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Review

Fission and proliferation of peroxisomes ☆

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ABSTRACT

Peroxisomes are remarkably dynamic, multifunctional organelles, which react to physiological changes in their cellular environment and adopt their morphology, number, enzyme content and metabolic functions accordingly. At the organelle level, the key molecular machinery controlling peroxisomal membrane elongation and remodeling as well as membrane fission is becoming increasingly established and defined. Key players in peroxisome division are conserved in animals, plants and fungi, and key fission components are shared with mitochondria. However, the physiological stimuli and corresponding signal transduction pathways regulating and modulating peroxisome maintenance and proliferation are, despite a few exceptions, largely unexplored. There is emerging evidence that peroxisomal dynamics and proper regulation of peroxisome number and morphology are crucial for the physiology of the cell, as well as for the pathology of the organism. Here, we discuss several key aspects of peroxisomal fission and proliferation and highlight their association with certain diseases. We address signaling and transcriptional events resulting in peroxisome proliferation, and focus on novel findings concerning the key division components and their interplay. Finally, we present an updated model of peroxisomal growth and division. This article is part of a Special Issue entitled: Metabolic Functions and Biogenesis of Peroxisomes in Health and Disease.

1. Introduction

Peroxisomes are dynamic, multifunctional organelles that contribute to numerous anabolic and catabolic pathways and are thus essential for human health and development. Common functions include the metabolism of hydrogen peroxide and the oxidation of fatty acids. However, several specialized functions have been acquired such as plasmalogen biosynthesis in mammals, photorespiration and glyoxylate cycle in plants, penicillin biosynthesis in fungi, and glycolysis in trypanosomes. In animals, peroxisomes are as well involved in the synthesis of bile acids, mediators of inflammation (e.g. leukotrienes) and docosahexaenoic acid, a modulator of neuronal function [1]. A new biological function for peroxisomes in anti-viral innate immunity and anti-viral (MAVS) signaling was recently discovered [2]. To adapt to the changing physiological requirements of a cell or organism, peroxisomes have to constantly adjust their morphology, number, enzyme content and metabolic functions accordingly. This requires dynamic processes which modulate peroxisome abundance, e.g. by peroxisome formation (biogenesis), degradation (pexophagy), or inheritance (cell division or budding) [3,4]. Peroxisomes can form by growth and division (fission) from pre-existing ones [5,6]. Alternatively, they can also arise from the ER [7–9]. This *de novo* formation was first discovered in mutant cells completely lacking peroxisomes after reintroduction of the deficient gene (PEX19, PEX3, or PEX16, which are thought to mediate peroxisome membrane biogenesis) (see Chapter 2, this issue). Recent publications indicate, that this process may also occur under normal conditions [10,11] involving the formation of vesicles containing a subset of peroxisomal membrane proteins (PMPs) budding from specialized ER sites [12,13]. Currently, however, the proportional contribution of both biogenesis pathways to the maintenance and abundance of peroxisomes is largely unknown and may vary considerably among different organisms. Here, we will focus mainly on peroxisome formation by growth and division and highlight recent advancements in the field. It is evident now, that an imbalance in peroxisome abundance, e.g. by impairment of regulatory pathways or defects in key division components can contribute to disorders displaying phenotypes, which often differ from those of classical peroxisome biogenesis disorders (see Chapter 3, this issue).

The terms “peroxisome proliferation” or “peroxisome multiplication” are commonly used to define the mode of peroxisome generation. Whereas “multiplication” refers to the maintenance of peroxisome numbers, peroxisome proliferation generally describes a pronounced increase in peroxisome number (usually after external

Abbreviations: ER, endoplasmic reticulum; Pex, peroxin; PGC-1α, peroxisome proliferator activated receptor γ coactivator-1α; PMP, peroxisomal membrane protein; PPAR, peroxisome proliferator activated receptor; PPRE, peroxisome proliferator response element; ROS, reactive oxygen species

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stimulation). In this review, the terms "multiplication" and "proliferation" will be used interchangeably, as both processes likely require the same machinery at the organelle level. Peroxisome proliferation has to be controlled by coordinated signaling events in the nucleus thus enhancing transcription of proliferation-relevant genes and concerted actions of biogenesis proteins at the cellular sites of peroxisome formation. Despite a few exceptions, the extracellular and intracellular signaling cascades involved in peroxisome proliferation are largely unknown. Key players in peroxisome division have, however, been identified during the last years and found to be conserved in animals, plants and fungi. Division of peroxisomes is preceded by elongation of the organelle membrane involving the conserved membrane protein Pex11p. Final fission requires dynamin-like proteins with GTPase activity and associated receptor and adaptor proteins (e.g. DLP1/Drp1 and its receptors Fis1 and Mff in mammals). Notably, these key components are shared with mitochondria which is a common strategy used by mammals, fungi and plants. Peroxisome formation from either the ER or by growth and division appears to follow a maturation process involving the recruitment of new membrane and matrix proteins.

In summary, peroxisome abundance is controlled at various stages and sites. On the one hand, it is regulated by controlled transcription of biogenesis- and division-related genes. On the other hand, peroxisome division requires a timely and spatially coordinated series of interactions between the various components involved. In the following, we will provide a comprehensive overview of our current knowledge on fission and proliferation of peroxisomes. We will first address signaling and transcriptional events resulting in peroxisome proliferation, and will afterwards focus on novel findings concerning the key components of the peroxisomal fission machinery and their interplay. The most recent findings have been incorporated in an updated model of peroxisomal growth and division.

2. Regulation of peroxisome proliferation

2.1. PPARα-controlled peroxisome proliferation — the classical scheme in mammals

The capability of peroxisomes to proliferate in response to exogenous stimuli has been described soon after their initial characterization in 1965 by Hess and coworkers [14], who treated rats with the hypolipidemic drug ethyl-chlorophenoxy-isobutyrate. However, it took another 10 years to link the hypolipidemic effect of the further on so-called "peroxisome proliferators" to peroxisomal fatty acid β-oxidation [15] (see Chapter 4, this issue). Treatment of rodents with classic peroxisome proliferators does not only result in a significant increase in organelle number, but also in changes in the peroxisomal protein composition. Whereas enzymes involved in fatty acid β-oxidation show an increase in both amounts and activities in response to the stimulation, proteins involved in other tasks – e.g., the H_2O_2 detoxifying enzyme catalase – are irresponsive or even decreased. Importantly, different species respond with variable intensities to synthetic peroxisome proliferators: potent hypolipidemic drugs such as fibrates, induce peroxisome proliferation [14] and expression of β-oxidation enzymes [15], but also the formation of liver tumors in rodent species [16]. Further studies showed that a massive peroxisome proliferation upon treatment with peroxisome proliferators is only observed in Muridae, whereas other organisms, including humans, are much more refractory [17] (see Section 2.2). Prolonged treatment with peroxisome proliferators has a carcinogenic effect in rodents leading to liver tumors [18–20] but apparently not in humans [21]. After the nuclear receptor Peroxisome Proliferator Activated Receptor α (PPARα), which belongs to the superfamily of steroid/thyroid/retinoid receptors, was identified as the responsible mediator for changing the expression of peroxisomal genes [22–24], it was possible to unveil that unsaturated long chain fatty acids are natural ligands of this receptor and thus transmit signals for the requirement of enhanced lipid catabolism [25] (Fig. 1). Later on, two related nuclear receptors, PPARγ and PPARβ/δ, were identified, which have partially overlapping substrate specificity but are not transmitting the signals of classical peroxisome proliferators [23,24]. Notably, constitutive expression of peroxisomal genes is not dependent on PPARα since the corresponding knockout mice proved to be viable, fertile and exhibit normal peroxisomes but are more susceptible to obesity [26,27]. Synthetic compounds triggering peroxisome proliferation via activation of PPARα are structurally remarkably different including fibrates, phthalate esters, polycyclic aromatic hydrocarbons, perfluorooctanoate and related compounds or dehydroepiandrosterone. Activation of PPARα does not only enhance the transcription of peroxisomal genes implicated in fatty acid β-oxidation but also those involved in peroxisome division, e.g. Pex11α (see Section 3.1, Table 1). However, PPARα-dependent peroxisome proliferators are capable of inducing peroxisome proliferation in a Pex11α knockout mouse model thus pointing to a potential functional compensation by the remaining Pex11 isoforms or to other, hitherto undetected factors [28]. Like all nuclear receptors, PPARs have to form dimers to attach to their correspondent DNA-binding sites (Fig. 1). For PPARα, ligand-binding induces conformational changes which permit an interaction with Retinoid X Receptor-α (RXRα), thus building the activated heterodimer capable of recognizing PPARα-responsive elements (PPREs) (Fig. 1). PPREs have been reported for all peroxisomal β-oxidation enzymes but also for several microsomal cytochrome P-450 subtypes and for apolipoproteins types I and II [29]. Thus, besides ligands for PPARα, full activation of the peroxisomal response depends as well on binding of 9-cis-retinoic acid to RXRα [30]. Further, it was shown that PPARα requires fatty acid-binding protein (FABP) for a full response to peroxisome proliferators [31], which may act as a mediator for nuclear transport of fatty acids.

2.2. Rats and mice are special — molecular background for species differences

Concerning the species differences in peroxisome proliferation, the affinities of endogenous or exogenous ligands to PPARα were not found to be responsible as was shown by experiments with species-specific PPARαs and reporter constructs based on the rat PPAR response element [32–34]. However, rats and mice exhibited a one-magnitude higher expression level of PPARα in liver than humans or guinea pigs [35,36], which would therefore allow a more frequent interaction between receptor and ligand. Moreover, primates exhibit significant sequence differences in both PPARα response elements and the corresponding DNA binding domain of the receptor, possibly leading to differential activation of PPAR-controlled genes. Indeed, insertion of murine response elements into human cell lines result in a comparable activation of the peroxisomal ACOX1 gene, encoding for acyl CoA oxidase 1, a key enzyme of peroxisomal β-oxidation [37]. PPARα-humanized mice (the human PPARα was introduced into the background of a PPARα knockout mouse line), however, still show a mouse-like activation of β-oxidation activities, but do not develop the proliferation-related tumors found in wild-type strains [38]. Thus, species differences in peroxisome proliferation appear to be caused by a species-specific coevolution of PPARα and its DNA-binding site elements allowing to adapt to individual physiological needs which are at the moment still not completely understood.

2.3. PPARα and then? — new regulating factors emerge

Physiologically, PPARα appears to regulate peroxisome number according to the requirements of increased lipolysis, e.g. in different tissues from fasting or hibernating animals, where peroxisome number and PPARα expression are up-regulated in parallel [39–41]. In brown adipose tissue, however, also PPARγ was suggested to

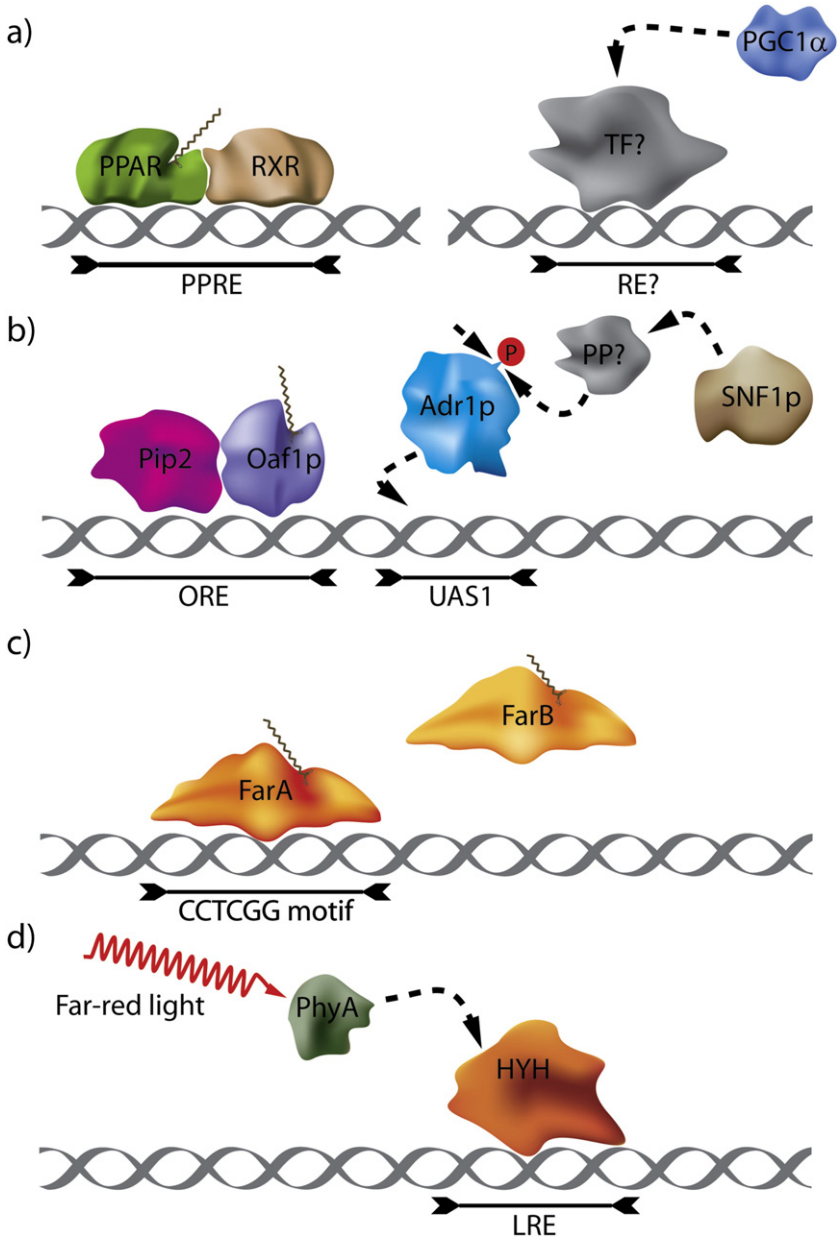

Fig. 1. Transcriptional regulation of peroxisome proliferation in different species. a) *Mus musculus*: Upon ligand binding, PPAR nuclear receptors and retinoid X receptors form heterodimers and interact with their cognate response elements (PPRE). The transcriptional coactivator PGC-1α regulates peroxisome abundance in concert with a hitherto unknown transcription factor. b) *Saccharomyces cerevisae*: Substrate-loaded heterodimers of the transcription factors Oaf1p and Pip2p induce transcription of peroxisomal genes by binding to Oaf1p response elements (ORE). Adr1p binding to UAS1 response elements cooperatively enhances the transcription of corresponding genes. Adr1p binding may be regulated by phosphorylation/dephosphorylation involving SNF1p. c) *Aspergillus nidulans*: The transcription factors FarA and FarB induce the transcription of peroxisomal genes after binding long and medium chain fatty acids, respectively. d) *Arabidopsis thaliana*: Far-red light activates phytochrome A, which induces binding of the transcription factor HYH to light responsible elements (LRE), e.g. in the promoter region of AtPex11b. See Section 2 for further details.

influence peroxisome abundance [40]. Recently, it was shown that peroxisome proliferation in brown adipose tissue during cold acclimatization can be a PPARα-independent process involving the transcriptional coactivator PGC-1α (peroxisome proliferator activated receptor γ coactivator-1α) in humans and mice [42] (Fig. 1). Since PGC-1α requires a DNA-binding transcription factor for mediating its action [43], a hitherto unidentified transcription factor has to be involved in the regulation of peroxisome numbers, since knockdown of PPARα and known interactors of PGC-1α (e.g. ERRα, NRF2, Foxo1) did not influence the PGC-1α-mediated proliferation. However, besides PPARα also PPARγ and δ have been proposed to possess the capability to induce peroxisome proliferation [44]. Remarkably, PPARγ has very recently been found to regulate peroxisome proliferation in hypothalamic neurons of mice on a fat-rich diet [45]. Subsequently, peroxisome abundance modulates neuronal ROS concentrations which influence the firing rates of neurons in the hypothalamus and by that the feeding behavior of the animals.

Besides PPAR-controlled proliferation, peroxisome numbers have been shown to increase in mammals in response to various other compounds, environmental factors or stimuli, which appear to be independent of this nuclear receptor. As a first compound, BM 15,766 was shown to induce peroxisome proliferation without elevating peroxisomal β-oxidation implying that both processes can be regulated independently [46]. Later, 4-phenylbutyrate was reported to induce peroxisome proliferation in the absence of PPARα [47] proving that there are other factors regulating peroxisome abundance. Growth

Table 1
Overview of the Pex11 proteins and their characteristics across species.

Model organism	Protein (*size*)	Transcriptional regulation	Membrane elongation	Membrane association and topology	Oligomerization		Interaction with Fis	Reference
					Homo-oligomers	Hetero-oligomers		
H. sapiens	Pex11α	✓	-	TMD	✓	✓ (αγ)	✓	[28,49,101–103,114,116,169,171]
	(*247aa*)	*PPARα*		N_{cyt}/C_{cyt}	*IP*	*IP*	*IP*	
	Pex11β	n.d.	✓	TMD	✓	✓ (βγ)	✓	
M. musculus	(*259aa*)			N_{cyt}/C_{cyt}	*IP*	*IP*	*IP*	
	Pex11γ	n.d.	✓	TMD	✓	✓ (αγ; βγ)	✓	
	(*241aa*)			N_{cyt}/C_{cyt}	*IP*	*IP*	*IP*	
A. thaliana	Pex11a	n.d.	(✓)	TMD	✓	✓ (all)	✓	[98,119,121,123]
	(*248aa*)			N_{cyt}/C_{matrix}	*BiFC*	*BiFC*	*BiFC*	
	Pex11b	✓	(✓)	TMD	✓	✓(all)	✓	
	(*227aa*)	*HYH*		N_{cyt}/C_{cyt}	*BiFC*	*BiFC*	*BiFC*	
	Pex11c	n.d.	✓	TMD	✓	✓(all)	✓	
	(*235aa*)			N_{cyt}/C_{cyt}	*BiFC*	*BiFC*	*BiFC*	
	Pex11d	n.d.	✓	TMD	✓	✓(all)	✓	
	(*236aa*)			N_{cyt}/C_{cyt}	*BiFC*	*BiFC*	*BiFC*	
	Pex11e	n.d.	-	TMD	✓	✓(all)	✓	
	(*231aa*)			N_{cyt}/C_{cyt}	*BiFC*	*BiFC*	*BiFC*	
S. cerevisiae	Pex11p	✓	✓	peripheral	✓	-	n.d.	[76–78,80,106,107,112,122,206]
	(*236aa*)	*Oaf1p-Pip2, Adr1p*			*CL, Y2H*			
	Pex25[a]	✓	✓	peripheral	✓	(✓) (25/27)	n.d.	
	(*394aa*)	*Oaf1p-Pip2, Adr1p*			*Y2H*	*Y2H*		
	Pex27	n.d.	-	peripheral	✓	(✓) (25/27)	n.d.	
	(*376aa*)				*Y2H*	*Y2H*		
A. nidulans	Pex11	✓	✓	n.d.	n.d.	n.d.	n.d.	[88,113,207]
	(*235aa*)	*FarA, FarB*						
	Pex11B	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	
	(*237aa*)							
	Pex11C	(✓)	n.d.	n.d.	n.d.	n.d.	n.d.	
	(*255aa*)	*putative FarA, FarB*						
T. brucei	Pex11	n.d.	✓	TMD	✓	-	n.d.	[108–110]
	(*218aa*)			N_{cyt}/C_{cyt}	*IP*			
	GIM5A	n.d.	n.d.	TMD	(✓)	✓ (5A/B)	n.d.	
	(*243aa*)			N_{cyt}/C_{cyt}	*IP*	*IP*		
	GIM5B	n.d.	n.d.	TMD	(✓)	✓(5A/B)	n.d.	
	(*241aa*)			N_{cyt}/C_{cyt}	*IP*	*IP*		

Abbreviations: n.d., not determined; TMD, transmembrane domain; CL, crosslinking studies; cyt, cytosolic; IP, immunoprecipitation; Y2H, yeast-2-hybrid; BiFC, bimolecular fluorescence complementation;

[a] Note that Pex25 has recently been implied in the *de novo* formation of peroxisomes from the ER in *H. polymorpha* and *S. cerevisiae* [111,112].

factors, arachidonic acid, UV light and reactive oxygen species (ROS) have been described to induce peroxisome elongation – a stage preceding proliferation (see Section 3) – in human HepG2 cells, a cell line refractory to the treatment with classic peroxisome proliferators [48,49]. Furthermore, peroxisome proliferation was reported in response to a plethora of chemical compounds not likely to interact directly with PPARα, such as endosulfan [50], cyclophosphamid [51], estrogenic compounds [52], acetyl salicylic acid [53] or dinitro-o-cresol [54]. Currently, it is not understood, how the elevation of peroxisome numbers is transduced in response to these treatments. The number of structurally different compounds may point to a more general stress response activating a hitherto undescribed signaling network. However, in specific cases also signaling cross-talk between different nuclear receptors, as e.g. described for PPARα/RXRα and estrogen receptor-α, may occur at the corresponding promoter response elements [55,56]. Concerning ROS, the scenario leading to peroxisome proliferation may be even more complicated. Reactive oxygen species have been implicated in modulating and influencing several signaling networks which can have cell survival or suicide functions [57] and are important messengers in pathological events such as cancer formation [58]. Thus, ROS can activate a multitude of different kinase networks and transcription factors depending on molecule species and concentration. In this context it is currently enigmatic by which factors and how peroxisomal abundance is regulated. Peroxisomes are both ROS scavenging organelles and potent ROS producers [59,60] (see Chapters 12 and 13, this issue). Unraveling their contribution to and regulation by redox sensitive signaling networks will be an important task for future research.

2.4. Enhanced peroxisome numbers are associated with particular diseases

In addition to induction by monocausal triggers, peroxisome proliferation was also reported to be associated with several liver diseases such as alcoholic and non-alcoholic steatosis as well as associated cirrhosis, cholestasis, and the different forms of hepatitis [61,62]. As these diseases do not mandatorily share a common etiologic background, the peroxisomal induction found may be caused by varying changes in the metabolic regulation systems associated. The peroxisome proliferation observed could be a sign of fatty acid overflow activating PPARα in steatohepatosis. Hashimoto and colleagues [63] showed a direct connection between disease formation and knock out of PPARα in mice. *Vice versa* treatment of mice with PPARα agonists was found to ameliorate liver steatosis [64,65]. Accordingly, down regulation of PPARα levels was observed in ethanol-infused rats as a model for alcoholic fatty liver disease [66,67]. Therefore, the elevated peroxisome levels accompanying the disease are unlikely to be caused by PPARα-activation, but are likely mediated by hitherto undiscovered signaling pathways. During alcoholic and non-alcoholic liver disease, ROS are produced by enhanced β-oxidation rates which are induced by an overflow of fatty acids in the liver [68,69]. Thus, peroxisome proliferation may represent a compensatory reaction to detoxify these harmful metabolites. However, numerous nuclear receptors and other

transcription factors are involved in the regulation of lipid homeostasis [70] and accordingly, the observed peroxisomal response may be induced by more than one causality.

A proliferation of peroxisomes in early disease stages of viral hepatitis has also been reported in humans and rodents [71,72]. As steatosis and increased ROS are common features observed in different forms of viral hepatitis [73,74], the factors discussed earlier may trigger peroxisomal responses in these diseases as well. Interestingly, however, Dixit and coworkers [2] recently showed that the anti-viral signaling protein MAVS is located, in addition to mitochondria, on peroxisomes and that viral infection induced an elongation of the compartment. This may be an initial step in peroxisome proliferation which is associated with the need of an increase in peroxisomal membrane surface, e.g. to facilitate MAVS signaling.

2.5. Peroxisome proliferation in fungi

In yeast, peroxisome proliferation has been exploited to identify peroxisome biogenesis (PEX) mutants [75]. Like animals, yeast species react with peroxisome proliferation upon growth on fatty acids as sole carbon source and likewise, transcription of Pex11 genes is induced [76,77]. Analogous to mammals, upon fatty acid stimulation *Saccharomyces cerevisae* forms heterodimers of the transcription factors Pip2 and Oaf1p – two proteins of the Zn-cluster family of transcription factors – and thereby activates the transcription of peroxisomal genes containing oleate-response elements (ORE) [78] (Fig. 1). Like PPARs, Oaf1p possesses functional fatty acid-binding domains, although embedded in a completely different molecular architecture [79]. Future studies have to reveal if both protein classes indeed share common ancestors as proposed by the authors, or are an example for analogous coevolution. However, unlike in animal species additional proteins were found to be involved in the process of transcriptional regulation of peroxisomal proliferation and protein expression (Fig. 1). Adr1p is an additional zinc-finger transcription factor sensing carbon status and controlling expression of peroxisomal genes [80]. Adr1p binds to upstream activating sequence 1 (UAS1) promoter sites under glucose depression and oleate induction conditions. UAS1 binding sites can be frequently found in proximity to OREs. Indeed, binding of Adr1p to promoters of peroxisomal genes enhances the affinity of Pip2/Oaf1p heterodimers to these promoters thus multiplying the transcriptional capacity of peroxisomal genes [81]. Currently, it is still unknown if the regulation system found in *S. cerevisae* is conserved among methylotrophic and n-alkane utilizing yeast species, which require a more modular peroxisomal response. However, ORE-like response elements were identified for peroxisomal genes of *Candida tropicalis*; furthermore, Mpp1p, a transcription factor of the binuclear Zn-cluster protein family with impact on peroxisome proliferation was described in *Hansenula polymorpha* (see [78] for detail). Recently, with Mxr1p (methanol expression regulator 1), a homolog of Adr1p was found in *Pichia pastoris* [82], whereas homologs in higher eukaryotes have not been described yet. Thus, methyl-induced peroxisome proliferation in the methylotrophic yeast *P. pastoris* seems to rely on a regulative mechanism which is conserved in different yeast species. Snf1p is an AMP-activated protein kinase found to be required for peroxisome proliferation in *Saccheromyces cerevisae* [83] (Fig. 1). Gurvitz and Rottensteiner hypothesized that Snf1p could be a kinase activating Oaf1p by phosphorylation [78]. However, although a phosphorylation of Oaf1p was detected, it was not abolished in a ΔSnf1-strain [81]. Recently, it was shown that Adr1p activation is controlled by dephosphorylation of Ser230 and that this event is dependent on Snf1p [84,85]. The authors hypothesize that Snf1p could accomplish this task by phosphorylation-dependent activation of a correspondent phosphatase or inhibition of a kinase responsible for Ser230 phosphorylation. In animals AMP-activated kinase (AMPK) is the homolog of Snf1 [86], but a direct influence on peroxisome proliferation has yet not been described. In filamentous fungi, FarA and FarB, two transcription factors of the Zn_2Cys_6 class, have been found to induce the transcription of genes implicated in fatty acid degradation as well as peroxisome biogenesis [87,88] (Fig. 1). Orthologs of these genes were found in ascomycetes [89,90], but also in several hemiascomycetes [91]. As described earlier, in other hemiascomycetes like *Saccharomyces* these transcription factors were replaced by the Pip2p/Oaf1p system.

2.6. Peroxisome proliferation in plants

In plants, ROS, UV radiation, salt stress, and even clofibrate, despite the lack of PPARs, are potent inducers of peroxisomal proliferation [92–95]. However, the molecular mechanisms regulating these processes remain enigmatic. In *Arabidopsis thaliana* treatment with clofibrate and wounding exhibit a similar activation of peroxisomal β-oxidation genes suggesting a regulation by jasmonate signaling in both cases. However, both phenomena showed no signs of interconnection since wounding and jasmonate treatment did not lead to detectable peroxisome proliferation [96]. In addition, induction of peroxisome proliferation was shown in response to light exposure in *A. thaliana*. During this process, glyoxysomes of seedlings involved in lipid metabolism are remodeled to leaf peroxisomes inhabiting enzymes of the glycolate pathway [97]. For this phenomenon a first regulatory mechanism was recently reported [98]: Like in animals and yeast, Pex11 and dynamin-related proteins are involved in peroxisomal elongation and division at the organelle level [99] (see Sections 3 and 4). In *Arabidopsis* light induces the expression of the Pex11-isoform Pex11b, which subsequently triggers peroxisome elongation thus initiating peroxisome division. This process was found to be mediated by the photoreceptor phytochrome A (phyA), which upon far-red light exposure translocates from the cytoplasm to the nucleus, where it interacts with transcription factors to activate light inducible genes [100] (Fig. 1). Further, the bZip transcription factor HYH, a downstream signaling component for several photoreceptors, was shown to bind directly to the Pex11b promoter and appears to be the direct transcriptional activator involved in light-induced peroxisome proliferation.

Taken together, individual control systems for peroxisome proliferation have emerged in all branches of the phylogenetic tree, which depend on similar but also diverging regulative concepts. To gain a more detailed understanding on how individual stimuli influence and regulate peroxisome abundance under physiological and pathological conditions, future investigations are required. To shed light on the relevance of peroxisome plasticity in health and disease, it will be important to unravel further interconnections between the numerous cellular signaling networks and the peroxisomal division machinery, e.g. with the various Pex11 isoforms found to be conserved across organisms.

3. Peroxin 11 (Pex11p) proteins

The peroxin 11 (Pex11) family is comprised of a number of conserved membrane proteins in fungi, plants and mammals that have been proposed to control peroxisome proliferation, and to function in the regulation of peroxisome morphology, size and number [49,76,77,101,102] (Table 1). Although Pex11 proteins are generally considered as key components of peroxisomal fission or division, they do not perform final membrane scission, which depends on dynamin-like proteins (DLPs/DRPs) (see Section 4). It is thought that Pex11 proteins mediate the initial step(s) of peroxisomal division and proliferation that is the growth and enlargement of the peroxisomal compartment (see Sections 3.2 and 3.3) prior to fission. In line with this, Pex11 proteins are supposed to recruit or assemble further components of the division machinery, e.g. Fis1, and thus DLPs (see Section 4). Loss of Pex11 function generally results in a decrease in peroxisome number and presence of enlarged peroxisomes, whereas overexpression of Pex11 leads to peroxisome elongation, subsequent division and an increase in peroxisome abundance. However, it should be noted that not all Pex11 isoforms in a given species

promote peroxisome proliferation or even membrane elongation pointing to distinct functions in peroxisome biogenesis (see later discussion). In line with this, the membrane association and topology of Pex11 may vary in different organisms (Table 1). Furthermore, not all Pex11 proteins can complement each other, although there is partial redundancy. It was recently reported that tagged variants of Pex11 proteins from plants, yeast and mammals are properly targeted to peroxisomes in plant and human cells and result in peroxisome proliferation when heterologously expressed [103].

3.1. Pex11 isoforms and Pex11-related proteins

While Pex11p (originally termed PMP31/32 according to its deduced molecular mass of approx. 30 kDa) was initially identified in *C. boidinii* as an inducible membrane protein upon peroxisome proliferation [104,105], its functional significance in this process was only recognized after deletion of its homolog in *S. cerevisae*, which led to the generation of one or two giant peroxisomal structures [76,77]. Conversely, overexpression was shown to result in peroxisome elongation and an increased number of small peroxisomes [76,77]. Besides Pex11, additional proteins with weak sequence similarity to Pex11 (so called Pex11-related or Pex11-like proteins) have been identified, mainly in *S. cerevisae*, and added to the Pex11 family (Table 1). These include the oleic acid-inducible Pex25p and the non-inducible Pex27p, whose deletions also influence peroxisome maintenance in *S. cerevisae* [106,107], as well as GIM5a and GIM5b, two Pex11-like proteins in *Trypanosoma brucei* [108–110]. Recently it was reported that Pex25p unlike Pex11p is involved in *de novo* formation of peroxisomes from the ER [111], whereas Pex27p appears to be a negative regulator of peroxisome proliferation [112]. Some yeast species like *Candida albicans*, *Yarrowia lipolytica*, *Hansenula polymorpha or Debaryomyces hensenii* contain Pex11C, another isoform with higher similarity to ScPex11p, thus resembling the situation in higher eukaryotes, where more than one isoform is present [113] (Table 1). In mammals, for example three Pex11p isoforms were shown to control peroxisome proliferation under both basal and induced conditions: Pex11pα, Pex11pβ and Pex11pγ [28,49,101,102,114–117]. This situation is analogously found in filamentous fungi, where as well three Pex11 isoforms, Pex11A-C, have been identified [113] (Table 1). In the filamentous fungus *Aspergillus oryzae*, Pex11 proteins not only induce peroxisome proliferation but were also reported to control the organelles' differentiation into Woronin bodies, a specialized peroxisomal derivate [118]. In the model plant *Arabidopsis thaliana*, even five obvious homologs were discovered, termed Pex11a-e [119] and categorized into three subfamilies: Pex11a, Pex11b and Pex11c-e (the latter showing the highest similarity to ScPex11p) [120] (Table 1). Thus, multiple Pex11 isoforms and/or related proteins appear to exist in all eukaryotes pointing to a functional variability in the process of peroxisome proliferation. In plants, despite some functional redundancy between the isoforms – as deletions of only a Pex11 subset has no obvious effect on plant physiology – differences in the expression pattern of the isoforms and in the morphological changes upon overexpression have been described [119,121]. Interestingly, not all isoforms induce peroxisome proliferation: only expression of Pex11a and Pex11e was reported to increase peroxisome number, whereas Pex11c and Pex11d induce peroxisome elongation without subsequent fission. Unlike the other forms, Pex11e was found to duplicate peroxisomes without any prominent membrane elongation, whereas Pex11b induced peroxisome aggregation [119].

Likewise, in mammals different expression patterns were observed for the three isoforms. While Pex11pβ is constitutively expressed, both Pex11pα and Pex11pγ show tissue-specific expression, but are most prominent in the liver [28,49,114,115,117]. Moreover, they differ in their transcriptional regulation: Pex11pα is a clofibrate-inducible protein in rat, while the related Pex11pβ was identified as its non-inducible homologue, sharing 40% sequence similarity [101]. In line with this, the Pex11pα gene is regulated by PPARα (see Section 2.1)[116], but is dispensable for PPAR-α mediated peroxisome proliferation in Pex11pα knockout (KO) mice suggesting functional redundancies between the three isoforms [28]. Regarding peroxisome morphology, there is a profound difference between Pex11pα, Pex11pβ and Pex11pγ-mediated peroxisome proliferation since only the latter two induce a pronounced peroxisome elongation prior to fission (Table 1)[49,114]. Concerning their functional importance, KO of Pex11pα in mice showed no obvious phenotypic alterations – except for some clustering of liver peroxisomes – suggesting functional compensation by the other isoforms. The KO of Pex11pβ, however, led to neonatal lethality and a Zellweger-like phenotype [28,114].

Across species all hitherto identified Pex11 isoforms are tightly associated with the peroxisomal membrane (Table 1). However, whereas the *S. cerevisae* proteins appear to be peripherally associated [77,106,107,122], mammalian and plant forms possess 1–2 or 3–4 predicted membrane spanning helices, respectively [49,101,102,119,121], with both the C- and N-termini (with exception of the plant Pex11a) protruding into the cytosol (Table 1).

All Pex11 forms hitherto identified including the Pex25 and Pex27 proteins found in most yeast species form homodimers and except for Pex11p in *S. cerevisae* and Pex11α/β in mammals can also heterodimerize with each other (Table 1) [103,106,107,122,123]. Homooligomerization of ScPex11p has been proposed to inhibit Pex11p function in peroxisome division [122], but the functional significance of homo- and heterooligomerization in other species remains to be determined.

3.2. Pex11-mediated membrane elongation and membrane remodeling

Studies with mammalian cell cultures expressing Pex11β initially revealed that peroxisome proliferation follows a multistep process including peroxisome membrane elongation (tubulation), membrane constriction, and final membrane fission (Figs. 2, 3) 1996 [49] . This model for peroxisomal “growth and division” is now generally accepted [5,6,99,124–127]. It should be noted that the aforementioned dynamic morphological changes of peroxisomes can as well be observed under routine culture conditions and in animal models for peroxisome proliferation [6]. Interestingly, Pex11β was observed to promote membrane elongation and to concentrate at the constriction sites [49], thus being the first peroxisomal membrane protein described to display a non-uniform membrane distribution (Fig. 3). We recently discovered that a Pex11pβ-YFP fusion protein can be used as a specific tool to further dissect the peroxisomal growth and division pathway by blocking peroxisome division at an early stage [128]. Expression of Pex11pβ carrying a monomeric YFP tag at the C-terminus inhibited constriction and division of peroxisomes in mammalian cells, but instead resulted in the formation of elongated pre-peroxisomal membrane structures, so called TPAs (tubular peroxisomal accumulations). In a similar study, the transient expression of various Pex11 family members led to the formation of protrusions which developed into large peroxisomal membrane stacks, termed juxtaposed elongated peroxisomes (JEPs) [103]. The JEPs, however, formed microtubule-dependent and disappeared after overexpression of Fis1, but not DLP1. As the division of the TPAs was blocked, single peroxisomes were apparently depleted from the cells. This observation challenges the current view that *de novo* formation from the ER and division of pre-existing peroxisomes may occur simultaneously in mammalian cells [10,129]. We might face a situation similar to yeast, where only the complete loss of peroxisomes triggers *de novo* formation [130]. Ultrastructural studies revealed that the pre-peroxisomal membrane compartment induced by Pex11pβ-YFP was composed of globular and extended tubular membrane domains. Interestingly, peroxisomal matrix proteins and PMPs distributed to distinct regions of the peroxisomal structures: matrix proteins and some PMPs (e. g. those with metabolic functions) were mainly targeted to

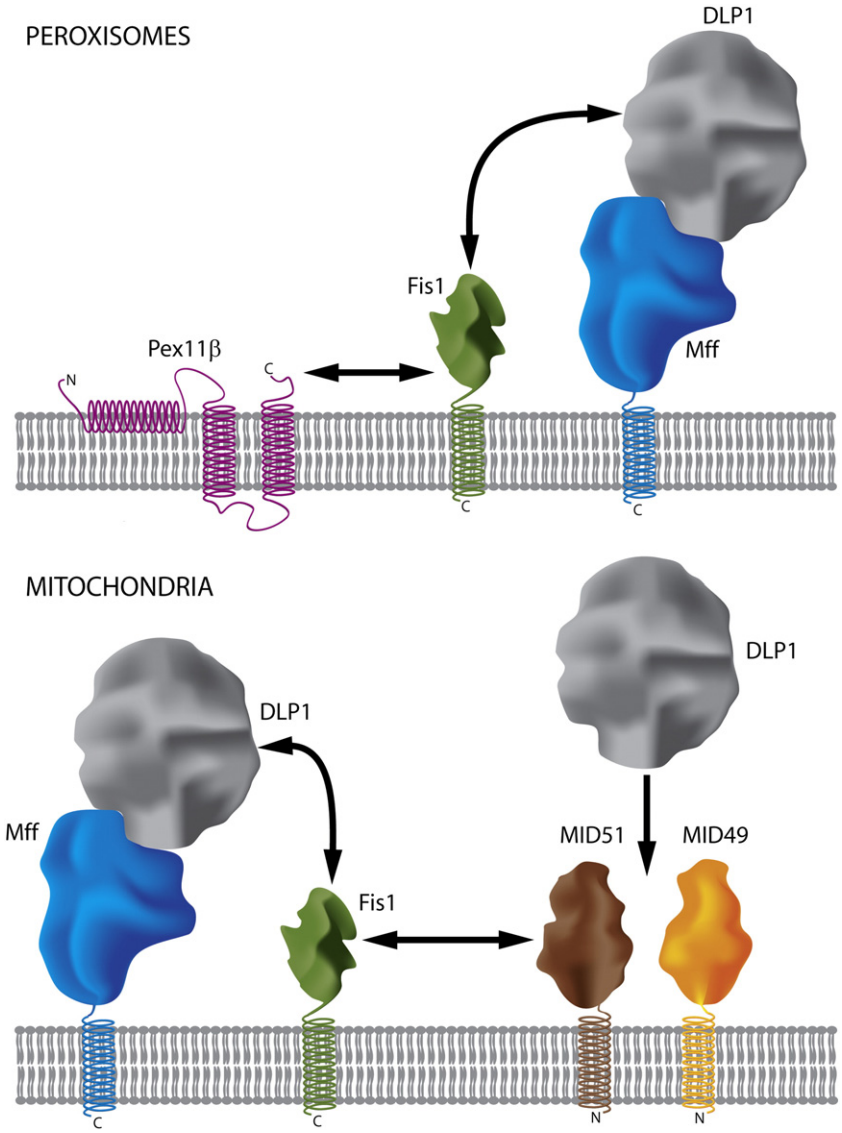

Fig. 2. Key fission proteins on peroxisomes and mitochondria in mammals. Peroxisomes and mitochondria share key components of their fission machineries. DLP1 is a GTPase performing the final scission of constricted membranes and is recruited to the organelle from the cytosol by the tail-anchored membrane receptors Mff and Fis1. Whereas Mff appears to be the essential DLP1 receptor for organelle fission, Fis1 might fulfil regulatory functions. On peroxisomes, the peroxin Pex11pβ that is known to regulate peroxisome abundance and to elongate membranes prior to fission, is supposed to interact with Fis1, which might result in the assembly and/or recruitment of other components of the fission machinery. On mitochondria, the N-terminally anchored proteins Mid51 and Mid49 may sequester DLP1 thus inhibiting its function. Fis1 can potentially regulate the inhibitory effect of MiD51 on DLP1 function and mitochondrial fission (see Section 4.3 for details). In yeast and plants additional receptor and adaptor proteins have been identified which are involved in mitochondrial and peroxisomal division (see Table 2).

the globular domains, the "early" peroxins required for membrane biogenesis (Pex16p, Pex19p, Pex3p) were uniformly/evenly distributed, whereas the majority of Pex11pβ and Fis1 localized to the tubular membrane domains (Fig. 3) [128]. These findings point to specific, yet undefined sorting and retention mechanisms within the peroxisomal membrane which require further investigation. Interestingly, a role for lipid rafts in peroxisome biogenesis has recently been proposed [131].

We as well demonstrated that Pex11pβ initially localizes to pre-existing spherical peroxisomes, where it induces the formation of a nose-like membrane protrusion which further extends resulting in a membrane tubule (Fig. 3). Again, these findings support the view that Pex11pβ is a peroxisome morphology protein that can shape and deform the peroxisomal membrane.

By applying the HaloTag technology for sequential labeling of catalase, we provided evidence that the membrane tubules contain only newly synthesized catalase, whereas pre-imported catalase is found in the spherical (mature) membrane compartment. These findings extend our previous model indicating that Pex11pβ-mediated growth (elongation) and division of peroxisomes follows a multistep maturation pathway, which is initiated by the formation of an early peroxisomal membrane compartment from a pre-existing peroxisome and its stepwise conversion into a mature, metabolically active peroxisome compartment (Fig. 3). Maturation is achieved by selective and stepwise import of certain PMPs, membrane lipids and matrix proteins. Our observations support the view that peroxisome division is an asymmetric process [132,133], which is far more complex than simple (symmetric) division of a pre-existing organelle. Interestingly, a maturation model is also proposed for *de novo* formation of peroxisomes from the ER [8,134].

Complementary to those findings, another recent study in *H. polymorpha* implied that Pex11p plays a key role in membrane reorganization prior to fission [135]. In fission arrested, Dnm1-deletion cells, tubular extensions protrude from the mother peroxisome, which show a differential distribution of membrane proteins with specific peroxins in the tubule (e.g. Pex8p, Pex10p, Pex14p, Pex25p), while

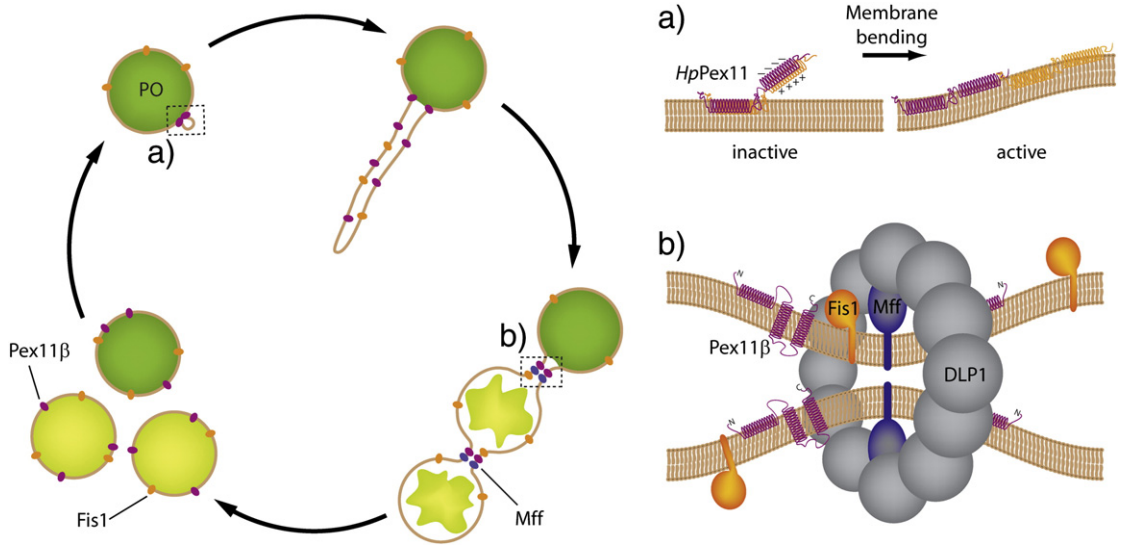

Fig. 3. Model of peroxisomal growth and division in mammalian cells. A well defined sequence of morphological changes of peroxisomes, including elongation (growth), constriction, and final fission (division) contributes to peroxisome proliferation in mammalian cells. Targeting to and/or activation of Pex11pβ at pre-existing peroxisomes initiates membrane remodeling and the formation of a tubular membrane extension on one side of the peroxisome. (a) Peroxisomal membrane remodeling via Pex11p is induced by the insertion of an amphipathic helix into one leaflet of the lipid bilayer which causes membrane asymmetry and bending (based on data obtained with HpPex11p). Homodimerization may keep Pex11p in an inactive form (see Section 3.3 for details). Subsequently, the extension grows and acquires a specific set of PMPs (e.g. Pex11pβ, Fis1), before it constricts and starts to import predominantly newly synthesized matrix proteins. Pex11pβ and the Mff-DLP1 complex concentrate at the sites of constriction, possibly driven by alterations in membrane curvature. (b) Cytosolic DLP1 is recruited by the membrane receptor Mff. After targeting, DLP1 self-assembles into large ring-like structures that hydrolyze GTP and sever the peroxisomal membrane. Fis1 may fulfil a regulatory function. Proper intracellular distribution of peroxisomes formed by division requires microtubules and motor proteins. It should be noted that elongated peroxisomes in mammalian cells can form and divide independent of microtubules and are even induced by microtubule-depolymerizing agents [172].

Pex11p remains enriched at the base of the membrane extension. Deletion studies indicated that Pex11p and specifically its N-terminal domain plays a key role in the acquisition and maintenance of the differential distribution of the PMPs. Ultrastructural studies suggest that initially a number of vesicular membrane structures are formed in a Pex11-dependent manner at the base of the Pex11p accumulation and that the membrane extension is formed out of these vesicles by the action of the myosin motor Myo2 and the peroxisomal inheritance protein Inp2 generating a pulling force [135]. This direct linkage between peroxisome proliferation and cell division in *H. polymorpha* may further explain the failure to retain peroxisomes in the mother cells upon deletion of HpPEX11 [136].

3.3. Mechanism of Pex11-induced membrane elongation

The biochemical properties of Pex11p have long been a matter of debate [125], but a recent study in *P. crysogenum* provided insight into the mechanism of Pex11p-induced membrane elongation [137]. Sequence comparison of yeast, fungal and human Pex11p isoforms revealed the presence of several conserved N-terminal helical motifs with amphipatic properties (i.e. hydrophobic and polar amino acids are segregated between the opposite faces of the α-helix). This distribution is well-suited for membrane binding and a model amphipathic helix adopts an orientation parallel to the membrane plane, inserting its hydrophobic residues between the fatty acyl-chains and its polar residues towards lipid polar heads of one leaflet, ultimately inducing membrane bending (Fig. 3) [138]. Within Pex11p, the so-called H3 motif formed the most extended helix in all species analyzed and derived peptides termed Pex11-Amph were used for further studies. Experiments using small unilamellar lipid vesicles (SUVs) revealed that Pex11-Amph peptides derived from different species preferentially bind to negatively charged SUVs that resemble the phospholipid composition of peroxisomes, inducing their tubulation. Notably, the tubulation induced by HsPex11pα was not as prominent, which is in line with previous findings [102]. Mutation analyses determined that the conservation of the amphipathic properties and the helix-forming abilities are essential for tubulation. The mechanical membrane-bending capabilities of the shared amphipatic helix motifs may further explain the reported complementing effects of heterologously expressed Pex11 proteins across species [103]. Additionally, the entire N-terminal domain of Pex11p was shown to exert membrane remodeling capacity, which was confirmed *in vivo* in *H. polymorpha*.

However, open questions remain in regard to the regulation of Pex11 activity. Early studies in *S. cerevisiae* provided evidence for dimerisation in later growth stages, indicating that Pex11p may act as a monomer whose action is blocked upon dimerisation (Fig. 3) [122]. Furthermore, ScPex11p contains cysteine residues of which the most N-terminal one – intriguingly indicated to be positioned in an amphipathic helix – was shown to affect dimer formation, thus providing a potential redox-sensitive conformational switch [122]. Besides regulation on the transcriptional and translational level, ScPex11p activity was recently shown to be influenced by post-translational modification [139]. ScPex11p was shown to be phosphorylated at S165/167, and the expression of phospho-mimicking mutants resulted either in a hyper-proliferative phenotype (Pex11-D "on") or in few and clustered peroxisomes (Pex11-A "off") resembling a deletion phenotype. Furthermore, overexpression of the cyclin-dependent kinase Pho85p resulted in hyperphosphorylation of Pex11p.

In contrast to higher eukaryotes, yeasts contain additional peroxins which influence peroxisome maintenance by interaction with or independent of Pex11 proteins. Deletion of the integral membrane proteins ScPex28 and ScPex29 (Pex24 in *Y. lipolytica*) led to the formation of clustered peroxisomes, thus implying a function in organelle separation [140]. ScPex30p, ScPex31p and ScPex32p were also reported to influence peroxisome numbers [141,142]. Deletion of Pex30, however, results in an increase in peroxisome number, implying a function as a negative regulator. The integral membrane protein ScPex34p, which acts independently, but also in concert with ScPex11p, ScPex25p and ScPex27p, increases peroxisome numbers when overexpressed [143]. In mammals, Pex11pα, β and γ are so far the only peroxins known to regulate peroxisome number and abundance.

4. The peroxisomal fission machinery

Whereas the role of Pex11 proteins in peroxisome proliferation has been linked to membrane elongation and deformation, it has become evident in the last years that final membrane scission of peroxisomes in all organisms studied so far depends on the assembly of dynamin-like (−related) proteins (DLPs/DRPs) at the peroxisomal membrane (Table 2). DLPs are large GTPases with mechanochemical properties that belong to the dynamin superfamily, whose members participate in various cellular membrane fission and fusion events [144]. DLPs are supposed to assemble into higher ordered ring-like structures in a GTP-dependent manner that wrap around membrane tubules to sever the membrane in a GTP hydrolysis-dependent process (Fig. 3) [145,146]. A recent cryo-electron microscopy study [147] revealed that *S. cerevisae* Dnm1 can form spirals with a much wider diameter (approx. 100 nm) than classical dynamins, that act in endocytosis (approx. 20 nm). However, the presence of other factors that may help to constrict the organelle membrane at defined sites to support assembly of DLPs *in vivo* is discussed [148]. DLPs contain a GTPase domain, followed by a middle domain and a GTPase effector domain, but they are lacking the proline rich domains and pleckstrin-homology domains (implicated in membrane binding) found in classical dynamins. With the majority present in the cytosol, DLPs have to be recruited to the peroxisome membrane for division. In mammals, the tail-anchored membrane receptor proteins Fis1 and Mff are supposed to provide an anchoring site for DLP1 [149–151] (Table 2) (Fig. 2). In *S. cerevisae*, peroxisome division depends on Fis1 and the WD40 domain-containing adaptor proteins Mdv1 and Caf4 [152,153], which are supposed to recruit Dnm1 to the peroxisomal membrane (Table 2). Furthermore, the DLP ScVps1, which is recruited by Pex19p, mediates peroxisome division in a Fis1-independent manner [154,155]. Mammalian homologs of Mdv1 and Caf4 have not been identified, and expression of Mff appears to be restricted to metazoans. In plants, DRP3A is recruited to peroxisomes by Fis1B [123,156]; however, PMD1 (Peroxisomal and Mitochondrial Division Factor 1), a plant-specific protein with a potential function in peroxisomal and mitochondrial division and/or positioning has recently been identified (Table 2) [157]. Interestingly, like Mff, PMD1 is supposed to be a tail-anchored membrane receptor containing coiled-coil domains. Despite these species-specific differences, it has been demonstrated that in many organisms peroxisomes and mitochondria share key components of the same DLP-based fission machinery (Table 2). Remarkably, sharing these components appears to be a common, evolutionary conserved strategy used by mammals, fungi and plants [6,158]. Moreover, these findings have further strengthened the disease-relevant concept of the "peroxisome-mitochondria connection" (see Section 4.2.1) [159] indicating that peroxisomes and mitochondria exhibit a much closer functional interplay than previously anticipated [158,160]. It is now evident that these organelles, besides metabolic cooperation in fatty acid β-oxidation in animals, also share a redox-sensitive relationship (see Chapter 12, this issue) and cooperate in anti-viral signaling [161] Furthermore, a novel vesicular trafficking pathway between mitochondria and peroxisomes has been proposed [162].

4.1. Do peroxisomes fuse?

In contrast to mitochondrial dynamics, which are regulated by balanced fusion and fission events [163–165], only peroxisomal fission events have so far been reported. There is firm evidence that mature peroxisomes in yeast and mammals do not fuse in a mechanism similar to mitochondrial fusion [130,132,166]. In line with this, mitochondrial fusion proteins such as the dynamin-related GTPases Mfn1 and Mfn2, or OPA1 were not found to localize to mammalian peroxisomes [166]. Interestingly, live cell imaging revealed that peroxisomes are engaged in transient and long term contacts, but without exchanging matrix or membrane markers [166]. However, fusion of peroxisomal subcompartments has been described as part of peroxisomal maturation in the yeast *Y. lipolytica* [167] that is mediated by the peroxins Pex1p and Pex6p. Furthermore, in live cells, reticular networks of peroxisomes have been described, which are extremely dynamic, with constant formation of tubular extensions interconnecting or detaching [168]. Thus, it can currently not be rigorously excluded that under certain metabolic or environmental conditions peroxisomes fuse to form more complex and dynamic structures to fulfil special metabolic functions more efficiently. However, these processes likely differ from mitochondrial fusion events.

4.2. Peroxisomal division in human diseases

4.2.1. DLP1 deficiency

Studies with mammalian cell cultures have revealed that functional loss of DLP1 (e.g. by siRNA-mediated silencing or the expression of dominant-negative mutants) inhibits peroxisomal (and mitochondrial) fission resulting in an elongated organelle morphology [148,169–171]. Interestingly, the elongated peroxisomes in DLP1 silenced cells exhibit a segmented, "beads on a string"-like morphology [148,172] (Fig. 3)

Table 2
Shared key components of peroxisomal and mitochondrial fission across organisms.

		Mammals		Plants		Yeast	
Function	Domain	Peroxisomes	Mitochondria	Peroxisomes	Mitochondria	Peroxisomes	Mitochondria
Membrane receptor (DLP1 recruitment)	C-TA TPR repeat	Fis1	Fis1	Fis1a, b	Fis1a, b	Fis1p	Fis1p
Membrane receptor (DLP1 recruitment)	C-TA Coiled-coil	Mff	Mff	-	-	-	-
Membrane receptor (segregation?)	C-TA Coiled-coil	-	-	PMD1	PMD1	-	-
Membrane receptor (DLP1 sequestration)	N-TA	-	MiD49 MiD51/MIEF1	-	-	-	-
Adaptor protein	WD 40 Others	?	?	Others[a]	ELM, others[a]	Mdv1 Caf4[b]	Mdv1 Caf4[b]
Membrane scission	Large GTPase	DLP1/Drp1	DLP1/Drp1	DRP3A, B DRP5B[c]	DRP3A, B DRP1C, E	Dnm1 Vps1[b]	Dnm1

Abbreviations: C-TA, C-terminally tail-anchored; TPR, tetratricopeptide repeat; N-TA, N-terminally tail-anchored.

[a] Recent work has suggested the existence of WD40 proteins with a similar domain structure as Mdv1/Caf4 in the Arabidopsis genome (At1g04510, At2g32950, At2g33340, At3g18860, At4g05410, At4g21130, At5g50230, At5g67320). The proteins share a central coiled-coil domain and a WD40 repeat region and range from 450–900aa in length. However, further studies need to determine localization and function [156].

[b] Note that Caf4 proteins appear to be only present in *S. cerevisiae* and *C. glabrata*. Similarly, although required for peroxisome division under glucose-grown conditions in *S. cerevisiae*, Vps1 is not present in other yeast species such as *H. polymorpha* [204,205]. Besides a role in peroxisome division, Vps1 is as well involved in vacuole formation.

[c] DRP5B mediates the division of both peroxisomes and chloroplasts [208].

indicating that DLP1 is not required for peroxisome constriction, but for final membrane scission. The factors that support constriction of the peroxisome membrane at defined sites to support assembly of DLP1 are still unknown.

Based on the reported peculiar peroxisome morphology in DLP1 silenced cells [148,170], a novel lethal disorder with defects in both peroxisomal and mitochondrial fission due to a heterozygous, dominant-negative missense mutation (A395D) in the middle domain of DLP1 was identified [173]. A recent biochemical study demonstrated that this mutation inhibits higher order assembly of DLP1 [174]. Other middle domain mutations (e.g. C452F; G363D, which may interfere with GTP hydrolysis) [175,176] or mutations in the GTPase domain (e.g. K38A, which inhibits GTP hydrolysis, but not GTP binding) are as well known to block DLP1 function leading to an elongated organelle morphology [170,171].

DLP1 deficiency represents the first member of a new group of combined peroxisomal–mitochondrial disorders. Its discovery further supports the concept of the "peroxisome–mitochondria connection" (see Section 4) [159]. The female patient, who died only few weeks after birth, showed microcephaly, abnormal brain development, optic atrophy and hypoplasia [173]. Several of the abnormalities were broadly similar to known disorders related to mitochondrial dynamics (e.g. Charcot–Marie–Tooth neuropathy, autosomal dominant optic atrophy), but the clinical course was more severe. Furthermore, elevated plasma levels of lactate and very-long chain fatty acids were detected pointing to defects in both mitochondrial and peroxisomal functions (mitochondrial respiration and peroxisomal β-oxidation, respectively). Elongated, constricted peroxisomes (and elongated mitochondria) similar to the ones described after loss of DLP1 function were observed in skin fibroblasts from the patient. Thus, the analysis of peroxisomal (and mitochondrial) morphology in patient cells is a valuable diagnostic tool for the determination of disorders based on defects in peroxisomal (mitochondrial) division.

The aforementioned findings have recently been confirmed by the generation and characterization of complete and brain-specific DLP1 knockout mice [177,178]. Complete knockouts displayed developmental abnormalities that resulted in embryonic lethality. Furthermore, peroxisomes and mitochondria exhibited an elongated and constricted morphology, thus confirming siRNA and mutational studies in cell culture. DLP1 function appears to be physiologically important for synapse formation and brain development in mice (for example by producing mitochondria, whose size is compatible with their movement and proper distributed within neurons). Despite the dramatic changes in mitochondrial morphology and dynamics, loss of DLP1 had no effect on mitochondrial respiration and ATP production. However, a C452F mutation in the DLP1 middle domain has been reported to result in dilated cardiomyopathy in mice [175].

It is presently unclear to what extent defects in mitochondrial or in peroxisomal function contribute to the clinical phenotype of the patient and to the pathological alterations observed in the knock out models. With respect to the functional interplay between peroxisomes and mitochondria (see Section 4), and the important role of peroxisomes in brain development and neurodegenerative diseases [179–181], the contribution of peroxisomes to the observed pathophysiologies should not be underestimated. In addition, DLP1 may fulfill additional functions in other subcellular locations. We have recently localized DLP1 at the Golgi complex in distinct cell types (but not in human fibroblasts), and proposed a role as a novel component of the apical sorting machinery at the trans-Golgi network [182]. In addition, cell-type specific requirements of DLP1 for mitochondrial division (e.g. in Purkinje neurons and granule cells) have been suggested [178]. Finally, DLP1 activity is highly regulated through a number of post-translational modifications including phosphorylation, S-nitrosylation, ubiquitination and sumoylation). If and how these modifications influence peroxisome dynamics and function has not yet been addressed. However, altered DLP1 activity via post-translational modifications is supposed to change mitochondrial dynamics in the course of neurodegenerative disorders [183,184].

4.3. The receptor proteins Fis1 and Mff

The potential receptor proteins for DLP1 on peroxisomes, Fis1 (Fission factor 1) and Mff (Mitochondrial fission factor) are both C-tail anchored membrane proteins, that are shared with mitochondria (Figs. 2, 3) (Table 2) [149,150,169]. Fis1 was identified in mammals based on sequence homology to ScFis1p and has been suggested to recruit DLP1 to mitochondria and peroxisomes [150,169,185–188]. Fis1 possesses an N-terminal tetratricopeptide repeat (TPR) domain, whereas Mff exposes its N-terminal part with a central coiled-coil motif into the cytosol [149,188]. Fis1 homodimerizes, which appears to be necessary for its function in organelle division [189]. Mff is supposed to act in a complex different from Fis1 [149].

Overexpression of Fis1 promotes peroxisomal (and mitochondrial) fragmentation, while silencing of Fis1 has been reported to result in elongated peroxisomes (and mitochondria) indicating that organelle division is blocked [150,169,187,188,190,191]. Furthermore, Fis1 was shown to be targeted to peroxisomes in a Pex19p-dependent manner [192] and to localize to highly purified peroxisomal fractions [150]. However, the effect of Fis1 silencing on peroxisome morphology was less pronounced than silencing of DLP1 [150]. Whereas DLP1 localizes in spots to potential division sites [188] (Fig. 3), Fis1 distributes uniformly over the peroxisomal (and mitochondrial) membrane, which does not quite fit to its proposed role as major membrane receptor for DLP1. In line with this, DLP1 can still be recruited to mitochondria following knockdown of Fis1 [186,193]. Moreover, targeted knockdown of Fis1 in mammalian cells was recently reported to have little if any effect on mitochondrial and peroxisomal morphology, and it was proposed that previous observations made through RNAi studies were the result of off-target effects [151]. Morphological alterations of peroxisomes after modulation of Fis1 expression levels might as well be indirectly induced by mitochondrial alterations (e.g. via functional peroxisome-mitochondria interplay; see Section 4) [159,160]. Based on these contradictory findings, the role of Fis1 as the main receptor for DLP1 in mammals and its contribution to organelle fission has recently been questioned [194] and it has been suggested that other proteins are involved in recruiting DLP1 to mitochondria and peroxisomes. There is growing evidence now that Mff is an essential factor for recruiting DLP1 to prospective fission sites on mitochondria and peroxisomes [151] (Fig. 2; Table 2). Loss of Mff function by RNAi results in elongated peroxisomes (and mitochondria) similar to silencing of DLP1 [149,151]. Furthermore, the elongated peroxisomes formed after silencing of Mff exhibit a constricted morphology as reported for silencing of DLP1 [148,170] (our unpublished results). This indicates that Mff (like DLP1) is likely not involved in the constriction of peroxisomes prior to fission. More importantly, as an elongated and constricted peroxisome morphology in patient fibroblasts may be the result of mutations in either DLP1 or Mff, both genes should be analyzed for potential mutations. In contrast to Fis, Mff localizes in spots on mitochondria (and peroxisomes; our unpublished results) (Fig. 3), and overexpression of Mff promotes the recruitment of DLP1 to mitochondria, and thus, mitochondrial division [151]. In summary, these findings strongly support a major role for Mff in recruiting DLP1 to mitochondria and peroxisomes.

If Mff is indeed the essential DLP1 receptor in mammals, what is the function of Fis1 on both organelles? On peroxisomes, Fis1 is supposed to interact with Pex11α and Pex11β [103,169] (Table 1), and is found to co-localize with Pex11β in tubular membrane domains which are formed prior to peroxisome division [128]. Physical interactions among all five *At*-Pex11 proteins and Fis1b have also been reported in *Arabidopsis* [123] (Table 1). Thus, Fis1 might function in the recruitment, assembly and/or regulation of the Mff-DLP1 fission machinery after activation of Pex11p (Fig. 2). Interestingly, Fis1 is also supposed to self-assemble and might play a role in membrane

constriction [189]. Its cytosolic domain was recently proposed to drive the association of two opposing bilayers prior to fission [195]. However, additional functions in apoptosis and autophagy have also been suggested [196,197].

Finally, MiD49 and MiD51/MIEF1, two novel N-terminally anchored mitochondrial membrane proteins, have been found to recruit DLP1 to mitochondria [198,199]) (Table 2). Like Mff, MiD proteins are not found in yeast, and present novel components of the mammalian mitochondrial fission machinery. In contrast to the Mff-DLP1 complex that promotes mitochondrial (and peroxisomal) fission, the MiD proteins have been suggested to sequester DLP1, thus inhibiting DLP1 function, and to promote mitochondrial fusion [200] (Fig. 2). Interestingly, in a mutually exclusive manner, MiD51 binds either to DLP1 or to Fis1. By that, Fis1 can potentially regulate the inhibitory effect of MiD51 on DLP1 function and mitochondrial fission. This scenario might as well explain some of the apparently contradictory results reported for the role of Fis1. However, MiD51 and MiD49 do not localize to peroxisomes (M. Ryan, LaTrobe University, Melbourne, personal communication, and our own unpublished results) and likely represent specific components of the mitochondrial fission machinery. This leaves us with the current opinion, that Fis1 is a major receptor for DLPs on mitochondria and peroxisomes in yeast and possibly plants (in cooperation with the adaptor proteins Mdv1 and Caf4), whereas Mff is the essential DLP1 recruitment factor in mammals (or metazoans), where Fis1 might fulfil a regulatory function (Figs. 2, 3).

5. Conclusions and future perspectives

The investigation of "peroxisomal dynamics" (i. e. addressing peroxisome morphology changes, peroxisome morphology proteins, membrane elongation and remodeling processes, peroxisome division and membrane fission, modes of peroxisome formation and maturation, regulation of peroxisome number, motility and distribution) has become an exciting new field in cell biology and biomedical sciences because of its potential relation to organelle functionality and its impact on, developmental and physiological processes [6,7,9,159,201].

At the organelle level, the key molecular machinery controlling peroxisomal morphology, dynamics and number is becoming more and more established and defined (Figs. 2, 3) (Tables 1, 2). It is likely that in the coming years many more proteins involved in peroxisome dynamics and morphology will be identified contributing to a better understanding of these complex mechanisms. However, information on the role of membrane lipids in peroxisome dynamics is scarce requiring further investigation. The expression and/or activation of Pex11 proteins (see Section 3) (Table 1) appears to be a common, initial event in yeasts, plants and mammals during peroxisome proliferation (Fig. 3). Some Pex11 proteins function as membrane-shaping proteins, and directly elongate the peroxisomal membrane prior to fission (see Sections 3.2 and 3.3). This activity depends on amphiphatic properties found in the N-terminal part of many Pex11 proteins. Pex11 proteins may as well support the recruitment and/or assembly of the fission machinery, which is composed of dynamin-like GTPases and organism-specific receptors (and adaptors) at the peroxisomal membrane (see Section 4) (Table 2). Remarkably, the key fission components are shared with mitochondria which is a common strategy used by mammals, fungi and plants (Table 2). There is emerging evidence that peroxisomes and mitochondria have a much closer interrelationship than previously assumed, which is supposed to have an impact on their cooperative functionality and contribution to diseases [158–160] (see Section 4).

While several key proteins involved in peroxisome dynamics and proliferation have been identified, their coordinated interplay and the regulation of these processes are not well understood. Post-translational modifications are likely to be involved in the regulation of peroxisome morphology proteins (e.g. Pex11p, DLP1); however, the signaling mechanisms acting upstream of Pex11p differ in mammals, plants and fungi (Fig. 1), and the cellular signals and the precise modulation of signal transduction pathways by physiological stimuli leading to peroxisome proliferation are, despite a few exceptions, largely unexplored, and require further investigation (see Section 2).

Although the field is young, there is emerging evidence that peroxisomal dynamics and proper regulation of peroxisome number and morphology are crucial for the physiology of the cell, as well as for the pathology of the organism and potentially, for host defence. Dysfunctions of peroxisome-shaping proteins can contribute to developmental disorders with characteristic peroxisome morphologies (see Sections 4.2 and 4.3) which can serve as valuable diagnostic indicators. Furthermore, alterations in peroxisome metabolism and proliferation are often associated with liver diseases or neurodegenerative disorders and have been linked to pathological conditions associated with oxidative stress and to cellular ageing [202,203]. In a very recent study, peroxisome proliferation and subsequent alterations in ROS levels have been demonstrated to set melanocortin tone and feeding in diet-induced obesity [45]. These findings further highlight the importance of peroxisome proliferation and regulation of peroxisome number in disease conditions. Understanding how peroxisomes manage to divide and proliferate, both on the organelle level and at the regulatory, signal transduction level will certainly contribute to therapeutic approaches for the treatment of patients with defects in peroxisome biogenesis and other disorders.

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References

[1] R.J.A. Wanders, H.R. Waterham, Biochemistry of mammalian peroxisomes revisited, Annu. Rev. Biochem. 75 (2006) 295–332.
[2] E. Dixit, S. Boulant, Y. Zhang, A.S. Lee, C. Odendall, B. Shum, N. Hacohen, Z.J. Chen, S.P. Whelan, M. Fransen, M.L. Nibert, G. Superti-Furga, J.C. Kagan, Peroxisomes are signaling platforms for antiviral innate immunity, Cell 141 (2010) 668–681.
[3] A. Fagarasanu, F.D. Mast, B. Knoblach, R.A. Rachubinski, Molecular mechanisms of organelle inheritance: lessons from peroxisomes in yeast, Nat. Rev. Mol. Cell Biol. 11 (2010) 644–654.
[4] M. Oku, Y. Sakai, Peroxisomes as dynamic organelles: autophagic degradation, FEBS J. 277 (2010) 3289–3294.
[5] P.B. Lazarow, Y. Fujiki, Biogenesis of peroxisomes, Annu. Rev. Cell Biol. 1 (1985) 489–530.
[6] M. Schrader, H.D. Fahimi, Growth and division of peroxisomes, Int. Rev. Cytol. 255 (2006) 237–290.
[7] E.H. Hettema, A.M. Motley, How peroxisomes multiply, J. Cell Sci. 122 (2009) 2331–2336.
[8] D. Hoepfner, D. Schildknegt, I. Braakman, P. Philippsen, H.F. Tabak, Contribution of the endoplasmic reticulum to peroxisome formation, Cell 122 (2005) 85–95.
[9] S. Nagotu, M. Veenhuis, I.J. van der Klei, Divide et impera: the dictum of peroxisomes, Traffic 11 (2010) 175–184.
[10] P.K. Kim, R.T. Mullen, U. Schumann, J. Lippincott-Schwartz, The origin and maintenance of mammalian peroxisomes involves a de novo PEX16-dependent pathway from the ER, J. Cell Biol. 173 (2006) 521–532.
[11] A. van der Zand, I. Braakman, H.F. Tabak, Peroxisomal membrane proteins insert into the endoplasmic reticulum, Mol. Biol. Cell 21 (2010) 2057–2065.
[12] G. Agrawal, S. Joshi, S. Subramani, Cell-free sorting of peroxisomal membrane proteins from the endoplasmic reticulum, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 9113–9118.
[13] S.K. Lam, N. Yoda, R. Schekman, A vesicle carrier that mediates peroxisome protein traffic from the endoplasmic reticulum, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) E51–E52.
[14] R. Hess, W. Staubli, W. Riess, Nature of the hepatomegalic effect produced by ethyl-chlorophenoxy-isobutyrate in the rat, Nature 208 (1965) 856–858.

[15] P.B. Lazarow, C. De Duve, A fatty acyl-CoA oxidizing system in rat liver peroxisomes; enhancement by clofibrate, a hypolipidemic drug, Proc. Natl. Acad. Sci. U. S. A. 73 (1976) 2043–2046.
[16] J.K. Reddy, S. Rao, D.E. Moody, Hepatocellular carcinomas in acatalasemic mice treated with nafenopin, a hypolipidemic peroxisome proliferator, Cancer Res. 36 (1976) 1211–1217.
[17] M. Islinger, M.J. Cardoso, M. Schrader, Be different—the diversity of peroxisomes in the animal kingdom, Biochim. Biophys. Acta 1803 (2010) 881–897.
[18] D.E. Moody, J.K. Reddy, B.G. Lake, J.A. Popp, D.H. Reese, Peroxisome proliferation and nongenotoxic carcinogenesis: commentary on a symposium, Fundam. Appl. Toxicol. 16 (1991) 233–248.
[19] J.K. Reddy, D.L. Azarnoff, C.E. Hignite, Hypolipidaemic hepatic peroxisome proliferators form a novel class of chemical carcinogens, Nature 283 (1980) 397–398.
[20] J.K. Reddy, J.R. Warren, M.K. Reddy, N.D. Lalwani, Hepatic and renal effects of peroxisome proliferators: biological implications, Ann. N. Y. Acad. Sci. 386 (1982) 81–110.
[21] P. Gariot, E. Barrat, L. Mejean, J.P. Pointel, P. Drouin, G. Debry, Fenofibrate and human liver. Lack of proliferation of peroxisomes, Arch. Toxicol. 53 (1983) 151–163.
[22] I. Issemann, S. Green, Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators, Nature 347 (1990) 645–650.
[23] S.R. Pyper, N. Viswakarma, S. Yu, J.K. Reddy, PPARalpha: energy combustion, hypolipidemia, inflammation and cancer, Nucl. Recept. Signal. 8 (2010) e002.
[24] M. Rakhshandehroo, B. Knoch, M. Muller, S. Kersten, Peroxisome proliferator-activated receptor alpha target genes, PPAR Res. 2010 (2010).
[25] C. Dreyer, H. Keller, A. Mahfoudi, V. Laudet, G. Krey, W. Wahli, Positive regulation of the peroxisomal beta-oxidation pathway by fatty acids through activation of peroxisome proliferator-activated receptors (PPAR), Biol. Cell 77 (1993) 67–76.
[26] F.J. Gonzalez, Recent update on the PPAR alpha-null mouse, Biochimie 79 (1997) 139–144.
[27] S.S. Lee, T. Pineau, J. Drago, E.J. Lee, J.W. Owens, D.L. Kroetz, P.M. Fernandez--Salguero, H. Westphal, F.J. Gonzalez, Targeted disruption of the alpha isoform of the peroxisome proliferator-activated receptor gene in mice results in abolishment of the pleiotropic effects of peroxisome proliferators, Mol. Cell. Biol. 15 (1995) 3012–3022.
[28] X. Li, E. Baumgart, G.X. Dong, J.C. Morrell, G. Jimenez-Sanchez, D. Valle, K.D. Smith, S.J. Gould, PEX11alpha is required for peroxisome proliferation in response to 4-phenylbutyrate but is dispensable for peroxisome proliferator-activated receptor alpha-mediated peroxisome proliferation, Mol. Cell. Biol. 22 (2002) 8226–8240.
[29] K. Schoonjans, B. Staels, J. Auwerx, Role of the peroxisome proliferator-activated receptor (PPAR) in mediating the effects of fibrates and fatty acids on gene expression, J. Lipid Res. 37 (1996) 907–925.
[30] S.A. Kliewer, K. Umesono, D.J. Noonan, R.A. Heyman, R.M. Evans, Convergence of 9-cis retinoic acid and peroxisome proliferator signalling pathways through heterodimer formation of their receptors, Nature 358 (1992) 771–774.
[31] C. Wolfrum, C.M. Borrmann, T. Borchers, F. Spener, Fatty acids and hypolipidemic drugs regulate peroxisome proliferator-activated receptors alpha- and gamma-mediated gene expression via liver fatty acid binding protein: a signaling path to the nucleus, Proc. Natl. Acad. Sci. U. S. A. 98 (2001) 2323–2328.
[32] M.T. Bility, J.T. Thompson, R.H. McKee, R.M. David, J.H. Butala, J.P. Vanden Heuvel, J.M. Peters, Activation of mouse and human peroxisome proliferator-activated receptors (PPARs) by phthalate monoesters, Toxicol. Sci. 82 (2004) 170–182.
[33] T.M. Willson, P.J. Brown, D.D. Sternbach, B.R. Henke, The PPARs: from orphan receptors to drug discovery, J. Med. Chem. 43 (2000) 527–550.
[34] S. Yu, W.Q. Cao, P. Kashireddy, K. Meyer, Y. Jia, D.E. Hughes, Y. Tan, J. Feng, A.V. Yeldandi, M.S. Rao, R.H. Costa, F.J. Gonzalez, J.K. Reddy, Human peroxisome proliferator-activated receptor alpha (PPARalpha) supports the induction of peroxisome proliferation in PPARalpha-deficient mouse liver, J. Biol. Chem. 276 (2001) 42485–42491.
[35] C.N. Palmer, M.H. Hsu, K.J. Griffin, J.L. Raucy, E.F. Johnson, Peroxisome proliferator activated receptor-alpha expression in human liver, Mol. Pharmacol. 53 (1998) 14–22.
[36] J.D. Tugwood, P.R. Holden, N.H. James, R.A. Prince, R.A. Roberts, A peroxisome proliferator-activated receptor-alpha (PPARalpha) cDNA cloned from guinea-pig liver encodes a protein with similar properties to the mouse PPARalpha: implications for species differences in responses to peroxisome proliferators, Arch. Toxicol. 72 (1998) 169–177.
[37] C.D. Kane, O.L. Francone, K.A. Stevens, Differential regulation of the cynomolgus, human, and rat acyl-CoA oxidase promoters by PPARalpha, Gene 380 (2006) 84–94.
[38] Q. Yang, T. Nagano, Y. Shah, C. Cheung, S. Ito, F.J. Gonzalez, The PPAR alpha-humanized mouse: a model to investigate species differences in liver toxicity mediated by PPAR alpha, Toxicol. Sci. 101 (2008) 132–139.
[39] Z. El Kebbaj, P. Andreoletti, D. Mountassif, M. Kabine, H. Schohn, M. Dauca, N. Latruffe, M.S. El Kebbaj, M. Cherkaoui-Malki, Differential regulation of peroxisome proliferator-activated receptor (PPAR)-alpha1 and truncated PPARalpha2 as an adaptive response to fasting in the control of hepatic peroxisomal fatty acid beta-oxidation in the hibernating mammal, Endocrinology 150 (2009) 1192–1201.
[40] H.M. Guardiola-Diaz, S. Rehnmark, N. Usuda, T. Albrektsen, D. Feltkamp, J.A. Gustafsson, S.E. Alexson, Rat peroxisome proliferator-activated receptors and brown adipose tissue function during cold acclimatization, J. Biol. Chem. 274 (1999) 23368–23377.
[41] M. Kabine, M.C. Clemencet, J. Bride, M.S. El Kebbaj, N. Latruffe, M. Cherkaoui--Malki, Changes of peroxisomal fatty acid metabolism during cold acclimatization in hibernating jerboa (Jaculus orientalis), Biochimie 85 (2003) 707–714.
[42] A. Bagattin, L. Hugendubler, E. Mueller, Transcriptional coactivator PGC-1alpha promotes peroxisomal remodeling and biogenesis, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 20376–20381.
[43] C. Handschin, The biology of PGC-1alpha and its therapeutic potential, Trends Pharmacol. Sci. 30 (2009) 322–329.
[44] K.L. DeCicco, T. Tanaka, F. Andreola, L.M. De Luca, The effect of thalidomide on non-small cell lung cancer (NSCLC) cell lines: possible involvement in the PPAR-gamma pathway, Carcinogenesis 25 (2004) 1805–1812.
[45] S. Diano, Z.W. Liu, J.K. Jeong, M.O. Dietrich, H.B. Ruan, E. Kim, S. Suyama, K. Kelly, E. Gyengesi, J.L. Arbiser, D.D. Belsham, D.A. Sarruf, M.W. Schwartz, A.M. Bennett, M. Shanabrough, C.V. Mobbs, X. Yang, X.B. Gao, T.L. Horvath, Peroxisome proliferation-associated control of reactive oxygen species sets melanocortin tone and feeding in diet-induced obesity, Nat. Med. 17 (2011) 1121–1127.
[46] E. Baumgart, A. Volkl, J. Pill, H.D. Fahimi, Proliferation of peroxisomes without simultaneous induction of the peroxisomal fatty acid beta-oxidation, FEBS Lett. 264 (1990) 5–9.
[47] C. Gondcaille, M. Depreter, S. Fourcade, M.R. Lecca, S. Leclercq, P.G. Martin, T. Pineau, F. Cadepond, M. ElEtr, N. Bertrand, A. Beley, S. Duclos, D. De Craemer, F. Roels, S. Savary, M. Bugaut, Phenylbutyrate up-regulates the adrenoleukodystrophy-related gene as a nonclassical peroxisome proliferator, J. Cell Biol. 169 (2005) 93–104.
[48] M. Schrader, K. Krieglstein, H.D. Fahimi, Tubular peroxisomes in HepG2 cells: selective induction by growth factors and arachidonic acid, Eur. J. Cell Biol. 75 (1998) 87–96.
[49] M. Schrader, B.E. Reuber, J.C. Morrell, G. Jimenez-Sanchez, C. Obie, T.A. Stroh, D. Valle, T.A. Schroer, S.J. Gould, Expression of PEX11beta mediates peroxisome proliferation in the absence of extracellular stimuli, J. Biol. Chem. 273 (1998) 29607–29614.
[50] T. Braunbeck, S. Appelbaum, Ultrastructural alterations in the liver and intestine of carp Cyprinus carpio induced orally by ultra-low doses of endosulfan, Dis. Aquat. Organ. 36 (1999) 183–200.
[51] P. Abraham, B. Isaac, Ultrastructural changes in the rat kidney after single dose of cyclophosphamide—possible roles for peroxisome proliferation and lysosomal dysfunction in cyclophosphamide induced renal damage, Hum. Exp. Toxicol. 30 (12) (2011) 1924–1930.
[52] M. Ortiz-Zarragoitia, M.P. Cajaraville, Effects of selected xenoestrogens on liver peroxisomes, vitellogenin levels and spermatogenic cell proliferation in male zebrafish, Comp. Biochem. Physiol. C Toxicol. Pharmacol. 141 (2005) 133–144.
[53] Y. Cai, A.K. Sohlenius, K. Andersson, C. Sundberg, J.W. DePierre, Effects of acetylsalicylic acid on parameters related to peroxisome proliferation in mouse liver, Biochem. Pharmacol. 47 (1994) 2213–2219.
[54] T. Braunbeck, A. Volkl, Induction of biotransformation in the liver of Eel (Anguilla anguilla L.) by sublethal exposure to dinitro-o-cresol: an ultrastructural and biochemical study, Ecotoxicol. Environ. Saf. 21 (1991) 109–127.
[55] H. Keller, F. Givel, M. Perroud, W. Wahli, Signaling cross-talk between peroxisome proliferator-activated receptor/retinoid X receptor and estrogen receptor through estrogen response elements, Mol. Endocrinol. 9 (1995) 794–804.
[56] S.B. Nunez, J.A. Medin, O. Braissant, L. Kemp, W. Wahli, K. Ozato, J.H. Segars, Retinoid X receptor and peroxisome proliferator-activated receptor activate an estrogen responsive gene independent of the estrogen receptor, Mol. Cell. Endocrinol. 127 (1997) 27–40.
[57] M.L. Circu, T.Y. Aw, Reactive oxygen species, cellular redox systems, and apoptosis, Free Radic. Biol. Med. 48 (2010) 749–762.
[58] W.S. Wu, The signaling mechanism of ROS in tumor progression, Cancer Metastasis Rev. 25 (2006) 695–705.
[59] N.A. Bonekamp, A. Volkl, H.D. Fahimi, M. Schrader, Reactive oxygen species and peroxisomes: struggling for balance, Biofactors 35 (2009) 346–355.
[60] M. Schrader, H.D. Fahimi, Peroxisomes and oxidative stress, Biochim. Biophys. Acta 1763 (2006) 1755–1766.
[61] D. De Craemer, M. Pauwels, C. Van den Branden, Alterations of peroxisomes in steatosis of the human liver: a quantitative study, Hepatology 22 (1995) 744–752.
[62] J.A. Litwin, K. Beier, A. Volkl, W.J. Hofmann, H.D. Fahimi, Immunocytochemical investigation of catalase and peroxisomal lipid beta-oxidation enzymes in human hepatocellular tumors and liver cirrhosis, Virchows Arch. 435 (1999) 486–495.
[63] T. Hashimoto, W.S. Cook, C. Qi, A.V. Yeldandi, J.K. Reddy, M.S. Rao, Defect in peroxisome proliferator-activated receptor alpha-inducible fatty acid oxidation determines the severity of hepatic steatosis in response to fasting, J. Biol. Chem. 275 (2000) 28918–28928.
[64] M. Fischer, M. You, M. Matsumoto, D.W. Crabb, Peroxisome proliferator-activated receptor alpha (PPARalpha) agonist treatment reverses PPARalpha dysfunction and abnormalities in hepatic lipid metabolism in ethanol-fed mice, J. Biol. Chem. 278 (2003) 27997–28004.
[65] E. Ip, G. Farrell, P. Hall, G. Robertson, I. Leclercq, Administration of the potent PPARalpha agonist, Wy-14,643, reverses nutritional fibrosis and steatohepatitis in mice, Hepatology 39 (2004) 1286–1296.
[66] A.A. Nanji, A.J. Dannenberg, K. Jokelainen, N.M. Bass, Alcoholic liver injury in the rat is associated with reduced expression of peroxisome proliferator-alpha (PPARalpha)-regulated genes and is ameliorated by PPARalpha activation, J. Pharmacol. Exp. Ther. 310 (2004) 417–424.
[67] Y.J. Wan, M. Morimoto, R.G. Thurman, H.K. Bojes, S.W. French, Expression of the peroxisome proliferator-activated receptor gene is decreased in experimental alcoholic liver disease, Life Sci. 56 (1995) 307–317.
[68] E. Albano, Oxidative mechanisms in the pathogenesis of alcoholic liver disease, Mol. Aspects Med. 29 (2008) 9–16.

[69] G.H. Koek, P.R. Liedorp, A. Bast, The role of oxidative stress in non-alcoholic steatohepatitis, Clin. Chim. Acta 412 (2011) 1297–1305.
[70] M.G. Sanal, The blind men 'see' the elephant—the many faces of fatty liver disease, World J. Gastroenterol. 14 (2008) 831–844.
[71] D. De Craemer, A. Bingen, M. Langendries, J.P. Martin, F. Roels, Alterations of hepatocellular peroxisomes in viral hepatitis in the mouse, J. Hepatol. 11 (1990) 145–152.
[72] D. De Craemer, M. Pauwels, M. Hautekeete, F. Roels, Alterations of hepatocellular peroxisomes in patients with cancer. Catalase cytochemistry and morphometry, Cancer 71 (1993) 3851–3858.
[73] C. Loguercio, A. Federico, Oxidative stress in viral and alcoholic hepatitis, Free Radic. Biol. Med. 34 (2003) 1–10.
[74] M. Persico, A. Iolascon, Steatosis as a co-factor in chronic liver diseases, World J. Gastroenterol. 16 (2010) 1171–1176.
[75] P.E. Purdue, P.B. Lazarow, Peroxisome biogenesis, Annu. Rev. Cell Dev. Biol. 17 (2001) 701–752.
[76] R. Erdmann, G. Blobel, Giant peroxisomes in oleic acid-induced Saccharomyces cerevisiae lacking the peroxisomal membrane protein Pmp27p, J. Cell Biol. 128 (1995) 509–523.
[77] P.A. Marshall, Y.I. Krimkevich, R.H. Lark, J.M. Dyer, M. Veenhuis, J.M. Goodman, Pmp27 promotes peroxisomal proliferation, J. Cell Biol. 129 (1995) 345–355.
[78] A. Gurvitz, H. Rottensteiner, The biochemistry of oleate induction: transcriptional upregulation and peroxisome proliferation, Biochim. Biophys. Acta 1763 (2006) 1392–1402.
[79] C. Phelps, V. Gburcik, E. Suslova, P. Dudek, F. Forafonov, N. Bot, M. MacLean, R.J. Fagan, D. Picard, Fungi and animals may share a common ancestor to nuclear receptors, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 7077–7081.
[80] A. Gurvitz, J.K. Hiltunen, R. Erdmann, B. Hamilton, A. Hartig, H. Ruis, H. Rottensteiner, Saccharomyces cerevisiae Adr1p governs fatty acid beta-oxidation and peroxisome proliferation by regulating POX1 and PEX11, J. Biol. Chem. 276 (2001) 31825–31830.
[81] I.V. Karpichev, J.M. Durand-Heredia, Y. Luo, G.M. Small, Binding characteristics and regulatory mechanisms of the transcription factors controlling oleate-responsive genes in Saccharomyces cerevisiae, J. Biol. Chem. 283 (2008) 10264–10275.
[82] G.P. Lin-Cereghino, L. Godfrey, B.J. de la Cruz, S. Johnson, S. Khuongsathiene, I. Tolstorukov, M. Yan, J. Lin-Cereghino, M. Veenhuis, S. Subramani, J.M. Cregg, Mxr1p, a key regulator of the methanol utilization pathway and peroxisomal genes in Pichia pastoris, Mol. Cell. Biol. 26 (2006) 883–897.
[83] M. Simon, M. Binder, G. Adam, A. Hartig, H. Ruis, Control of peroxisome proliferation in Saccharomyces cerevisiae by ADR1, SNF1 (CAT1, CCR1) and SNF4 (CAT3), Yeast 8 (1992) 303–309.
[84] S. Ratnakumar, N. Kacherovsky, E. Arms, E.T. Young, Snf1 controls the activity of adr1 through dephosphorylation of Ser230, Genetics 182 (2009) 735–745.
[85] S. Ratnakumar, E.T. Young, Snf1 dependence of peroxisomal gene expression is mediated by Adr1, J. Biol. Chem. 285 (2010) 10703–10714.
[86] D.G. Hardie, D. Carling, M. Carlson, The AMP-activated/SNF1 protein kinase subfamily: metabolic sensors of the eukaryotic cell? Annu. Rev. Biochem. 67 (1998) 821–855.
[87] M.J. Hynes, S.L. Murray, A. Duncan, G.S. Khew, M.A. Davis, Regulatory genes controlling fatty acid catabolism and peroxisomal functions in the filamentous fungus Aspergillus nidulans, Eukaryot. Cell 5 (2006) 794–805.
[88] M.J. Hynes, S.L. Murray, G.S. Khew, M.A. Davis, Genetic analysis of the role of peroxisomes in the utilization of acetate and fatty acids in Aspergillus nidulans, Genetics 178 (2008) 1355–1369.
[89] K. Reiser, M.A. Davis, M.J. Hynes, AoxA is a major peroxisomal long chain fatty acyl-CoA oxidase required for beta-oxidation in A. nidulans, Curr. Genet. 56 (2010) 139–150.
[90] K. Reiser, M.A. Davis, M.J. Hynes, Aspergillus nidulans contains six possible fatty acyl-CoA synthetases with FaaB being the major synthetase for fatty acid degradation, Arch. Microbiol. 192 (2010) 373–382.
[91] N. Poopanitpan, S. Kobayashi, R. Fukuda, H. Horiuchi, A. Ohta, An ortholog of farA of Aspergillus nidulans is implicated in the transcriptional activation of genes involved in fatty acid utilization in the yeast Yarrowia lipolytica, Biochem. Biophys. Res. Commun. 402 (2010) 731–735.
[92] E. Lopez-Huertas, W.L. Charlton, B. Johnson, I.A. Graham, A. Baker, Stress induces peroxisome biogenesis genes, EMBO J. 19 (2000) 6770–6777.
[93] S. Mitsuya, M. El-Shami, I.A. Sparkes, W.L. Charlton, M. Lousa Cde, B. Johnson, A. Baker, Salt stress causes peroxisome proliferation, but inducing peroxisome proliferation does not improve NaCl tolerance in Arabidopsis thaliana, PLoS One 5 (2010) e9408.
[94] J.M. Palma, M. Garrido, M.I. Rodriguez-Garcia, L.A. del Rio, Peroxisome proliferation and oxidative stress mediated by activated oxygen species in plant peroxisomes, Arch. Biochem. Biophys. 287 (1991) 68–74.
[95] A.M. Sinclair, C.P. Trobacher, N. Mathur, J.S. Greenwood, J. Mathur, Peroxule extension over ER defined paths constitutes a rapid subcellular response to hydroxyl stress, Plant J. 59 (2) (2009) 231–242.
[96] M.C. Castillo, L.M. Sandalio, L.A. Del Rio, J. Leon, Peroxisome proliferation, wound-activated responses and expression of peroxisome-associated genes are cross-regulated but uncoupled in Arabidopsis thaliana, Plant Cell Environ. 31 (2008) 492–505.
[97] L.J. Olsen, W.F. Ettinger, B. Damsz, K. Matsudaira, M.A. Webb, J.J. Harada, Targeting of glyoxysomal proteins to peroxisomes in leaves and roots of a higher plant, Plant Cell 5 (1993) 941–952.
[98] M. Desai, J. Hu, Light induces peroxisome proliferation in Arabidopsis seedlings through the photoreceptor phytochrome A, the transcription factor HY5 HOMOLOG, and the peroxisomal protein PEROXIN11b, Plant Physiol. 146 (2008) 1117–1127.
[99] J. Hu, Molecular basis of peroxisome division and proliferation in plants, Int. Rev. Cell Mol. Biol. 279 (2010) 79–99.
[100] H. Wang, X.W. Deng, Dissecting the phytochrome A-dependent signaling network in higher plants, Trends Plant Sci. 8 (2003) 172–178.
[101] I. Abe, Y. Fujiki, cDNA cloning and characterization of a constitutively expressed isoform of the human peroxin Pex11p, Biochem. Biophys. Res. Commun. 252 (1998) 529–533.
[102] I. Abe, K. Okumoto, S. Tamura, Y. Fujiki, Clofibrate-inducible, 28-kDa peroxisomal integral membrane protein is encoded by PEX11, FEBS Lett. 431 (1998) 468–472.
[103] J. Koch, K. Pranjic, A. Huber, A. Ellinger, A. Hartig, F. Kragler, C. Brocard, PEX11 family members are membrane elongation factors that coordinate peroxisome proliferation and maintenance, J. Cell Sci. 123 (2010) 3389–3400.
[104] J.M. Goodman, J. Maher, P.A. Silver, A. Pacifico, D. Sanders, The membrane proteins of the methanol-induced peroxisome of Candida boidinii. Initial characterization and generation of monoclonal antibodies, J. Biol. Chem. 261 (1986) 3464–3468.
[105] M. Moreno, R. Lark, K.L. Campbell, J.M. Goodman, The peroxisomal membrane proteins of Candida boidinii: gene isolation and expression, Yeast 10 (1994) 1447–1457.
[106] H. Rottensteiner, K. Stein, E. Sonnenhol, R. Erdmann, Conserved function of pex11p and the novel pex25p and pex27p in peroxisome biogenesis, Mol. Biol. Cell 14 (2003) 4316–4328.
[107] Y.Y. Tam, J.C. Torres-Guzman, F.J. Vizeacoumar, J.J. Smith, M. Marelli, J.D. Aitchison, R.A. Rachubinski, Pex11-related proteins in peroxisome dynamics: a role for the novel peroxin Pex27p in controlling peroxisome size and number in Saccharomyces cerevisiae, Mol. Biol. Cell 14 (2003) 4089–4102.
[108] P. Lorenz, A.G. Maier, E. Baumgart, R. Erdmann, C. Clayton, Elongation and clustering of glycosomes in Trypanosoma brucei overexpressing the glycosomal Pex11p, EMBO J. 17 (1998) 3542–3555.
[109] A. Maier, P. Lorenz, F. Voncken, C. Clayton, An essential dimeric membrane protein of trypanosome glycosomes, Mol. Microbiol. 39 (2001) 1443–1451.
[110] F. Voncken, J.J. van Hellemond, I. Pfisterer, A. Maier, S. Hillmer, C. Clayton, Depletion of GIM5 causes cellular fragility, a decreased glycosome number, and reduced levels of ether-linked phospholipids in trypanosomes, J. Biol. Chem. 278 (2003) 35299–35310 (Epub 32003 Jun 35226).
[111] R. Saraya, A.M. Krikken, M. Veenhuis, I.J. van der Klei, Peroxisome reintroduction in Hansenula polymorpha requires Pex25 and Rho1, J. Cell Biol. 193 (2011) 885–900.
[112] A. Huber, J. Koch, F. Kragler, C. Brocard, A. Hartig, A subtle interplay between three Pex11 proteins shapes de novo formation and fission of peroxisomes, Traffic 13 (1) (2011) 157–167.
[113] J.A. Kiel, M. Veenhuis, I.J. van der Klei, PEX genes in fungal genomes: common, rare or redundant, Traffic 7 (2006) 1291–1303.
[114] X. Li, E. Baumgart, J.C. Morrell, G. Jimenez-Sanchez, D. Valle, S.J. Gould, PEX11 beta deficiency is lethal and impairs neuronal migration but does not abrogate peroxisome function, Mol. Cell. Biol. 22 (2002) 4358–4365.
[115] M. Passreiter, M. Anton, D. Lay, R. Frank, C. Harter, F.T. Wieland, K. Gorgas, W.W. Just, Peroxisome biogenesis: involvement of ARF and coatomer, J. Cell Biol. 141 (1998) 373–383.
[116] M. Shimizu, A. Takeshita, T. Tsukamoto, F.J. Gonzalez, T. Osumi, Tissue-selective, bidirectional regulation of PEX11 alpha and perilipin genes through a common peroxisome proliferator response element, Mol. Cell. Biol. 24 (2004) 1313–1323.
[117] A. Tanaka, K. Okumoto, Y. Fujiki, cDNA cloning and characterization of the third isoform of human peroxin Pex11p, Biochem. Biophys. Res. Commun. 300 (2003) 819–823.
[118] C.S. Escano, P.R. Juvvadi, F.J. Jin, T. Takahashi, Y. Koyama, S. Yamashita, J. Maruyama, K. Kitamoto, Disruption of the Aopex11-1 gene involved in peroxisome proliferation leads to impaired Woronin body formation in Aspergillus oryzae, Eukaryot. Cell 8 (2009) 296–305.
[119] M.J. Lingard, R.N. Trelease, Five Arabidopsis peroxin 11 homologs individually promote peroxisome elongation, division without elongation, or aggregation, J. Cell Sci. 119 (2006) 1961–1972.
[120] N. Kaur, J. Hu, Dynamics of peroxisome abundance: a tale of division and proliferation, Curr. Opin. Plant Biol. 12 (2009) 781–788.
[121] T. Orth, S. Reumann, X. Zhang, J. Fan, D. Wenzel, S. Quan, J. Hu, The PEROXIN11 protein family controls peroxisome proliferation in Arabidopsis, Plant Cell 19 (2007) 333–350.
[122] P.A. Marshall, J.M. Dyer, M.E. Quick, J.M. Goodman, Redox-sensitive homodimerization of Pex11p: a proposed mechanism to regulate peroxisomal division, J. Cell Biol. 135 (1996) 123–137.
[123] M.J. Lingard, S.K. Gidda, S. Bingham, S.J. Rothstein, R.T. Mullen, R.N. Trelease, Arabidopsis PEROXIN11c-e, FISSION1b, and DYNAMIN-RELATED PROTEIN3A cooperate in cell cycle-associated replication of peroxisomes, Plant Cell 20 (2008) 1567–1585.
[124] A. Fagarasanu, M. Fagarasanu, R.A. Rachubinski, Maintaining peroxisome populations: a story of division and inheritance, Annu. Rev. Cell Dev. Biol. 23 (2007) 321–344.
[125] S. Thoms, R. Erdmann, Dynamin-related proteins and Pex11 proteins in peroxisome division and proliferation, FEBS J. 272 (2005) 5169–5181.
[126] M. Yan, N. Rayapuram, S. Subramani, The control of peroxisome number and size during division and proliferation, Curr. Opin. Cell Biol. 17 (2005) 376–383.
[127] L. Opalinski, M. Veenhuis, I.J. van der Klei, Peroxisomes: membrane events accompanying peroxisome proliferation, Int. J. Biochem. Cell Biol. 43 (2011) 847–851.

[128] H.K. Delille, B. Agricola, S.C. Guimaraes, H. Borta, G.H. Luers, M. Fransen, M. Schrader, Pex11pbeta-mediated growth and division of mammalian peroxisomes follows a maturation pathway, J. Cell Sci. 123 (2010) 2750–2762.
[129] H.K. Delille, G. Dodt, M. Schrader, Pex11pbeta-mediated maturation of peroxisomes, Commun. Integr. Biol. 4 (2011) 51–54.
[130] A.M. Motley, E.H. Hettema, Yeast peroxisomes multiply by growth and division, J. Cell Biol. 178 (2007) 399–410.
[131] J. Woudenberg, K.P. Rembacz, M. Hoekstra, A. Pellicoro, F.A. van den Heuvel, J. Heegsma, S.C. van Ijzendoorn, A. Holzinger, T. Imanaka, H. Moshage, K.N. Faber, Lipid rafts are essential for peroxisome biogenesis in HepG2 cells, Hepatology 52 (2010) 623–633.
[132] S.J. Huybrechts, P.P. Van Veldhoven, C. Brees, G.P. Mannaerts, G.V. Los, M. Fransen, Peroxisome dynamics in cultured mammalian cells, Traffic 10 (2009) 1722–1733.
[133] J. Koch, C. Brocard, Membrane elongation factors in organelle maintenance: the case of peroxisome proliferation, Biomol Concepts 2 (2011) 353–364.
[134] W.H. Kunau, Peroxisome biogenesis: end of the debate, Curr. Biol. 15 (2005) R774–R776.
[135] M.N. Cepinska, M. Veenhuis, I.J. van der Klei, S. Nagotu, Peroxisome fission is associated with reorganization of specific membrane proteins, Traffic 12 (2011) 925–937.
[136] A.M. Krikken, M. Veenhuis, I.J. van der Klei, Hansenula polymorpha pex11 cells are affected in peroxisome retention, FEBS J. 276 (2009) 1429–1439.
[137] L. Opalinski, J.A. Kiel, C. Williams, M. Veenhuis, I.J. van der Klei, Membrane curvature during peroxisome fission requires Pex11, EMBO J. 30 (2011) 5–16.
[138] G. Drin, B. Antonny, Amphipathic helices and membrane curvature, FEBS Lett. 584 (2010) 1840–1847.
[139] B. Knoblach, R.A. Rachubinski, Phosphorylation-dependent activation of peroxisome proliferator protein PEX11 controls peroxisome abundance, J. Biol. Chem. 285 (2010) 6670–6680.
[140] F.J. Vizeacoumar, J.C. Torres-Guzman, Y.Y. Tam, J.D. Aitchison, R.A. Rachubinski, YHR150w and YDR479c encode peroxisomal integral membrane proteins involved in the regulation of peroxisome number, size, and distribution in Saccharomyces cerevisiae, J. Cell Biol. 161 (2003) 321–332.
[141] L.A. Brown, A. Baker, Peroxisome biogenesis and the role of protein import, J. Cell Mol. Med. 7 (2003) 388–400.
[142] F.J. Vizeacoumar, J.C. Torres-Guzman, D. Bouard, J.D. Aitchison, R.A. Rachubinski, Pex30p, Pex31p, and Pex32p form a family of peroxisomal integral membrane proteins regulating peroxisome size and number in Saccharomyces cerevisiae, Mol. Biol. Cell 15 (2004) 665–677.
[143] R.J. Tower, A. Fagarasanu, J.D. Aitchison, R.A. Rachubinski, The peroxin Pex34p functions with the Pex11 family of peroxisomal divisional proteins to regulate the peroxisome population in yeast, Mol. Biol. Cell 22 (2011) 1727–1738.
[144] G.J. Praefcke, H.T. McMahon, The dynamin superfamily: universal membrane tubulation and fission molecules? Nat. Rev. Mol. Cell Biol. 5 (2004) 133–147.
[145] E. Ingerman, E.M. Perkins, M. Marino, J.A. Mears, J.M. McCaffery, J.E. Hinshaw, J. Nunnari, Dnm1 forms spirals that are structurally tailored to fit mitochondria, J. Cell Biol. 170 (2005) 1021–1027.
[146] Y. Yoon, K.R. Pitts, M.A. McNiven, Mammalian dynamin-like protein DLP1 tubulates membranes, Mol. Biol. Cell 12 (2001) 2894–2905.
[147] J.A. Mears, L.L. Lackner, S. Fang, E. Ingerman, J. Nunnari, J.E. Hinshaw, Conformational changes in Dnm1 support a contractile mechanism for mitochondrial fission, Nat. Struct. Mol. Biol. 18 (2011) 20–26.
[148] A. Koch, G. Schneider, G.H. Luers, M. Schrader, Peroxisome elongation and constriction but not fission can occur independently of dynamin-like protein 1, J. Cell Sci. 117 (2004) 3995–4006.
[149] S. Gandre-Babbe, A.M. van der Bliek, The novel tail-anchored membrane protein Mff controls mitochondrial and peroxisomal fission in mammalian cells, Mol. Biol. Cell 19 (2008) 2402–2412.
[150] A. Koch, Y. Yoon, N.A. Bonekamp, M.A. McNiven, M. Schrader, A role for fis1 in both mitochondrial and peroxisomal fission in mammalian cells, Mol. Biol. Cell 16 (2005) 5077–5086.
[151] H. Otera, C. Wang, M.M. Cleland, K. Setoguchi, S. Yokota, R.J. Youle, K. Mihara, Mff is an essential factor for mitochondrial recruitment of Drp1 during mitochondrial fission in mammalian cells, J. Cell Biol. 191 (2010) 1141–1158.
[152] K. Kuravi, S. Nagotu, A.M. Krikken, K. Sjollema, M. Deckers, R. Erdmann, M. Veenhuis, I.J. van der Klei, Dynamin-related proteins Vps1p and Dnm1p control peroxisome abundance in Saccharomyces cerevisiae, J. Cell Sci. 119 (2006) 3994–4001.
[153] A.M. Motley, G.P. Ward, E.H. Hettema, Dnm1p-dependent peroxisome fission requires Caf4p, Mdv1p and Fis1p, J. Cell Sci. 121 (2008) 1633–1640.
[154] D. Hoepfner, M. van den Berg, P. Philippsen, H.F. Tabak, E.H. Hettema, A role for Vps1p, actin, and the Myo2p motor in peroxisome abundance and inheritance in Saccharomyces cerevisiae, J. Cell Biol. 155 (2001) 979–990.
[155] F.J. Vizeacoumar, W.N. Vreden, G.A. Eitzen, J.D. Aitchison, R.A. Rachubinski, The dynamin-like protein Vps1p of the yeast Saccharomyces cerevisiae associates with peroxisomes in a Pex19p-dependent manner, J. Biol. Chem. 281 (2006) 12817–12823.
[156] R. Pan, J. Hu, The conserved fission complex on peroxisomes and mitochondria, Plant Signal. Behav. 6 (2011) 870–872.
[157] K. Aung, J. Hu, The Arabidopsis Tail-anchored protein PEROXISOMAL AND MITOCHONDRIAL DIVISION FACTOR1 is involved in the morphogenesis and proliferation of peroxisomes and mitochondria, Plant Cell (2011) Dec. 9 Epub ahead of print doi:org/10.1105/tpc.111.090142.
[158] H.K. Delille, R. Alves, M. Schrader, Biogenesis of peroxisomes and mitochondria: linked by division, Histochem. Cell Biol. 131 (2009) 441–446.
[159] F. Camoes, N.A. Bonekamp, H.K. Delille, M. Schrader, Organelle dynamics and dysfunction: a closer link between peroxisomes and mitochondria, J. Inherit. Metab. Dis. 32 (2009) 163–180.
[160] M. Schrader, Y. Yoon, Mitochondria and peroxisomes: are the 'Big Brother' and the 'Little Sister' closer than assumed? Bioessays 29 (2007) 1105–1114.
[161] O. Ivashchenko, P.P. Van Veldhoven, C. Brees, Y.S. Ho, S.R. Terlecky, M. Fransen, Intraperoxisomal redox balance in mammalian cells: oxidative stress and interorganellar cross-talk, Mol. Biol. Cell 22 (2011) 1440–1451.
[162] M. Neuspiel, A.C. Schauss, E. Braschi, R. Zunino, P. Rippstein, R.A. Rachubinski, M.A. Andrade-Navarro, H.M. McBride, Cargo-selected transport from the mitochondria to peroxisomes is mediated by vesicular carriers, Curr. Biol. 18 (2008) 102–108.
[163] S. Hoppins, L. Lackner, J. Nunnari, The machines that divide and fuse mitochondria, Annu. Rev. Biochem. 76 (2007) 751–780.
[164] K. Okamoto, J.M. Shaw, Mitochondrial morphology and dynamics in yeast and multicellular eukaryotes, Annu. Rev. Genet. 39 (2005) 503–536.
[165] B. Westermann, Mitochondrial fusion and fission in cell life and death, Nat. Rev. Mol. Cell Biol. 11 (2010) 872–884.
[166] N.A. Bonekamp, P. Sampaio, G.H. Luers, M. Schrader, Peroxisomal dynamics: do mammalian peroxisomes fuse with each other? Open European Peroxisome Meeting 2010, Lunteren, The Netherlands, 2010.
[167] V.I. Titorenko, R.A. Rachubinski, Dynamics of peroxisome assembly and function, Trends Cell Biol. 11 (2001) 22–29.
[168] M. Schrader, S.J. King, T.A. Stroh, T.A. Schroer, Real time imaging reveals a peroxisomal reticulum in living cells, J. Cell Sci. 113 (2000) 3663–3671.
[169] S. Kobayashi, A. Tanaka, Y. Fujiki, Fis1, DLP1, and Pex11p coordinately regulate peroxisome morphogenesis, Exp. Cell Res. 313 (2007) 1675–1686.
[170] A. Koch, M. Thiemann, M. Grabenbauer, Y. Yoon, M.A. McNiven, M. Schrader, Dynamin-like protein 1 is involved in peroxisomal fission, J. Biol. Chem. 278 (2003) 8597–8605.
[171] X. Li, S.J. Gould, The dynamin-like GTPase DLP1 is essential for peroxisome division and is recruited to peroxisomes in part by PEX11, J. Biol. Chem. 278 (2003) 17012–17020.
[172] M. Schrader, J.K. Burkhardt, E. Baumgart, G. Luers, H. Spring, A. Volkl, H.D. Fahimi, Interaction of microtubules with peroxisomes. Tubular and spherical peroxisomes in HepG2 cells and their alterations induced by microtubule-active drugs, Eur. J. Cell Biol. 69 (1996) 24–35.
[173] H.R. Waterham, J. Koster, C.W. van Roermund, P.A. Mooyer, R.J. Wanders, J.V. Leonard, A lethal defect of mitochondrial and peroxisomal fission, N. Engl. J. Med. 356 (2007) 1736–1741.
[174] C.R. Chang, C.M. Manlandro, D. Arnoult, J. Stadler, A.E. Posey, R.B. Hill, C. Blackstone, A lethal de novo mutation in the middle domain of the dynamin-related GTPase Drp1 impairs higher order assembly and mitochondrial division, J. Biol. Chem. 285 (2010) 32494–32503.
[175] H. Ashrafian, L. Docherty, V. Leo, C. Towlson, M. Neilan, V. Steeples, C.A. Lygate, T. Hough, S. Townsend, D. Williams, S. Wells, D. Norris, S. Glyn-Jones, J. Land, I. Barbaric, Z. Lalanne, P. Denny, D. Szumska, S. Bhattacharya, J.L. Griffin, I. Hargreaves, N. Fernandez-Fuentes, M. Cheeseman, H. Watkins, T.N. Dear, A mutation in the mitochondrial fission gene Dnm1l leads to cardiomyopathy, PLoS Genet. 6 (2010) e1001000.
[176] A. Tanaka, S. Kobayashi, Y. Fujiki, Peroxisome division is impaired in a CHO cell mutant with an inactivating point-mutation in dynamin-like protein 1 gene, Exp. Cell Res. 312 (2006) 1671–1684.
[177] N. Ishihara, M. Nomura, A. Jofuku, H. Kato, S.O. Suzuki, K. Masuda, H. Otera, Y. Nakanishi, I. Nonaka, Y. Goto, N. Taguchi, H. Morinaga, M. Maeda, R. Takayanagi, S. Yokota, K. Mihara, Mitochondrial fission factor Drp1 is essential for embryonic development and synapse formation in mice, Nat. Cell Biol. 11 (2009) 958–966.
[178] J. Wakabayashi, Z. Zhang, N. Wakabayashi, Y. Tamura, M. Fukaya, T.W. Kensler, M. Iijima, H. Sesaki, The dynamin-related GTPase Drp1 is required for embryonic and brain development in mice, J. Cell Biol. 186 (2009) 805–816.
[179] M. Baes, P. Aubourg, Peroxisomes, myelination, and axonal integrity in the CNS, Neuroscientist 15 (2009) 367–379.
[180] L. Hulshagen, O. Krysko, A. Bottelbergs, S. Huyghe, R. Klein, P.P. Van Veldhoven, P.P. De Deyn, R. D'Hooge, D. Hartmann, M. Baes, Absence of functional peroxisomes from mouse CNS causes dysmyelination and axon degeneration, J. Neurosci. 28 (2008) 4015–4027.
[181] C.M. Kassmann, C. Lappe-Siefke, M. Baes, B. Brugger, A. Mildner, H.B. Werner, O. Natt, T. Michaelis, M. Prinz, J. Frahm, K.A. Nave, Axonal loss and neuroinflammation caused by peroxisome-deficient oligodendrocytes, Nat. Genet. 39 (2007) 969–976.
[182] N.A. Bonekamp, K. Vormund, R. Jacob, M. Schrader, Dynamin-like protein 1 at the Golgi complex: a novel component of the sorting/targeting machinery en route to the plasma membrane, Exp. Cell Res. 316 (2010) 3454–3467.
[183] V. Costa, M. Giacomello, R. Hudec, R. Lopreiato, G. Ermak, D. Lim, W. Malorni, K.J. Davies, E. Carafoli, L. Scorrano, Mitochondrial fission and cristae disruption increase the response of cell models of Huntington's disease to apoptotic stimuli, EMBO Mol. Med. 2 (2010) 490–503.
[184] X. Qi, M.H. Disatnik, N. Shen, R.A. Sobel, D. Mochly-Rosen, Aberrant mitochondrial fission in neurons induced by protein kinase C{delta} under oxidative stress conditions in vivo, Mol. Biol. Cell 22 (2011) 256–265.
[185] D.I. James, P.A. Parone, Y. Mattenberger, J.C. Martinou, hFis1, a novel component of the mammalian mitochondrial fission machinery, J. Biol. Chem. 278 (2003) 36373–36379.
[186] Y.J. Lee, S.Y. Jeong, M. Karbowski, C.L. Smith, R.J. Youle, Roles of the mammalian mitochondrial fission and fusion mediators Fis1, Drp1, and Opa1 in apoptosis, Mol. Biol. Cell 15 (2004) 5001–5011.
[187] D. Stojanovski, O.S. Koutsopoulos, K. Okamoto, M.T. Ryan, Levels of human Fis1 at the mitochondrial outer membrane regulate mitochondrial morphology, J. Cell Sci. 117 (2004) 1201–1210.

[188] Y. Yoon, E.W. Krueger, B.J. Oswald, M.A. McNiven, The mitochondrial protein hFis1 regulates mitochondrial fission in mammalian cells through an interaction with the dynamin-like protein DLP1, Mol. Cell. Biol. 23 (2003) 5409–5420.
[189] M.N. Serasinghe, Y. Yoon, The mitochondrial outer membrane protein hFis1 regulates mitochondrial morphology and fission through self-interaction, Exp. Cell Res. 314 (2008) 3494–3507.
[190] M.A. Karren, E.M. Coonrod, T.K. Anderson, J.M. Shaw, The role of Fis1p-Mdv1p interactions in mitochondrial fission complex assembly, J. Cell Biol. 171 (2005) 291–301.
[191] A.D. Mozdy, J.M. McCaffery, J.M. Shaw, Dnm1p GTPase-mediated mitochondrial fission is a multi-step process requiring the novel integral membrane component Fis1p, J. Cell Biol. 151 (2000) 367–380.
[192] H.K. Delille, M. Schrader, Targeting of hFis1 to peroxisomes is mediated by Pex19p, J. Biol. Chem. 283 (2008) 31107–31115.
[193] S. Wasiak, R. Zunino, H.M. McBride, Bax/Bak promote sumoylation of DRP1 and its stable association with mitochondria during apoptotic cell death, J. Cell Biol. 177 (2007) 439–450.
[194] H. Otera, K. Mihara, Discovery of the membrane receptor for mitochondrial fission GTPase Drp1, Small GTPases 2 (2011) 167–172.
[195] R.C. Wells, R.B. Hill, The cytosolic domain of Fis1 binds and reversibly clusters lipid vesicles, PLoS One 6 (2011) e21384.
[196] L.C. Gomes, L. Scorrano, High levels of Fis1, a pro-fission mitochondrial protein, trigger autophagy, Biochim. Biophys. Acta 1777 (2008) 860–866.
[197] D.F. Suen, K.L. Norris, R.J. Youle, Mitochondrial dynamics and apoptosis, Genes Dev. 22 (2008) 1577–1590.
[198] C.S. Palmer, L.D. Osellame, D. Laine, O.S. Koutsopoulos, A.E. Frazier, M.T. Ryan, MiD49 and MiD51, new components of the mitochondrial fission machinery, EMBO Rep. 12 (2011) 565–573.
[199] J. Zhao, T. Liu, S. Jin, X. Wang, M. Qu, P. Uhlen, N. Tomilin, O. Shupliakov, U. Lendahl, M. Nister, Human MIEF1 recruits Drp1 to mitochondrial outer membranes and promotes mitochondrial fusion rather than fission, EMBO J. 30 (2011) 2762–2778.
[200] D. Dikov, A.S. Reichert, How to split up: lessons from mitochondria, EMBO J. 30 (2011) 2751–2753.
[201] K.A. Sacksteder, S.J. Gould, The genetics of peroxisome biogenesis, Annu. Rev. Genet. 34 (2000) 623–652.
[202] A. Cimini, E. Benedetti, B. D'Angelo, L. Cristiano, S. Falone, S. Di Loreto, F. Amicarelli, M.P. Ceru, Neuronal response of peroxisomal and peroxisome-related proteins to chronic and acute Abeta injury, Curr. Alzheimer Res. 6 (2009) 238–251.
[203] V.I. Titorenko, S.R. Terlecky, Peroxisome metabolism and cellular aging, Traffic 12 (2011) 252–259.
[204] S. Nagotu, A.M. Krikken, M. Otzen, J.A. Kiel, M. Veenhuis, I.J. van der Klei, Peroxisome fission in Hansenula polymorpha requires Mdv1 and Fis1, two proteins also involved in mitochondrial fission, Traffic 9 (2008) 1471–1484.
[205] S. Nagotu, R. Saraya, M. Otzen, M. Veenhuis, I.J. van der Klei, Peroxisome proliferation in Hansenula polymorpha requires Dnm1p which mediates fission but not de novo formation, Biochim. Biophys. Acta 1783 (2008) 760–769.
[206] J.J. Smith, M. Marelli, R.H. Christmas, F.J. Vizeacoumar, D.J. Dilworth, T. Ideker, T. Galitski, K. Dimitrov, R.A. Rachubinski, J.D. Aitchison, Transcriptome profiling to identify genes involved in peroxisome assembly and function, J. Cell Biol. 158 (2002) 259–271.
[207] J.A. Kiel, I.J. van der Klei, Proteins involved in microbody biogenesis and degradation in Aspergillus nidulans, Fungal Genet. Biol. 46 (Suppl. 1) (2009) S62–S71.
[208] X. Zhang, J. Hu, The Arabidopsis chloroplast division protein DYNAMIN-RELATED PROTEIN5B also mediates peroxisome division, Plant Cell 22 (2010) 431–442.