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REVIEW

Biogenesis of peroxisomes and mitochondria: linked by division

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Abstract Peroxisomes and mitochondria are metabolically linked organelles, which are crucial to human health and development. The search for components involved in their dynamics and maintenance led to the interesting finding that mitochondria and peroxisomes share components of their division machinery. Recently, it became clear that this is a common strategy used by mammals, fungi and plants. Furthermore, a closer interrelationship between peroxisomes and mitochondria has been proposed, which might have an impact on functionality and disease conditions. Here, we briefly highlight the major findings, views and open questions concerning peroxisomal formation, division, and interrelationship with mitochondria.

Keywords Peroxisomes · Mitochondria · Biogenesis · Dynamin · Fis1

Abbreviations

DLP	Dynamin-like protein
ER	Endoplasmic reticulum
PMP	Peroxisomal membrane protein
TA	Tail-anchored

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Formation of peroxisomes: classical and novel views

Peroxisomes are pleomorphic, single-membrane-bound organelles that house a wide variety of critical metabolic pathways (Wanders and Waterham 2006). They are crucial for lipid metabolism and free radical detoxification, development, differentiation and morphogenesis from yeasts to humans. The significance of peroxisomes to human health is exemplified by several genetic diseases such as the Zellweger syndrome or X-linked adrenoleukodystrophy.

Peroxisomes are able to respond to environmental changes and extracellular stimuli by altering their enzyme content, morphology, and abundance. Peroxisome formation, multiplication/proliferation and maintenance have been debated for a long time, and the debate is not over. According to the classical view, peroxisomes represent autonomous organelles, which form out of pre-existing peroxisomes by growth and division (Lazarow and Fujiki 1985). The "growth and division" model was supported by the discovery of the synthesis of peroxisomal proteins on free ribosomes, their post-translational transport into peroxisomes, and the observations of interconnections between peroxisomes. Furthermore, peroxisomes have been reported to divide, and recently proteins of the peroxisomal division machinery have been identified in yeast, mammalian and plant cells (see below) (Fagarasanu et al. 2007; Mullen and Trelease 2006; Schrader and Fahimi 2006). In contrast, the ER-maturation concept proposes that the ER contributes to peroxisome formation (Tabak et al. 2006; Titorenko and Mullen 2006). The degree of this contribution is, however, controversially discussed. Whereas there is general agreement that the ER provides the lipids for the formation of the peroxisomal membrane, its role in the delivery of peroxisomal membrane proteins (PMPs) is hotly debated. Opinions are swinging from a major

function of the ER in the indirect delivery of most (or all) PMPs (Tabak et al. 2008) to an ER function in comprising some (few) but essential PMPs (e.g., Pex3p and Pex16p) (semi-autonomous model) (Haan et al. 2006; Hoepfner et al. 2005; Kim et al. 2006; Kragt et al. 2005; Motley and Hettema 2007; Mullen and Trelease 2006; Tam et al. 2005). The ER-maturation-model received strong support by the observation that a loss of the peroxins Pex3p, Pex16p, or Pex19p, which are required for peroxisomal membrane biogenesis and PMP targeting/insertion (Van Ael and Fransen 2006), resulted in the absence of detectable peroxisomes/peroxisomal membranes, whereas reintroduction led to a de novo formation of peroxisomes from the ER. The Pex3p and Pex19p have been observed to initially localize to the ER before maturing into import-competent peroxisomes (Haan et al. 2006; Hoepfner et al. 2005; Tam et al. 2005), indicating that the ER is the source of the newly synthesized membrane and organelle. However, recent findings in *S. cerevisiae* indicate that in wild-type cells, peroxisomes multiply by growth and division and do not form de novo. Only cells lacking peroxisomes, as a result of a segregation defect, were observed to form peroxisomes de novo out of the ER (Motley and Hettema 2007; Nagotu et al. 2008b). Furthermore, evidence has been presented that Pex3p is directly transported to peroxisomes in a novel Pex19p- and Pex16p-dependent manner in mammalian cells (Matsuzaki and Fujiki 2008). Thus, the physiological significance of the mechanism of de novo formation in comparison to the classical pathway of growth and division is debatable. The de novo formation of peroxisomes from the ER may represent a rescue mechanism that becomes functional in some organisms only in case peroxisomes are lost (e.g., due to failure in inheritance). Most of the studies addressing de novo peroxisome formation out of the ER have been performed in yeast/fungi, and at present there is only one report in mammalian cells (Kim et al. 2006). It is interesting to note that in yeast PMPs are often misdirected to the ER under conditions of peroxisomal dysfunction, whereas in mammalian cells they are mistargeted to mitochondria (Van Ael and Fransen 2006). The concept of an indirect targeting of PMPs from the ER to peroxisomes has brought up several yet unanswered questions. This novel trafficking pathway is supposed to involve ER-derived vesicular or pre-peroxisomal structures, which either fuse with existing peroxisomes or develop into mature organelles (Motley and Hettema 2007; Tabak et al. 2008). Current studies in the field try to elucidate if and how the PMPs enter and leave the ER, how they are sorted and packaged, what the nature and composition of the ER-derived structures is, how fusion with peroxisomes is mediated, and if a retrograde, peroxisome-to-ER pathway exists (Halbach et al. 2008; Matsuzaki and Fujiki 2008; Mullen and Trelease 2006). In a recent report, it has been demonstrated that lipids are directly transferred from the ER to peroxisomes by a nonvesicular pathway suggesting that ER to peroxisome vesicular transport is not required to provide lipids for peroxisomal growth (Raychaudhuri and Prinz 2008). It is long known from ultrastructural studies that peroxisomes are often found in close contact with the ER. Thus, specific ER subdomains (contact sites) might mediate the transport of phospholipids to the growing peroxisomes by a transfer mechanism that has yet to be elucidated.

Division of peroxisomes

In the last few years great progress has been made in the identification of factors involved in the division of peroxisomes (Table 1; Fig. 1). First, dynamin-like proteins (DLPs) (namely, yeast Vps1 and mammalian DLP1/Drp1) were shown to be involved in the division step of peroxisomal biogenesis (Hoepfner et al. 2001; Koch et al. 2003; Li and Gould 2003). Dynamins are large GTPases known to perform fission of (tubulated) membranes (Praefcke and McMahon 2004). In line with this, silencing of DLP1 leads to highly elongated peroxisomal tubules which are constricted, but cannot be divided (Koch et al. 2004). Interestingly, DLP1 is also involved in mitochondrial division (reviewed in Hoppins et al. 2007; Okamoto and Shaw 2005) and was therefore the first component identified to divide two different organelles (Fig. 1). Furthermore, mammalian hFis1 (Fission 1), a tail-anchored protein of the outer mitochondrial membrane (reviewed in Hoppins et al. 2007; Okamoto and Shaw 2005), was likewise found on peroxisomes, and its involvement in peroxisomal division was demonstrated (Kobayashi et al. 2007; Koch et al. 2005) (Table 1; Fig. 1). The hFis1 is supposed to act as an adaptor molecule for the recruitment of DLP1 and regulate organelle morphology and fission through self-interaction (Serasinghe and Yoon 2008). An increase of hFis1 promotes mitochondrial and peroxisomal division, while its loss of function inhibits the division of both organelles (Kobayashi et al. 2007; Koch et al. 2005). Based on these findings the existence of other shared components of peroxisomal and mitochondrial division has been proposed (Schrader 2006). Very recently, the mammalian tail-anchored protein mitochondrial fission factor (Mff) was identified to be the third factor involved in mitochondrial and peroxisomal division (Gandre-Babbe and van der Bliek 2008) (Table 1; Fig. 1). Similar to hFis1, loss of Mff function results in the elongation of both organelles. The Mff is supposed to act as an adaptor protein as well, but in a complex different from hFis1. It is possible that Mff is involved in the assembly of the constriction machinery. Components involved in organelle constriction prior to fission have so far not been identified, and the process is currently not well understood

Table 1 Shared components of the peroxisomal and mitochondrial division machinery across organisms

Plants		Yeast		Mammals			
Peroxisomes	Mitochondria	Peroxisomes	Mitochondria	Peroxisomes	Mitochondria	Family	Function
Fis1a, b	Fis1a, b	Fis1	Fis1	hFis1	hFis1	TA protein TPR motif	Membrane adapter protein
		-	-	Mff	Mff	TA protein	Membrane adapter protein?
?	ELM[a]	Mdv1 Caf4[b]	Mdv1 Caf4[b]	?	?	WD protein other	Cytosolic linker protein
DRP3A, B	DRP3A, B DRP1C, E	Dnm1 Vps1[c]	Dnm1	Drp1/DLP1	Drp1/DLP1	large GTPase	Final scission
Pex11 (a-e)		Pex11	Mmm1, 2 Mdm (10, 12, 31-33)	Pex11 (α,β,γ)			Membrane tubulation

[a] Identified in *A. thaliana* (Arimura et al. 2008)

[b] Only present in *S. cerevisae* and *C. glabrata*

[c] Required in *S. cerevisae* but not in *H. polymorpha*

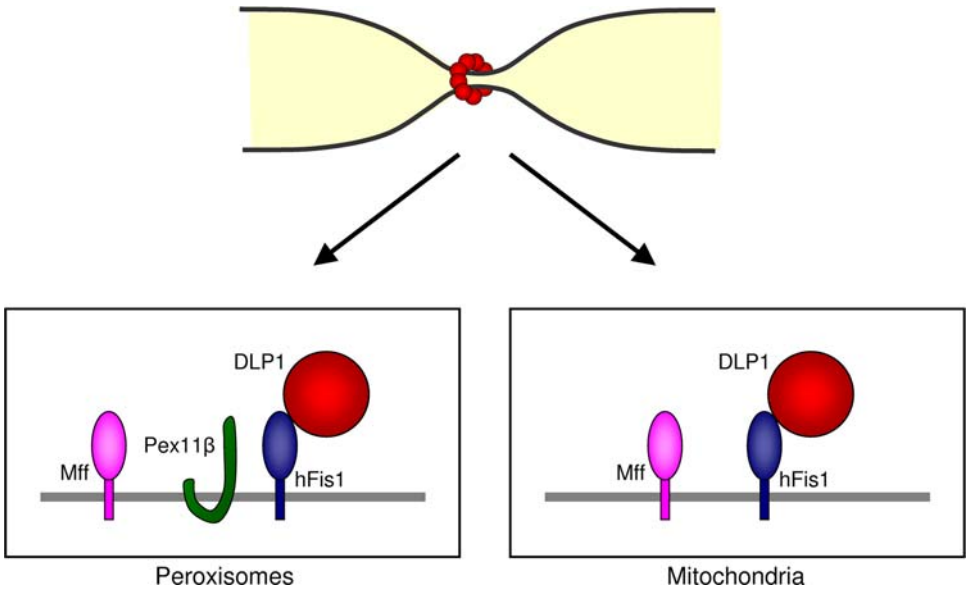

Fig. 1 Organelle division in mammals. Peroxisomes and mitochondria are divided by similar machineries. *DLP1* is a GTPase performing the final scission of constricted membranes and is recruited from the cytosol by the TA-protein *hFis1*, which might regulate organelle morphology and fission through self-interaction. hFis1 is supposed to interact with the peroxin Pex11*β*, which is known to regulate peroxisomal abundance and to tubulate membranes. *Mff* is a novel TA-protein involved in peroxisomal and mitochondrial division. It is supposed to function in a complex different from hFis1. In yeast, additional linker proteins (Mdv1, Caf4) have been identified which are involved in mitochondrial and peroxisomal division (see Table 1)

(Schrader and Fahimi 2006). Alternatively, hFis1 might play a role in membrane constriction (Serasinghe and Yoon 2008).

Sharing the key components of the division machinery appears to be a ubiquitous and general principle of peroxisomes and mitochondria in many eukaryotes, as homologous components were identified to act on both organelles in fungi and plants (Table 1). Members of the DRP3 subfamily of DLPs as well as the Fis1 homologs, Fis1a and Fis1b, have been implicated in peroxisomal and mitochondrial division in *Arabidopsis thaliana* (Lingard et al. 2008; Mano et al. 2004; Zhang and Hu 2008). In yeast, two independent pathways of peroxisomal division have been identified. The major DLP required for peroxisomal fission in glucose-grown *S. cerevisiae* appears to be vacuolar protein sorting-associated protein 1 (Vps1) (Hoepfner et al. 2001). The Vps1 was initially shown to be required for vacuolar protein sorting but is not involved in mitochondrial fission. However, cells grown in peroxisome-inducing growth conditions (oleate) have been reported to require the yeast DLP Dnm1, yeast Fis1, and the soluble molecular linkers Mdv1 and the closely related Caf4 (Kuravi et al. 2006; Motley and Hettema 2007; Motley et al. 2008) (Table 1). Mdv1 and Caf4 are cytosolic WD proteins that bind to Fis1 and Dnm1 in yeast. In addition, the four proteins are key components of mitochondrial division in yeast

(reviewed in Hoppins et al. 2007; Okamoto and Shaw 2005). Dnm1 (but not Vps1), Fis1 and Mdv1 are also required for peroxisomal (and mitochondrial) fission in *H. polymorpha* (Nagotu et al. 2008a; Nagotu et al. 2008b). Interestingly, Caf4 proteins appear to be present only in *Saccharomyces* species and *Candida glabrata*, but not in other yeast and fungi (including *H. polymorpha* and *P. pastoris*). However, all species tested contain Dnm1, Vps1 as well as Fis1 orthologs (Nagotu et al. 2008a). The de novo formation of peroxisomes via the ER (see above) appears to be independent of Vps1 and Dnm1 (Motley and Hettema 2007; Nagotu et al. 2008b).

Interestingly, there are no homologs for the linker proteins Mdv1 or Caf4 in metazoans, while Mff appears to be metazoan-specific (Gandre-Babbe and van der Bliek 2008) (Table 1). It is an interesting question if other Fis1-interacting linker proteins (functionally similar to Mdv1 and Caf4) exist in higher eukaryotes, which might be involved in the specific regulation and assembly of the division machineries on mitochondria and peroxisomes.

Besides the overlap in some components of the peroxisomal and mitochondrial division machinery, there is so far no evidence for shared components in other steps of their biogenesis. Membrane proteins of the Pex11 family have been shown to induce proliferation of peroxisomes by elongation (growth) of the organelle membrane, and subsequent division in mammals, yeast, and plants (Lingard et al. 2008; Schrader and Fahimi 2006; Thoms and Erdmann 2005; Yan et al. 2005) (Table 1; Fig. 1). However, the mode of action of the Pex11 proteins is still not fully understood. In mammals only three Pex11 proteins (α, β, and γ) have been reported to be involved in the regulation of peroxisome abundance/proliferation, whereas in yeast several peroxins affecting peroxisome abundance have been identified. It has been shown that the Pex11 proteins interact with the respective Fis1 proteins but not with the DLPs (Kobayashi et al. 2007; Koch et al. 2005; Lingard et al. 2008). The function of this interaction is still unclear. Interestingly, several mitochondrial membrane proteins required for the formation of mitochondrial tubules have been identified in fungi but not yet in higher eukaryotes (reviewed in Hoppins et al. 2007; Okamoto and Shaw 2005) (Table 1).

There is great interest now in the identification of further components involved in peroxisomal and/or mitochondrial division. It is likely, that the dynamic multistep process of peroxisome elongation (growth), constriction, final scission, and proper intracellular distribution via the cytoskeleton and motor proteins involves the assembly of distinct, complex machineries. Keeping this in mind, we are presumably just looking at the tip of an iceberg.

Another important issue is the regulation of peroxisomal and mitochondrial division. What determines the specific assembly of the shared division components on either peroxisomes or mitochondria, and how is their division coordinated? How are membrane proteins such as Fis1 and Mff targeted to both peroxisomes and mitochondria? It is likely that there is already regulation at the targeting level of these proteins to both organelles. As hFis1 recruits DLP1 to mitochondria and peroxisomes (Yu et al. 2005), the hFis1 levels in the respective membrane might be critical for the regulation of division. Recently, it was shown that the targeting of hFis1 to peroxisomes depends on Pex19p, an import factor involved in peroxisomal membrane protein import (Delille and Schrader 2008). In contrast, targeting of hFis1 to mitochondria does not require any known mitochondrial transport components (Kemper et al. 2008; Setoguchi et al. 2006), and appears to be independent from peroxisomal targeting. Furthermore, DLP1 is subject to several posttranslational modifications such as phosphorylation, ubiquitination, and sumoylation, which contribute to its regulation (reviewed in Cerveny et al. 2007).

Interrelationship of peroxisomes and mitochondria

There is emerging new evidence that peroxisomes and mitochondria exhibit a far greater co-dependent relationship than previously assumed (see also Schrader and Yoon 2007). Peroxisomes and mitochondria are metabolically linked organelles. They cooperate in the β-oxidation of fatty acids and in the metabolism of reactive oxygen species. In addition, a novel vesicular transport pathway from mitochondria to peroxisomes has been described (Neuspiel et al. 2008). Therefore, it is meaningful that their biogenesis is coordinated and that they share components of their division machinery (Schrader 2006) (Table 1; Fig. 1). Moreover, peroxisomal alterations in metabolism, biogenesis, dynamics and proliferation can potentially influence mitochondrial functions and vice versa. The close interrelationship between peroxisomes and mitochondria is not only supposed to have an impact on their cooperative functionality, but might also contribute to diseases (Camoes et al. 2008). Peroxisomal and mitochondrial dysfunctions are often associated with neurological and developmental defects. Furthermore, peroxisomes and mitochondria have been suggested to contribute to pathological conditions associated with oxidative stress and have been linked to ageing as well (Terlecky et al. 2006). In line with this, it has recently been shown that elevating peroxisomal catalase levels in late passage human cells restores mitochondrial integrity (Koepke et al. 2007), whereas compromised catalase activity may be linked to mitochondrial dysfunction (Koepke et al. 2008).

The first case of a newborn with a division defect in peroxisomes and mitochondria has been described recently (Waterham et al. 2007). Genetic analysis revealed a

missense mutation in the central domain of DLP1. Skin fibroblasts from the patient displayed elongated peroxisomes and mitochondria indicative for a block in DLP1-dependent organelle fission. A similar phenotype was described after inhibition of the DLP1 function (Koch et al. 2003; Koch et al. 2004; Li and Gould 2003), indicating that the determination of peroxisome morphology is a useful tool to identify patients with a division defect. The patient died only few weeks after birth and showed combined features of peroxisomal and mitochondrial dysfunction (e.g., defects in peroxisomal fatty acid β-oxidation and mitochondrial respiration). However, it has to be elucidated as to what extent the clinical phenotype reflects defects in mitochondrial or peroxisomal function. As mentioned above, it will be a great challenge in the future to dissect the contribution of mitochondria and peroxisomes to the progression of pathologies such as neurodegeneration and ageing.

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