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Current Opinion in Cell Biology

How peroxisomes partition between cells. A story of yeast, mammals and filamentous fungi

Barbara Knoblach and Richard A Rachubinski

Eukaryotic cells are subcompartmentalized into discrete, membrane-enclosed organelles. These organelles must be preserved in cells over many generations to maintain the selective advantages afforded by compartmentalization. Cells use complex molecular mechanisms of organelle inheritance to achieve high accuracy in the sharing of organelles between daughter cells. Here we focus on how a multi-copy organelle, the peroxisome, is partitioned in yeast, mammalian cells, and filamentous fungi, which differ in their mode of cell division. Cells achieve equidistribution of their peroxisomes through organelle transport and retention processes that act coordinately, although the strategies employed vary considerably by organism. Nevertheless, we propose that mechanisms common across species apply to the partitioning of all membrane-enclosed organelles.

Address
Department of Cell Biology, University of Alberta, Edmonton, Alberta T6G 2H7, Canada

Corresponding author: Rachubinski, Richard A (rick.rachubinski@ualberta.ca)

Current Opinion in Cell Biology 2016, **41**:73–80

This review comes from a themed issue on **Cell Organelles**

Edited by **Pedro Carvalho** and **Davis Ng**

For a complete overview see the Issue and the Editorial

Available online 26th April 2016

http://dx.doi.org/10.1016/j.ceb.2016.04.004

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Introduction

The cell is the self-propagating unit of all living organisms. Eukaryotic cells are equipped with a set of membrane-enclosed compartments called organelles that are each specialized for distinct biochemical functions. To maintain the benefits of compartmentalization, cells must transmit their organelles to future generations through a process termed organelle inheritance. While certain aspects of cell division, such as DNA replication and segregation, have long been recognized to occur with a high level of precision, organelle inheritance has traditionally been thought of as being random, with each daughter cell just needing to receive some 'seed' material to expand the organelle compartment [1]. However, numerous factors involved in the inheritance of different organelles have been identified in recent years [2], making it increasingly apparent that cells stringently regulate the inheritance of their organelles. Here we discuss strategies for organelle inheritance used by cells that divide asymmetrically, by median fission, and by hyphal growth (Figure 1). We focus on a multi-copy organelle, the peroxisome, but discuss other organelles to illustrate regulatory mechanisms specific for their inheritance.

Why study peroxisome inheritance?

Peroxisomes are ubiquitous, single-membrane-delimited organelles involved in a variety of cellular processes, including notably the β-oxidation of fatty acids and the metabolism of reactive oxygen species. The existence of congenital peroxisome biogenesis disorders [3] has prompted intensive research into the molecular biology of the organelle. As yeast peroxisome assembly mutants are conditionally viable, the core biogenic machinery of peroxisomes has been identified in yeast and shown to be largely conserved across species [4].

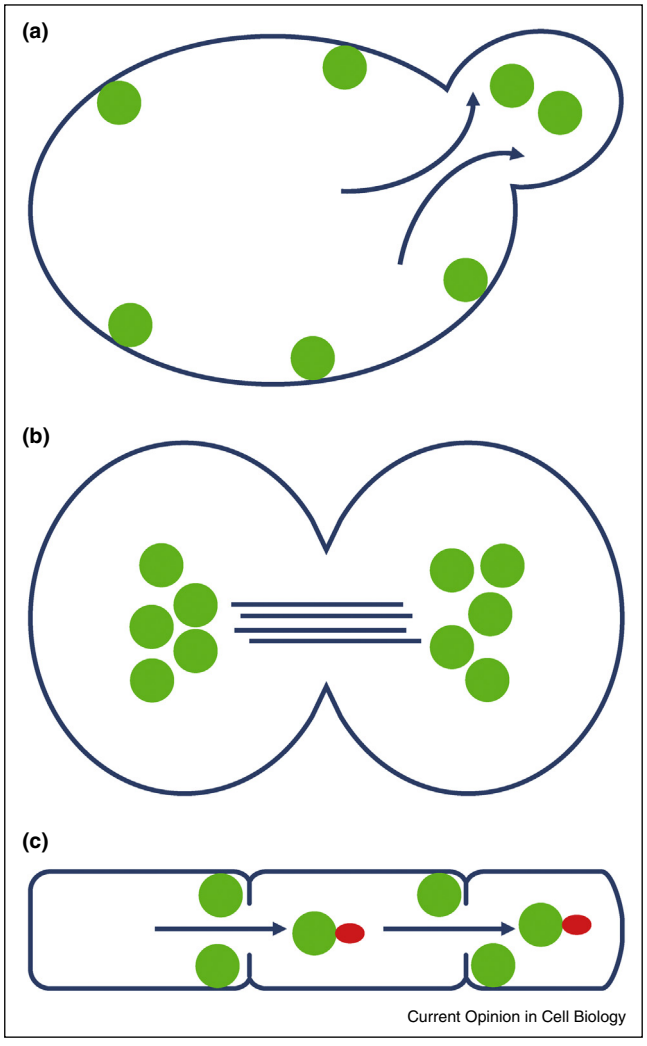
Peroxisomes originate at the endoplasmic reticulum (ER) through the formation of precursor vesicles that later acquire import competency for peroxisomal enzymes [5]. The peroxins Pex3p and Pex19p in yeast and, additionally, Pex16p in mammals are early acting peroxisome biogenesis factors. Pex3p is co-translationally inserted into the ER membrane [6,7] where it interacts with the cytosolic chaperone Pex19p to initiate budding of pre-peroxisomal vesicles [8,9]. In mammalian cells, Pex16p is also targeted to the ER, where it helps in peroxisomal membrane protein recruitment to make peroxisomes de novo [10,11]. Peroxisomes contain distinct machineries for the import of proteins from the cytosol [12,13]. In yeast, peroxisomes are not routinely made de novo but instead are duplicated and separated equitably between mother and daughter cell at cytokinesis [14].

Peroxisome partitioning in budding yeast

Cells of baker's yeast, *Saccharomyces cerevisiae*, undergo a repetitive pattern of growth and division termed budding in which they produce a bud that is initially very small. Yeast actively partition organelles between mother cell and bud to achieve an equidistribution of organelles at cytokinesis. Vectorial delivery of some organelles to the bud is balanced by retention of the remaining organelles in the mother cell. Attributes like these make budding yeast an attractive model with which to study organelle inheritance [15].

Yeast cells segregate their organelles in an actomyosin-dependent manner. The actin cytoskeleton of yeast is

Figure 1



Peroxisome partitioning in different model systems. (**a**) Yeast cells divide asymmetrically, with the production of a bud that is initially much smaller than its mother cell. Peroxisome partitioning can be dissected into transport and retention processes, which are linked by peroxisome division. (**b**) Mammalian cells divide by median fission but actively segregate their peroxisomes via microtubule-dependent and actin-dependent transport. (**c**) Filamentous fungi contain two types of peroxisome-derived organelles, one of which tethers to the septal region of hyphae and the other which travels on microtubules by hitchhiking on another organelle (early endosome). Green, peroxisomes; red, early endosomes.

highly polarized toward sites of growth and spatially arranged to drive organelle movement [16]. Two class V myosin motors, Myo2p and Myo4p, walk along actin cables using their N-terminal head domains, while binding organelle cargo with their C-terminal tail domains [17]. Processivity of transport, which is required for efficient delivery of cargo, is established through dimerization of Myo2p [18] and multimerization of Myo4p [19]. While Myo4p powers only the movement of cortical ER [20], Myo2p moves all other membrane-enclosed organelles except the nucleus, which is segregated along microtubules [15]. Individual organelles attach to class V myosins via organelle-specific adaptors.

Organelle adaptors bind at two sites on the surface of the Myo2p globular tail [21,22]. Eight of the nine known adaptors overlap in their binding at one site, which forces organelles to compete for access to Myo2p [23•]. The availability of Myo2p adaptors on the surface of organelles may dictate the timing of organelle movement and hence choreograph the inheritance of different organelle populations [24]. Myo2p does in fact move distinct cargoes at distinct times in the cell cycle, for example, peroxisome inheritance always precedes lipid droplet inheritance [25].

The integral membrane protein Inp2p is the peroxisomal adaptor for Myo2p [26]. Inp2p peaks in expression in G1 when most peroxisomes are inserted into the nascent bud, and is turned over at the end of the cell cycle. Mutants of Myo2p that cannot bind Inp2p fail to actively transport peroxisomes to the bud [24] and upregulate the abundance of Inp2p to compensate for the lack of peroxisome inheritance [24]. Phosphorylation of the vacuolar Myo2p adaptor Vac17p at Cdk1p sites leads to the initiation of vacuole inheritance [27], whereas phosphorylation at a threonine located in the PEST motif of Vac17p leads to recruitment of ubiquitin ligase, proteasomal degradation of Vac17p, and termination of vacuole inheritance. Since the ubiquitin ligase is recruited to the transport complex only after the vacuole has entered the bud, the movement of vacuoles is controlled both spatially and temporally [28••].

A study recently showed that not only does the cell cycle dictate the timing of organelle inheritance, but conversely organelle inheritance could provide a cell cycle checkpoint [29]. The vacuole is an essential organelle. When vacuole inheritance fails, a new vacuole can quickly be generated in the bud. However, mutants combining a vacuole biogenesis defect with a vacuole inheritance defect arrest early in G1. Presence of the vacuole in the bud is therefore prerequisite for cell cycle progression.

The controlled delivery of some organelles to the bud must be balanced by retention of the remaining organelles in the mother cell. This is explicitly evident in mutants in which the balancing act between organelle transport and retention is perturbed. Yeast mother cells lacking the peroxisome tethering protein Inp1p drive their entire peroxisome population to the bud [30]. Mutants of Pex3p that are peroxisome biogenic but unable to recruit Inp1p to the peroxisomal membrane display a peroxisome retention defect akin to that of *inp1Δ* cells [31], which suggested that Inp1p and Pex3p interact directly. Inp1p contains at least two binding sites for Pex3p, and this divalency is used by Inp1p to bridge

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