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Mitochondrial anchors: Positioning mitochondria and more

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ABSTRACT

The shape and position of mitochondria are intimately connected to both mitochondrial and cellular function. Mitochondrial anchors play a central role in mitochondrial positioning by exerting spatial, temporal, and contextual control over the cellular position of the organelle. Investigations into the molecular mechanisms of mitochondrial anchoring are still in the early stages, and we are beginning to appreciate the number and variety of anchors that exist. From the insight gained thus far, it is clear that mitochondrial anchoring has functional and physiological consequences that extend beyond mitochondrial positioning to other critical cellular processes.

1. Introduction

While it is well appreciated that mitochondrial division, fusion, and motility all contribute to the overall distribution of mitochondria within a cell, the critical contributions of actively anchoring the organelle to specific cellular sites and structures are becoming increasingly evident. Mitochondria make many contacts within the cell. These contacts, which are mediated by tether proteins, can be very dynamic and transient or stable and maintained over long periods of time. Here we will focus on our current understanding of the molecular bases, mechanisms, and physiological functions of tethers that function to stably anchor and position mitochondria.

2. The molecular mechanisms of mitochondrial anchoring

2.1. General anchoring mechanisms

While there is evidence of mitochondrial anchoring in various cell types, the molecular basis of this activity is poorly understood. From studies in which the identity of the anchoring protein(s) has been elucidated, it is clear that there is not one specific mechanism used by cells to anchor mitochondria. Tethering proteins may function to anchor mitochondria to other cellular membranes, such as the endoplasmic reticulum and plasma membrane, to cytoskeletal structures, such as microtubules and the actin network, or to motor proteins (Fig. 1). The molecular basis and mechanism for tether protein-mitochondria interactions also differ. Some tethers make direct contact with the mitochondrial membrane, while others interact with proteins anchored in the mitochondrial membrane or themselves are membrane anchored. While the list of anchoring proteins continues to grow and their mechanisms of anchoring are elucidated, the challenge will be to understand how the tethering activity of these proteins is regulated to position mitochondria in the right place at the right time.

2.2. Insight into the molecular mechanism of mitochondrial anchoring from studies in yeast

Similar to the impact yeast has had on the mitochondrial dynamics field, studies in yeast have and will continue to provide valuable insight into fundamental mechanisms used by cells to construct and regulate anchoring complexes that position mitochondria. Three tethers involved in mitochondrial positioning have been identified in yeast: the mitochondria-ER-cortex anchor (MECA), Mmr1, and Mfb1.

MECA is an extended multi-subunit structure composed of at least two proteins, Num1 and Mdm36, and three organelles, mitochondria, the endoplasmic reticulum (ER), and the plasma membrane [1–3]. Num1, the core protein component of MECA, assembles into clusters of limited mobility and dynamics at the cell cortex in mother cells and large buds and functions to stably tether mitochondria to the plasma membrane at these sites [3–7]. MECA interacts directly with the mitochondrial and plasma membranes via two distinct lipid binding domains within Num1 [8]. An unpredicted membrane binding region within the N-terminal

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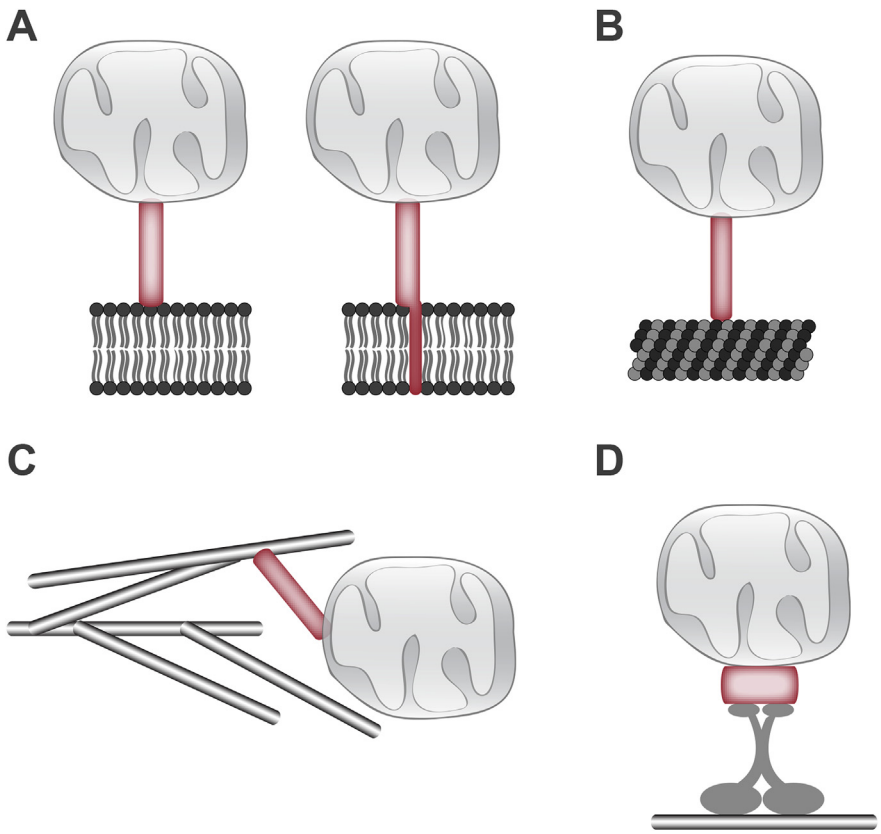

Fig. 1. General mechanisms for stable anchoring of mitochondria. Tethering proteins function to anchor mitochondria to a variety of cellular components using a variety of mechanisms. Mitochondria can be anchored to other cellular membranes via proteins with integral or peripheral membrane binding domains (A). Tethering proteins can also stably anchor mitochondria to cytoskeletal structures, such as microtubules (B) or actin (C), or to motor proteins (D), which drive organelle trafficking.

coiled-coil region of Num1 interacts directly with the mitochondrial outer membrane exhibiting a preference for the mitochondrial specific lipid cardiolipin [3,6,8], and a C-terminal PH domain interacts with $PI_{4,5}P_2$ in the plasma membrane [9,10]. The preferential binding of Num1 to cardiolipin and $PI_{4,5}P_2$, organelle-specific lipids that play key structural, regulatory, and signaling roles [11,12], may provide a mechanism to integrate the tethering capacity of MECA with mitochondrial and cellular functions. In contrast to integral membrane domains, the peripheral membrane interactions mediated by Num1's lipid binding domains allow for rapid membrane association and dissociation. In addition, as Num1 assembly likely enhances interactions with its membrane binding partners and, consequently, the ability of Num1 to robustly tether mitochondria, assembly may be exploited as a mechanism to regulate tether function.

While MECA functions to tether mitochondria to the plasma membrane at sites relatively evenly distributed along the cell cortex of mothers and large buds, recent work identified the protein Mfb1 in functioning to tether mitochondria to the distal end of the mother cell, also referred to as the mother tip [13]. Unlike MECA-mediated tethering, which occurs in proximity to cortical ER [3], the ER does not appear to be required for Mfb1-mediated anchoring. The mechanism by which Mfb1, a non-canonical F-box protein, tethers mitochondria is unknown, but the localization of the protein to mitochondria at the mother cell tip suggests a direct role in anchoring is possible [13–15].

In contrast to MECA and Mfb1, which function primarily in the mother-specific retention of mitochondria [1,3,7,13], the function of Mmr1 in mitochondrial positioning is daughter specific. Mmr1 serves to tether mitochondria to Myo2 for myosin-driven actin-based transport of mitochondria into the bud [16–18]. Mmr1 is also proposed to function in the retention of mitochondria in buds by tethering mitochondria to cortical ER sheets at the bud tip [19]. If and how Mmr1 switches between its roles in mitochondrial transport and anchoring is unclear. Mmr1 is a soluble protein that interacts with the mitochondrial outer membrane in a peripheral manner [16]. While both the transport and tethering roles of Mmr1 require an interaction with mitochondria, the molecular basis and mechanism of the interaction are unknown.

MECA, Mfb1, and Mmr1 work at spatially distinct locations at specific times to ensure the proper distribution of mitochondria between the mother and daughter over the course of the yeast cell cycle. Mmr1 functions early in the cell cycle to transport mitochondria to and tether mitochondria in buds prior to MECA assembly in and Mfb1 localization to buds late in the cell cycle. In mothers, MECA and Mfb1 function to retain mitochondria throughout the cell cycle. How the localization and activity of these tethers are regulated in space and time to coordinately govern the distribution and inheritance of the essential mitochondrial network is an outstanding question.

2.3. Mitochondrial anchoring in neurons

In neurons, roughly one-third of mitochondria are mobile while the remaining two-thirds remain stationary [20]. This distribution is not fixed; the mobility state of one mitochondrion can be rapidly switched, and neuronal activity can alter the fraction of stationary versus mobile mitochondria in specific regions of the cell, such as dendrites, nodes of Ranvier, and synaptic boutons. The coordinate regulation of transport and anchoring mechanisms is critical to

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