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Organelle remodeling at membrane contact sites

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ABSTRACT

Cellular organelles must execute sophisticated biological processes to persist, and often communicate with one another to exchange metabolites and information. Recent studies suggest inter-organelle membrane contact sites (MCSs) are hubs for this cellular cross-talk. MCSs also govern membrane remodeling, thus controlling aspects of organelle shape, identity, and function. Here, we summarize three emerging phenomena that MCSs appear to govern: 1) organelle identity via the non-vesicular exchange of lipids, 2) mitochondrial shape and division, and 3) endosomal migration in response to sterol trafficking. We also discuss the role for ER-endolysosomal contact sites in cholesterol metabolism, and the potential biomedical importance this holds. Indeed, the emerging field inter-organellar cross-talk promises substantial advances in the fields of lipid metabolism and cell signaling.

1. Introduction

Eukaryotic cells harbor numerous membrane bound organelles, and must cope with significant spatial constraints to properly contain and compartmentalize organelles efficiently. As a result, organelles are often in very close proximity. Even in early electron micrographs from Keith Porter and George Palade, the ability of organelles like the Endoplasmic Reticulum (ER) to physically touch mitochondria or the plasma membrane (PM) was noted, but these phenomena were generally ignored (Porter and Palade, 1957; Porter and Machado, 1960). More recently, elegant microscopy, genetic, and biochemical studies have revealed numerous proteins and protein complexes specifically tasked with tethering organelles together. Moreover, these proteins function in numerous cellular pathways, including lipid synthesis and trafficking, Ca^{2+} signaling, and organelle movement and identity. These functions are also intimately connected to organelle shape and function.

The purpose of this short review is to highlight recent findings that illustrate the importance of membrane contact sites on organelle reshaping, and how inter-organelle communication contributes to organelle structure and function. Particular focus will be placed on contacts formed between the ER and mitochondria, as well as with the endomembrane system. In addition, we will examine the state of the membrane contact site field, and discuss exciting future directions that should be investigated. As Membrane Contact Sites (MCSs) are emerging as important sites of inter-organelle nutrient exchange, we also postulate upon the function of organelle contacts in metabolic decision-making.

2. ER-PM contact sites in organelle identity and membrane remodeling

The lipid composition of an organelle contributes significantly to its identity and function. At the plasma membrane (PM) of both yeast and mammals, the phosphoinositide phospholipid PtdIns4P is generated as a precursor to PtdIns(4,5)P2 (also known simply as PIP2). PIP2 serves as a biomarker of PM identity, and coordinates numerous cellular responses at the cell surface, including clathrin-mediated endocytosis and actin turnover (Jost et al., 1998; Miki et al., 1996). PtdIns4P itself accumulates at the Golgi as well as the cell surface, and thus PtdIns4P levels at the PM must be carefully regulated to ensure proper organelle distinction.

How are PtdIns4P levels regulated? A series of recent studies using both yeast and mammalian systems suggest ER-PM contact sites serve as hubs for the regulation of PM-localized PtdIns4P, and thus “hotspots” for membrane remodeling at the PM. Initial studies identified numerous proteins that physically tether the ER to the PM (Manford et al., 2012; Toulmay and Prinz, 2012). To date, at least three ER-resident protein families—the Tricalbins (E-Syts in mammals), Scs2/22 (VAPs in mammals) and Ist2 (Tmem16 in mammals)—contribute to ER-PM tethering. All three were found to co-purify with Sac1, the ER-resident PtdIns4P phosphatase, indicating that PtdIns4P turnover is coupled to ER-PM

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contacts. Consistent with this, deletion of these tethers causes PM-localized PtdIns4P levels to increase substantially (Manford et al., 2012).

Although the reason for this PtdIns4P increase requires additional study, it may be explained by recent models proposed by De Camilli, Drin, and colleagues (Chung et al., 2015; Moser von Filseck et al., 2014, 2015). Using both yeast and mammalian model systems, they demonstrate that members of the Oxysterol-binding Protein (OSBP)-related family (ORP) are able to efficiently exchange PtdIns4P between the PM and ER at contact sites. In mammals, this required ORP5 and ORP8. This mechanism requires a dual-switch model, where PtsIns4P is initially extracted from the PM by the ORP protein, shuttled across the cytoplasm, and deposited in the ER membrane. Here, the phosphatase Sac1 can efficiently hydrolyze PtdIns4P to phosphoinositol (PtdIns). In exchange for releasing PtdIns4P, the ORP protein retrieves phosphatidylserine (PtdSer), which is normally synthesized at the ER, but accumulates at the PM. PtdSer is subsequently shuttled to the PM via the ORP, thus completing the 1:1 lipid exchange cycle (Fig. 1). In this way, both lipids are efficiently exchanged between organelles in a timely manner, allowing for localized membrane remodeling. A similar mechanism using OSBP has been proposed for the cycling of sterols with PtdIns4P at the ER-Golgi interface (Mesmin et al., 2013).

Although this lipid exchange cycle elegantly explains the bidirectional shuttling of lipids, several questions remain. How are sites of lipid exchange chosen and demarcated? How is this exchange coupled to the synthesis of new PtdIns4P and PtdSer? Earlier studies of phospholipid synthesis indicate that synthesis enzymes can be coupled to organelle-organelle junctions, suggesting regulatory pathways exist that couple synthesis with shuttling (Stone and Vance, 2000).

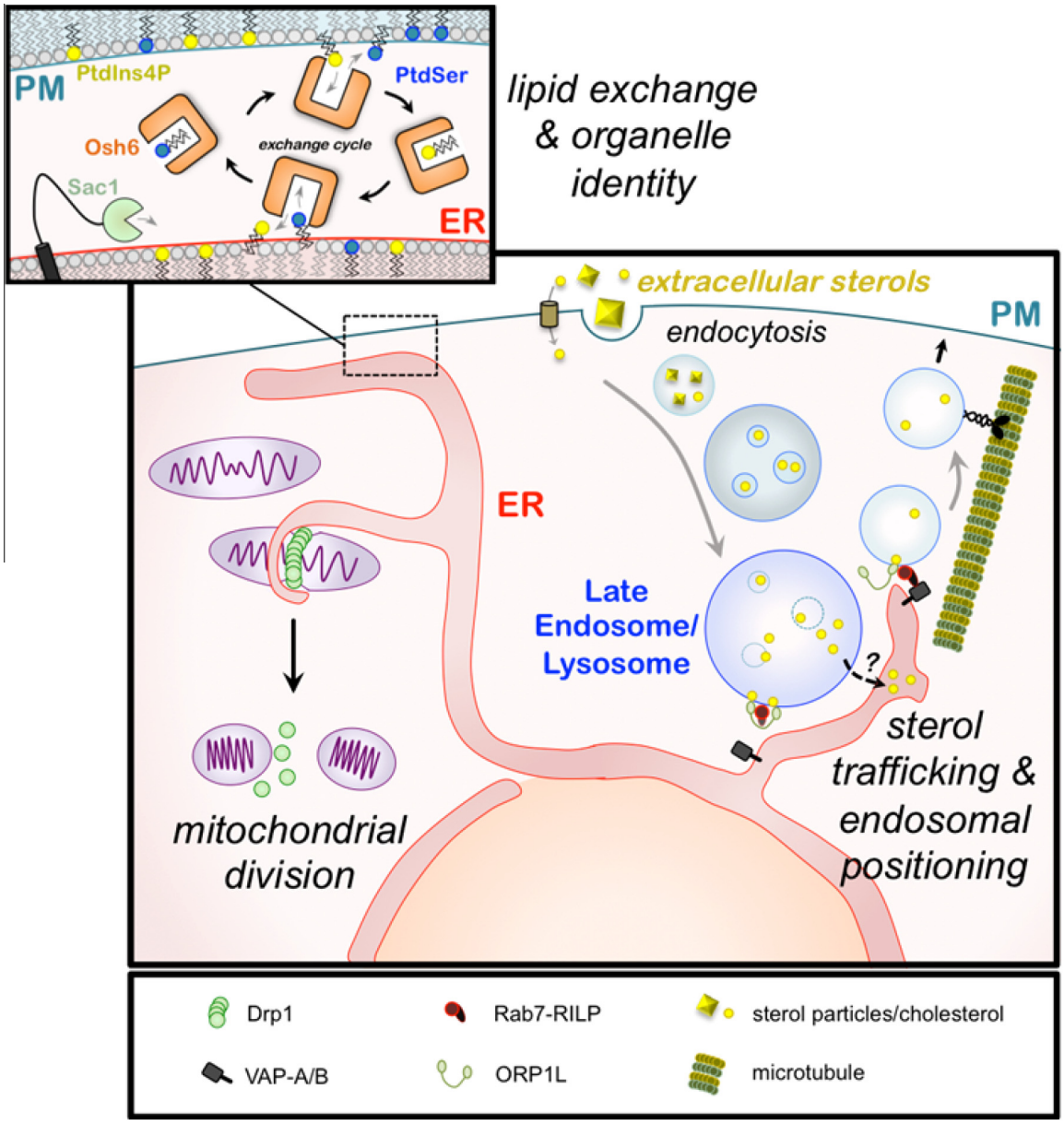

Fig. 1. An example of three biological processes mediated by inter-organelle contact sites: 1) organelle-organelle lipid exchange (and thus organelle identity), 2) mitochondrial division, and 3) sterol trafficking and its role in late endosomal positioning within cells.

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