J Inherit Metab Dis (2015) 38:681–702
DOI 10.1007/s10545-015-9819-7

SSIEM 2014

Peroxisome-mitochondria interplay and disease

Michael Schrader · Joseph Costello · Luis F. Godinho · Markus Islinger

Received: 15 December 2014 / Revised: 21 January 2015 / Accepted: 26 January 2015 / Published online: 17 February 2015

Abstract Peroxisomes and mitochondria are ubiquitous, highly dynamic organelles with an oxidative type of metabolism in eukaryotic cells. Over the years, substantial evidence has been provided that peroxisomes and mitochondria exhibit a close functional interplay which impacts on human health and development. The so-called "peroxisome-mitochondria connection" includes metabolic cooperation in the degradation of fatty acids, a redox-sensitive relationship, an overlap in key components of the membrane fission machineries and cooperation in anti-viral signalling and defence. Furthermore, combined peroxisome-mitochondria disorders with defects in organelle division have been revealed. In this review, we present the latest progress in the emerging field of peroxisomal and mitochondrial interplay in mammals with a particular emphasis on cooperative fatty acid β-oxidation, redox interplay, organelle dynamics, cooperation in anti-viral signalling and the resulting implications for disease.

Presented at the Annual Symposium of the Society for the Study of Inborn Errors of Metabolism, Innsbruck, Austria, 2–5 September 2014

Communicated by: Jerry Vockley

M. Schrader (✉) · J. Costello
College of Life and Environmental Sciences, Biosciences, University of Exeter, Geoffrey Pope Building, Stocker Road, Exeter EX4 4QD, UK
e-mail: m.schrader@exeter.ac.uk

M. Schrader · L. F. Godinho
Centre for Cell Biology & Department of Biology, University of Aveiro, 3810-193 Aveiro, Portugal

M. Islinger
Neuroanatomy, Center for Biomedicine and Medical Technology Mannheim, University of Heidelberg, 68167 Mannheim, Germany

Introduction

Peroxisomes represent a class of ubiquitous and dynamic single membrane-bound organelles in eukaryotic cells. They are devoid of DNA, but are similar to mitochondria in that they show an oxidative type of metabolism. Peroxisomes fulfil important functions in hydrogen peroxide and lipid metabolism, which renders them essential for human health and development (Wanders and Waterham 2006). In addition, peroxisomes can act as important intracellular signalling platforms in redox-, lipid-, inflammatory-, and innate immunity signalling (Odendall and Kagan 2013; Nordgren and Fransen 2014). In order to perform their multiple functions, peroxisomes are supposed to closely cooperate and interact with other cellular organelles, including mitochondria (Fig. 1), the endoplasmic reticulum (ER), and lipid droplets (Schrader et al 2013). In this review we will mainly focus on findings obtained in mammals and mammalian cells.

Over the years, substantial evidence has been provided that peroxisomes and mitochondria exhibit a close functional interplay (Schrader and Yoon 2007; Schrader et al 2013) (Fig. 2). This is perhaps best illustrated by the metabolic cooperation of mitochondria and peroxisomes in the β-oxidation of fatty acids to maintain lipid homeostasis (Fig. 3) (Wanders 2013) (see Metabolic cooperation of peroxisomes and mitochondria section). More recently it has become evident that peroxisomes and mitochondria contribute to cellular ROS homeostasis and share a redox-sensitive relationship (Fig. 4a) (Fransen et al 2012) (see Peroxisomal and mitochondrial redox relationship section). Remarkably, both organelles also share key proteins of their division machinery which highlights a coordinated biogenesis under certain conditions and demands organised targeting and recruitment of those proteins (Fig. 5) (Delille et al 2009; Schrader et al 2012) (see Peroxisomal and mitochondrial membrane dynamics

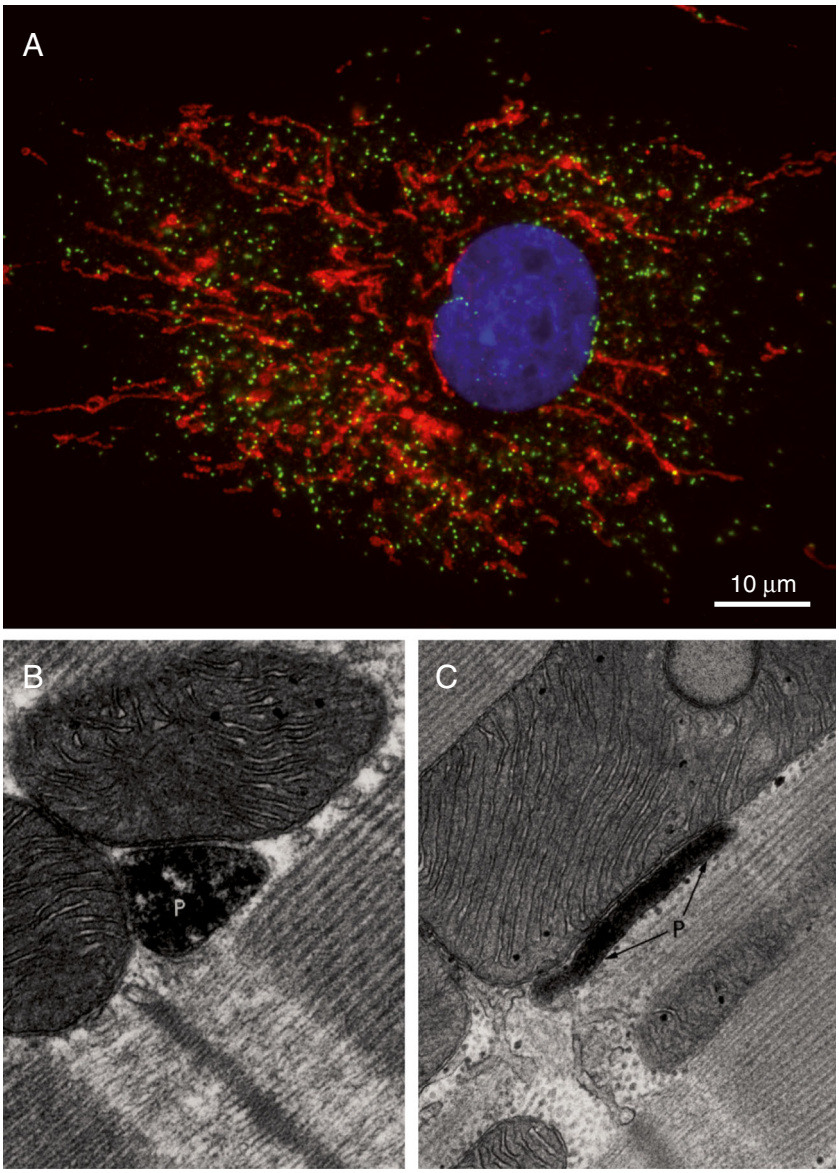

Fig. 1 Mitochondria and peroxisomes in mammalian cells. (**a**) Immunofluorescence microscopy showing the distribution and morphology of mitochondria (red) and peroxisomes (green) in human skin fibroblasts. Cells were stained with antibodies to Pex14, a peroxisomal membrane protein, and to mitochondrial Tom20. (**b-c**) Electron micrographs showing intimate physical interactions of peroxisomes (P) (black) and mitochondria in the myocardium of rodents and primates. (**b**) Rabbit Heart, Mag. 57,000 ×; (**c**) Elongated peroxisome; Heart of *Macaca java*, Mag. 52,500×(from Hicks and Fahimi 1977). Peroxisomes were stained by catalase cytochemistry using the alkaline diamino-benzidine technique

section). Furthermore, peroxisomes and mitochondria cooperate in anti-viral signalling and defence (Fig. 4b) (Dixit et al 2010; Kagan 2012) (see Cooperative roles of peroxisomes and mitochondria in viral combat section). The mechanisms of communication between the two organelles are still elusive, but diffusion processes (e.g. via PXMP2, a channel-forming peroxisomal membrane protein), physical contact sites (Fig. 1) and vesicular transport have all been implicated (Antonenkov and Hiltunen 2012; Horner et al 2011; Neuspiel et al 2008). The latter mechanism is based on the observation that a class of mitochondria-derived vesicles (MDVs) interact and fuse with peroxisomes (Sugiura et al 2014). However, the physiological role of this process is still unclear, and evidence for a vesicular transport route from peroxisomes to mitochondria is missing.

Based on the above findings, we proposed the medically relevant concept of the "peroxisome-mitochondrion connection" suggesting that peroxisomal alterations in metabolism, biogenesis, dynamics and proliferation can potentially influence mitochondrial functions, and *vice versa* (Camoes et al 2009; Schrader et al 2013). In early studies, morphological and biochemical alterations of mitochondria were already reported in parallel with the absence of peroxisomes in the livers and kidneys of patients suffering from Zellweger syndrome (Goldfischer et al 1973). Consequently, it was initially considered that Zellweger patients were suffering from either a peroxisomal or a mitochondrial defect (Kelley 1983) before the loss of peroxisome integrity and function was identified as the primary cause of this severe peroxisomal biogenesis disorder (Borst 1983, 1986; Singh et al 1984).

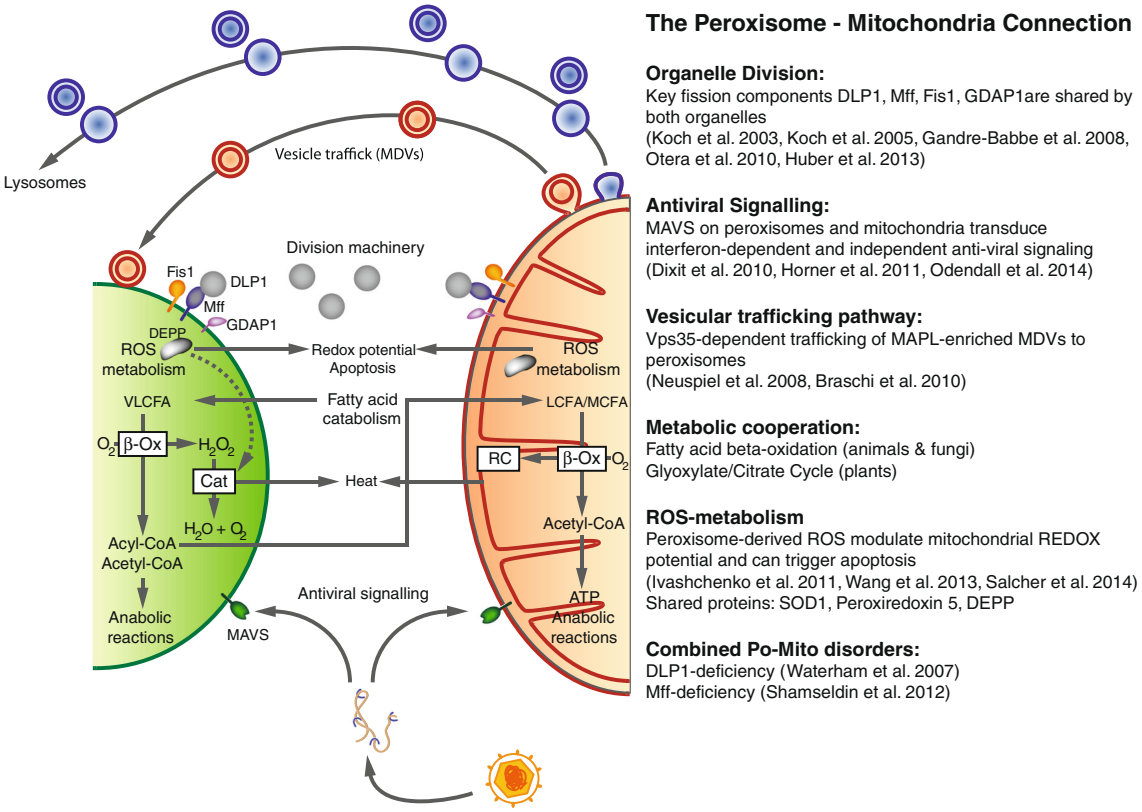

Fig. 2 Overview of the interconnections between peroxisomes (left) and mitochondria (right) in mammals. β-Ox, fatty acid β-oxidation; Cat, peroxisomal catalase; RC, respiratory chain; VLCFA, LCFA, MCFA, very long-chain, long-chain and medium chain fatty acids (adapted from Islinger et al 2012)

Moreover, ultrastructural (e.g. swollen mitochondria, alterations at the inner mitochondrial membrane) and functional alterations of mitochondria (e.g. impaired activity of respiratory chain complexes) were reported in knockout mouse models for peroxisomal disorders (Baumgart et al 2001; McGuinness et al 2003; Dirkx et al 2005; Ferrer et al 2005). In a recent study loss of peroxisomal metabolism in hepatocytes by liver-specific knockdown of PEX5 revealed perturbation of the mitochondrial inner membrane, depletion of mitochondrial DNA, increased oxidative stress and promotion of mitochondrial biogenesis independent of PGC-1α (Peeters et al 2014). Acute deletion of PEX5 in vivo using adeno-Cre virus mimicked these effects, suggesting that mitochondrial perturbations rapidly occur following loss of functional peroxisomes (Peeters et al 2014). In line with this, features of a concomitant mitochondrial myopathy were reported in Zellweger patients underscoring the role of secondary mitochondrial dysfunction in Zellweger syndrome, potentially contributing to the clinical phenotype (Salpietro et al 2014). These findings are in support of a tight interplay between peroxisomes and mitochondria and highlight potential compensatory roles between both organelles.

Metabolic cooperation of peroxisomes and mitochondria

The cooperation of peroxisomes and mitochondria in the β-oxidation of fatty acids is perhaps the best known example for peroxisome-mitochondria crosstalk (Figs. 2 and 3). Below we will address the fatty acid β-oxidation pathways in mammals in detail (Fatty acid β-oxidation — the principal pathways in mammals), highlight their regulation (PPARα and beyond — regulators for peroxisomal and mitochondrial fatty acid β-oxidation), and discuss functional aspects of peroxisomal and mitochondrial β-oxidation (Functional aspects of β-oxidation in peroxisomes and mitochondria). Furthermore, we will address organelle interplay and fatty acid metabolism disorders (The fatty acid metabolism disorders — incidence for a mitochondrial-peroxisomal interplay?). It should be noted that crosstalk between both organelles is not restricted to fatty acid β-oxidation and that other metabolic pathways in peroxisomes also depend on mitochondria for subsequent metabolism. Examples include the detoxification of glyoxylate, which in humans requires the enzyme alanine-glyoxylate aminotransferase (AGT) that converts glyoxylate and alanine into glycine and pyruvate in peroxisomes. Glycine is then routed to mitochondria for oxidation by the glycine cleavage pathway

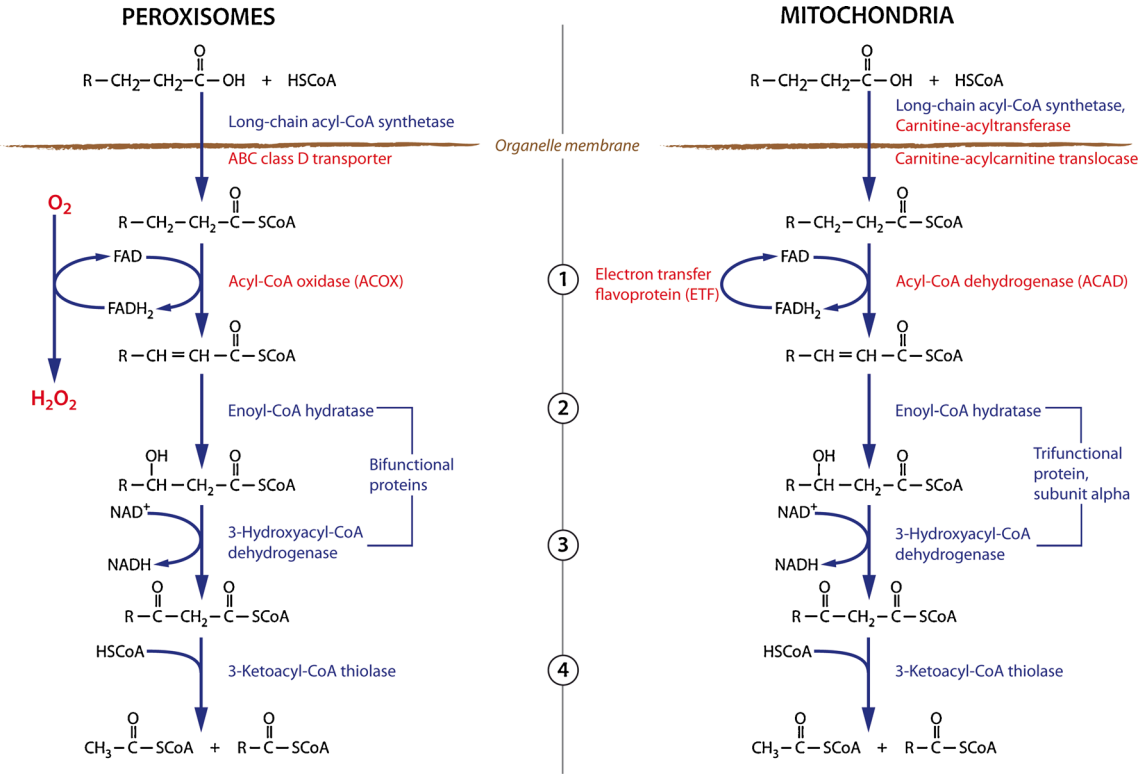

Fig. 3 Comparison of peroxisomal and mitochondrial fatty acid β-oxidation pathways. As long-chain fatty acids cannot pass the organelle membranes by mere diffusion, fatty acids have to be actively transported across both peroxisomal and mitochondrial membranes. Prior to transport, fatty acids are activated outside the organelle by conjugation to either coenzyme A (peroxisomes) or carnitine (mitochondria). The activated long-chain fatty acids are imported into the organelles by specific import systems, whereas short- and medium chain fatty acids are supposed to enter mitochondria by diffusion prior to activation. Subsequently, fatty acids are degraded by β-oxidation in peroxisomes and mitochondria in four consecutive reactions (① - ④). Concerning substrate specificity, peroxisomes degrade long- to very long-chain fatty acids (> C16) down to a chain length of 6–8 carbon atoms. The chain-shortened fatty acids are subsequently exported to mitochondria, which preferentially metabolize long- to short chain fatty acids. Mechanistic differences in fatty acid import and the catabolic reactions carried out in peroxisomes and mitochondria are marked in red; note that the enzyme sets required for steps ② to ④ show a phylogenetic relationship in both organelles, whereas ACOX appear to be a peroxisomal invention. Steps ② and ③ are combined in bifunctional enzymes (D-BP, L-BP) in peroxisomes. Mitochondria possess both, individual enzymes for each step of the pathway as well as a trifunctional enzyme consisting of two polypeptide chains (HadhA, HadhB) combining steps ② to ④ (from Camoes et al 2014)

(Wanders et al 2011). In addition, peroxisomal α-oxidation of phytanic acid relies on mitochondria. The peroxisomal enzyme phytanoyl-CoA hydroxylase catalyses the hydroxylation of phytanoyl-CoA into 2-hydroxyphytanoyl-CoA using 2-oxoglutarate as co-substrate with succinate and CO_2 as products. The 2-oxoglutarate can be regenerated from succinate via part of the citric acid cycle in mitochondria further highlighting the crosstalk between both organelles (Wanders et al 2011). Furthermore, continued peroxisomal fatty acid α-oxidation requires ATP which is most likely generated by the mitochondrial oxidative phosphorylation system (Wanders et al 2011).

Fatty acid β-oxidation — the principal pathways in mammals

The identification of a peroxisomal fatty acid β-oxidation system in mammals (Lazarow and De Duve 1976) may be regarded as an initiating discovery for the functional interconnection between peroxisomes and mitochondria. Indeed, both organelles possess an astonishingly similar enzyme inventory for the catabolism of fatty acids (Fig. 3). During the subsequent decade research on peroxisomes was primarily focused on deciphering the functional differences between the peroxisomal and mitochondrial pathways, which show differential but overlapping substrate spectra. Generally, the terminology for fatty acids with different chain length varies among literature, especially if β-oxidation is viewed from a "peroxisomal" or "mitochondrial" perspective. In this review we will refer to "very long-chain" for fatty acids with a backbone>C20, "long-chain" between C20 and C16, "medium-chain" between C14 and C8 and "short-chain"<C8. Prior to degradation by β-oxidation, fatty acids have to enter the organelles. Short- and medium-chain fatty acids are comparably water-soluble and may enter organelles by diffusion through unselective pores (Antonenkov and Hiltunen 2012). The hydrophobic long- and very long-chain fatty acids (VLCFAs), however, require special transporters to cross cellular membranes (Fig. 3). In both organelles this transport requires a previous

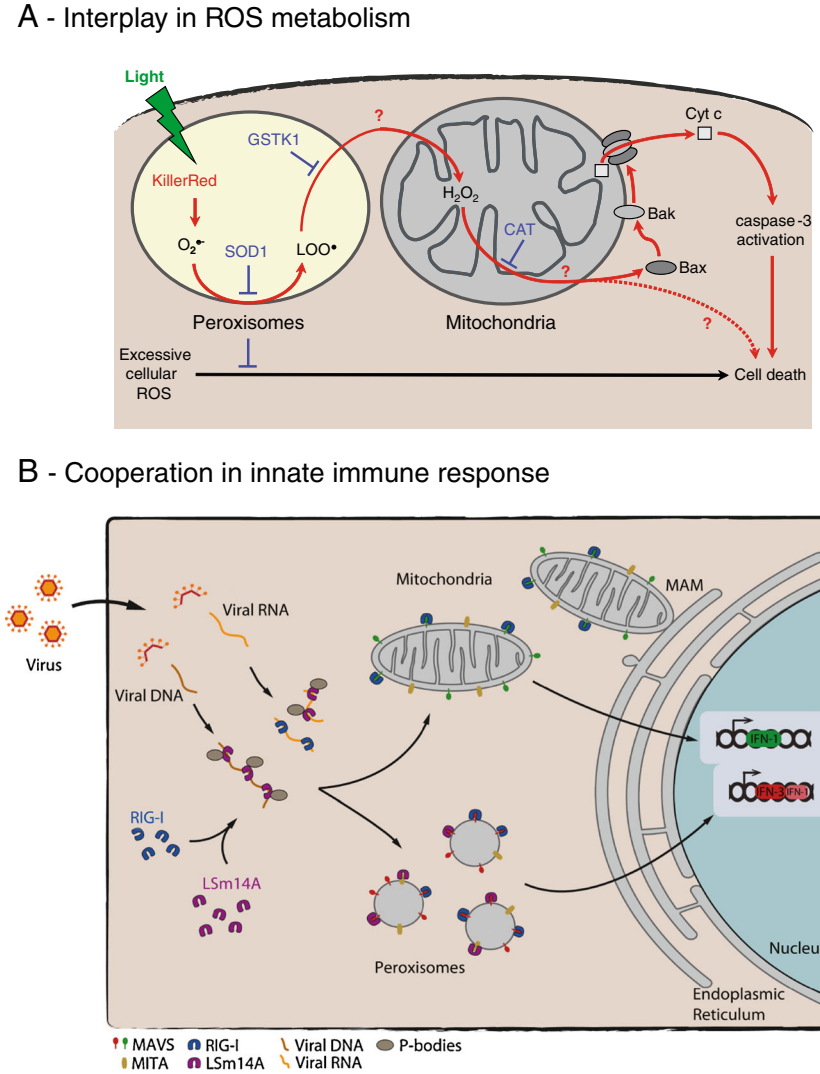

Fig. 4 (**a**) Redox-sensitive relationship between peroxisomes and mitochondria. Oxidative stress generated in peroxisomes by the genetically-encoded photosensitizer KillerRed induces mitochondria-mediated cell death. KillerRed is supposed to generate superoxide radicals in peroxisomes and to result in lipid peroxidation. Peroxisomal KillerRed results in the generation of H_2O_2 in mitochondria which initiates cell death, partially mediated by Bax, Bak, cytochrome c and caspase-3 activation. This process can be counteracted by targeted overexpression of peroxisomal glutathione-S-transferase kappa 1 (GSTK1), superoxide dismutase 1 (SOD1) and mitochondrial (but not peroxisomal) catalase (CAT). See text for details (from Wang et al 2013). (**b**) Cooperation of mitochondria and peroxisomes in cellular antiviral innate immune response. Upon viral infection, viral RNA is recognized by the RNA helicase RIG-I (retinoic acid-inducible gene 1 protein) or LSm14A, a processing body-associated protein, in the cytosol. Active RIG-I interacts with MAVS (mitochondrial antiviral-signalling protein), a membrane adaptor protein which localizes to mitochondria, peroxisomes and mitochondria-associated membranes (MAM). Viral DNA can be recognized by LSm14A, which interacts with MITA (mediator of IRF3 activation) at peroxisomes. Each recognition pathway mediates an anti-viral response with different kinetics and downstream effectors. See text for details

activation step producing acyl-CoA. To this end peroxisomes and mitochondria in mammals possess various acyl-CoA synthetases associated to the protein families of long-chain acyl-CoA synthetases (ACSL) and fatty acid transport proteins (FATP). However, there is still some uncertainty as to which proteins reside on peroxisomes and mitochondria. Originally, palmitoyl-CoA synthetase (ACSL1) was described as a protein shared by peroxisomes, mitochondria and the ER (Bronfman et al 1984). Following the identification of several ACSL isoforms, two subsequent studies, using ACSL-specific antibodies, suggested that ACSL5 localizes to mitochondria, ACSL4 to peroxisomes and ACSL1 to microsomes (Lewin et al 2001, 2002). In contrast, recent quantitative proteomic studies showed an enrichment of ACSL1 and ACSL5 in peroxisomal fractions (Wiese et al 2007; Islinger et al 2010; Gronemeyer et al 2013), but failed to identify ACSL4. Moreover, ACSL3 was recently described as a constituent of mitochondria and the endoplasmic reticulum (Wu et al 2011). Besides ACSL, mitochondria and peroxisomes appear to contain acyl-CoA synthetases of the FATP-class: FATP1 and FATP2,

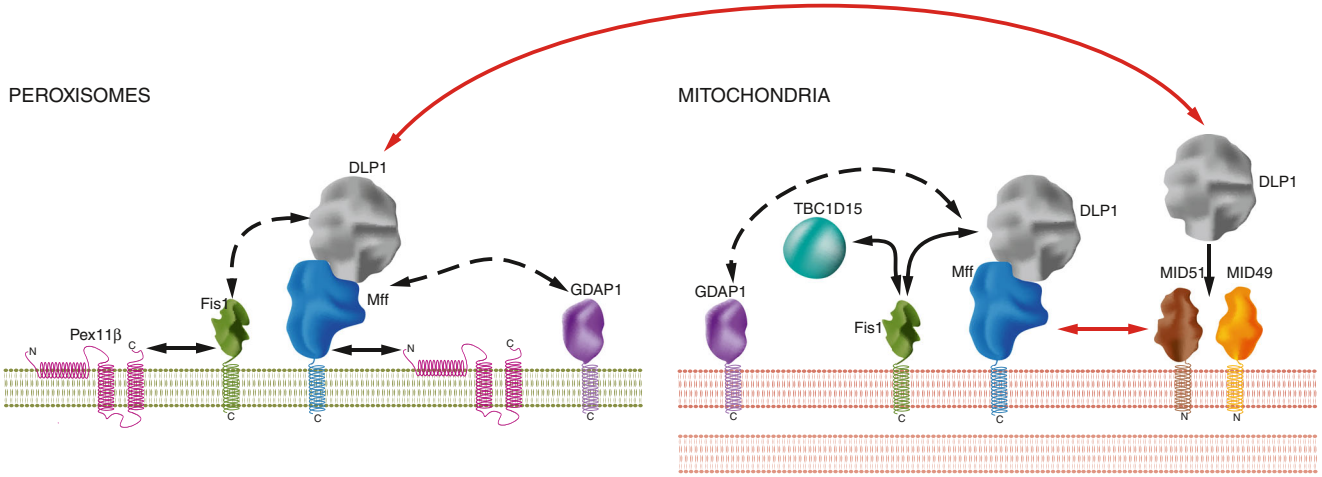

Fig. 5 Schematic view of the key fission proteins and interaction partners on peroxisomes and mitochondria in mammals. Shared key components of the mitochondrial and peroxisomal fission machineries include DLP1, a large dynamin-like GTPase involved in final membrane scission of constricted membranes, and the DLP1-membrane adaptor proteins Mff and Fis1. Mff is supposed to be the major DLP1 receptor for organelle fission. GDAP1 can regulate both mitochondrial and peroxisomal morphology and division in an Mff and DLP1-dependent manner. The peroxin Pex11pβ is an exclusively peroxisomal membrane protein involved in the regulation of peroxisome abundance and in membrane deformation/elongation prior to fission. Pex11pβ can oligomerize and interacts with both Fis1 and Mff, which can homodimerize as well. Mid51 and Mid49 are mitochondrial membrane adaptors which can sequester DLP1 and inhibit its function. This process may be regulated by mitochondrial Fis1, which interacts with TBC1D15, a Rab GTPase activating protein. Upregulation of Mid49 on mitochondria can deplete DLP1 from peroxisomes resulting in peroxisome elongation due to reduced division (red arrow). See text for details

respectively (Sebastian et al 2009; Falcon et al 2010). FATP2 was earlier described as a very long-chain synthetase (VLACS) localized to peroxisomes and microsomes (Uchida et al 1996). In knockdown experiments, Falcon et al (2010) demonstrated that FATP2 is involved in the cellular uptake of long- and VLCFAs at the plasma membrane and peroxisomes, where it contributes to approximately 50 % of fatty acid import. Besides these findings, the mechanistic contribution of FATP2 to peroxisomal fatty acid import remains mysterious. At the plasma membrane FATP2 was reported to be directly involved in the transport of fatty acids prior to CoA coupling (Melton et al 2013). In line with this, acyl-CoA synthetase activity of VLACS was localized inside peroxisomes (Lazo et al 1990). Thus, it remains to be clarified if peroxisomal FATP2 is more than just a VLACS and also involved in fatty acid transport. In addition, other shuttle systems for acyl-CoA exist in peroxisomes and mitochondria and differ substantially between both organelles. The relatively small and medium chain-fatty acids are supposed to be able to enter the mitochondria by diffusion, whereas long chain fatty acids (C14–C20) require a transport system. In mitochondrial fatty acid import, acyl-groups are first transferred from CoA to carnitine, translocated across the inner mitochondrial membrane as carnitine-esters and finally the carnitine-group is re-exchanged to CoA for further processing (Fig. 3). For this process, mitochondria in mammals contain a single carnitine palmitoyl-transferase – CPT2 – and a single carnitine acyl-carnitine translocase (CACT) at the inner mitochondrial membrane. For the initial conversion of acyl-CoA to acyl-carnitine, however, they possess three CPT1 isoforms (a-c), which are encoded by individual genes (Bonnefont et al 2004). Peroxisomes also likely inhabit a carnitine shuttle. However, in contrast to mitochondria, the peroxisomal CPTs have a preference for acetyl- and medium-chain acyl-CoAs and are supposed to contribute to the export of the respective fatty acids (Antonenkov and Hiltunen 2012). For fatty acid import, peroxisomes utilize three membrane proteins of the ABC transporter class (ABCD1-3) (Morita and Imanaka 2012) (Fig. 3). In plants, peroxisomal ABC transporters appear to cleave the CoA-group from the fatty acyl-chain prior to transport across the membrane. Once inside the organelle the fatty acids are reactivated by intrinsic peroxisomal acyl-CoA synthetases (VLACS) physically interacting with the transporters (De Marcos Lousa et al 2013). By contrast, mammalian peroxisomal ABC transporters were reported to directly import the acyl-CoA without the requirement of further enzymatic activities (Wiesinger et al 2013). All three mammalian transporters were recently functionally characterized by heterologous expression in a yeast strain where the endogenous orthologues have been deleted (van Roermund et al 2008, 2011, 2014). Indeed, all three are half transporters and act as dimers, which are able to transport fatty acyl-CoA across the peroxisomal membrane with a distinct but overlapping substrate spectrum. ABCD1 exhibited highest affinities to the very hydrophobic saturated VLCFAs (C24:0–C26;0), ABCD2 to slightly more hydrophilic very long-chain to long chain-fatty acids (C22:0–C24:0, C22:6) and ABCD3 to the most hydrophilic fatty acid species (C20:5) as well as dicarboxylic acids (C16:0DCA). The data for ABCD1 and ABCD2 are corroborated by the elevated levels of VLCFAs found in the respective knockout

mouse models (Lu et al 1997; Ferrer et al 2005). The recently generated ABCD3 knockout extended the spectrum of transported substrates, as the mice also showed elevated levels of bile acids (Ferdinandusse et al 2014). Thus, the individual fatty acid transporter systems function as initial filters, which according to their substrate spectrum, preferentially direct peroxisomal β-oxidation towards VLCFAs whereas mitochondria are specialized for fatty acids with shorter chain length. After import the activated fatty acyl-CoAs are degraded in both organelles in mechanistically quite similar pathways (Fig. 3). Generally, peroxisomes and mitochondria chain-shorten fatty acids stepwise by two C-atoms producing acetyl-CoA in four consecutive reactions: (1) the CoA-activated fatty acid chain is oxidized by introduction of a double bond between C2 and C3, (2) the 2-enoyl-CoA generated is hydrated forming 3-hydroxyacyl-CoA, (3) a subsequent dehydrogenation reaction produces 3-oxoacyl-CoA, which is (4) finally thiolytically cleaved into acetyl-CoA and the shortened acyl-CoA chain to be further degraded in subsequent reaction cycles. While the enzymatic reactions for steps 2–4 are comparable in both organelles, step 1 is catalyzed by an acyl-CoA oxidase (ACOX) in peroxisomes but an acyl-CoA dehydrogenase (ACAD) in mitochondria. Both proteins belong to the superfamily of flavoenzymes and share distant sequence homologies, but are mechanistically distinct. ACOXs transfer the electrons accepted during the oxidation of acyl-CoA directly to molecular oxygen thereby producing heat and the cytotoxic H_2O_2, whereas ACADs deliver the electrons to the electron transfer protein ETF1 for further integration into the ATP generating mitochondrial electron transfer chain of the inner membrane (Figs. 2 and 3). Thus, mitochondrial β-oxidation is able to generate an additional two ATP molecules per cleavage cycle if compared to the peroxisomal system. With regard to the enzyme inventory responsible for the pathway, both organelles contain several enzymes for each reaction step, which have different affinities for individual fatty acid species. Mammalian peroxisomes possess three ACOXs: (1) ACOX1 — with a substrate spectrum of saturated and unsaturated straight chain as well as dicarboxylic acids, (2) ACOX2 — acting on 2-methylacyl-CoAs, and (3) ACOX3 which is able to process both methyl-branched and straight chain fatty acids (Van Veldhoven 2010). Furthermore, the animal genome is predicted to contain a fourth ACOX gene (ACOXL) with different splice variants with and without a peroxisomal targeting signal (PTS1). However, no experimental data on the localization and enzymatic properties of this ACOX exist to date. Mammalian mitochondria contain up to eight ACADs for the first step in β-oxidation (Shen et al 2009). According to their substrate specificity the most prominent ones are named very long-chain (ACADV), long-chain (ACADL), medium-chain (ACADM), short-chain (ACADS) and short branched-chain (ACDSB) acyl-CoA dehydrogenase. More recently, three additional ACADs (ACAD9-11) have been identified. All three were reported to possess enzymatic activities to very long- and long-chain fatty acids (Zhang, Zhang et al 2002; He et al 2007; He et al 2011). Interestingly, ACAD11 has been shown to also be targeted to peroxisomes in mammals and fungi (Islinger et al 2007; Wiese et al 2007; Camoes et al 2014) and resides predominantly in peroxisomes of rodent liver (Camoes et al 2014) which suggests that ACAD11 is an ancient peroxisomal protein. The second and third steps of the pathway are catalyzed by a single enzyme in both subcellular compartments (Fig. 3). In peroxisomes there are two bifunctional enzymes (PBE) with different stereoselectivity — the L- and the D-PBE combining enoyl-CoA hydratase and 3-hydoxyacly CoA dehydrogenase functions. Interestingly, both proteins are not phylogenetically linked, since the two L-PBE domains are true members of the crotonase and 3-hydoxyacly CoA dehydrogenase protein families whereas the D-PBE is a fusion of a short chain dehydrogenase and a hot dog superfamily member. In this respect, the L-PBE shares more similarities with the respective mitochondrial enzymes. With regard to their function, the D-PBE seems to be majorly involved in the processing of very long-chain and branched-chain fatty acids, whereas the physiological role of the L-PBE is not fully understood (Wanders et al 2010), but appears to be involved in the degradation of long- to medium-chain dicarboxylic acids produced during microsomal fatty acid ω-oxidation (Houten et al 2012; Ding et al 2013). In mitochondria the respective reactions for long- to medium-chain fatty acids are performed by a similar fusion protein, the α-subunit of the trifunctional enzyme (TFP), which is acting in a multi-enzyme complex with the 3-ketoacyl-CoA thiolase β-subunit (Fig. 3). Medium– to short-chain fatty acids, however, are processed by individual hydratases, dehydrogenases and thiolases (Bartlett and Eaton 2004). The last step of peroxisomal β-oxidation is again performed by two enzymes: the classic peroxisomal 3-ketoacyl-COA thiolase (ACAA1) and SCP-X, a fusion between a sterol carrier protein and a thiolase domain (Fig. 3). Whereas the ACAA1 metabolizes only straight-chain fatty acids, SCP-X shows a broader substrate range and is able to also process branched-chain fatty acids and bile acid precursors (Wanders et al 2010). In addition to these inventories for the principle steps of β-oxidation in peroxisomes and mitochondria, both organelles house several auxiliary enzymes for the degradation of mono- and polyunsaturated fatty acids including enoyl-CoA isomerase and di-enoyl-CoA reductase enzymes as well as racemases. A detailed description of these enzymes is beyond the scope of this review (see Houten and Wanders 2010; Van Veldhoven 2010) for further details).

PPARα and beyond — regulators for peroxisomal and mitochondrial fatty acid β-oxidation

Mitochondrial and peroxisomal β-oxidation is under metabolic control of intermediates of this pathway which are described in closer detail in recent reviews (Saggerson 2008; Hunt et al 2014). However, lipid metabolism in both organelles is also coordinated at the level of gene expression. Indeed, in parallel with the initial biochemical characterization of peroxisomes by Christian de Duve in 1965 (de Duve 1965) the effect of fibrates on peroxisome numbers and lipid metabolism was detected (Hess et al 1965; Svoboda and Azarnoff 1966). However, the mechanistic explanation for this phenomenon remained undiscovered for another 25 years, when Issemann and Green (1990) discovered the peroxisome proliferation activating nuclear receptor (PPAR) α and its impact on cellular peroxisome abundance. Since then three members of this nuclear receptor subfamily have been characterized in humans (PPARα, γ, δ) and all have been shown to be involved in the transcriptional control of lipid homeostasis but show distinct ligand affinities, tissue specific expression patterns and target different genes (Menendez-Gutierrez et al 2012). With respect to their individual function, PPARα, which is most prominently expressed in liver and kidney, is focused on the activation of lipid catabolic processes. Correspondingly, PPARα induces the transcription of genes regulating peroxisome biogenesis in response to saturated and unsaturated long-chain fatty acids and associated intermediates in lipid metabolism, which are presumably its natural ligands, but also more specifically upregulates protein expression of peroxisomal β-oxidation and auxiliary enzymes (Pyper et al 2010; Reddy and Hashimoto 2001). Likewise, genes of the mitochondrial β-oxidation systems are induced by PPARα, guaranteeing a concerted regulation of both organellar systems (Cook et al 2000; Mandard et al 2004). Compared to peroxisomes, however, upregulation of β-oxidation in response to peroxisome proliferators is preferentially at the enzyme expression level, whereas a mitochondrial proliferation is much less prominent (Paget 1963; Eggens et al 1980). The functional significance of PPARα activity is most obvious during fasting. PPARα-null mice fed a standard chow develop normally, are fertile but show an increase in adipose tissue if compared to controls in later life stages (Costet et al 1998). During fasting, however, the knockout animals develop severe hypoglycemia, hypothermia, hypoketonemia and hepatic steatosis (Kersten et al 1999; Hashimoto et al 2000), emphasizing the importance of PPARα for a parallel control of both β-oxidation pathways. According to its tissue abundance, PPARα-induced activation of peroxisomal and mitochondrial β-oxidation is most prominent in the liver (Cook et al 2000). However, weak but significant activation of β-oxidation as well as peroxisome proliferation has been reported in the liver of PPARα-null mice after application of PPARγ and PPARδ agonists. Thus, it is tempting to ask, whether these transcription factors coordinate peroxisomal and mitochondrial β-oxidation in tissues, where they show higher expression rates. Indeed, PPARδ, which shows a broader tissue distribution than its two relatives, has been reported to control expression of mitochondrial and peroxisomal β-oxidation enzymes in mouse adipocytes and cardiomyocytes, resembling PPARα activation in liver (Wang et al 2003; Cheng et al 2004).

PPARγ is required for adipocyte and cardiocyte differentiation during development (Barak et al 1999). In adults activated PPARγ was reported to stimulate the expression of genes involved in fatty acid catabolism in the liver of diabetic mice (Suzuki et al 2000) but anabolic lipid pathways in adipocytes opposing PPARδ (Roberts et al 2011). Interestingly, in neurons and astrocytes PPARγ ligands seem to induce peroxisomal biogenesis (Diano et al 2011; Zanardelli et al 2014). Moreover, results from differentiated neuroblastoma cells suggest that PPARγ activation could in parallel induce mitochondrial proliferation (Corona et al 2014). However, PPARγ-mediated peroxisome and mitochondria proliferation does not include a specific activation of β-oxidation capacities besides activating biogenesis induces genes involved in the degradation of ROS (e.g. mitochondrial SOD1 or peroxisomal catalase) (Gray et al 2012; Corona et al 2014).

Peroxisome proliferator activating receptor γ co-activators (PGC) interact with PPARs in order to modulate the tissue specificity of nuclear receptor-controlled gene expression (Handschin and Spiegelman 2006). However, PGCs, which include PGC-1α, PGC-1β and PRC (PGC-1-related co-activator), interact with a variety of other nuclear receptors such as the estrogen receptor-related receptors (ERRα), hepatocyte nuclear factors (HNF4α) or muscle enhancer factors (MEF2) (Puigserver 2005). Overall, PGCs are thereby involved in the stimulation of mitochondrial oxidative metabolism and biogenesis and are abundant in tissues with high energy demands. Interestingly, PGC-1α has been recently shown to promote peroxisomal proliferation independent from PPARα in brown adipose tissue (Bagattin et al 2010). Also other transcription factors known to interact with PGC-1α like ERRα, NRF2 and Foxo1 could not be identified as factors mediating the peroxisomal PGC-response. Nevertheless, this report implies that mitochondria and peroxisomes share further transcriptional regulation systems, which are controlled by yet unknown transcription factors. In this respect, future research will likely identify additional regulative networks, which are involved in a synchronized coordination of peroxisomal and mitochondrial metabolic functions.

Functional aspects of β-oxidation in peroxisomes and mitochondria

As outlined above, peroxisomes and mitochondria metabolize an overlapping, but nevertheless substantially different fatty

acid spectrum. Under conditions of unrestricted access to fatty acids, peroxisomes metabolize preferentially long-chain fatty acids (C14–C18) (Lazarow 1978; Osmundsen et al 1979), substantially overlapping with mitochondrial capacities. In this respect, peroxisomal β-oxidation capacities mirror the enzymatic substrate specificities of the ACOXs, which have highest affinities towards long-chain fatty acids (Van Veldhoven et al 1992). In vivo, however, cellular fatty acids are majorly bound to fatty acid binding proteins and free fatty acid concentrations are low. Under such conditions, mitochondrial β-oxidation is the dominating pathway for the degradation of long-chain fatty acids, which are the most frequent fatty acids in fat deposits (Mannaerts et al 1979; Foerster et al 1981). In contrast, under such conditions peroxisomes are specialized on degradation of very long-chain and branched-chain fatty acids, which accumulate in inherited peroxisomal disorders (see below). Thus the physiological role of peroxisomal β-oxidation is not determined by the enzymatic capacities of their ACOXs but by the transport systems across their membrane. In this respect, the peroxisomal ABC-transporters, according to their transport capacities, ensure that peroxisomes receive preferentially the less frequent but toxic VLCFAs for degradation (van Roermund et al 2011, 2014). Nevertheless, the estimations for the actual contribution of peroxisomes to the total cellular β-oxidation vary substantially, depending on experimental conditions, ranging from<5 % to up to 30 % for rodent hepatocytes (Thomas et al 1980; Kondrup and Lazarow 1985). After import, peroxisomes degrade fatty acids not to completion, and according to the substrate affinities of their respective enzymes only chain-shorten fatty acids to chain length of approx. C8-C6. These medium-chain fatty acids appear to be exported to mitochondria for subsequent degradation. For this reason, peroxisomes likely contain a carnitine shuttle system, as they possess medium-chain and short-chain specific acylcarnitine transferases (Markwell et al 1973; Farrell and Bieber 1983). However, until now the existence of a respective membrane translocase could not be convincingly proven (Antonenkov and Hiltunen 2012). Moreover, as an export alternative, peroxisomal thioesterases produce internal medium-chain fatty acids which are able to freely diffuse through peroxisomal membrane pores into the surrounding cytosol (Westin et al 2008).

Taken together, the contribution of mitochondria and peroxisomes to β-oxidation in animals appears to be adapted towards most efficient energy production, as mitochondria produce two additional ATP molecules in the first reaction step per degradation cycle. In this scenario, peroxisomes preferentially metabolize those fatty acids, which do not meet the substrate range of the mitochondria. Indeed, as revealed by fatty acid metabolizing deficiencies, mitochondrial and peroxisomal β-oxidation systems are not able to complement each other, since an up-regulation of the remaining β-oxidation system by intrinsic or pharmacological induction of PPARα does not compensate for the loss of function in the other pathway (Hashimoto et al 1999; Djouadi and Bastin 2008). From an evolutionary stand point it may appear slightly puzzling why mitochondria have not acquired the ability to also metabolize VLCFAs. In plants, which do not utilize fatty acids for energy production but to generate acetyl-CoA required in anabolic reactions, β-oxidation is entirely peroxisomal. Yeast species do also rely exclusively on peroxisomal β-oxidation but use fatty acids for energy production (Tanaka et al 1982; Kurihara et al 1992). Like in animals, in most fungi β-oxidation is shared by both compartments and has similar substrate preferences (Maggio-Hall and Keller 2004; Klose and Kronstad 2006; Freitag et al 2012; Kretschmer et al 2012a, b; Camoes et al 2014). These fungi are able to use peroxisomal β-oxidation for energy production and growth (Kretschmer et al 2012a, b). Theoretically, the energy gain from mitochondrial β-oxidation if compared to the peroxisomal system in animal cells is less than anticipated at a first glance. Provided that acetyl-CoA generated in peroxisomes can be integrated into the mitochondrial citric acid cycle, the degradation of palmitate could produce 122 ATP when performed in peroxisomes (considering octanoate is exported to mitochondria) compared to 130 ATP when entirely performed in mitochondria (Tolbert 1981). Thus the net ATP gain of an exclusively mitochondrial β-oxidation of palmitate in mammalian cells is roughly 10 %. For lignocerate (C24) the difference is already nearly 20 % as more ATP is lost during the peroxisomal β-oxidation cycles. Thus, the β-oxidation of VLCFAs has to have an advantage over the mitochondrial system which can compete with the waste of ATP. Recently it was hypothesized that mitochondrial fatty acid β-oxidation increases radical formation by an elevation of the $FADH_2$/NADH ratio if compared to carbohydrate metabolism (Speijer 2011). As $FADH_2$ enters the mitochondrial electron transport chain at complex II and NADH at complex I, high $FADH_2$ concentrations result in higher reduction rates of ubiquinone, which is then not able to accept enough electrons delivered from NADH via complex I. In the absence of its physiological electron acceptor, those electrons are surpassed to O_2 forming highly reactive superoxide radicals. As peroxisomal ACOXs do not produce $FADH_2$, which is accessible for the mitochondrial electron transport chain, but instead reduce O_2 to H_2O_2, peroxisomal β-oxidation is able to reduce the cellular $FADH_2$/NADH ratio. As the $FADH_2$/NADH ratio increases with fatty acid chain length, peroxisomal β-oxidation gets more favorable the longer the fatty acids are. Thus, the disadvantages in energy production would be compensated by the reduced production of superoxide radicals in mitochondria thus favoring peroxisomal VLCFA oxidation. In a subsequent publication the author (Speijer 2014) claimed that the radical formation in mitochondrial β-oxidation induced the evolution of peroxisomes from the ER, since key components of peroxisomal β-oxidation show significant similarities to α-proteobacterial

proteins. Indeed, enzymes for the last three steps of peroxisomal β-oxidation appear to be direct mitochondrial descendants and entered peroxisomes already in the last eukaryotic common ancestor (LECA) (Bolte et al 2014). Others, like the L-PBE, have mitochondrial paralogs but are only found in animals indicating that transitions of enzymes from mitochondria to peroxisomes also occurred at different evolutionary time points (Gabaldon and Capella-Gutierrez 2010; Camoes et al 2014). In contrast, the ACOX genes have no α-proteobacterial counterparts and their evolutionary origin and original function remains unknown (Shen et al 2009; Bolte et al 2014; Gabaldon 2014). Strikingly, the members of the ACAD11 family have α-proteobacterial relatives and are ancient peroxisomal constituents presumably already found in the LECA (Camoes et al 2014). They may have therefore been involved in early peroxisomal β-oxidation. Currently, there is no compelling evidence, that peroxisome evolution preceded mitochondrial endosymbiosis or that mitochondria induced the formation of peroxisomes from the ER by retargeting mitochondrial β-oxidation enzymes. Nevertheless, phylogenetic protein comparisons undoubtedly show that the β-oxidation pathways of both organelles co-evolved during eukaryotic evolution influencing each other's functions. Indeed, enzymatic systems of both pathways have to deal with the reactive molecular oxygen, however, at different enzymatic stages. Both organelles have developed different enzymatic strategies for the first step of β-oxidation: mitochondria produce oxygen radicals in the electron transport chain, and peroxisomes generate H_2O_2 by direct reduction of molecular oxygen. As both organelles have to handle and control the generation of reactive oxygen species they have evolved intertwined signaling systems which link peroxisomal with mitochondrial physiology (Fig. 4a).

The fatty acid metabolism disorders — incidence for a mitochondrial-peroxisomal interplay?

Mutations in β-oxidation enzymes of both the mitochondrial and the peroxisomal pathways lead to severe inherited metabolic disorders with differing phenotypes. Mitochondrial deficiencies in β-oxidation target tissues with high energy demands, such as liver, skeletal muscle and heart. Typically, the patients present with episodic symptoms during phases of glycogen depletion like fasting, stress and prolonged exercise (Kompare and Rizzo 2008). The individual disorders manifest according to the gene disrupted and quality of the mutation with differing severity but if undiagnosed can lead to severe developmental defects and even mortality. However, if the disease is diagnosed in early childhood and phases of energy depletion are avoided, symptoms can often be significantly ameliorated (Saudubray et al 1999; Spiekerkoetter et al 2009). The phenotypes differ substantially between individuals and can be classified into an early onset form with hypoketotic hypoglycemia and Reye-like syndrome, another infant form with cardiomyopathy and arrhythmias and a milder adult onset disease characterized by exercise-induced myopathy and rhabdomyolysis (Houten and Wanders 2010). Defects in more than 20 of the proteins involved in or associated with mitochondrial β-oxidation are known to be responsible for mitochondrial fatty acid oxidation disorders and include fatty acid transporters, enzymes of all four steps of the pathway and the electron acceptor proteins of the pathway's first step (Rinaldo et al 2002; Vockley and Whiteman 2002; Kompare and Rizzo 2008). Thus, according to the substrate specificity of the disrupted gene and the severity of the mutation, the phenotypes of the disorders vary significantly. However, there is no clear correlation between genotypes and phenotypes of single gene defects and the reasons for this significant variability are currently not completely understood.

As for mitochondrial β-oxidation, multiple gene defects have also been described for peroxisomal β-oxidation disorders. Affected genes code for the fatty acyl-CoA transporters ABCD1 and ABCD3 as well as ACOX1, D-PBE, SCPX and AMACR (2-methylacyl-CoA racemase), an auxiliary enzyme required for the degradation of 2-methyl-branched fatty acids and bile acids (Van Veldhoven 2010; Ferdinandusse et al 2014). Although exhibiting broad phenotype variability, peroxisomal gene defects show a pathology which is quite different from mitochondrial disorders and which cannot be ameliorated by avoiding periods of fasting. Peroxisomal β-oxidation deficiencies most commonly lead to neurological abnormalities and/or hepatomegaly and exhibit elevated levels of VLCFA and/or bile acid intermediates in line with a disruption of peroxisomal β-oxidation. Consequently, disruption of individual genes required for peroxisomal β-oxidation can result in similar pathologies. For example, deficiencies in ACBD1, ACOX1 and MFP2 can cause (among other more gene-specific phenotypes) different forms of adrenoleukodystrophy (X-ALD, pseudo-neonatal, neonatal ALD), which exhibit a very severe etiopathology and usually lead to death during childhood.

While a detailed description of the cell biological and clinical aspects of the numerous mitochondrial and peroxisomal gene defects is beyond the scope of this article (see Wanders and Waterham 2006; Kompare and Rizzo 2008), a closer look at the potential reciprocal changes induced in the organelle unaffected by the gene defect may shed light on the functional interplay of peroxisomes and mitochondria. X-linked adrenoleukodystrophy is the most frequent peroxisomal disorder. It is caused by disruption of the peroxisomal ABC transporter ABCD1 (Bezman et al 2001), which is involved in the import of VLCFAs into peroxisomes (van Roermund et al 2011). Indeed, mitochondrial structural alterations in adrenal gland cells were reported in 12 month-old X-ALD mice (McGuinness et al 2003). Although these findings were not corroborated for skeletal muscle mitochondria (Oezen et al

2005), more recent studies suggested that mitochondria may be compromised in neuronal tissues of ACBD1 knockout mice and X-ALD patients due to elevated levels in VLCFAs (Hein et al 2008; Galino et al 2011; Lopez-Erauskin et al 2013). In particular, the authors showed that supraphysiological levels of VLCFAs (40–100 μM) lead to impaired membrane potential across the inner mitochondrial membrane, increased production of ROS and impairment of mitochondrial oxidative phosphorylation in neuronal and glial cell culture systems. At VLCFA levels of 1–5 μM, which correspond to concentrations found in the plasma of X-ALD patients, no such abnormalities were observed in wild-type cultured oligodendrocytes (Baarine et al 2012a), whereas increased production of superoxide and hydrogen peroxide could be measured after knockdown of ACBD1 and ACOX1, respectively (Baarine et al 2012b). Additionally, glial cell lines showed an altered expression of mitochondrial genes and a decreased mitochondrial biogenesis after knockdown of ABCD1 (Baarine et al 2014). Interestingly, a knockout of ABCD2, the paralog of ABCD1 with overlapping substrate spectrum, leads to a similar mitochondrial phenotype (Ferrer et al 2005). Mechanistically, the oxidative damage found in mitochondrial respiratory complex V may be explained by increasing amounts of VLCFAs incorporated into the mitochondrial inner membrane (Lopez-Erauskin et al 2013). The altered membrane lipid composition could consequently lead to electron leakage and elevated ROS production thus initiating cellular degeneration (Fourcade et al 2014). According to the pathology of X-ALD, mitochondrial alterations have been largely investigated in brain associated tissue or cells. Elevated VLCFA plasma concentrations, however, should also target mitochondria in other tissues if VLCFA-induced ROS generation is a primary cause of the disease. Ultrastructural mitochondrial alterations have been reported in the adrenal cortex of ABCD1 knockout mice (McGuinness et al 2003), and fibroblasts from patients with an X-ALD phenotype were reported to exhibit reduced mitochondrial respiration rates (Singh and Giri 2014). Enhanced protein oxidation, which could point to a disturbed mitochondrial respiratory chain, has been described in adrenal cortex and periadrenal fat tissue as well as fibroblasts from X-ALD patients (Powers et al 2005; Fourcade et al 2008). Nevertheless, there is no information on mitochondrial abnormalities in other tissues with high peroxisomal β-oxidation rates such as liver or kidney. In this respect, future work has to clarify, if mitochondrial disruption and associated ROS production is crucial for the etiology of the disease or why this is only the case in selected cell types. Strikingly, X-ALD knockout mice almost totally retain their capacity to degrade VLCFAs (McGuinness et al 2003). On the one hand this may be explained by the remaining ABC-transporters ABCD2 and ABCD3 which could compensate the ABCD1 deficiency. However, ACOX1 deficient fibroblasts also show reduced but still significant residual straight-chain β-oxidation activity (Ferdinandusse et al 2007). Likely, ACOX2 is responsible for a great part of the residual activity; however, a minor portion of VLCFAs may also enter the mitochondrial β-oxidation pathway under elevated cellular concentrations. Since ROS production during mitochondrial β-oxidation was supposed to increase with fatty acid chain length (Speijer 2011), a misguided degradation of VLCFAs in mitochondria under condition when the peroxisomal β-oxidation system is compromised may also directly damage the mitochondrial respiratory complexes and thus contribute to the pathology of peroxisomal β-oxidation disorders. According to the current knowledge it remains to be determined if VLCFA-induced mitochondrial disruption is a primary cause in X-ALD or if mitochondrial alterations establish under physiological VLCFA concentrations only secondary after ongoing demyelination of neurons leads to an inflammatory response in nervous tissue. Nevertheless, the intermingled disturbance of peroxisomal and mitochondrial physiology found in X-ALD underlines the close interconnection between both organelles, even if they may not be caused by a direct elevation of VLFA concentrations.

With respect to the peroxisomal potential for long-chain fatty acid degradation it may be pertinent to ask if a disruption of the mitochondrial β-oxidation pathway is influencing the peroxisomal physiology. Currently, information on peroxisomes in mitochondrial β-oxidation deficiencies remains scarce. Studies on the correction of β-oxidation activities in fibroblasts with VLCAD and CPTII deficiencies using PPARα agonists were only able to significantly restore fatty acid catabolism when the mutant proteins retained partial enzyme activities (Djouadi et al 2005; Djouadi and Bastin 2008). Thus, the peroxisomal β-oxidation system appears to be unable to compensate for the loss of mitochondrial β-oxidation activities. Nevertheless, a recent publication reports that peroxisomes sequester lauric acid (C12) in CPTII- and CACT-deficient human fibroblasts (Violante et al 2013). To this end, the inability of peroxisomes to compensate for the loss in mitochondrial β-oxidation may be in part attributed to the low abundance and induction rates of peroxisomes in extrahepatic tissues (Cook et al 2000). Consequently, increased long-chain fatty acid concentrations in patients with mitochondrial β-oxidation disorders may influence the peroxisomal metabolism and may lead to the activation of signaling systems coordinating the interplay between both organelles. In this respect, peroxisomes may contribute to the pathology of mitochondrial disorders (Camoes et al 2009) and may be a reasonable target of future research.

Peroxisomal and mitochondrial redox relationship

Reactive oxygen species (ROS) are generated as a side product of mitochondrial respiration as well as being produced in a

variety of reactions in peroxisomes (Schrader and Fahimi 2006a, b; Antonenkov et al 2010; Fransen et al 2012). If left unchecked these highly reactive molecules can accumulate and cause extensive cellular damage. Excess ROS, predominantly in the form of superoxide radicals or H_2O_2, is removed in a number of different ways, principally using catalase in peroxisomes and via the SOD and peroxiredoxin pathways in the mitochondria (Murphy 2009). It is now widely recognized that ROS are not only a toxic side-product of metabolic reactions but also an important signalling molecule (D'Autreaux and Toledano 2007). Reversible oxidation and reduction of proteins with exposed reactive groups, generally cysteine residues, is directly coordinated by the levels of ROS in the local environment. This redox system leads to a myriad of effects on the cell with the extent and context of the modification determining a particular proteins reactivity to ROS (Go and Jones 2013). Throughout the cell, including the mitochondria, there are a variety of redox-sensitive factors whose activity varies depending on redox balance and thus many essential processes are redox sensitive (Brandes and Kreuzer 2005; Mesecke et al 2005). This balance is finely tuned and it has been estimated that just a twofold difference in steady-state H_2O_2 levels is enough to switch the cellular mode from proliferative to apoptotic (Boveris and Cadenas 2000).

There is a growing body of evidence demonstrating that alterations to ROS levels in peroxisomes rapidly lead to alterations in ROS activity in mitochondria. The best characterized link is that mediated by peroxisomal catalase. Reduction in peroxisomal catalase levels or activity, either through chemical treatment (Koepke et al 2008; Walton and Pizzitelli 2012), or loss of peroxisomal import competency (Legakis et al 2002; Terlecky et al 2006), results in elevated ROS levels in the mitochondria with a subsequent decrease in redox-sensitive mitochondrial enzyme activity. H_2O_2 is able to freely diffuse across membranes but under normal conditions it is estimated that very little H_2O_2 would be released from peroxisomes to the cytosol (Boveris and Cadenas 2000). Therefore it makes sense that uncoupling catalase from one of the major sites of H_2O_2 production, i.e. peroxisomes, would impact levels in the rest of the cell.

The significance of this observation becomes more apparent if one considers the role of both peroxisomes and mitochondria during ageing (Giordano and Terlecky 2012; Fransen et al 2013). It has been observed that in mid to late passage cells significant cytosolic mis-localization of catalase occurs due to a reduction in peroxisomal import capacity. This results in peroxisomes switching from being a site of ROS degradation to a potent source of ROS and causes redox sensitive enzymes in the mitochondria to become oxidized and inactivated, compromising mitochondrial function. At this point the hallmarks of cell ageing, such as loss of mitochondrial inner membrane potential become apparent. Significantly this scenario can be partially rescued by expression of ectopic catalase carrying a more efficient C-terminal peroxisomal targeting signal (SKL) (Legakis et al 2002; Terlecky et al 2006; Koepke et al 2007). It should, however, be noted that a weak peroxisomal targeting signal (which, strikingly, is a common feature of catalase enzymes from different organisms) may be required to allow proper folding of catalase prior to import into peroxisomes and to avoid aggregation and subsequent loss of function (Williams et al 2012).

A potential clinical aspect of this phenomenon was highlighted by the observation that targeting catalase to mitochondria increases the lifespan of mice (Schriner et al 2005) perhaps in part due to reduced ROS levels leading to delays in cellular senescence (Baker et al 2011). Furthermore catalase expression in mitochondria has been shown to enhance exercise performance and increase radio-resistance in mice (Epperly et al 2009; Li et al 2009). However mitochondrial targeting of catalase may disrupt the normal redox-balance in the organelle, presumably the reason that cells generally lack mitochondrial catalase, resulting in secondary effects (Bai et al 1999). A different approach could be to address peroxisomal protein import (e.g. of catalase) which decreases with age (Williams et al 2012). Interestingly, Pex5, the cycling import receptor for peroxisomal matrix proteins, is a redox-sensitive protein whose activity can be affected by the redox state of the cytosol (Apanasets et al 2014).

Recent experiments using genetically-encoded redox sensors and modulators have provided evidence for a more orchestrated redox relationship between peroxisomes and mitochondria (Fransen et al 2013) (Fig. 4a). Fransen and coworkers employed a peroxisomal variant of KillerRed, a red fluorescent photosensitizer that efficiently generates ROS upon green light illumination (Bulina et al 2006), to study the downstream effects of peroxisome-derived ROS. They revealed that generation of excess ROS inside peroxisomes perturbs the mitochondrial redox balance and leads to mitochondrial fragmentation and cell death (Ivashchenko et al 2011; Wang et al 2013) (Fig. 4a). These findings support previous observations that the production of excess H_2O_2 inside peroxisomes can cause pancreatic β-cell dysfunction and ultimately cell death (Elsner et al 2011). It was further demonstrated that apoptotic signal pathways were induced only when KillerRed was activated in peroxisomes or mitochondria, but not in the cytoplasm (Ivashchenko et al 2011; Wang et al 2013). The authors provide evidence that the main reactive oxygen species involved in the propagation of KillerRed-mediated cell death is most likely superoxide, and not H_2O_2. The superoxide-radicals produced by KillerRed are suggested to trigger chain reactions in polyunsaturated fatty acids, which lead to membrane lipid peroxidation. As overexpression of mitochondrially-targeted catalase (but not peroxisomal catalase) was able to counteract the cytotoxic effects of peroxisomal KillerRed, the initial mitochondrial damage resulting from excess peroxisomal ROS is supposed to be caused by

intra-mitochondrial H_2O_2 (Wang et al 2013) (Fig. 4a). Taken together these experiments provide evidence for a more complex signalling system as opposed to simple diffusion of excess ROS from peroxisomes spreading to the cytoplasm and into the mitochondria. In this context, it should be noted that a disturbance in the peroxisomal oxidative balance by inhibition of catalase activity results in a decrease of the mitochondrial inner membrane potential and increase in the mitochondrial redox state (Walton and Pizzitelli 2012). Furthermore, dysfunctional peroxisomes in X-linked adrenoleukodystrophy cells impair mitochondrial oxidative phosphorylation and generate mitochondrial ROS (Lopez-Erauskin et al 2013).

Two recent studies have identified two more proteins which may play a role in the redox-link. One of these is the starvation-induced protein DEPP (Fig. 2). Salcher et al (2014) found DEPP present on both peroxisomes and mitochondria and suggested that DEPP may act as a sensitizer for ROS-induced apoptosis. As part of the cellular stress response the transcription factor FOXO3 is activated, leading to an induction of apoptosis (Calnan and Brunet 2008). DEPP is a key target of FOXO3 and induction of DEPP expression leads to reduced catalase activity and an increase in the cellular levels of ROS. Depletion of DEPP leads to an increase in catalase activity, a subsequent reduction in ROS levels and increased resistance to H_2O_2. In yeast a potential role for Opt2 as a peroxisome-specific glutathione transporter was recently demonstrated (Elbaz-Alon et al 2014). Deletion of Opt2 not only led to alterations in peroxisomal glutathione balance but also had an impact on mitochondria. As there is no known Opt2 homologue in mammals, it remains to be elucidated if there is a similar system in higher eukaryotes.

How redox communication between peroxisomes and mitochondria is mediated is currently unclear (Fig. 4a) but so far simple diffusion (e.g. via PXMP2, a non-selective pore-forming peroxisomal membrane protein) (Antonenkov and Hiltunen 2012), potential contact sites (Horner et al 2011) or vesicular transport (e.g. via mitochondria-derived vesicles) (Neuspiel et al 2008) have been suggested as possible mechanisms. Further work in this area should help to decipher the significance such processes play in peroxisome and mitochondria interplay.

Peroxisomal and mitochondrial membrane dynamics

Peroxisomes and mitochondria are dynamic organelles with high membrane plasticity which undergo constant changes in membrane shape and morphology (Fig. 1). Whereas mitochondrial morphology is regulated by constant fusion and fission events (Westermann 2010, 2012), only peroxisomal fission (division) has been demonstrated so far (Bonekamp et al 2012; Schrader et al 2012). Mitochondrial dynamics have been linked to changes in metabolism, cell development and cell death and facilitate apoptosis, organelle transport, distribution, inheritance, quality control and turnover. Even mild defects in mitochondrial dynamics can affect normal development and have been implicated in neurodegenerative diseases (Chen and Chan 2009).

Peroxisome division is a well-coordinated multistep maturation process, which consecutively involves membrane elongation, constriction and final fission (Schrader et al 2012). Initially, spherical peroxisomes deform their membranes and generate small membrane extensions. Those further grow and elongate before adapting a typical “beads on a string” morphology which indicates constriction. The “beads” are finally separated by membrane fission and new peroxisomes are distributed within the cytoplasm in a microtubule-dependent manner. As the growing membrane protrusions are initially devoid of peroxisomal matrix proteins, which are subsequently imported, peroxisome division also represents a maturation process which contributes to the formation of new peroxisomes and to peroxisome multiplication (Delille et al 2010; Schrader et al 2012). Furthermore, peroxisomes may change their morphology to meet the requirements for enhanced metabolite transport, membrane signaling or protection against ROS. Tubular protrusions of peroxisomes may also facilitate interorganellar communication (Schrader et al 2000; Sinclair et al 2009).

Over the years, it was discovered that peroxisomes and mitochondria share key components of their division machinery (Schrader and Fahimi 2006a, b; Schrader and Yoon 2007) (Figs. 2 and 5). Sharing these components is an evolutionary conserved strategy among mammals, fungi and plants (Schrader and Fahimi 2006a, b; Delille et al 2009). Shared key components include the large dynamin-like/related GTPase DLP1/Drp1 and its membrane adaptor proteins Fis1 (fission factor 1) and Mff (mitochondrial fission factor), which recruit the cytosolic DLP1 to both peroxisomal and mitochondrial constriction sites (Fig. 5). Another shared protein is ganglioside-induced differentiation-associated protein 1 (GDAP1), a putative glutathione-S transferase, which has been linked to Charcot-Marie-Tooth neuropathy (Huber et al 2013). DLP1 belongs to the dynamin superfamily and is supposed to self-oligomerize forming ring- or spiral like structures around constricted membranes in a GTP-dependent manner and to mediate final membrane fission through GTP hydrolysis. New insights into DLP1 structure, oligomerization and organelle remodeling have recently been revealed (Frohlich et al 2013). In contrast to classical dynamins, cytosolic DLP1 lacks a lipid–binding PH domain and depends on adaptor proteins for membrane recruitment. Furthermore, ER-mitochondria contacts contribute to mitochondrial fission. ER tubules have been found to wrap around mitochondria in yeast and mammalian cells, thus marking fission sites and driving mitochondrial constriction (Friedman et al 2011; Korobova et al 2013). If peroxisomal division is also ER-assisted is currently unknown.

Clinical features of the first patient reported with a defect in DLP1 include microcephaly, abnormal brain development, optic atrophy and hypoplasia (Waterham et al 2007). An aberrant elongated morphology of peroxisomes and mitochondria was revealed in the patient's skin fibroblasts. Similar elongated peroxisomes had previously been reported after loss of DLP1 function in cultured cells (Koch et al 2003, 2004; Li and Gould 2003). Indeed, genetic analysis of the patient revealed a heterozygous, dominant-negative missense mutation (A395D) in the DLP1 middle domain (Waterham et al 2007), which inhibits its oligomerization and thus function in membrane scission (Chang et al 2010). The female patient, who died only a few weeks after birth, combined features of mitochondrial (e.g. autosomal dominant optic atrophy, neuropathy) and peroxisomal (dysmyelination, severity) disorders. In line with this, elevated plasma levels of lactate (indicative of defects in mitochondrial respiration) and slightly elevated levels of VLCFA (indicative of mild defects in peroxisomal ß-oxidation) were reported. However, in contrast to the classical peroxisome biogenesis disorders (PBDs) (e.g. Zellweger syndrome), metabolic biomarkers were not grossly altered. This complicates the diagnosis of this novel group of peroxisome-mitochondria based disorders beyond the mere analysis of classical biomarkers such as VLCFA and underlines the importance of organelle morphology in diagnostics. Meanwhile, DLP1 knockout mice have been generated (Ishihara et al 2009; Wakabayashi et al 2009), which display similar defects, e.g. in synapse formation and brain development resulting in embryonic lethality. Recent findings indicate that DLP1 fulfils additional functions, e.g. in apical sorting at the trans-Golgi network (Bonekamp et al 2010) or in the regulation of synaptic vesicle morphology and membrane dynamics during endocytosis in hippocampal neurons (Li et al 2013), which may contribute to the severity of DLP1 deficiency.

Whereas no patients with a defect in Fis1 are known, two patients with a mutation in Mff were recently reported (Shamseldin et al 2012). A homozygous truncating mutation (Q64X) in the MFF gene of two Saudi Arabian brothers was identified which is supposed to remove the C-terminal transmembrane domain. This would result in a cytosolic localization of Mff and diminish recruitment of DLP1 to the peroxisomal and mitochondrial fission complex. Mff appears to represent the major receptor for DLP1 on peroxisomes and mitochondria in mammals (Otera et al 2010; Itoyama et al 2013). Whereas its C-terminus contains a single transmembrane domain, its N-terminus, which exhibits two short repeat motifs and a central coiled-coil domain, is exposed to the cytosol and binds DLP1 (Gandre-Babbe and van der Bliek 2008). Human MFF contains nine coding exons, and at least eight Mff splice variants are predicted. Similar to DLP1 deficiency, abnormally elongated mitochondria and peroxisomes were detected in skin fibroblasts from Mff patients. This is in line with observations in cell culture after silencing of MFF (Gandre-Babbe and van der Bliek 2008; Otera et al 2010). Clinical features of one of the patients, a 4.5-year-old boy, included delayed psychomotor development, abnormal intensity of the globus pallidus (by MRI), microcephaly, pale optic discs, and mild hypertonia. The younger brother showed similar developmental delay with initial diagnosis of mitochondrial encephalopathy. Biochemical parameters (e.g. lactate and VLCFA levels, mitochondrial respiratory chain complex profiles) of skin fibroblasts from the Mff patient were normal. This is similar to the reported DLP1 patient indicating that metabolic parameters of the organelles are not or only slightly affected.

Recently, the glutathione S-transferase GDAP1 was found to localize to both peroxisomes and mitochondria and to influence their dynamics and division (Huber et al 2013) (Fig. 5). Mutations in GDAP1 have been associated with Charcot-Marie-Tooth disease, the most common inherited peripheral neuropathy (Niemann et al 2005, 2006, 2009). Loss of GDAP1 function results in peroxisomal (and mitochondrial) elongation, which with respect to peroxisomes is less prominent than that observed after loss of DLP1 or Mff. GDAP1 overexpression on the other hand induces peroxisomal (and mitochondrial) division in a Mff and DLP1 dependent manner. Whereas C-terminal alterations in a hydrophobic domain of GDAP1 or at the C-terminal tail affect both peroxisomal and mitochondrial fission, N-terminal autosomal recessively inherited disease mutations are still able to promote peroxisomal but not mitochondrial fission (Niemann et al 2009; Huber et al 2013). These findings suggest that the pathophysiological alterations of the corresponding patients are likely caused by changes in mitochondrial and not peroxisomal dynamics. However, peroxisomal functions have not yet been investigated in detail in patients, and peroxisomes may contribute to some degree to the clinical features of Charcot-Marie-Tooth disease.

Whereas key division components are shared by peroxisomes and mitochondria, the key proteins for mitochondrial fusion (e.g. the dynamin-related GTPases Mfn1, Mfn2 or OPA1) are not present on peroxisomes. In contrast to mitochondria, mature peroxisomes have not been observed to fuse (Huybrechts et al 2009; Bonekamp et al 2012). However, live cell imaging studies provided evidence for peroxisome-peroxisome interactions with transient and long-term contacts, but without exchange of matrix or membrane markers (Bonekamp et al 2012). In combination with microtubule-dependent transport these interactions are supposed to contribute to the equilibration of the peroxisomal compartment in mammalian cells.

Furthermore, the mitochondrial membrane proteins MiD49 and MID51 which are involved in the sequestration of DLP1 (Palmer et al 2013), as well as the mitochondrial Rab GTPase-activating protein TBC1D15, a binding partner of Fis1 at

mitochondria (Onoue et al 2013; Yamano et al 2014), do not localize to peroxisomes indicating organelle-specific differences in the regulation of division (Fig. 5). In line with this, increased expression of MiD51 leads to enhanced recruitment of DLP1 to mitochondria. Interestingly, this renders DLP1 less available for peroxisomal division causing peroxisome elongation (Palmer et al 2013) and highlights how alterations in the recruitment of division components at one organelle can influence the dynamics of the other (Fig. 5).

Peroxisome-specific division factors include members of the Pex11 family of peroxisomal membrane proteins. Pex11 proteins regulate and promote peroxisomal membrane deformation and elongation as well as fission and proliferation processes (Fig. 5). Loss of Pex11 function is associated with reduced peroxisome number and the formation of enlarged peroxisomes, whereas overexpression promotes peroxisome elongation and proliferation (Thoms and Erdmann 2005; Schrader et al 2012). Of the three Pex11 proteins identified in humans, Pex11β has recently been linked to disease (Ebberink et al 2012; Thoms and Gartner 2012). Human Pex11β is a peroxisome-specific integral membrane protein with the N- and C-termini exposed to the cytosol (Schrader et al 1998; Bonekamp et al 2013). This widely expressed division factor combines interesting properties: Pex11β forms homo-oligomers, interacts with Fis1 and Mff, and likely with membrane lipids to deform and shape the peroxisomal membrane; furthermore, the N-terminus contains amphipathic helices required for membrane elongation in vitro and in vivo as well as for dimerization (Fig. 5) (Kobayashi et al 2007; Opalinski et al 2011; Koch and Brocard 2012; Bonekamp et al 2013; Itoyama et al 2013).

The first patient identified displayed a homozygous nonsense mutation in the PEX11β gene leading to a truncation of the protein after 21 amino acids (Q22X) (Ebberink et al 2012). Meanwhile, seven additional patients have been identified (Ebberink et al 2014) with null mutations in the PEX11β gene. All patients presented with congenital cataracts. The older patients all had mild intellectual disability, ataxia and sensorineural deafness. In addition, most of them presented with short stature and convulsions. Similar to the DLP1 and Mff patients, biochemical parameters of peroxisomes were normal. However, analysis of patient skin fibroblasts often revealed enlarged and elongated peroxisomes indicative of a defect in peroxisome division or proliferation. In contrast to the patients, PEX11β knockout in mice is neonatal lethal and causes severe, Zellweger-like abnormalities (Li et al 2002a, b). Peroxisome numbers in cultured mouse fibroblasts were reduced, but similar to the patients peroxisomal metabolism was normal or only slightly affected. Knockout of PEX11α in mice on the other hand did not result in a severe disease-phenotype under standard housing conditions (Li et al 2002a, b). Currently, no patient with a defect in human PEX11α is known. In addition, Pex11α was not able to complement the peroxisomal alterations in fibroblasts from PEX11β patients (Ebberink et al 2012).

Cooperative roles of peroxisomes and mitochondria in viral combat

Despite the vast knowledge acquired thus far concerning peroxisome functions, a new role for these organelles has emerged recently in which they, either alone or in concert with mitochondria, play an important role in the innate immune response of the host cell to combat viral and bacterial infections (Figs. 2 and 4b). The innate immune response, which provides the first line of defence against pathogen invasion, depends on pattern recognition receptors (PRRs) which recognize pathogen components such as bacterial lipopolysaccharides, flagellin, lipoproteins and double stranded RNA (dsRNA), among others. Activated PRRs deliver signals to specific adaptor proteins that, in turn, orchestrate complex host defence mechanisms. This includes the activation of several transcription factors (e.g. NF-κB, interferon regulatory factors (IRFs)) which lead to the production of pro-inflammatory and immune-modulatory factors (e.g. type 1 interferons and inflammatory cytokines) by the host (Medzhitov and Horng 2009; Dixit et al 2010; Chen and Jiang 2013). PRRs such as RIG-I-like receptors (RLRs) are present in the cytosol of mammalian cells. RLRs are RNA helicases that function in virtually all mammalian cells to detect viral and bacterial nucleic acids in the cytosol (Odendall and Kagan 2013). The mitochondrial antiviral signalling protein (MAVS) functions as an adaptor protein for retinoic acid-inducible gene 1 protein (RIG-I) (Fig. 4b). Remarkably, MAVS was recently found to localize to both mitochondria and peroxisomes (Medzhitov and Horng 2009; Dixit et al 2010). The authors showed that peroxisomes undergo morphological changes upon viral infection and that RNA viruses can activate MAVS-dependent signalling from peroxisomes. MAVS responses from both peroxisomes and mitochondria were required for maximal antiviral activity. Initially it was reported that peroxisomal MAVS elicits a rapid but transient, type I IFN-independent innate immune responses, whereas the mitochondrial MAVS induces a type I interferon-dependent, sustained response with delayed kinetics (Medzhitov and Horng 2009; Dixit et al 2010). These findings were extended by Horner et al (2011) who demonstrated that peroxisomal MAVS was able to induce an interferon-dependent response. Furthermore, MAVS was localized to mitochondria-associated ER membranes (MAMs) and it was reported that dynamic MAM tethering to mitochondria and peroxisomes coordinates MAVS localization to form a signalling synapse between membranes (Horner et al 2011). Remarkably, the hepatitis C virus NS3-4A protease specifically targets these sites for MAVS proteolysis to ablate RIG-I signalling of

immune defences (Horner et al 2011). Moreover, LSm14A, a processing body-associated sensor of viral RNA and DNA of the LSm family, translocates to peroxisomes upon viral infection (Fig. 4b). Interestingly, after binding to viral RNA, LSm14A requires RIG-I and MAVS for IRF-3 activation but its translocation to peroxisomes is RIG-I or MAVS independent (Li et al 2012). On the other hand, when LSm14A binds to viral DNA, it requires the adaptor protein MITA (Mediator of IRF3 activation; also known as STING/TMEM173/ERIS), which was found on peroxisomes, for IFN-β induction in the early phase of viral infection (Fig. 4b) (Li et al 2012).

Recent studies have also highlighted the role of peroxisomes in the innate immune responses to genomic HIV RNA (Berg et al 2012) and as signalling platforms for the induction of type III interferon response upon cellular infection by several other viruses (e.g. Sendai virus and Dengue virus) as well as cytosolic bacteria (Odendall et al 2014). This response is thought to complement the actions of the type I interferon responses induced from mitochondria. Overall, both mitochondria and peroxisomes are capable of inducing RLR-mediated interferon responses, allowing the cell to mediate its antiviral response according to the type and possibly the stage of pathogen infection.

In addition to inducing an antiviral immune response, viruses such as rotavirus, HIV and influenza, were shown to exploit peroxisomes and mitochondria for intracellular replication in mammalian cells (Lazarow 2011; Ruggieri et al 2014). Peroxisomes can be targeted by viral proteins directly or through peroxisomal proteins and are also used as assembly points for viral replication (Lazarow 2011). The rotavirus VP4 protein has a peroxisomal targeting signal (PTS1) at its C-terminus and targets peroxisomes when cultured cells are infected with rotavirus (Mohan et al 2002). The Nef protein from HIV and the NS1 protein from influenza virus were found to indirectly target peroxisomes via interaction with a peroxisomal thioesterase and the multifunctional β-oxidation protein type 2 (MFP-2), respectively (Wolff et al 1996; Cohen et al 2000). Several other viral proteins with putative peroxisomal targeting sequences were identified by bioinformatics, though additional studies are required to verify their peroxisomal localization and function (Mohan and Atreya 2003). Despite the clear link between peroxisomes and viral proteins, it is still unclear how viruses benefit from this relationship. Besides using peroxisomes and other organelles as scaffolds for replication and assembly, pathogens might exploit peroxisomes as a source of lipids (Boncompain et al 2014; Tanner et al 2014). Furthermore, viruses may attempt to interfere with the anti-viral signalling pathways associated with peroxisomes and mitochondria. In line with this, the pestivirus N terminal protease N(pro) (e.g. from swine fever virus or bovine viral diarrhea virus) was found to redistribute to mitochondria and peroxisomes (Jefferson et al 2014). Mitochondrial and peroxisomal N(pro) was shown to inactivate IRF3, a central regulator of interferon production. N(pro) inhibited the stress-induced intrinsic mitochondrial apoptotic pathway through inhibition of IRF-3-dependent Bax activation. These results implicate mitochondria and peroxisomes as new sites for IRF-3 regulation by N(pro), and highlight the role of these organelles in the anti-viral pathway.

Recent studies on the hepatitis B virus X protein (hBx), a viral protein that also binds to MAVS (Kumar et al 2011), revealed that its function is influenced by its subcellular localization. Predominantly found in the cytoplasm, hBx was also reported to localize to the membranes of both mitochondria and peroxisomes (Ma et al 2011; Han et al 2014). Association of hBx with mitochondria altered the organellar membrane potential increasing cellular ROS generation, NFκB-activation and apoptosis (Ma et al 2011). Peroxisome-associated hBx triggered even stronger production of ROS and NFκB-activation (Han et al 2014), which increased the expression of matrix-metalloproteinases. This scenario is supposed to contribute to hepatitis B induced progression of hepatocellular carcinoma.

Finally, peroxisomes may also modulate inflammatory immune responses. In line with this, it has been shown that a peroxisome deficiency in Drosophila larvae causes an increase in the expression of genes involved in innate immunity and humoral responses (Mast et al 2011). Furthermore, the immune system is activated in nestin-PEX5 knockout mice (Bottelbergs et al 2012). The molecular mechanisms underlying these alterations are currently unclear. However, it is possible that the upregulation of innate immunity genes reflects a response to increased levels of accumulating peroxisomal metabolites (Mast et al 2011).

Although our information on the role of peroxisomes and mitochondria in viral pathogenesis as well as host-defense still remains very limited, our current knowledge already points to an important role of both organelles in both health-related processes. Further work in this research area will help to clarify the molecular mechanisms by which peroxisomes and mitochondria cooperate in order to combat pathogen infections but also how both organelles are exploited from the invading organisms. Increasing knowledge for both processes may lead to novel strategies for treating viral and bacterial infections.

Perspectives

There is emerging evidence that the functional relationship between peroxisomes and mitochondria is the result of an organellar co-evolution originating in the early ancestors of all eukaryotes. This fundamental interconnection between peroxisomes and mitochondria is reflected by an increasing number of cooperative functions, such as fatty acid β-oxidation, innate immune response, maintenance of ROS homeostasis or even regulation of apoptosis and cell survival (Fig. 2). In this

respect both organelles have to coordinate their biogenesis and abundance as reflected by the utilization of shared components of their division machineries (Fig. 5). Furthermore, both organelles share a significant number of proteins linked to the cellular processes listed above or contain an enzymatic inventory, which descended from common precursors. According to this phylogenetic relationship, reaction pathways originally located in mitochondria may have hitchhiked peroxisomal precursor organelles to outsource detrimental metabolic processes to a more specialized compartment. This hypothesis, however, does not shed light on the primary role of peroxisomes in ancient eukaryotes and thus cannot explain why peroxisomes presumably descended from the ER as semi-autonomous compartments. In this respect, future research on the phylogeny of the peroxisomal proteome may help to decipher their ancient protein inventory and attributed functions, which will certainly help to understand why mitochondria and peroxisomes gained such intensive interconnections. Furthermore, there is a growing body of evidence demonstrating that alterations to ROS levels in peroxisomes rapidly lead to alterations in ROS activity in mitochondria (Fig. 4a). How redox communication between peroxisomes and mitochondria is mediated is currently unclear but so far simple diffusion, potential contact sites or vesicular transport have been suggested as possible mechanisms. The importance of this redox relationship in health and disease is highlighted by studies demonstrating an imbalance in mitochondrial ROS in peroxisomal disorders as well as other conditions, such as ageing, where peroxisomal function is reduced. Additionally, peroxisomes and mitochondria have an essential role in the response of the host cell to combat pathogens (Fig. 4b). Their cooperation provides the first line of defence against pathogen infection, which also renders them important targets for the invading organisms. Deciphering how organelle dynamics and peroxisome-mitochondria interactions influence the antiviral signalling pathways operating from both organelles remains a future challenge. A better understanding of these processes will help to develop novel therapies to combat invading pathogens.

Acknowledgements We would like to thank H. Dariush Fahimi (Heidelberg) and Marc Fransen (Leuven) for kindly providing images and members of the laboratory for stimulating discussions and comments on the manuscript. We apologize to those whose work has not been cited owing to space limitations. This work was supported by BBSRC (BB/K006231/1), the Portuguese Foundation for Science and Technology (FCT) and FEDER/COMPETE (PTDC/BIA-BCM/118605/2010) to M. S., SFRH/BPD/90084/2012 to L. G.) and FP-7-PEOPLE-2012-Marie Curie-ITN 316723 PERFUME.

Compliance with Ethics Guidelines This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of interest None.

References

Antonenkov VD, Hiltunen JK (2012) Transfer of metabolites across the peroxisomal membrane. Biochim Biophys Acta 1822:1374–1386

Antonenkov VD, Grunau S, Ohlmeier S, Hiltunen JK (2010) Peroxisomes are oxidative organelles. Antioxid Redox Signal 13: 525–537

Apanasets O, Grou CP, Van Veldhoven PP et al (2014) PEX5, the shuttling import receptor for peroxisomal matrix proteins, is a redox-sensitive protein. Traffic 15(1):94–103

Baarine M, Ragot K, Athias A et al (2012a) Incidence of Abcd1 level on the induction of cell death and organelle dysfunctions triggered by very long chain fatty acids and TNF-α on oligodendrocytes and astrocytes. Neurotoxicology 33:212–228

Baarine M, Andreoletti P, Athias A et al (2012b) Evidence of oxidative stress in very long chain fatty acid–treated oligodendrocytes and potentialization of ROS production using RNA interference-directed knockdown of ABCD1 and ACOX1 peroxisomal proteins. Neuroscience 213:1–18

Baarine M, Beeson C, Singh A, Singh I (2014) ABCD1 deletion-induced mitochondrial dysfunction is corrected by SAHA: implication for adrenoleukodystrophy. J Neurochem. doi:10.1111/jnc.12992

Bagattin A, Hugendubler L, Mueller E (2010) Transcriptional coactivator PGC-1alpha promotes peroxisomal remodeling and biogenesis. Proc Natl Acad Sci U S A 107:20376–20381

Bai J, Rodriguez AM, Melendez JA, Cederbaum AI (1999) Overexpression of catalase in cytosolic or mitochondrial compartment protects HepG2 cells against oxidative injury. J Biol Chem 274:26217–26224

Baker MJ, Tatsuta T, Langer T (2011) Quality control of mitochondrial proteostasis. Cold Spring Harb Perspect Biol 3. doi: 10.1101/cshperspect.a007559

Barak Y, Nelson MC, Ong ES et al (1999) PPAR gamma is required for placental, cardiac, and adipose tissue development. Mol Cell 4:585–595

Bartlett K, Eaton S (2004) Mitochondrial beta-oxidation. Eur J Biochem 271(3):462–469

Baumgart E, Vanhorebeek I, Grabenbauer M et al (2001) Mitochondrial alterations caused by defective peroxisomal biogenesis in a mouse model for Zellweger syndrome (PEX5 knockout mouse). Am J Pathol 159:1477–1494

Berg RK, Melchjorsen J, Rintahaka J et al (2012) Genomic HIV RNA induces innate immune responses through RIG-I-dependent sensing of secondary-structured RNA. PLoS One 7:e29291

Bezman L, Moser AB, Raymond GV et al (2001) Adrenoleukodystrophy: incidence, new mutation rate, and results of extended family screening. Ann Neurol 49(4):512–517

Bolte K, Rensing SA, Maier UG (2014) The evolution of eukaryotic cells from the perspective of peroxisomes: phylogenetic analyses of peroxisomal beta-oxidation enzymes support mitochondria-first models of eukaryotic cell evolution. BioEssays. doi:10.1002/bies.201400151

Boncompain G, Muller C, Meas-Yedid V, Schmitt-Kopplin P, Lazarow PB, Subtil A (2014) The intracellular bacteria Chlamydia hijack peroxisomes and utilize their enzymatic capacity to produce bacteria-specific phospholipids. PLoS One 9:e86196

Bonekamp NA, Vormund K, Jacob R, Schrader M (2010) 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 316:3454–3467

Bonekamp NA, Sampaio P, de Abreu FV, Luers GH, Schrader M (2012) Transient complex interactions of mammalian peroxisomes without exchange of matrix or membrane marker proteins. Traffic 13:960–978

Bonekamp NA, Grille S, Cardoso MJ et al (2013) Self-interaction of human Pex11pbeta during peroxisomal growth and division. PLoS One 8:e53424

Bonnefont JP, Djouadi F, Prip-Buus C, Gobin S, Munnich A, Bastin J (2004) Carnitine palmitoyltransferases 1 and 2: biochemical, molecular and medical aspects. Mol Aspects Med 25:495–520

Borst P (1983) Animal peroxisomes (microbodies), lipid biosynthesis and the Zellweger syndrome. Trends Biochem Sci 8:269–272

Borst P (1986) How proteins get into microbodies (peroxisomes, glyoxysomes, glycosomes). Biochim Biophys Acta 866:179–203

Bottelbergs A, Verheijden S, Van Veldhoven PP, Just W, Devos R, Baes M (2012) Peroxisome deficiency but not the defect in ether lipid synthesis causes activation of the innate immune system and axonal loss in the central nervous system. J Neuroinflammation 9:61

Boveris A, Cadenas E (2000) Mitochondrial production of hydrogen peroxide regulation by nitric oxide and the role of ubisemiquinone. IUBMB Life 50:245–250

Brandes RP, Kreuzer J (2005) Vascular NADPH oxidases: molecular mechanisms of activation. Cardiovasc Res 65:16–27

Bronfman M, Inestrosa NC, Nervi FO, Leighton F (1984) Acyl-CoA synthetase and the peroxisomal enzymes of beta-oxidation in human liver. Quantitative analysis of their subcellular localization. Biochem J 224:709–720

Bulina ME, Chudakov DM, Britanova OV et al (2006) A genetically encoded photosensitizer. Nat Biotechnol 24:95–99

Calnan DR, Brunet A (2008) The FoxO code. Oncogene 27:2276–2288

Camoes F, Bonekamp NA, Delille HK, Schrader M (2009) Organelle dynamics and dysfunction: a closer link between peroxisomes and mitochondria. J Inherit Metab Dis 32:163–180

Camoes F, Islinger M, Guimaraes SC et al (2014) New insights into the peroxisomal protein inventory: Acyl-CoA oxidases and -dehydrogenases are an ancient feature of peroxisomes. Biochim Biophys Acta 1853:111–125

Chang CR, Manlandro CM, Arnoult D et al (2010) 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 285:32494–32503

Chen H, Chan DC (2009) Mitochondrial dynamics–fusion, fission, movement, and mitophagy–in neurodegenerative diseases. Hum Mol Genet 18:R169–R176

Chen H, Jiang Z (2013) The essential adaptors of innate immune signaling. Protein Cell 4:27–39

Cheng L, Ding G, Qin Q et al (2004) Peroxisome proliferator-activated receptor delta activates fatty acid oxidation in cultured neonatal and adult cardiomyocytes. Biochem Biophys Res Commun 313:277–286

Cohen GB, Rangan VS, Chen BK, Smith S, Baltimore D (2000) The human thioesterase II protein binds to a site on HIV-1 Nef critical for CD4 down-regulation. J Biol Chem 275:23097–23105

Cook WS, Yeldandi AV, Rao MS, Hashimoto T, Reddy JK (2000) Less extrahepatic induction of fatty acid beta-oxidation enzymes by PPAR alpha. Biochem Biophys Res Commun 278:250–257

Corona JC, de Souza SC, Duchen MR (2014) PPARgamma activation rescues mitochondrial function from inhibition of complex I and loss of PINK1. Exp Neurol 253:16–27

Costet P, Legendre C, More J, Edgar A, Galtier P, Pineau T (1998) Peroxisome proliferator-activated receptor alpha-isoform deficiency leads to progressive dyslipidemia with sexually dimorphic obesity and steatosis. J Biol Chem 273:29577–29585

D'Autreaux B, Toledano MB (2007) ROS as signalling molecules: mechanisms that generate specificity in ROS homeostasis. Nat Rev Mol Cell Biol 8:813–824

de Duve C (1965) Function of microbodies (peroxisomes). J Cell Biol 27: 25A–26A

De Marcos Lousa C, van Roermund CW, Postis VL et al (2013) Intrinsic acyl-CoA thioesterase activity of a peroxisomal ATP binding cassette transporter is required for transport and metabolism of fatty acids. Proc Natl Acad Sci U S A 110:1279–1284

Delille HK, Alves R, Schrader M (2009) Biogenesis of peroxisomes and mitochondria: linked by division. Histochem Cell Biol 131:441–446

Delille HK, Agricola B, Guimaraes SC et al (2010) Pex11pbeta-mediated growth and division of mammalian peroxisomes follows a maturation pathway. J Cell Sci 123(Pt 16):2750–2762

Diano S, Liu ZW, Jeong JK et al (2011) Peroxisome proliferation-associated control of reactive oxygen species sets melanocortin tone and feeding in diet-induced obesity. Nat Med 17:1121–1127

Ding J, Loizides-Mangold U, Rando G et al (2013) The peroxisomal enzyme L-PBE is required to prevent the dietary toxicity of medium-chain fatty acids. Cell Rep 5:248–258

Dirkx R, Vanhorebeek I, Martens K et al (2005) Absence of peroxisomes in mouse hepatocytes causes mitochondrial and ER abnormalities. Hepatology 41:868–878

Dixit E, Boulant S, Zhang Y et al (2010) Peroxisomes are signaling platforms for antiviral innate immunity. Cell 141:668–681

Djouadi F, Bastin J (2008) PPARs as therapeutic targets for correction of inborn mitochondrial fatty acid oxidation disorders. J Inherit Metab Dis 31:217–225

Djouadi F, Aubey F, Schlemmer D et al (2005) Bezafibrate increases very-long-chain acyl-CoA dehydrogenase protein and mRNA expression in deficient fibroblasts and is a potential therapy for fatty acid oxidation disorders. Hum Mol Genet 14:2695–2703

Ebberink MS, Koster J, Visser G et al (2012) A novel defect of peroxisome division due to a homozygous non-sense mutation in the PEX11beta gene. J Med Genet 49:307–313

Ebberink M, Koster J, Stark Z, et al (2014) PEX11β deficiency: a novel human peroxisome biogenesis disorder affecting peroxisome division. J Inherit Metab Dis 37(Suppl. 1): O-053.

Eggens I, Brunk U, Dallner G (1980) Effects of clofibrate administration to rats on their hepatocytes. Exp Mol Pathol 32:115–127

Elbaz-Alon Y, Morgan B, Clancy A et al (2014) The yeast oligopeptide transporter Opt2 is localized to peroxisomes and affects glutathione redox homeostasis. FEMS Yeast Res 14:1055–1067

Elsner M, Gehrmann W, Lenzen S (2011) Peroxisome-generated hydrogen peroxide as important mediator of lipotoxicity in insulin-producing cells. Diabetes 60:200–208

Epperly MW, Melendez JA, Zhang X et al (2009) Mitochondrial targeting of a catalase transgene product by plasmid liposomes increases radioresistance in vitro and in vivo. Radiat Res 171:588–595

Falcon A, Doege H, Fluitt A et al (2010) FATP2 is a hepatic fatty acid transporter and peroxisomal very long-chain acyl-CoA synthetase. Am J Physiol Endocrinol Metab 299:E384–E393

Farrell SO, Bieber LL (1983) Carnitine octanoyltransferase of mouse liver peroxisomes: properties and effect of hypolipidemic drugs. Arch Biochem Biophys 222:123–132

Ferdinandusse S, Denis S, Hogenhout EM et al (2007) Clinical, biochemical, and mutational spectrum of peroxisomal acyl-coenzyme A oxidase deficiency. Hum Mutat 28:904–912

Ferdinandusse S, Jimenez-Sanchez G, Koster J, et al (2014) A novel bile acid biosynthesis defect due to a deficiency of peroxisomal ABCD3. Hum Mol Genet

Ferrer I, Kapfhammer JP, Hindelang C et al (2005) Inactivation of the peroxisomal ABCD2 transporter in the mouse leads to late-onset ataxia involving mitochondria, Golgi and endoplasmic reticulum damage. Hum Mol Genet 14:3565–3577

Foerster EC, Fahrenkemper T, Rabe U, Graf P, Sies H (1981) Peroxisomal fatty acid oxidation as detected by H2O2 production in intact perfused rat liver. Biochem J 196:705–712

Fourcade S, López-Erauskin J, Galino J et al (2008) Early oxidative damage underlying neurodegeneration in X-adrenoleukodystrophy. Hum Mol Genet 17:1762–1773

Fourcade S, Lopez-Erauskin J, Ruiz M, Ferrer I, Pujol A (2014) Mitochondrial dysfunction and oxidative damage cooperatively fuel

axonal degeneration in X-linked adrenoleukodystrophy. Biochimie 98:143–149
Fransen M, Nordgren M, Wang B, Apanasets O (2012) Role of peroxisomes in ROS/RNS-metabolism: implications for human disease. Biochim Biophys Acta 1822(9):1363–1373
Fransen M, Nordgren M, Wang B, Apanasets O, Van Veldhoven PP (2013) Aging, age-related diseases and peroxisomes. Subcell Biochem 69:45–65
Freitag J, Ast J, Bolker M (2012) Cryptic peroxisomal targeting via alternative splicing and stop codon read-through in fungi. Nature 485: 522–525
Friedman JR, Lackner LL, West M, DiBenedetto JR, Nunnari J, Voeltz GK (2011) ER tubules mark sites of mitochondrial division. Science 334:358–362
Frohlich C, Grabiger S, Schwefel D et al (2013) Structural insights into oligomerization and mitochondrial remodelling of dynamin 1-like protein. EMBO J 32:1280–1292
Gabaldon T (2014) Evolutionary considerations on the origin of peroxisomes from the endoplasmic reticulum, and their relationships with mitochondria. Cell Mol Life Sci 71:2379–2382
Gabaldon T, Capella-Gutierrez S (2010) Lack of phylogenetic support for a supposed actinobacterial origin of peroxisomes. Gene 465:61–65
Galino J, Ruiz M, Fourcade S et al (2011) Oxidative damage compromises energy metabolism in the axonal degeneration mouse model of X-adrenoleukodystrophy. Antioxid Redox Signal 15:2095–2107
Gandre-Babbe S, van der Bliek AM (2008) The novel tail-anchored membrane protein Mff controls mitochondrial and peroxisomal fission in mammalian cells. Mol Biol Cell 19:2402–2412
Giordano CR, Terlecky SR (2012) Peroxisomes, cell senescence, and rates of aging. Biochim Biophys Acta 1822:1358–1362
Go YM, Jones DP (2013) The redox proteome. J Biol Chem 288:26512–26520
Goldfischer S, Moore CL, Johnson AB et al (1973) Peroxisomal and mitochondrial defects in the cerebro-hepato-renal syndrome. Science 182:62–64
Gray E, Ginty M, Kemp K, Scolding N, Wilkins A (2012) The PPAR-gamma agonist pioglitazone protects cortical neurons from inflammatory mediators via improvement in peroxisomal function. J Neuroinflammation 9:63
Gronemeyer T, Wiese S, Ofman R et al (2013) The proteome of human liver peroxisomes: identification of five new peroxisomal constituents by a label-free quantitative proteomics survey. PLoS One 8: e57395
Han JM, Kang JA, Han MH et al (2014) Peroxisome-localized hepatitis Bx protein increases the invasion property of hepatocellular carcinoma cells. Arch Virol 159:2549–2557
Handschin C, Spiegelman BM (2006) Peroxisome proliferator-activated receptor gamma coactivator 1 coactivators, energy homeostasis, and metabolism. Endocr Rev 27:728–735
Hashimoto T, Fujita T, Usuda N et al (1999) Peroxisomal and mitochondrial fatty acid beta-oxidation in mice nullizygous for both peroxisome proliferator-activated receptor alpha and peroxisomal fatty acyl-CoA oxidase. Genotype correlation with fatty liver phenotype. J Biol Chem 274:19228–19236
Hashimoto T, Cook WS, Qi C, Yeldandi AV, Reddy JK, Rao MS (2000) Defect in peroxisome proliferator-activated receptor alpha-inducible fatty acid oxidation determines the severity of hepatic steatosis in response to fasting. J Biol Chem 275:28918–28928
He M, Rutledge SL, Kelly DR et al (2007) A new genetic disorder in mitochondrial fatty acid beta-oxidation: ACAD9 deficiency. Am J Hum Genet 81:87–103
He M, Pei Z, Mohsen AW et al (2011) Identification and characterization of new long chain acyl-CoA dehydrogenases. Mol Genet Metab 102:418–429
Hein S, Schonfeld P, Kahlert S, Reiser G (2008) Toxic effects of X-linked adrenoleukodystrophy-associated, very long chain fatty acids on glial cells and neurons from rat hippocampus in culture. Hum Mol Genet 17:1750–1761
Hess R, Staubli W, Riess W (1965) Nature of the hepatomegalic effect produced by ethyl-chlorophenoxy-isobutyrate in the rat. Nature 208: 856–858
Hicks L, Fahimi HD (1977) Peroxisomes (microbodies) in the myocardium of rodents and primates. A comparative Ultrastructural cytochemical study. Cell Tissue Res 175(4):467–481
Horner SM, Liu HM, Park HS, Briley J, Gale M Jr (2011) Mitochondrial-associated endoplasmic reticulum membranes (MAM) form innate immune synapses and are targeted by hepatitis C virus. Proc Natl Acad Sci U S A 108:14590–14595
Houten SM, Wanders RJ (2010) A general introduction to the biochemistry of mitochondrial fatty acid beta-oxidation. J Inherit Metab Dis 33(5):469–477
Houten SM, Denis S, Argmann CA, Jia Y, Ferdinandusse S, Reddy JK, Wanders RJ (2012) Peroxisomal L-bifunctional enzyme (Ehhadh) is essential for the production of medium-chain dicarboxylic acids. J Lipid Res 53:1296–1303
Huber N, Guimaraes S, Schrader M, Suter U, Niemann A (2013) Charcot-Marie-Tooth disease-associated mutants of GDAP1 dissociate its roles in peroxisomal and mitochondrial fission. EMBO Rep 14:545–552
Hunt MC, Tillander V, Alexson SE (2014) Regulation of peroxisomal lipid metabolism: the role of acyl-CoA and coenzyme A metabolizing enzymes. Biochimie 98:45–55
Huybrechts SJ, Van Veldhoven PP, Brees C, Mannaerts GP, Los GV, Fransen M (2009) Peroxisome dynamics in cultured mammalian cells. Traffic 10(11):1722–1733
Ishihara N, Nomura M, Jofuku A et al (2009) Mitochondrial fission factor Drp1 is essential for embryonic development and synapse formation in mice. Nat Cell Biol 11:958–966
Islinger M, Luers GH, Li KW, Loos M, Volkl A (2007) Rat liver peroxisomes after fibrate treatment. A survey using quantitative mass spectrometry. J Biol Chem 282:23055–23069
Islinger M, Li KW, Loos M et al (2010) Peroxisomes from the heavy mitochondrial fraction: isolation by zonal free flow electrophoresis and quantitative mass spectrometrical characterization. J Proteome Res 9:113–124
Islinger M, Grille S, Fahimi HD, Schrader M (2012) The peroxisome: an update on mysteries. Histochem Cell Biol 137:547–574
Issemann I, Green S (1990) Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators. Nature 347: 645–650
Itoyama A, Michiyuki S, Honsho M et al (2013) Mff functions with Pex11pbeta and DLP1 in peroxisomal fission. Biol Open 2:998–1006
Ivashchenko O, Van Veldhoven PP, Brees C, Ho YS, Terlecky SR, Fransen M (2011) Intraperoxisomal redox balance in mammalian cells: oxidative stress and interorganellar cross-talk. Mol Biol Cell 22:1440–1451
Jefferson M, Whelband M, Mohorianu I, Powell PP (2014) The pestivirus N terminal protease N(pro) redistributes to mitochondria and peroxisomes suggesting new sites for regulation of IRF3 by N(pro.). PLoS One 9:e88838
Kagan JC (2012) Signaling organelles of the innate immune system. Cell 151:1168–1178
Kelley RI (1983) Review: the cerebrohepatorenal syndrome of Zellweger, morphologic and metabolic aspects. Am J Med Genet 16:503–517
Kersten S, Seydoux J, Peters JM, Gonzalez FJ, Desvergne B, Wahli W (1999) Peroxisome proliferator-activated receptor alpha mediates the adaptive response to fasting. J Clin Invest 103(11):1489–1498
Klose J, Kronstad JW (2006) The multifunctional beta-oxidation enzyme is required for full symptom development by the biotrophic maize pathogen Ustilago maydis. Eukaryot Cell 5:2047–2061

Kobayashi S, Tanaka A, Fujiki Y (2007) Fis1, DLP1, and Pex11p coordinately regulate peroxisome morphogenesis. Exp Cell Res 313: 1675–1686

Koch J, Brocard C (2012) PEX11 proteins attract Mff and human Fis1 to coordinate peroxisomal fission. J Cell Sci 125:3813–3826

Koch A, Thiemann M, Grabenbauer M, Yoon Y, McNiven MA, Schrader M (2003) Dynamin-like protein 1 is involved in peroxisomal fission. J Biol Chem 278:8597–8605

Koch A, Schneider G, Luers GH, Schrader M (2004) Peroxisome elongation and constriction but not fission can occur independently of dynamin-like protein 1. J Cell Sci 117:3995–4006

Koepke JI, Nakrieko KA, Wood CS et al (2007) Restoration of peroxisomal catalase import in a model of human cellular aging. Traffic 8: 1590–1600

Koepke JI, Wood CS, Terlecky LJ, Walton PA, Terlecky SR (2008) Progeric effects of catalase inactivation in human cells. Toxicol Appl Pharmacol 232:99–108

Kompare M, Rizzo WB (2008) Mitochondrial fatty-acid oxidation disorders. Semin Pediatr Neurol 15:140–149

Kondrup J, Lazarow PB (1985) Flux of palmitate through the peroxisomal and mitochondrial beta-oxidation systems in isolated rat hepatocytes. Biochim Biophys Acta 835:147–153

Korobova F, Ramabhadran V, Higgs HN (2013) An actin-dependent step in mitochondrial fission mediated by the ER-associated formin INF2. Science 339:464–467

Kretschmer M, Klose J, Kronstad JW (2012a) Defects in mitochondrial and peroxisomal beta-oxidation influence virulence in the maize pathogen Ustilago maydis. Eukaryot Cell 11:1055–1066

Kretschmer M, Wang J, Kronstad JW (2012b) Peroxisomal and mitochondrial beta-oxidation pathways influence the virulence of the pathogenic fungus Cryptococcus neoformans. Eukaryot Cell 11: 1042–1054

Kumar M, Jung SY, Hodgson AJ, Madden CR, Qin J, Slagle BL (2011) Hepatitis B virus regulatory HBx protein binds to adaptor protein IPS-1 and inhibits the activation of beta interferon. J Virol 85:987–995

Kurihara T, Ueda M, Okada H et al (1992) Beta-oxidation of butyrate, the short-chain-length fatty acid, occurs in peroxisomes in the yeast Candida tropicalis. J Biochem 111:783–787

Lazarow PB (1978) Rat liver peroxisomes catalyze the beta oxidation of fatty acids. J Biol Chem 253:1522–1528

Lazarow PB (2011) Viruses exploiting peroxisomes. Curr Opin Microbiol 14:458–469

Lazarow PB, De Duve C (1976) A fatty acyl-CoA oxidizing system in rat liver peroxisomes; enhancement by clofibrate, a hypolipidemic drug. Proc Natl Acad Sci U S A 73:2043–2046

Lazo O, Contreras M, Singh I (1990) Topographical localization of peroxisomal acyl-CoA ligases: differential localization of palmitoyl-CoA and lignoceroyl-CoA ligases. Biochemistry 29:3981–3986

Legakis JE, Koepke JI, Jedeszko C et al (2002) Peroxisome senescence in human fibroblasts. Mol Biol Cell 13:4243–4255

Lewin TM, Kim JH, Granger DA, Vance JE, Coleman RA (2001) Acyl-CoA synthetase isoforms 1, 4, and 5 are present in different subcellular membranes in rat liver and can be inhibited independently. J Biol Chem 276:24674–24679

Lewin TM, Van Horn CG, Krisans SK, Coleman RA (2002) Rat liver acyl-CoA synthetase 4 is a peripheral-membrane protein located in two distinct subcellular organelles, peroxisomes, and mitochondrial-associated membrane. Arch Biochem Biophys 404:263–270

Li X, Gould SJ (2003) The dynamin-like GTPase DLP1 is essential for peroxisome division and is recruited to peroxisomes in part by PEX11. J Biol Chem 278:17012–17020

Li X, Baumgart E, Dong GX et al (2002a) 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 22:8226–8240

Li X, Baumgart E, Morrell JC, Jimenez-Sanchez G, Valle D, Gould SJ (2002b) PEX11 beta deficiency is lethal and impairs neuronal migration but does not abrogate peroxisome function. Mol Cell Biol 22:4358–4365

Li D, Lai Y, Yue Y, Rabinovitch PS, Hakim C, Duan D (2009) Ectopic catalase expression in mitochondria by adeno-associated virus enhances exercise performance in mice. PLoS One 4:e6673

Li Y, Chen R, Zhou Q et al (2012) LSm14A is a processing body-associated sensor of viral nucleic acids that initiates cellular antiviral response in the early phase of viral infection. Proc Natl Acad Sci U S A 109:11770–11775

Li H, Alavian KN, Lazrove E et al (2013) A Bcl-xL-Drp1 complex regulates synaptic vesicle membrane dynamics during endocytosis. Nat Cell Biol 15:773–785

Lopez-Erauskin J, Galino J, Ruiz M et al (2013) Impaired mitochondrial oxidative phosphorylation in the peroxisomal disease X-linked adrenoleukodystrophy. Hum Mol Genet 22:3296–3305

Lu JF, Lawler AM, Watkins PA et al (1997) A mouse model for X-linked adrenoleukodystrophy. Proc Natl Acad Sci U S A 94:9366–9371

Ma J, Sun T, Park S, Shen G, Liu J (2011) The role of hepatitis B virus X protein is related to its differential intracellular localization. Acta Biochim Biophys Sin 43:583–588

Maggio-Hall LA, Keller NP (2004) Mitochondrial beta-oxidation in Aspergillus nidulans. Mol Microbiol 54:1173–1185

Mandard S, Muller M, Kersten S (2004) Peroxisome proliferator-activated receptor alpha target genes. Cell Mol Life Sci 61:393–416

Mannaerts GP, Debeer LJ, Thomas J, De Schepper PJ (1979) Mitochondrial and peroxisomal fatty acid oxidation in liver homogenates and isolated hepatocytes from control and clofibrate-treated rats. J Biol Chem 254:4585–4595

Markwell MA, McGroarty EJ, Bieber LL, Tolbert NE (1973) The subcellular distribution of carnitine acyltransferases in mammalian liver and kidney. A new peroxisomal enzyme. J Biol Chem 248:3426–3432

Mast FD, Li J, Virk MK, Hughes SC, Simmonds AJ, Rachubinski RA (2011) A Drosophila model for the Zellweger spectrum of peroxisome biogenesis disorders. Dis Model Mech 4:659–672

McGuinness MC, Lu JF, Zhang HP et al (2003) Role of ALDP (ABCD1) and mitochondria in X-linked adrenoleukodystrophy. Mol Cell Biol 23:744–753

Medzhitov R, Horng T (2009) Transcriptional control of the inflammatory response. Nat Rev Immunol 9:692–703

Melton EM, Cerny RL, DiRusso CC, Black PN (2013) Overexpression of human fatty acid transport protein 2/very long chain acyl-CoA synthetase 1 (FATP2/Acsvl1) reveals distinct patterns of trafficking of exogenous fatty acids. Biochem Biophys Res Commun 440:743–748

Menendez-Gutierrez MP, Roszer T, Ricote M (2012) Biology and therapeutic applications of peroxisome proliferator- activated receptors. Curr Top Med Chem 12:548–584

Mesecke N, Terziyska N, Kozany C et al (2005) A disulfide relay system in the intermembrane space of mitochondria that mediates protein import. Cell 121:1059–1069

Mohan KV, Atreya CD (2003) Novel organelle-targeting signals in viral proteins. Bioinformatics 19:10–13

Mohan KV, Som I, Atreya CD (2002) Identification of a type 1 peroxisomal targeting signal in a viral protein and demonstration of its targeting to the organelle. J Virol 76:2543–2547

Morita M, Imanaka T (2012) Peroxisomal ABC transporters: structure, function and role in disease. Biochim Biophys Acta 1822:1387–1396

Murphy MP (2009) How mitochondria produce reactive oxygen species. Biochem J 417:1–13

Neuspiel M, Schauss AC, Braschi E et al (2008) Cargo-selected transport from the mitochondria to peroxisomes is mediated by vesicular carriers. Curr Biol 18:102–108

Niemann A, Ruegg M, La Padula V, Schenone A, Suter U (2005) Ganglioside-induced differentiation associated protein 1 is a regulator of the mitochondrial network: new implications for Charcot-Marie-Tooth disease. J Cell Biol 170:1067–1078

Niemann A, Berger P, Suter U (2006) Pathomechanisms of mutant proteins in Charcot-Marie-Tooth disease. Neuromol Med 8:217–242

Niemann A, Wagner KM, Ruegg M, Suter U (2009) GDAP1 mutations differ in their effects on mitochondrial dynamics and apoptosis depending on the mode of inheritance. Neurobiol Dis 36:509–520

Nordgren M, Fransen M (2014) Peroxisomal metabolism and oxidative stress. Biochimie 98:56–62

Odendall C, Kagan JC (2013) Peroxisomes and the antiviral responses of Mammalian cells. Subcell Biochem 69:67–75

Odendall C, Dixit E, Stavru F et al (2014) Diverse intracellular pathogens activate type III interferon expression from peroxisomes. Nat Immunol 15:717–726

Oezen I, Rossmanith W, Forss-Petter S et al (2005) Accumulation of very long-chain fatty acids does not affect mitochondrial function in adrenoleukodystrophy protein deficiency. Hum Mol Genet 14:1127–1137

Onoue K, Jofuku A, Ban-Ishihara R et al (2013) Fis1 acts as a mitochondrial recruitment factor for TBC1D15 that is involved in regulation of mitochondrial morphology. J Cell Sci 126:176–185

Opalinski L, Kiel JA, Williams C, Veenhuis M, van der Klei IJ (2011) Membrane curvature during peroxisome fission requires Pex11. EMBO J 30:5–16

Osmundsen H, Neat CE, Norum KR (1979) Peroxisomal oxidation of long chain fatty acids. FEBS Lett 99:292–296

Otera H, Wang C, Cleland MM et al (2010) Mff is an essential factor for mitochondrial recruitment of Drp1 during mitochondrial fission in mammalian cells. J Cell Biol 191:1141–1158

Paget GE (1963) Experimental studies of the toxicity of Atromid with particular reference to fine structural changes in the livers of rodents. J Atheroscler Res 3:729–736

Palmer CS, Elgass KD, Parton RG, Osellame LD, Stojanovski D, Ryan MT (2013) Adaptor proteins MiD49 and MiD51 can act independently of Mff and Fis1 in Drp1 recruitment and are specific for mitochondrial fission. J Biol Chem 288:27584–27593

Peeters A, Shinde AB, Dirkx R et al (2014) Mitochondria in peroxisome-deficient hepatocytes exhibit impaired respiration, depleted DNA, and PGC-1alpha independent proliferation. Biochim Biophys Acta 1853:285–298

Powers JM, Pei Z, Heinzer AK et al (2005) Adreno-leukodystrophy: oxidative stress of mice and men. J Neuropathol Exp Neurol 64:1067–1079

Puigserver P (2005) Tissue-specific regulation of metabolic pathways through the transcriptional coactivator PGC1-alpha. Int J Obes 29(Suppl 1):S5–S9

Pyper SR, Viswakarma N, Yu S, Reddy JK (2010) PPARalpha: energy combustion, hypolipidemia, inflammation and cancer. Nucl Recept Signal 16:e002

Reddy JK, Hashimoto T (2001) Peroxisomal beta-oxidation and peroxisome proliferator-activated receptor alpha: an adaptive metabolic system. Annu Rev Nutr 21:193–230

Rinaldo P, Matern D, Bennett MJ (2002) Fatty acid oxidation disorders. Annu Rev Physiol 64:477–502

Roberts LD, Murray AJ, Menassa D, Ashmore T, Nicholls AW, Griffin JL (2011) The contrasting roles of PPARdelta and PPARgamma in regulating the metabolic switch between oxidation and storage of fats in white adipose tissue. Genome Biol 12:R75

Ruggieri V, Mazzoccoli C, Pazienza V, Andriulli A, Capitanio N, Piccoli C (2014) Hepatitis C virus, mitochondria and auto/mitophagy: exploiting a host defense mechanism. World J Gastroenterol 20:2624–2633

Saggerson D (2008) Malonyl-CoA, a key signaling molecule in mammalian cells. Annu Rev Nutr 28:253–272

Salcher S, Hagenbuchner J, Geiger K et al (2014) C10ORF10/DEPP, a transcriptional target of FOXO3, regulates ROS-sensitivity in human neuroblastoma. Mol Cancer 13:224

Salpietro V, Phadke R, Saggar A, et al (2014) Zellweger syndrome and secondary mitochondrial myopathy. Eur J Pediatr

Saudubray JM, Martin D, de Lonlay P et al (1999) Recognition and management of fatty acid oxidation defects: a series of 107 patients. J Inherit Metab Dis 22:488–502

Schrader M, Fahimi HD (2006a) Growth and division of peroxisomes. Int Rev Cytol 255:237–290

Schrader M, Fahimi HD (2006b) Peroxisomes and oxidative stress. Biochim Biophys Acta 1763:1755–1766

Schrader M, Yoon Y (2007) Mitochondria and peroxisomes: are the 'big brother' and the 'little sister' closer than assumed? BioEssays 29:1105–1114

Schrader M, Reuber BE, Morrell JC et al (1998) Expression of PEX11beta mediates peroxisome proliferation in the absence of extracellular stimuli. J Biol Chem 273:29607–29614

Schrader M, King SJ, Stroh TA, Schroer TA (2000) Real time imaging reveals a peroxisomal reticulum in living cells. J Cell Sci 113:3663–3671

Schrader M, Bonekamp NA, Islinger M (2012) Fission and proliferation of peroxisomes. Biochim Biophys Acta 1822:1343–1357

Schrader M, Grille S, Fahimi HD, Islinger M (2013) Peroxisome interactions and cross-talk with other subcellular compartments in animal cells. Subcell Biochem 69:1–22

Schriner SE, Linford NJ, Martin GM et al (2005) Extension of murine life span by overexpression of catalase targeted to mitochondria. Science 308:1909–1911

Sebastian D, Guitart M, Garcia-Martinez C et al (2009) Novel role of FATP1 in mitochondrial fatty acid oxidation in skeletal muscle cells. J Lipid Res 50:1789–1799

Shamseldin HE, Alshammari M, Al-Sheddi T et al (2012) Genomic analysis of mitochondrial diseases in a consanguineous population reveals novel candidate disease genes. J Med Genet 49:234–241

Shen YQ, Lang BF, Burger G (2009) Diversity and dispersal of a ubiquitous protein family: acyl-CoA dehydrogenases. Nucleic Acids Res 37:5619–5631

Sinclair AM, Trobacher CP, Mathur N, Greenwood JS, Mathur J (2009) Peroxule extension over ER-defined paths constitutes a rapid subcellular response to hydroxyl stress. Plant J 59:231–242

Singh J, Giri S (2014) Loss of AMP-activated protein kinase in X-linked adrenoleukodystrophy patient-derived fibroblasts and lymphocytes. Biochem Biophys Res Commun 445:126–131

Singh I, Moser AE, Goldfischer S, Moser HW (1984) Lignoceric acid is oxidized in the peroxisome: implications for the Zellweger cerebro-hepato-renal syndrome and adrenoleukodystrophy. Proc Natl Acad Sci U S A 81:4203–4207

Speijer D (2011) Oxygen radicals shaping evolution: why fatty acid catabolism leads to peroxisomes while neurons do without it: FADH(2)/NADH flux ratios determining mitochondrial radical formation were crucial for the eukaryotic invention of peroxisomes and catabolic tissue differentiation. BioEssays 33:88–94

Speijer D (2014) How the mitochondrion was shaped by radical differences in substrates: what carnitine shuttles and uncoupling tell us about mitochondrial evolution in response to ROS. BioEssays 36:634–643

Spiekerkoetter U, Lindner M, Santer R et al (2009) Management and outcome in 75 individuals with long-chain fatty acid oxidation defects: results from a workshop. J Inherit Metab Dis 32:488–497

Sugiura A, McLelland GL, Fon EA, McBride HM (2014) A new pathway for mitochondrial quality control: mitochondrial-derived vesicles. EMBO J 33:2142-2156

Suzuki A, Yasuno T, Kojo H, Hirosumi J, Mutoh S, Notsu Y (2000) Alteration in expression profiles of a series of diabetes-related genes

in db/db mice following treatment with thiazolidinediones. Jpn J Pharmacol 84:113–123
Svoboda DJ, Azarnoff DL (1966) Response of hepatic microbodies to a hypolipidemic agent, ethyl chlorophenoxyisobutyrate (CPIB). J Cell Biol 30:442–450
Tanaka A, Osumi M, Fukui S (1982) Peroxisomes of alkane-grown yeast: fundamental and practical aspects. Ann N Y Acad Sci 386:183–199
Tanner LB, Chng C, Guan XL, Lei Z, Rozen SG, Wenk MR (2014) Lipidomics identifies a requirement for peroxisomal function during influenza virus replication. J Lipid Res 55:1357–1365
Terlecky SR, Koepke JI, Walton PA (2006) Peroxisomes and aging. Biochim Biophys Acta 1763:1749–1754
Thomas J, Debeer LJ, De Schepper PJ, Mannaerts GP (1980) Factors influencing palmitoyl-CoA oxidation by rat liver peroxisomal fractions. Substrate concentration, organelle integrity and ATP. Biochem J 190:485–494
Thoms S, Erdmann R (2005) Dynamin-related proteins and Pex11 proteins in peroxisome division and proliferation. FEBS J 272:5169–5181
Thoms S, Gartner J (2012) First PEX11beta patient extends spectrum of peroxisomal biogenesis disorder phenotypes. J Med Genet 49:314–316
Tolbert NE (1981) Metabolic pathways in peroxisomes and glyoxysomes. Annu Rev Biochem 50:133–157
Uchida Y, Kondo N, Orii T, Hashimoto T (1996) Purification and properties of rat liver peroxisomal very-long-chain acyl-CoA synthetase. J Biochem 119:565–571
van Roermund CW, Visser WF, Ijlst L et al (2008) The human peroxisomal ABC half transporter ALDP functions as a homodimer and accepts acyl-CoA esters. FASEB J 22:4201–4208
van Roermund CW, Visser WF, Ijlst L, Waterham HR, Wanders RJ (2011) Differential substrate specificities of human ABCD1 and ABCD2 in peroxisomal fatty acid beta-oxidation. Biochim Biophys Acta 1811:148–152
van Roermund CW, Ijlst L, Wagemans T, Wanders RJ, Waterham HR (2014) A role for the human peroxisomal half-transporter ABCD3 in the oxidation of dicarboxylic acids. Biochim Biophys Acta 1841:563–568
Van Veldhoven PP (2010) Biochemistry and genetics of inherited disorders of peroxisomal fatty acid metabolism. J Lipid Res 51:2863–2895
Van Veldhoven PP, Vanhove G, Assselberghs S, Eyssen HJ, Mannaerts GP (1992) Substrate specificities of rat liver peroxisomal acyl-CoA oxidases: palmitoyl-CoA oxidase (inducible acyl-CoA oxidase), pristanoyl-CoA oxidase (non-inducible acyl-CoA oxidase), and trihydroxycoprostanoyl-CoA oxidase. J Biol Chem 267:20065–20074
Violante S, Ijlst L, Te Brinke H et al (2013) Peroxisomes contribute to the acylcarnitine production when the carnitine shuttle is deficient. Biochim Biophys Acta 1831:1467–1474
Vockley J, Whiteman DA (2002) Defects of mitochondrial beta-oxidation: a growing group of disorders. Neuromuscul Disord 12:235–246
Wakabayashi J, Zhang Z, Wakabayashi N et al (2009) The dynamin-related GTPase Drp1 is required for embryonic and brain development in mice. J Cell Biol 186:805–816
Walton PA, Pizzitelli M (2012) Effects of peroxisomal catalase inhibition on mitochondrial function. Front Physiol 3:108
Wanders RJ (2013) Peroxisomes in human health and disease: metabolic pathways, metabolite transport, interplay with other organelles and signal transduction. Subcell Biochem 69:23–44
Wanders RJ, Waterham HR (2006) Peroxisomal disorders: the single peroxisomal enzyme deficiencies. Biochim Biophys Acta 1763:1707–1720
Wanders RJ, Ferdinandusse S, Brites P, Kemp S (2010) Peroxisomes, lipid metabolism and lipotoxicity. Biochim Biophys Acta 1801:272–280
Wanders RJ, Komen J, Ferdinandusse S (2011) Phytanic acid metabolism in health and disease. Biochim Biophys Acta 1811:498–507
Wang YX, Lee CH, Tiep S et al (2003) Peroxisome-proliferator-activated receptor delta activates fat metabolism to prevent obesity. Cell 113:159–170
Wang B, Van Veldhoven PP, Brees C et al (2013) Mitochondria are targets for peroxisome-derived oxidative stress in cultured mammalian cells. Free Radic Biol Med 65:882–894
Waterham HR, Koster J, van Roermund CW, Mooyer PA, Wanders RJ, Leonard JV (2007) A lethal defect of mitochondrial and peroxisomal fission. N Engl J Med 356:1736–1741
Westermann B (2010) Mitochondrial fusion and fission in cell life and death. Nat Rev Mol Cell Biol 11:872–884
Westermann B (2012) Bioenergetic role of mitochondrial fusion and fission. Biochim Biophys Acta 1817:1833–1838
Westin MA, Hunt MC, Alexson SE (2008) Short- and medium-chain carnitine acyltransferases and acyl-CoA thioesterases in mouse provide complementary systems for transport of beta-oxidation products out of peroxisomes. Cell Mol Life Sci 65:982–990
Wiese S, Gronemeyer T, Ofman R et al (2007) Proteomics characterization of mouse kidney peroxisomes by tandem mass spectrometry and protein correlation profiling. Mol Cell Proteomics 6:2045–2057
Wiesinger C, Kunze M, Regelsberger G, Forss-Petter S, Berger J (2013) Impaired very long-chain acyl-CoA β-oxidation in human X-linked adrenoleukodystrophy fibroblasts is a direct consequence of ABCD1 transporter dysfunction. J Biol Chem 288:19269–19279
Williams C, Bener Aksam E, Gunkel K, Veenhuis M, van der Klei IJ (2012) The relevance of the non-canonical PTS1 of peroxisomal catalase. Biochim Biophys Acta 1823:1133–1141
Wolff T, O'Neill RE, Palese P (1996) Interaction cloning of NS1-I, a human protein that binds to the nonstructural NS1 proteins of influenza A and B viruses. J Virol 70:5363–5372
Wu M, Cao A, Dong B, Liu J (2011) Reduction of serum free fatty acids and triglycerides by liver-targeted expression of long chain acyl-CoA synthetase 3. Int J Mol Med 27:655–662
Yamano K, Fogel AI, Wang C, van der Bliek AM, Youle RJ (2014) Mitochondrial Rab GAPs govern autophagosome biogenesis during mitophagy. eLife 3:e01612
Zanardelli M, Micheli L, Cinci L et al (2014) Oxaliplatin neurotoxicity involves peroxisome alterations. PPARgamma agonism as preventive pharmacological approach. PLoS One 9:e102758
Zhang J, Zhang W, Zou D et al (2002) Cloning and functional characterization of ACAD-9, a novel member of human acyl-CoA dehydrogenase family. Biochem Biophys Res Commun 297:1033–1042