

# The mitochondria–plasma membrane contact site

Benedikt Westermann

Mitochondria are dynamic organelles that are highly motile and frequently fuse and divide. It has recently become clear that their complex behavior is governed to a large extent by interactions with other cellular structures. This review will focus on a mitochondria–plasma membrane tethering complex that was recently discovered and molecularly analyzed in budding yeast, the Num1/Mdm36 complex. This complex attaches mitochondria to the cell cortex and ensures that a portion of the organelles is retained in mother cells during cell division. At the same time, it supports mitochondrial division and integrates mitochondrial dynamics into cellular architecture. Recent evidence suggests that similar mechanisms might exist also in mammalian cells.

## Address

Institut für Zellbiologie, Universität Bayreuth, Bayreuth 95440, Germany

Corresponding author: Westermann, Benedikt  
 ([benedikt.westermann@uni-bayreuth.de](mailto:benedikt.westermann@uni-bayreuth.de))

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## Introduction

Mitochondria are semi-autonomous organelles. Even though they possess their own genome encoding a handful of proteins required for oxidative phosphorylation, mitochondrial biogenesis largely depends on extra-mitochondrial processes. Hundreds of nuclear-encoded proteins are translated by cytosolic ribosomes and subsequently imported into the organelle, and most of the membrane lipids are imported from the ER. Furthermore, mitochondrial inheritance requires division of the mitochondrial membranes by dynamin-related proteins assembling from the cytosolic side on the mitochondrial outer membrane, and mitochondrial partitioning often requires cytoskeleton-dependent transport of mitochondria. Thus, growth, division, and inheritance of mitochondria are largely orchestrated from the outside of the organelle. On the other hand, mitochondria contribute to the biogenesis of other organelles, most notably because they are involved in the biosynthesis of several

phospholipids that are exchanged with the organelles of the secretory pathway.

In recent years it became clear that the ER plays a major role in the coordination of mitochondrial biogenesis and inheritance. Contact sites of ER and mitochondria are hubs for the exchange of membrane lipids and determine the sites of assembly of the mitochondrial division machinery [1,2]. However, mitochondria are known to communicate also with other organelles, albeit these interactions are less well understood. For example mitochondria are found in close contact with lipid droplets or peroxisomes in several cell types [1–3], they deliver contents to peroxisomes and lysosomes by mitochondrion-derived vesicles (MDVs) [4], and recently a mitochondrion–vacuole contact site was identified in yeast [5,6]. Rather little is known about contacts of mitochondria with the plasma membrane and their molecular constituents. This review will focus on the recent discovery of a molecular anchor connecting mitochondria to the plasma membrane in yeast and briefly refer to the relevance of mitochondria–plasma membrane contacts in mammalian cells.

## A mitochondria–plasma membrane anchor in yeast

Budding yeast *Saccharomyces cerevisiae* is a valuable model organism to study the mechanisms of asymmetric cell division. At the beginning of each cell cycle cells become polarized, select a site for bud emergence, and most of the cellular transport is directed towards the growing bud. As the bud approaches the size of the mother, a septum is formed that separates the daughter cell from its mother. Before cytokinesis nuclei and organelles are partitioned by active cytoskeleton-dependent transport of organelles to the growing bud concomitant with retention of a portion of the organelles in the mother cell [7,8].

Num1 is a large 313 kDa protein that was first discovered through its role in nuclear migration [9] (proteins discussed in this review are listed in [Table 1](#)). It is bound to the plasma membrane and interacts with dynein and microtubules to control migration of the nucleus from the mother cell to the emerging bud during late anaphase [10]. Num1 assembles into punctate structures in the mother cell at S/G2 phase and mitosis and appears in the bud only late in the cell cycle [11–13]. A screen of the yeast deletion collection revealed an additional role of Num1 in mitochondrial distribution and morphology [14]. Live cell microscopy showed that tips of mitochondrial tubules extending into the mother cell are frequently associated with Num1 punctae [15<sup>•</sup>, 16<sup>••</sup>, 17<sup>•</sup>], and mitochondria of mutants lacking Num1 are abnormally motile

Table 1

## Proteins discussed in this review.

| Protein                                              | Role in mitochondrial dynamics                                                                                                                    | References                                                                                  |
|------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Caf4 (CCR4-associated factor 4)                      | Dnm1 adaptor protein, not crucial for mitochondrial fission                                                                                       | [15 <sup>**</sup> ,30,31]                                                                   |
| Dnm1 (dynamin-related 1)                             | Key factor of mitochondrial fission                                                                                                               | [15 <sup>**</sup> ,17 <sup>*</sup> ]                                                        |
| Fzo1 (fuzzy onions 1)                                | Key factor of mitochondrial outer membrane fusion                                                                                                 | [15 <sup>**</sup> ]                                                                         |
| Mdm36 (mitochondrial distribution and morphology 36) | Component of a cell cortex anchor important for retention of mitochondria in the mother cell                                                      | [14,15 <sup>**</sup> ,16 <sup>**</sup> ,18 <sup>*</sup> ]                                   |
| Mmr1 (mitochondrial Myo2 receptor-related 1)         | Outer membrane protein of bud-localized mitochondria; participates in binding of Myo2 to mitochondria and/or retention of mitochondria in the bud | [16 <sup>**</sup> ,26–29]                                                                   |
| Myo2 (myosin 2)                                      | Myosin motor powering actin-dependent anterograde mitochondrial transport                                                                         | [16 <sup>**</sup> ,23,24,28]                                                                |
| Num1 (nuclear migration 1)                           | Major component of a cell cortex anchor important for retention of mitochondria in the mother cell                                                | [14,15 <sup>**</sup> ,16 <sup>**</sup> ,17 <sup>*</sup> ,18 <sup>*</sup> ,20 <sup>*</sup> ] |

and located away from the cell cortex [18<sup>\*</sup>]. Furthermore, Num1 tethers mitochondrial tips to fixed sites at the cell cortex, while the rest of the organelle moves around in the cell [15<sup>\*\*</sup>,16<sup>\*\*</sup>]. These observations demonstrate that Num1 is part of an anchor that attaches parts of the mitochondrial network to the plasma membrane.

Mdm36 is a soluble protein that is peripherally bound to the mitochondrial surface [18<sup>\*</sup>]. It was found in a complex with Num1, and the localization patterns of Mdm36 and Num1 in foci on the cortical side of mitochondrial tubules are interdependent [15<sup>\*\*</sup>]. Mitochondrial morphology defects in  $\Delta$ *mdm36* mutants and increased mitochondrial motility are indiscernible from  $\Delta$ *num1* mutants [18<sup>\*</sup>]. These data suggest that Num1 and Mdm36 cooperate in mitochondrial morphogenesis and are both components of a mitochondria–plasma membrane tether complex.

Num1 contains an N-terminal coiled-coil (CC) domain, an EF hand-like domain, a region of twelve 64 amino acids repeats, and a C-terminal pleckstrin homology (PH) domain [9] (Figure 1). The PH domain has high affinity to phosphatidylinositol 4,5-bisphosphate and is required for attachment of Num1 to the plasma membrane [19]. Structure–function analyses showed that the CC and PH domains are both crucial for the mitochondrial functions of Num1, while the 64 aa repeat region is dispensable. Num1 constructs lacking the CC domain still localize to the cortex but fail to associate with mitochondria. In contrast, constructs lacking the PH domain do associate with mitochondria, but fail to stably bind to the cell cortex [15<sup>\*\*</sup>,20<sup>\*</sup>]. The CC domain is necessary and sufficient for binding of Mdm36 [15<sup>\*\*</sup>]. It is conceivable that Mdm36 facilitates correct localization and function of Num1 on mitochondria via its interaction with the Num1 CC domain (Figure 1) [15<sup>\*\*</sup>]. Mitochondrial membrane proteins interacting with Num1 or Mdm36 are currently unknown.

Immunoprecipitations from cross-linked whole-cell extracts identified several ER proteins as potential interaction partners of Num1, and fluorescence microscopy

revealed that the cortical ER is in close vicinity of Num1-mediated mitochondria–plasma membrane tethering sites, suggesting that the ER is a critical component of a mitochondria–ER–cortex-anchor, termed MECA [15<sup>\*\*</sup>]. On the other hand, electron tomography revealed direct contacts of the mitochondrial outer membrane with invaginations of the plasma membrane that could be observed without participation of the ER [16<sup>\*\*</sup>]. Strikingly, these invaginations resemble eisosomes, which are specialized sites of plasma membrane organization, and eisosomal proteins could be co-purified with Num1 [15<sup>\*\*</sup>]. However, a role of eisosomes in the formation of mitochondria–plasma membrane tethers could not be demonstrated (unpublished results), and the exact nature of these structures remains elusive.

The role of Num1 in mitochondrial anchoring appears to be independent of its role in nuclear migration, and both functions involve distinct interaction partners. Complex formation of Num1 with Mdm36 is specific for mitochondria [15<sup>\*\*</sup>,18<sup>\*</sup>], whereas Num1 interactions with dynein are specific for nuclear migration [10,12,20<sup>\*</sup>]. Recently, Num1 was found to also interact with the ER protein Scs2 [13]. Scs2 and septins form an ER diffusion barrier at the mother bud neck that is important to polarize the ER and establish mother and bud domains. It was proposed that Num1 interactions with Scs2 at plasma membrane-associated ER confine the distribution of Num1 to the mother cell until M phase [13]. Thus, it appears that Num1 actively controls the distribution of mitochondria (as outlined below) and nuclei, while its own distribution is controlled by the ER.

### Mitochondrial partitioning

During mitotic growth mitochondria are transported to the bud where they are attached to retention sites at the bud tip. At the same time, a portion of the mitochondrial network must be retained in the mother cell. Mitochondria are partitioned in dividing yeast cells by balanced, bi-directional actin-dependent movement [21,22]. Anterograde transport is powered by the myosin motor protein,

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