochondria contacts, among them phosphatidylserine synthase (PSS) and fatty acid-CoA ligase 4 (FACL4). C, ER–mitochondria contacts have been shown to represent nucleation spots for autophagosomes via ATG14 enrichment. D, Metabolic regulator complex mTORC2 is present at MAM, and increases there in response to growth factor stimulation. E, ER–mitochondria contacts contain proteins involved in protein homeostasis, such as the proteases presenilins, quality control lectin calnexin and sorting factor PACS-2. F, Proteins that regulate organelle dynamics are present in MAM, such as the mitochondrial constriction GTPase Drp-1, and the mitochondrial fusion GTPase Mfn-2.