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Peroxisomes Are Oxidative Organelles

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Abstract

Peroxisomes are multifunctional organelles with an important role in the generation and decomposition of reactive oxygen species (ROS). In this review, the ROS-producing enzymes, as well as the antioxidative defense system in mammalian peroxisomes, are described. In addition, various conditions leading to disturbances in peroxisomal ROS metabolism, such as abnormal peroxisomal biogenesis, hypocatalasemia, and proliferation of peroxisomes are discussed. We also review the role of mammalian peroxisomes in some physiological and pathological processes involving ROS that lead to mitochondrial abnormalities, defects in cell proliferation, and alterations in the central nervous system, alcoholic cardiomyopathy, and aging. *Antioxid. Redox Signal.* 13, 525–537.

Introduction

PEROXISOMES ARE ESSENTIAL CELLULAR ORGANELLES that perform important metabolic functions in such diverse organisms as mammals, plants, and unicellular eukaryotes, including yeast and *Tetrahymena*. Mammalian peroxisomes harbor more than 100 enzymes and other proteins. The main function of these particles is the oxidative degradation of long- and very long-chain fatty acids, including branched-chain (e.g., phytanic acid) and polyunsaturated fatty acids, dicarboxylic acids, and a side chain of bile acid precursors (di- and trihydroxycoprostanoyl-CoA). In addition, mammalian peroxisomes carry out a wide range of other reactions such as the oxidation of purines, L-α-hydroxy acids, polyamines, and some amino acids as well as the synthesis of plasmalogenes, waxes, and ketone bodies (Table 1, reviewed in Refs. 85 and 107). These organelles play a key role in the production and utilization of reactive oxygen species (ROS). The importance of peroxisomes for cellular metabolism is emphasized by the existence of a group of inherited diseases (Zellweger syndrome, neonatal adrenoleukodystrophy, infantile Refsum's disease, and rhizomelic chondrodysplasia punctata) caused by severe impairment of one or more peroxisomal functions (reviewed in Refs. 101 and 108).

The unique feature of peroxisomes is their central role in the metabolism of compounds poorly soluble in water or lipids (Table 1). Most of them are amphipathic molecules (e.g., various fatty acids, steroids including bile acid precursors, and several hydrophobic hydroxy- and amino acids). Other metabolites that are poorly soluble in water and insoluble in lipids include purines (xanthine, hypoxanthine, and uric acid) and oxalates. Interestingly, if the transport and metabolism of these compounds is inefficient, they accumulate in the human body, which leads to the development of pathological conditions such as atherosclerosis, gout, kidney stones, and gallstones, and the accumulation of very long-chain fatty acids in some inherited diseases (24, 42, 65, 101, 108). Most of these abnormalities are accompanied by disturbances in ROS metabolism.

Although the main peroxisomal metabolic pathways have already been characterized, the functional roles of the systems responsible for the generation and degradation of ROS in peroxisomes are poorly understood. Peroxisomal oxygen metabolism may represent a chain of interconnected events that are highly coordinated and prevent the destructive effects of ROS on cellular functions. In the current review, we describe the basic mechanisms involved in ROS metabolism in mammalian peroxisomes and discuss new developments in the study of the pathobiology of these organelles.

Morphology of Mammalian Peroxisomes

Peroxisomes belong to a group of organelles called 'microbodies.' The group also includes glyoxysomes from plant seeds (45), glycosomes from *Tetrahymena* species (79), and Woronin bodies from filamentous fungi (70). All these organelles share similar morphology and biogenesis although they differ in protein composition and function. Mammalian peroxisomes from liver and kidney are spherical or oval particles with a diameter of 0.5–1.0 μm surrounded by a single membrane and filled with an electron-dense granular matrix (Fig. 1).Peroxisomes usually contain characteristic core-like structures called nucleoids that represent natural crystals of the enzyme urate oxidase. Rather smaller are microperoxisomes (0.1–0.45 μm in diameter) which can be found in tissues other than liver and kidney (34). These particles are difficult to discriminate from the structures formed by smooth endoplasmic reticulum when using conventional electron microscopy.

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Table 1. Main Metabolic Pathways in Mammalian Peroxisomes

Pathway	*Substrate*	*Product*
β-Oxidation of long- and very-long chain fatty acids.	Long- and very long-chain fatty acids (saturated and unsaturated).	Medium-chain fatty acids plus acetyl-CoA.
β-Oxidation of dicarboxylic fatty acids.	Dicarboxylic long- and medium-chain fatty acids.	Dicarboxylic short-chain acids including succinate plus acetyl-CoA.
β-Oxidation of methyl branched fatty acids.	Long and medium-chain methyl-branched fatty acids (pristanic acid).	Short- and medium-chain branched fatty acids plus acetyl-CoA and propionyl-CoA.
α-Oxidation of branched-chain fatty acids.	3*R*-Methyl-branched fatty acids (phytanic acid).	2*R*-Methyl-branched fatty acids (pristanic acid).
Last steps in the formation of bile acids (β-oxidation and conjugation with amino acids).	Di- and trihydroxycholestanoic acids (DHCA and THCA).	Chenodeoxycholic, cholic, taurocholic, and glycocholic acids.
Ketogenesis	Acetyl-CoA.	Acetoacetate.
Ether-phospholipid (plasmalogen) biosynthesis.	Dihydroxyacetone phosphate and acyl-CoA's.	Alkyl-glycerol-3-phosphate.
Glyoxylate metabolism.	Glycolate.	Glycine.
Amino acids oxidation.	L- and/or D-isomers of some amino acids.	2-oxoacids.
Polyamine oxidation.	*N*-acetyl derivatives of spermine and spermidine.	Spermidine, putrescine, and 3-acetamidopropanal.
Oxidative part of pentose phosphate pathway.	Glucose-6-phosphate.	Ribose-5-phosphate.

Therefore, a method has been developed to detect microperoxisomes by tissue staining with 3,3'-diaminobenzidine (DAB) that is converted to an electron-dense insoluble material in the peroxidase reaction of catalase, a peroxisomal marker (Fig. 1E).

Biogenesis of Peroxisomes

Peroxisomes lack DNA, and therefore all peroxisomal proteins are coded for in the nucleus and synthesized on free polyribosomes in the cytoplasm. Unlike mitochondria and

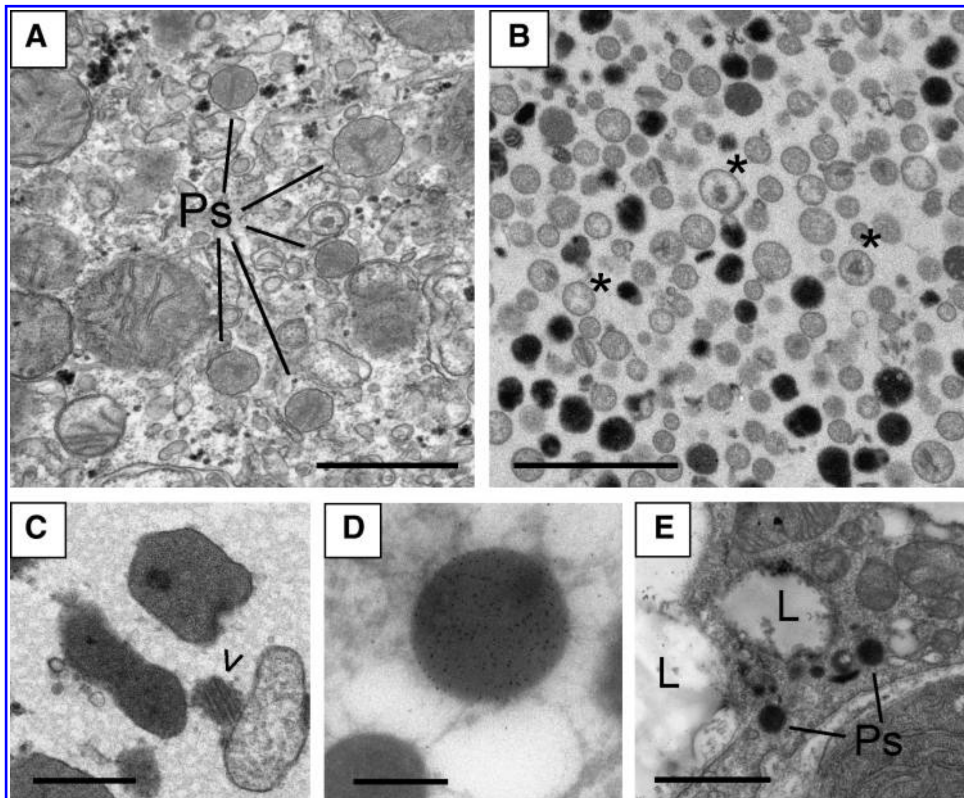

FIG. 1. Morphology of mammalian peroxisomes. (**A**) Cluster of mouse liver peroxisomes (Ps). The particles are surrounded by a single membrane, contain a homogeneous matrix and electron-dense 'worm'-like nucleoids. Bar, 1000 nm. (**B**) Peroxisomes purified from normal mouse liver. Note the differences in electron density of the particles due to leakage of soluble matrix proteins during isolation. Structures that contain membrane and nucleoid but lack matrix (peroxisomal 'ghosts') are marked by *asterisks*. Bar, 2000 nm. (**C**) Peroxisomes isolated from rat liver. A nucleoid released during isolation with a clear visible crystalline structure is marked by an *arrowhead.* Bar, 500 nm. (**D**) Immunogold staining of rat liver peroxisomes for the marker enzyme 3-oxoacyl-CoA thiolase. Note that the gold particles are highly concentrated in the organelle, indicating that the enzyme is a truly peroxisomal constituent. Bar, 500 nm. (**E**) DAB staining of peroxisomes (Ps) in the fat pad tissue of mouse mammary glands. Lipid droplets are marked (L). Bar, 500 nm.

chloroplasts, peroxisomes can import folded, fully assembled proteins (73). To facilitate their transport into peroxisomes, most peroxisomal proteins possess a targeting sequence, the so-called peroxisomal targeting signal (PTS). Two distinct signals for matrix proteins have been described. PTS1 represents a tripeptide with a consensus sequence: (S/A/C)-(K/H/Q/R)-(L/M), which is located at the extreme C-terminus of a protein.

PTS2, with a consensus sequence: (R/K)-(L/I/V)-X_5-(H/Q)-(L/A/F), is located near the N-terminus of a protein. Some proteins that have no PTS can be imported into peroxisomes after oligomerization with other proteins that contain a PTS. This pathway is designated a 'piggyback' mechanism. PTS's are recognized in the cytoplasm by their corresponding receptor proteins Pex5 (PTS1) and Pex7 (PTS2), which transfer their cargo to the peroxisomal membrane (Fig. 2). How the cargo proteins are transferred across the membrane is still unknown. The mechanism of this transportation is a subject of hot discussions (reviewed in Ref. 33).

Main Metabolic Pathways in Mammalian Peroxisomes

Peroxisomes play an important role in mammalian cellular metabolism and physiology. The repertoire of enzyme activities in these particles varies greatly depending on the species or tissues, which reflects the contribution of these organelles to the metabolism of host cells. Peroxisomes are also remarkable in that their number, size, and enzyme profiles respond to various stimuli (see, for example, Fig. 3). Because of their multiple metabolic functions, peroxisomes are linked to a number of inherited or acquired human diseases. The metabolic functions performed by peroxisomes include a wide range of degradative and synthetic reactions summarized in Table 1 (reviewed in Ref. 107). Frequently, the peroxisomal metabolite breakdown processes include a hydrogen peroxide (H_2O_2) generating oxidation step.

A common feature of peroxisomes from different species is that they carry out fatty acid β-oxidation. In most fungi as well as in plants, this seems to be solely a peroxisomal process. In mammals, however, fatty acid β-oxidation also takes place in mitochondria. All the known peroxisomal β-oxidation pathways have multifunctional proteins displaying both 2E-enoyl-CoA hydratase and 3-hydroxyacyl-CoA dehydrogenase activities. Interestingly, mammals have two of these proteins (peroxisomal multifunctional enzymes types 1 and 2) showing different evolutionary origins and catalyzing the conversion of 2E-enoyl-CoA esters to 3-oxoacyl-CoA esters either through 3S- or 3R-hydroxyacyl-CoA intermediates,

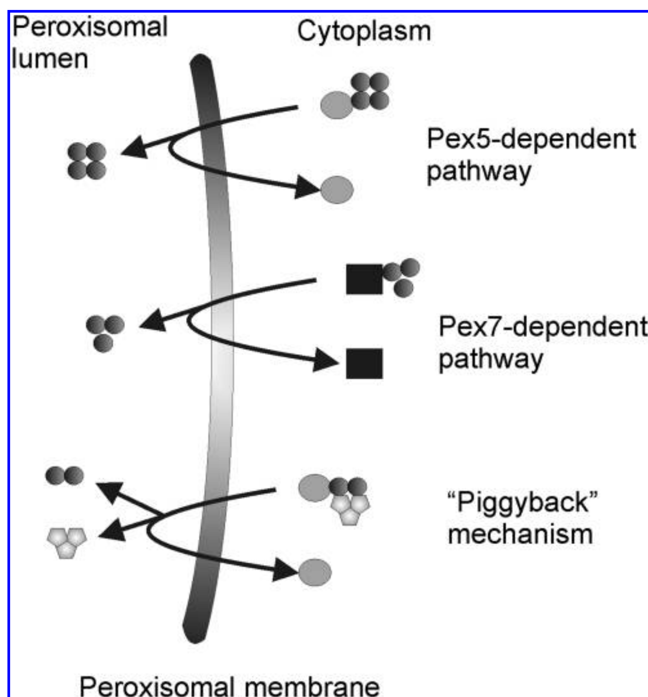

FIG. 2. Transfer of matrix proteins into peroxisomes. *Dark gray circles*: matrix proteins that are folded and fully assembled as oligomers. *Light gray circles*: Pex5 receptor recognizing proteins containing PTS1. *Black squares*: Pex7 receptor recognizing proteins containing PTS2. *Light gray pentagons*: oligomeric protein molecule that is delivered into the peroxisome by the so-called 'piggyback' mechanism. Note that the receptors are shuttled between the cytoplasm and peroxisomes. Pex7 delivers cargo proteins into peroxisomes only after complex formation with Pex5.

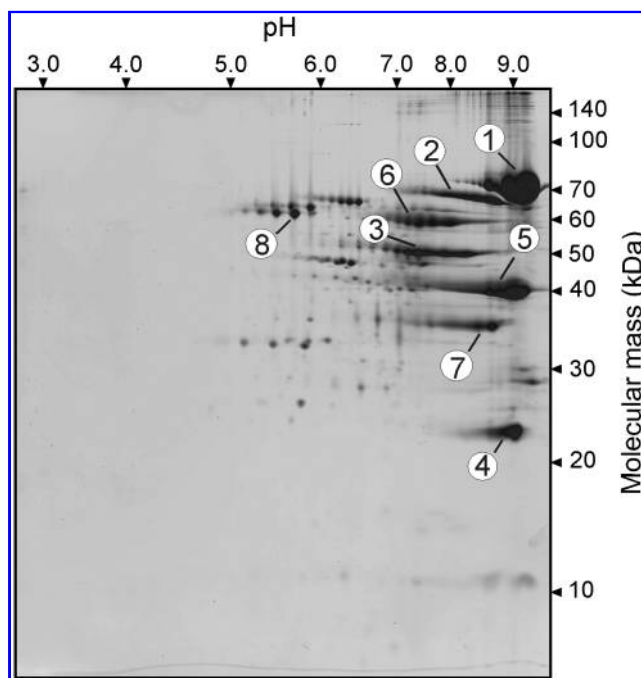

FIG. 3. Two-dimensional electrophoresis of peroxisomal matrix proteins that demonstrates the relative abundance of the proteins in the particles. Peroxisomes were isolated from clofibrate-treated mouse liver. Apparent pI and molecular mass values are indicated. The main protein components were detected using mass spectrometry: (1) Multifunctional enzyme 1 catalyzing the second (hydratase) and third (dehydrogenase) steps in peroxisomal β-oxidation of fatty acids; (2) Palmitoyl-CoA oxidase, full-length peptide; (3) Palmitoyl-CoA oxidase, N-terminal fragment. The enzyme undergoes a limited proteolytic cleavage after import into peroxisomes; (4) Palmitoyl-CoA oxidase, C-terminal fragment; (5) 3-Oxoacyl-CoA thiolase; (6) Catalase; (7) Urate oxidase; (8) Epoxide hydrolase. Note the abundance of proteins involved in production (palmitoyl-CoA oxidase, urate oxidase) and decomposition (catalase) of H_2O_2.

respectively (36, 47). Some polyunsaturated fatty acids are not accepted as substrates by the β-oxidation enzymes. Therefore, peroxisomes have acquired a set of auxiliary enzymes to transform the acyl-CoA esters of these fatty acids to intermediates suitable for breakdown by β-oxidation (47, 85).

Transfer of Metabolites Across the Peroxisomal Membrane

Carbon flow through peroxisomal pathways requires a continuous transfer of metabolites across the peroxisomal membrane. The mechanism of this transfer represents a long-standing problem in the physiology of peroxisomes. The key question that was unanswered for more than 40 years is whether metabolites are transferred across the membrane by specific transporters like in the inner mitochondrial membrane or whether they cross the membrane through nonselective channels similar to the mechanism of permeation of the outer mitochondrial or nuclear membranes (6, 85, 106, 107). It now seems that both concepts are valid for peroxisomes (10, 11, 92) since the membrane of these organelles contains nonselective channels side by side with transporters highly selective for certain compounds (Fig. 4). The channels allow the transmembrane passage of small solutes with a molecular mass below 400 Da while the transporters are responsible for the transfer of 'bulky' solutes (molecular mass over 400 Da) such as ATP (81) and long-chain acyl-CoA derivatives (106). Therefore, the peroxisomal lumen and the surrounding cytoplasm share a common pool of small solutes including nearly all the intermediates of peroxisomal metabolic pathways. In contrast, these two compartments possess their own pools of 'bulky' solutes (ATP and cofactors such as NAD/H and NADP/H) and acyl-CoA derivatives. These predictions are important for understanding the physiology of mammalian peroxisomes. For instance, one can suggest that molecules of reduced glutathione (GSH, molecular mass 307.3 Da) freely penetrate the peroxisomal membrane. GSH effectively reduces peroxides and free radicals nonenzymatically with the formation of oxidized glutathione (GSSG). The hexapeptide molecule of GSSG (molecular mass 612.2 Da) is a 'bulky' solute that is unable to use channels to pass through the peroxisomal membrane. Consequently, an active transport of GSSG out of peroxisomes by means of specific transporters can be predicted.

Peroxisomal Enzymes Producing ROS

Mammalian peroxisomes are densely populated by enzymes that form ROS (Table 2). Most of them are FAD (or FMN)-dependent oxidases generating H_2O_2 as a reaction by-product. In addition, some observations indicate the presence in peroxisomes of the O_2-producing enzyme xanthine oxidoreductase (4) and the inducible form of nitric oxide synthase (72).

Acyl-CoA oxidases

Rat liver peroxisomes contain three acyl-CoA oxidases with overlapping substrate specificities: palmitoyl-CoA oxidase (ACOX1), trihydroxycoprostanoyl-CoA oxidase (ACOX2) and pristanoyl-CoA oxidase (ACOX3). In addition to their specific substrates (Table 2), all of them oxidize long and very-long straight-chain acyl-CoA's with varying efficiency (104). Only ACOX1 is inducible by clofibrate and other peroxisome proliferators (see section below and Fig. 3). As in rodents, the human genome contains three genes for peroxisomal acyl-CoA oxidases (17). However, expression of one of them, the homolog of rat ACOX3, is somehow suppressed. The protein product of this gene was only detected in human prostate tissue and in some prostate cancer cell lines (117). In all other human tissues, peroxisomal ACOX2 is responsible not only for oxidation of bile acid intermediates but also for degradation of 2-methyl-branched fatty acids. Considering the abundance of acyl-CoA oxidases, especially ACOX1, in peroxisomes (Fig. 3) and the availability of their substrates, these enzymes may be the main source of H_2O_2 in the particles.

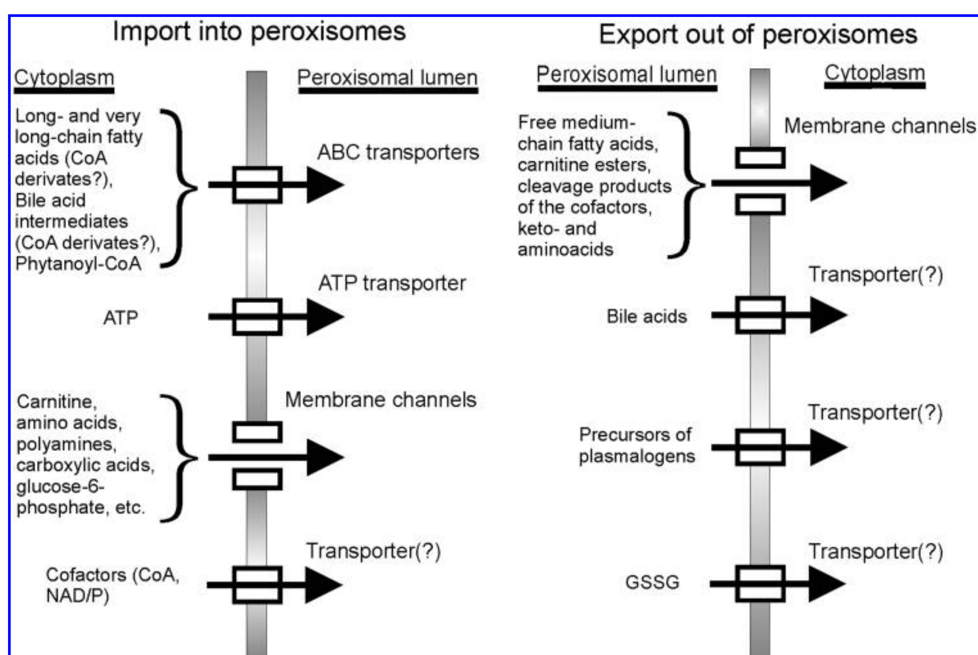

FIG. 4. Transfer of metabolites across the peroxisomal membrane. Note the presence of nonselective channels side by side with transporters specific for 'bulky' solutes or lipid soluble compounds. In contrast to channels, transporters are able to transfer metabolites against their concentration gradient.

Table 2. Enzymes in Mammalian Peroxisomes that Generate ROS

Enzyme	*Substrate*	*ROS*
Palmitoyl-CoA oxidase	Long- and very long-chain fatty acids, dicarboxylic fatty acids, glutaryl-CoA	H_2O_2
Pristanoyl-CoA oxidase	2-Methyl-branched fatty acids	H_2O_2
Trihydroxycoprostanoyl-CoA oxidase	Bile acids intermediates	H_2O_2
Urate oxidase	Uric acid	H_2O_2
L-α-hydroxyacid oxidases	Glycolate, lactate, medium- and long-chain 2-hydroxyacids	H_2O_2
Polyamine oxidase	*N*-acetyl spermine/spermidine	H_2O_2
Pipecolic acid oxidase	L-Pipecolic acid	H_2O_2
Sarcosine oxidase	Sarcosine, L-proline	H_2O_2
D-amino acid oxidase	D-isomers of neutral and basic amino acids	H_2O_2
D-aspartate oxidase	D-isomers of acidic amino acids	H_2O_2
Xanthine oxidase	Hypoxanthine, xanthine	O_{2-}
NO synthase	L-arginine	NO

Urate oxidase

This enzyme, which does not require an organic co-factor for catalysis, is a principal component of peroxisomal nucleoids in some mammals. These natural crystals of urate oxidase were detected only in liver and kidney peroxisomes (Fig. 1). In all other tissues the enzyme is not expressed. The biological significance of the formation of nucleoids is not clear. Primates, including humans, have no nucleoids due to the absence of the urate oxidase protein. The human urate oxidase gene contains two nonsense mutations and thus does not encode a functional protein (114). Uric acid is a powerful antioxidant that scavenges singlet oxygen, peroxynitrite and free radicals (2, 49). Therefore, the prediction has been made that the loss of urate oxidase function is beneficial since it allows maintenance of an elevated, relative to other mammals, content of uric acid in body fluids and tissues of primates (2). However, a knockout of the urate oxidase gene in mice that led to a drastic increase in the body content of uric acid did not reveal any beneficial effect (112). Moreover, these animals displayed symptoms characteristic for gout, a human disease caused by the accumulation of urate crystals in kidney and joints. On the other hand, the administration of uric acid has been shown to inhibit CNS inflammation, blood–CNS barrier permeability changes, and tissue damage in a mouse model of multiple sclerosis (49). Recently, a moderately elevated concentration of uric acid has been detected in the body fluids of mice deficient in the peroxisomal membrane channel protein Pxmp2 (92). This animal model may be useful for *in vivo* analysis of the antioxidant defense potential of uric acid.

2-Hydroxyacid oxidase

Two isoforms of this enzyme have been detected in rodents: (i) Glycolate oxidase (isoform A) oxidizes glycolic, lactic, and glyoxylic acids; (ii) 2-Hydroxyacid oxidase (isoform B) is specific towards short (2-hydroxybutyrate) and medium-chain 2-hydroxyacids (64). Three human peroxisomal 2-hydroxyacid oxidases have been characterized: HAOX1, HAOX2, and HAOX3 (67). HAOX1 is in fact glycolate oxidase. HAOX3 is reactive towards the medium chain acid 2-hydroxyoctanoate, while HAOX2 shows activity with 2-hydroxyoctanoate and with the long-chain fatty acid 2-hydroxypalmitate as substrates. In mammals, the long-chain 2-hydroxy acids are most abundant in brain where they represent ~ 6% of the total amount of fatty acids (37).

N¹-Acetyl polyamine oxidase

Polyamines—putrescine, spermine (SPM), and spermidine (SPD)—are essential for the growth, maintenance, and function of mammalian cells (76). The intracellular concentration of these compounds is under tight regulation that depends on the enzymes involved in the synthesis and the degradation of polyamines. The main degradation pathway starts in the cytosol by the action of acetyl-CoA:SPD/SPM N^1-acetyltransferase. The enzyme converts biologically active SPM and SPD to their inactive N-acetylated forms, N^1-acetyl-SPM and N^1-acetyl-SDP, respectively (76). As a next step, the acetylated polyamines are oxidized by peroxisomal N^1-acetyl polyamine oxidase, resulting in the formation of SPD from N^1-acetyl-SPM, putrescine from N^1-acetyl-SDP as well as 3-acetamidopropanal and H_2O_2 as by-products (111). Therefore, by producing SPD and putrescine, the oxidase partially reverses an inactivating effect of the acetyltransferase on polyamines. Apart from peroxisomes, the cytosol also contains polyamine oxidase that reacts with SPM, but not with acetylated polyamines (76). The biological significance of the coexistence of two polyamine oxidases in the same cells is not clear.

Pipecolic acid and sarcosine oxidases

One of the routes for L-lysine degradation is the L-pipecolate pathway. L-pipecolic acid is oxidized by peroxisomal L-pipecolate oxidase with the production of Δ1-piperideine-6-carboxylate (30). The other pathway for lysine catabolism includes the formation of glutaryl-CoA that can be oxidized in peroxisomes, most probably in a side reaction catalyzed by palmitoyl-CoA oxidase (104). The structural similarity between L-pipecolic acid, sarcosine, and L-proline indicates that all these amino acids can be oxidized by the same enzyme. Indeed, both—peroxisomal sarcosine oxidase and L-pipecolic acid oxidase—accept these substrates (30, 91). Whether sarcosine and L-pipecolic acid oxidases co-localize in the same organelle or whether different mammalian species contain only one type of oxidase specific for both substrates, sarcosine and L-pipecolic acid, remains to be established.

D-amino acid and D-aspartate oxidases

D-amino acid oxidase was one of the first enzymes detected in mammalian peroxisomes (27). However, its functional role remains a mystery since only traces of D-amino acids, most

probably of bacterial origin, were detected in mammals. The enzyme oxidizes D-isomers of neutral and basic amino acids. D-aspartate oxidase is specific towards D-isomers of acidic amino acids. In addition to kidney and liver, the enzyme is also present in the brain where D-aspartate specifically accumulates (115, 116). Evidence of a possible role for D-aspartate in native synaptic transmission as an agonist of glutamate receptors has been reported (43).

Xanthine oxidase

The enzyme is a complex molybdoflavoprotein that is transformed from an oxidoreductase (NAD-dependent) to an oxidase form under various conditions such as proteolysis or ischemia (4, 46). This is a rate-limiting enzyme in purine catabolism accepting hypoxanthine and xanthine as substrates. The by-products of the oxidase reaction are O_{2-} and H_2O_2. In addition, the enzyme catalyzes the reduction of nitrates and nitrites to nitric oxide (NO), acting as a source of both NO and peroxynitrite (46). Rodent liver peroxisomes contain mainly the oxidase form of the enzyme while the oxidoreductase form is present in the cytoplasm of various cell types in liver, kidney and intestine (4, 38).

Nitric oxide synthase

NO is a free radical serving as an important messenger molecule involved in the regulation of a number of cellular functions as well as cell viability (1). The production of NO from arginine is catalyzed by nitric oxide synthase (NOS) and requires oxygen, NADPH, tetrahydrobiopterin, and FAD. There are at least three known forms of mammalian NOS including constitutive NOS (cNOS) and inducible NOS (iNOS). Peroxisomal and the cytosolic pools of iNOS were detected in cytokine-stimulated hepatocytes (102). The peroxisomal pool mainly consists of an enzymatically inactive monomeric form of iNOS while the cytosolic pool is composed of both active dimers and monomers (72). Whether the peroxisomal iNOS is somehow activated and produces NO inside the particles is not clear. Interestingly, the nitroalkene derivatives of long- and very long-chain unsaturated fatty acids, which supposedly can be generated in peroxisomes, are able to serve as endogenous PPAR ligands (16). Therefore, one of the roles of intraperoxisomal NO may be signaling related to the functional state of peroxisomal β-oxidation. NO has a high affinity for O_{2-} that is generated in peroxisomes by xanthine oxidase. The reaction between the two radicals reduces NO bioavailability and at the same time leads to the production of peroxynitrite, an extremely active ROS that may inactivate peroxisomal enzymes.

Peroxisomal Antioxidant Defense Systems

Considering the abundance of ROS-producing enzymes in peroxisomes, it is not surprising that these particles are well equipped with antioxidant defense systems composed mainly of enzymes involved in the decomposition of H_2O_2 and O_{2-} (Table 3).

Catalase

This is the most abundant antioxidant defense enzyme in mammalian peroxisomes (Fig. 3). In rodent liver peroxisomes, rough estimates indicate that each molecule of H_2O_2-producing oxidase possesses at least one molecule of catalase as a functional counterpart. The very high content of catalase in peroxisomes explains the latency of this enzyme in the particles (see Ref. 6 for details) and led to the experimentally based prediction that peroxisomes serve as an intracellular sink for H_2O_2 (74, 110). Catalase decomposes H_2O_2 in dismutase: $2H_2O_2 \rightarrow H_2O + O_2$, and peroxidase: $H_2O_2 + RH_2 \rightarrow 2H_2O + R$ reactions, where RH_2 may be phenols, formic acid, formaldehyde, and short-chain alcohols such as methanol and ethanol. Apparently, the role of catalase in the oxidation of ethanol is especially important in organs with low alcohol dehydrogenase activity, including heart and brain (118). Each subunit of a tetrameric catalase molecule contains a tightly bound NADPH that is believed to prevent inactivation of the enzyme under conditions of intensive H_2O_2 production (61). Oxidized bound NADP can be converted back to the reduced form by soluble NADPH or NADH (39). Catalase shows a very high K_m for H_2O_2 ($\geq 1\,M$), which may be a reason for the relative inefficiency of the dismutase activity of this enzyme at low H_2O_2 concentrations (74). This in turn explains the presence in peroxisomes of other enzymes capable of decomposing H_2O_2 (see below).

Table 3. Antioxidative Defense Enzymes in Mammalian Peroxisomes

Enzyme	*Substrate*
Catalase	H_2O_2
Peroxiredoxine V (PMP20)	H_2O_2
Cu/Zn-superoxide dismutase	O_{2-}
Mn-superoxide dismutase	O_{2-}
Epoxide hydrolase	Epoxides
Soluble glutathione S-transferase (member of kappa family)	Hydroperoxides
Membrane bound ('microsomal') glutathione S-transferase	Lipid hydroperoxides

Superoxide dismutase

The enzyme catalyzes a dismutation of superoxide anions: $2O_{2-} + 2H^+ \rightarrow H_2O_2 + O_2$ with the production of H_2O_2 that in turn is a substrate for peroxisomal catalase. Therefore, superoxide dismutase (SOD) and catalase comprise a short metabolic route protecting cells from damage by ROS (reviewed in Ref. 69). Two forms of SOD—Cu,ZnSOD and MnSOD—have been identified in mammalian cells. MnSOD is a mitochondrial enzyme. The dual localization of Cu,ZnSOD in cytoplasm and peroxisomes of rat liver, human fibroblasts, and hepatoma cells was verified using different experimental approaches including mass spectrometric analysis of peroxisomal proteins (28, 57). Interestingly, Cu,ZnSOD is targeted in peroxisomes using its physiological interaction partner called copper chaperon of SOD as a shuttle by means of a piggyback import mechanism (52). Data on the presence of MnSOD in mammalian peroxisomes (99) are less convincing. Detection of the enzyme in the peroxisomal fraction may be due to mitochondrial contamination.

Peroxiredoxin V

The protein peroxiredoxin V (PrxV), also named as PMP20, AOEB166, PRDX5, or ACR1, belongs to a large family of peroxidases reacting with H_2O_2 or alkyl hydroxyperoxides (62, 97, 113). PrxV is also active as a peroxynitrite reductase

(31). The enzyme contains two redox-active cysteine residues that can be oxidized to a sulfenic acid by a peroxide substrate and then recycled back to a thiol. PrxV contains both the N-terminal mitochondrial targeting presequence and the C-terminal PTS1 (SQL). The enzyme was detected in peroxisomes, mitochondria, cytosol, and to a lesser extent in nuclei. Some data indicate that PrxV is tightly associated with the peroxisomal membrane (113). The nature of the reducing agent for peroxisomal PrxV is not clear. Thioredoxins are widely considered as physiological electron donors for peroxiredoxins. However, thioredoxins and their functional counterpart, thioredoxin reductase, have not been detected in mammalian peroxisomes. In *in vitro* experiments, dithiothreitol was active as a reducing agent for sulfhydryl groups in PrxV (113). This suggests a possible role of reduced glutathione in the reactivation of oxidized PrxV in peroxisomes.

Soluble epoxide hydrolase

This prominent protein component of mammalian peroxisomes (Fig. 3) catalyzes the hydrolysis of epoxides, highly reactive oxygen containing electrophilic compounds especially damaging to nucleic acids and unsaturated lipids. In addition to peroxisomes the enzyme is also localized in the cytoplasm. It is genetically different from microsomal epoxide hydrolase that is an abundant component of the endoplasmic reticulum (13). The potential substrates for peroxisomal epoxide hydrolase are epoxides derived from lipids including prostaglandins, cholesterol, arachidonic and other polyunsaturated fatty acids (80).

Glutathione S-transferase kappa

This is the first enzyme identified as a peroxisomal constituent by means of a proteomics approach (59). Glutathione S-transferases (GSTs) promote the conjugation of a wide variety of electrophilic compounds, including xenobiotics and products of lipid peroxidation, to glutathione. The enzymes also catalyze the glutathione peroxidase reaction using lipid hydroperoxides (but not H_2O_2) as substrates (77).

Interestingly, some data indicate that GST kappa is, in fact, a disulfide-bond A oxidoreductase (DsbA) that functions as protein disulfide isomerase (71). In particular, the DsbA may be responsible for adiponectin multimerization during hormone secretion from adipocytes and other cell types including hepatocytes (71). However, there is a little chance that DsbA (GST kappa) is somehow involved in the formation of proper disulfide bonds in peroxisomal proteins since the highly reductive environment in the particles apparently maintains most SH groups in the reduced form. The precise function of GST kappa in peroxisomes remains to be established.

Membrane-bound glutathione S-transferase

The protein membrane-bound glutathione S-transferase (mGST) is a prominent component of peroxisomal membranes in rodent livers. (53, Antonenkov, unpublished results). It shows multiple subcellular localizations and is detected in the endoplasmic reticulum, the outer membrane of mitochondria, and peroxisomes. The enzyme, which has no sequence homology to soluble GSTs, forms homotrimers with one thiol group per subunit. This thiol group is important for mGST function since its modification (alkylation, disulfide bond or sulfenic acid formation) leads to activation of the enzyme. mGST has broad substrate specificity towards lipid hydroperoxides and several other products of oxidative metabolism (3).

Fatty aldehyde dehydrogenase

The presence of membrane-associated long-chain aldehyde dehydrogenase activity inducible by the peroxisome proliferator clofibrate was established more than 20 years ago (9). Later on it was suggested that the enzyme is involved in the α-oxidation of branched-chain fatty acids converting pristanal to pristanic acid (reviewed in Refs. 101 and 108). In addition, the dehydrogenase protects cells from the cytotoxic effects of medium-chain aldehydes derived from peroxidation of unsaturated fatty acids. Several splicing variants of fatty aldehyde dehydrogenase (FALDH) have been described in mammalian cells. One variant, FALDH-V, was exclusively detected in the peroxisomal membranes (14).

Pxmp2, Mpv17 and MP-L proteins

These integral membrane proteins share significant sequence similarity and were initially detected in peroxisomes (21, 50, 119). Recently, at least two of them—Mpv17 and MP-L proteins—have been implicated in ROS metabolism (66, 100, 105, 119). Pxmp2, the most abundant protein component of the rat liver peroxisomal membrane, was recently described as a channel-forming protein partially responsible for membrane permeability to solutes (92). On the basis of sequence similarity, the same function was predicted for the other members of the family. However, more recent observations indicated that Mpv17 and MP-L are localized in the inner mitochondrial membrane (66, 100). The discrepancies in the results concerning the subcellular localization of the Mpv17 and MP-L proteins may be at least partially explained by the tendency to use cell lines where the protein of interest is heavily overexpressed. This frequently leads to mislocalization of the expressed protein. Deletion of the *Mpv17* gene in mice is accompanied by disturbances in ROS production (119), the appearance of mitochondrial abnormalities including mitochondrial DNA depletion and suppression of oxidative phosphorylation (100), and leads to the development of glomerulosclerosis and deafness (105, 119). Apparently, the MP-L protein is involved in protection against mitochondrial oxidative stress and apoptosis by activation of the Omi/HtrA2 protease, which is suggested to cleave misfolded and damaged proteins (66).

Peroxisomal lipid-binding proteins

Several lines of evidence indicate that lipid-binding proteins such as the fatty acid binding protein (FABP) and the sterol-carrier protein 2 (SCP2), which are partially localized in mammalian peroxisomes (12, 96), are participants in the antioxidant defense system protecting unsaturated fatty acids from peroxidation (25, 109). The third peroxisomal protein with the potential to bind fatty acids is the so-called UK114. It belongs to the YjgF/Yer057p/UK114 family of proteins that is highly conserved from bacteria to mammals (7). However, the real function of the UK114 protein is still elusive.

NADP-dependent dehydrogenases

NADPH is required in peroxisomes to remove double bonds from unsaturated fatty acids in the auxiliary reactions

of β-oxidation (reviewed in Ref. 85) and also in reactions involved in ROS metabolism such as defending catalase against oxidative damage, biosynthesis of NO, and apparently reduction of oxidized glutathione catalyzed by glutathione reductase. The resulting $NADP^+$ is unable to penetrate the peroxisomal membrane (11) and has to be converted to the reduced form (NADPH) inside the particles. To accomplish this task, mammalian peroxisomes contain two enzymatic systems: (i) The oxidative part of the pentose phosphate pathway consisting of glucose-6-phosphate and 6-phosphogluconate dehydrogenases (5) and (ii) NADP-dependent isocitrate dehydrogenase (41). The enzymes catalyze nearly irreversible reactions that guarantee a steady supply of NADPH in peroxisomes. It seems that the dehydrogenases found in peroxisomes are the same proteins responsible for $NADP^+$ reduction in the cytoplasm and in mitochondria.

Other enzymes with apparent peroxisomal localization

In addition to the enzymes mentioned above, several other components of an antioxidant defense system appear to be localized in mammalian peroxisomes. They include glutathione peroxidase (98), peroxiredoxin1 (51), hypoxia-inducible factors, and hypoxia-inducible factor regulatory hydroxylases (58). However, the presence of these proteins in peroxisomes has not been verified independently by using alternative experimental approaches. It should be emphasized that verification of the presence of a certain proteins in peroxisomes is not an easy task since these particles are not as abundant as other organelles, very leaky during isolation, and exploit a flexible mechanism of biogenesis which allows transfer into the particles not only of proteins containing PTS1 or PTS2 targeting signals but also proteins able to use so-called 'piggyback' translocation (see section 'Biogenesis of peroxisomes').

Peroxisomes and Mitochondria

Peroxisomes and mitochondria cooperate in the maintenance of several metabolic pathways including the complete oxidative degradation of fatty acids. In some cases the particles share the same functions such as β-oxidation of long-chain fatty acids or ketogenesis (94). Recently, direct contacts between peroxisomes and mitochondria by means of cargo-selective transport by vesicular carriers were described in mammalian cells (78). Like peroxisomes, the mitochondria have a key role in both the production and scavenging of ROS. The mitochondrial electron transport chain is a major site of free radical generation with a rate of cellular output comparable to or even higher than peroxisomal ROS production. Not surprisingly, abnormalities in peroxisomal metabolic machinery may lead to mitochondrial malfunction, which in turn aggravates cellular damage. Indeed, defective biogenesis (Pex5 knockout mouse model) leading to functional incompetence of peroxisomes causes the proliferation and clustering of mitochondria with severe ultrastructural alterations accompanied by changes in the expression and the activities of mitochondrial respiratory chain complexes (18, 29). The ultrastructural abnormalities in mitochondria were similar to those found in disorders associated with oxidative stress. Moreover, a significant upregulation of mitochondrial Mn-SOD was detected in the liver of Pex5-deficient mice, which strengthens the prediction that ROSs may be key players in peroxisome-dependent mitochondrial pathology (18). Mitochondrial damage accompanied by elevated levels of the products of peroxidative degradation of DNA (8-hydroxy-2′-deoxyguanosine) and proteins (carbonyls) was also detected in livers of mice consuming the peroxisome proliferator clofibrate (86).

Hypocatalasemia

The disorder is a hereditary deficiency of catalase activity in blood erythrocytes and in peroxisomes of human tissues resulting in two clinical variants. The Swiss variant is asymptomatic, whereas the Japanese variant (Takahara disease) is often manifested by recurrent infections or ulceration of gums and related oral structures caused by peroxide-generating bacteria such as streptococci and pneumococci. Some minor changes in carbohydrate and lipid metabolism were also detected. Importantly, in patients of both groups (Swiss and Japanese variants) only partial reduction of catalase activity has been reported, which may explain the low manifestation of the disease (reviewed in Ref. 32).

Several transgenic animal models have been established to assess the role of catalase in ROS metabolism and aging. Cells of the nematode *Caenorhabditis elegans* contain two forms of catalase, peroxisomal and cytosolic, encoded by different genes. Deletion of the gene coding for the peroxisomal enzyme caused a progeric phenotype while deficiency in the cytosolic catalase had no effect (84). In contrast, overexpression of human catalase in murine peroxisomes did not affect the life-span of the animals (95) and caused no alterations in their sensitivity to γ-irradiation (23). However, if the same enzyme was targeted into mitochondria, the medium and maximum life-spans were significantly increased with evident improvement in the diagnostic indices of aging (95). Similarly, mice lacking catalase developed normally, they were not more vulnerable to hypoxia-induced lung injury, and their lenses did not show any increased susceptibility to oxidative stress generated by photochemical reactions. However, the animals showed differential sensitivity to oxidant tissue injury in brain (48). The authors of this study did not describe potential age-related abnormalities in catalase-deficient mice. As a whole, the phenotypic abnormalities described so far for catalase transgenic mice are surprisingly scarce. This may indicate that despite the absence of catalase, the peroxisomal metabolic machinery of rodentis is well protected against oxidative damage by H_2O_2.

Proliferation of Mammalian Peroxisomes and Carcinogenesis

The administration of peroxisome proliferators, which include some hypolipidemic drugs (clofibrate), herbicides, plasticizers, and leukotriene antagonists, causes the development of hepatomegalia and drastic increases in the number and size of hepatic peroxisomes in rodents (89). If the administration is continued for several months, the animals develop hepatic carcinomas. Peroxisome proliferators in general are not genotoxic (40), and sustain a PPARα-dependent activation of the H_2O_2-generating enzymes ACOX-1 and CYP4A and a decline in the activities of H_2O_2-degrading catalase and glutathione peroxidase (87, 88). These changes result in the accumulation of the oxidative stress marker lipofuscin and the formation of 8-hydroxy-2′-deoxyguanosine DNA adducts in liver cells (55, 90). Thus hepatic carcinogen-

esis in rodents fed with peroxisome proliferators may be due to oxidative stress and damage to liver DNA. This idea, however, is challenged, for instance, by the observation that *Acox*$^{-/-}$ mice that are deficient in peroxisomal β-oxidation at the H_2O_2-generating oxidation of acyl-CoA, still develop liver tumors (89). The tumors are thought to arise due to sustained activation of PPARα by unmetabolized substrates of ACOX-1. This hypothesis is supported by a DNA microarray of the expression profiles of these tumors that show an overall commonality with tumors induced by peroxisome proliferators, but not with tumors generated by genotoxic carcinogens (75). Therefore, the current view favors the idea that hepatic carcinogenesis promoted by peroxisome proliferators is not only due to hepatic oxidative stress but also related to abnormalities in cell growth and communication (22, 103).

Peroxisomes and the Nervous System

Data on several transgenic mouse models created for analysis of the function of peroxisomes revealed a prominent role of these particles in the development and maintenance of the central nervous system (15, 20, 54). These data corroborate with the results of clinical and pathomorphological examination of patients that suffer from inherited peroxisomal disorders such as Zellweger syndrome and X-linked adrenoleukodystrophy (reviewed in Refs. 101 and 108). The pathological manifestations include impaired neuronal migration, axonal degeneration, and progressive subcortical demyelination. A role of ROS in the development of these abnormalities was proposed on the basis of observations of the mouse model with a selectively inactivated import receptor Pex5 in oligodendrocytes that led to dysfunction of peroxisomes only in this cell type (56). Oligodendrocytes are highly effective in scavenging H_2O_2 and O_{2-} and the peroxisomes of these glial cells apparently protect neuronal axons from deleterious effects of ROS (56).

Peroxisomes and Heart Failure

Strong evidence points to the role of alcohol-induced oxidative stress in the pathogenesis of alcoholic cardiomyopathy that is the cause of sudden cardiac death (26). The link between prolonged consumption of alcohol and alterations in heart peroxisomes was established more than 30 years ago (35, 60). Chronic consumption by rodents of an alcohol-containing diet results in the activation of the heart peroxisomal enzymes catalase and acyl-CoA oxidase (60, 82) and is accompanied by a drastic elevation of nonenzymatic peroxidation of membrane lipids (82). Moreover, when mice consuming alcohol were treated with the catalase inhibitor 3-amino-1,2,4-triazole, an excess of lipid peroxidation products accumulated in the heart (8), and cardiomyocytes showed morphological abnormalities characteristic of human alcoholic cardiomyopathy (60). Finally, cardiac-specific overexpression of catalase rescues ventricular myocytes from an ethanol-induced cardiac contractile defect (118). It would be interesting to use a catalase-deficient mouse model to study the destructive effects of ethanol on heart tissue.

Peroxisomes and Aging

Aging is a complex, multifactorial process leading to modification and damage of cellular components, abnormal regulation of homeostasis, and impaired cell function. It is believed that the key factor triggering cellular senescence may be disturbances in the metabolism of ROS, including their synthesis and degradation in peroxisomes (19, 83). However, experimental results linking peroxisomal abnormalities with aging are controversial and do not discriminate between the two possibilities: (i) Defects in peroxisomal metabolism lead to aging; (ii) Cellular senescence negatively affects peroxisomal morphology and function. For example, age-related alterations in the morphology of hepatic peroxisomes in rodents were detected in several studies (reviewed in Ref. 83) although it is not clear whether these changes provoke an aging spiral or are a consequence of senescence. The latter option seems more attractive since defects in peroxisomal biogenesis in aging cells, especially the import of PTS1-containing proteins into the particles, are well documented (68). Most reports focus on the role of peroxisomal catalase in aging. Detailed epidemiological studies on hypocatalasemic individuals revealed an elevated frequency of age-related diseases, including atherosclerosis, anemia, tumors, type 2 diabetes, and eye disorders—cataracts and macular degeneration (32, 44). Similarly, experimental manipulations of catalase activity in cell cultures alter ROS metabolism and in some cases lead to the appearance of senescence markers (63). However, catalase-deficient mouse models did not provide strong evidences for the crucial importance of catalase in aging, at least in mammals (48, 93). This may be due to compensatory activation of the components of antioxidative defense system in catalase-deficient mice. The development of animal models with conditional knockout of catalase may be beneficial to resolve this issue.

Conclusion

Mammalian peroxisomes harbor many ROS-producing enzymes and are well equipped with powerful antioxidant defense systems. This ensures an important role of these organelles in the generation and scavenging of ROS, which implies considerable involvement of peroxisomes in processes leading to oxidative stress. However, questions about the ROS-related mechanisms responsible for cellular damage caused by peroxisome malfunction remain unanswered. Even less is known about the participation of peroxisomal ROS, especially H_2O_2 and NO, in the cellular signaling that plays a pivotal role in the pathogenesis of aging and carcinogenesis. There is growing evidence that tissue-specific abnormalities in peroxisomal ROS metabolism lead to liver and kidney failure, heart disease, and inflammatory changes in the nervous system. The functional plasticity of mammalian peroxisomes, which is mainly under the control of PPAR-related mechanisms, provides an opportunity for the development of therapeutic applications directed toward the cure of diseases caused by peroxisomal dysfunction. The above-mentioned problems are only some of the challenges that future studies of mammalian peroxisomes will encounter; studies that deserve serious attention from the scientific community.

References

1. Alderton WK, Cooper CE, and Knowles RG. Nitric oxide synthases: Structure, function and inhibition. *Biochem J* 357: 593–615, 2001.
2. Ames BN, Cathcart R, Schwiers E, and Hochstein P. Uric acid provides an antioxidant defense in humans against

oxidant- and radical-caused aging and cancer: A hypothesis. *Proc Natl Acad Sci USA* 78: 6858–6862, 1981.
3. Andersson C, Mosialou E, Weinander R, and Morgenstern R. Enzymology of microsomal glutathione S-transferase. *Adv Pharmacol* 27: 19–35, 1994.
4. Angermüller S, Bruder G, Völkl A, Wesch H, and Fahimi HD. Localization of xanthine oxidase in crystalline cores of peroxisomes. A cytochemical and biochemical study. *Eur J Cell Biol* 45: 137–144, 1987.
5. Antonenkov VD. Dehydrogenases of the pentose phosphate pathway in rat liver peroxisomes. *Eur J Biochem* 183: 75–82, 1989.
6. Antonenkov VD and Hiltunen JK. Peroxisomal membrane permeability and solute transfer. *Biochim Biophys Acta* 1763: 1697–1706, 2006.
7. Antonenkov VD, Ohlmeier S, Sormunen RT, and Hiltunen JK. UK114, a YjgF/Yer057p/UK114 family protein highly conserved from bacteria to mammals, is localized in rat liver peroxisomes. *Biochem Biophys Res Commun* 357: 252–257, 2007.
8. Antonenkov VD and Panchenko LF. Effect of chronic ethanol treatment under partial catalase inhibition on the activity of enzymes related to peroxide metabolism in rat liver and heart. *Int J Biochem* 20: 823–828, 1988.
9. Antonenkov VD, Pirozhkov SV, and Panchenko LF. Intraparticulate localization and some properties of a clofibrate-induced peroxisomal aldehyde dehydrogenase from rat liver. *Eur J Biochem* 149: 159–167, 1985.
10. Antonenkov VD, Rokka A, Sormunen RT, Benz R, and Hiltunen JK. Solute traffic across mammalian peroxisomal membrane–single channel conductance monitoring reveals pore-forming activities in peroxisomes. *Cell Mol Life Sci* 62: 2886–2895, 2005.
11. Antonenkov VD, Sormunen RT, and Hiltunen JK. The rat liver peroxisomal membrane forms a permeability barrier for cofactors but not for small metabolites *in vitro*. *J Cell Sci* 117: 5633–5642, 2004.
12. Antonenkov VD, Sormunen RT, Ohlmeier S, Amery L, Fransen M, Mannaerts GP, and Hiltunen JK. Localization of a portion of the liver isoform of fatty-acid-binding protein (L-FABP) to peroxisomes. *Biochem J* 394: 475–484, 2006.
13. Arand M, Knehr M, Thomas H, Zeller HD, and Oesch F. An impaired peroxisomal targeting sequence leading to an unusual bicompartmental distribution of cytosolic epoxide hydrolase. *FEBS Lett* 294: 19–22, 1991.
14. Ashibe B, Hirai T, Higashi K, Sekimizu K, and Motojima K. Dual subcellular localization in the endoplasmic reticulum and peroxisomes and a vital role in protecting against oxidative stress of fatty aldehyde dehydrogenase are achieved by alternative splicing. *J Biol Chem* 282: 20763–20773, 2007.
15. Baes M, Gressens P, Baumgart E, Carmeliet P, Casteels M, Fransen M, Evrard P, Fahimi D, Declercq PE, Collen D, van Veldhoven PP, and Mannaerts GP. A mouse model for Zellweger syndrome. *Nat Genet* 17: 49–57, 1997.
16. Baker PR, Lin Y, Schopfer FJ, Woodcock SR, Groeger AL, Batthyany C, Sweeney S, Long MH, Iles KE, Baker LM, Branchaud BP, Chen YE, and Freeman BA. Fatty acid transduction of nitric oxide signaling: Multiple nitrated unsaturated fatty acid derivatives exist in human blood and urine and serve as endogenous peroxisome proliferator-activated receptor ligands. *J Biol Chem* 280: 42464–42475, 2005.
17. Baumgart E, Vanhooren JC, Fransen M, Marynen P, Puype M, Vandekerckhove J, Leunissen JA, Fahimi HD, Mannaerts GP, and van Veldhoven PP. Molecular characterization of the human peroxisomal branched-chain acyl-CoA oxidase: cDNA cloning, chromosomal assignment, tissue distribution, and evidence for the absence of the protein in Zellweger syndrome. *Proc Natl Acad Sci USA* 93: 13748–13753, 1996.
18. Baumgart E, Vanhorebeek I, Grabenbauer M, Borgers M, Declercq PE, Fahimi HD, and Baes M. Mitochondrial alterations caused by defective peroxisomal biogenesis in a mouse model for Zellweger syndrome (PEX5 knockout mouse). *Am J Pathol* 159: 1477–1494, 2001.
19. Beckman KB and Ames BN. The free radical theory of aging matures. *Physiol Rev* 78: 547–581, 1998.
20. Brites P, Motley AM, Gressens P, Mooyer PA, Ploegaert I, Everts V, Evrard P, Carmeliet P, Dewerchin M, Schoonjans L, Duran M, Waterham HR, Wanders RJ, and Baes M. Impaired neuronal migration and endochondral ossification in Pex7 knockout mice: A model for rhizomelic chondrodysplasia punctata. *Hum Mol Genet* 12: 2255–2267, 2003.
21. Brosius U, Dehmel T, and Gärtner J. Two different targeting signals direct human peroxisomal membrane protein 22 to peroxisomes. *J Biol Chem* 277: 774–784, 2002.
22. Cattley RC. Peroxisome proliferators and receptor-mediated hepatic carcinogenesis. *Toxicol Pathol* 32: 6–11, 2004.
23. Chen X, Liang H, Van Remmen H, Vijg J, and Richardson A. Catalase transgenic mice: Characterization and sensitivity to oxidative stress. *Arch Biochem Biophys* 422: 197–210, 2004.
24. Danpure CJ. Primary hyperoxaluria type 1: AGT mistargeting highlights the fundamental differences between the peroxisomal and mitochondrial protein import pathways. *Biochim Biophys Acta* 1763: 1776–1784, 2006.
25. Dansen TB, Kops GJ, Denis S, Jelluma N, Wanders RJ, Bos JL, Burgering BM, and Wirtz KW. Regulation of sterol carrier protein gene expression by the forkhead transcription factor FOXO3a. *J Lipid Res* 45: 81–88, 2004.
26. Das SK and Vasudevan DM. Alcohol-induced oxidative stress. *Life Sci* 81: 177–187, 2007.
27. De Duve C and Baudhuin P. Peroxisomes (microbodies and related particles). *Physiol Rev* 46: 323–357, 1966.
28. Dhaunsi GS, Gulati S, Singh AK, Orak JK, Asayama K, and Singh I. Demonstration of Cu-Zn superoxide dismutase in rat liver peroxisomes. Biochemical and immunochemical evidence. *J Biol Chem* 267: 6870–6873, 1992.
29. Dirkx R, Vanhorebeek I, Martens K, Schad A, Grabenbauer M, Fahimi D, Declercq P, Van Veldhoven PP, and Baes M. Absence of peroxisomes in mouse hepatocytes causes mitochondrial and ER abnormalities. *Hepatology* 41: 868–878, 2005.
30. Dodt G, Kim DG, Reimann SA, Reuber BE, McCabe K, Gould SJ, and Mihalik SJ. L-Pipecolic acid oxidase, a human enzyme essential for the degradation of L-pipecolic acid, is most similar to the monomeric sarcosine oxidases. *Biochem J* 345: 487–494, 2000.
31. Dubuisson M, Vander Stricht D, Clippe A, Etienne F, Nauser T, Kissner R, Koppenol WH, Rees JF, and Knoops B. Human peroxiredoxin 5 is a peroxynitrite reductase. *FEBS Lett* 571: 161–165, 2004.
32. Eaton JW and Ma M. Acatalasemia. In: *The metabolic and molecular bases of inherited diseases.* 2nd ed. Sciver CR, Beaudett AL, Sly WS, and Valle D. (Eds). New York: McGraw Hill, 1995, pp. 2371–2381.
33. Erdmann R and Schliebs W. Peroxisomal matrix protein import: The transient pore model. *Nat Rev Mol Cell Biol* 6: 738–742, 2005.

34. Fahimi HD. Peroxisomes: 40 years of histochemical staining, personal reminiscences. *Histochem Cell Biol* 131: 437–440, 2009.
35. Fahimi HD, Kino M, Hicks L, Thorp KA, and Abelman WH. Increased myocardial catalase in rats fed ethanol. *Am J Pathol* 96: 373–390, 1979.
36. Filppula SA, Sormunen RT, Hartig A, Kunau WH, and Hiltunen JK. Changing stereochemistry for a metabolic pathway *in vivo*. Experiments with the peroxisomal beta-oxidation in yeast. *J Biol Chem* 270: 27453–27457, 1995.
37. Foulon V, Sniekers M, Huysmans E, Asselberghs S, Mahieu V, Mannaerts GP, Van Veldhoven PP, and Casteels M. Breakdown of 2-hydroxylated straight chain fatty acids via peroxisomal 2-hydroxyphytanoyl-CoA lyase: A revised pathway for the alpha-oxidation of straight chain fatty acids. *J Biol Chem* 280: 9802–9812, 2005.
38. Frederiks WM and Vreeling–Sindelárová H. Ultrastructural localization of xanthine oxidoreductase activity in isolated rat liver cells. *Acta Histochem* 104: 29–37, 2002.
39. Gaetani GF, Ferraris AM, Sanna P, and Kirkman HN. A novel NADPH:(bound) NADP + reductase and NADH:(bound) NADP + transhydrogenase function in bovine liver catalase. *Biochem J* 385: 763–768, 2005.
40. Galloway SM, Johnson TE, Armstrong MJ, and Ashby J. The genetic toxicity of the peroxisome proliferator class of rodent hepatocarcinogen. *Mutat Res* 448: 153–158, 2000.
41. Geisbrecht BV and Gould SJ. The human PICD gene encodes a cytoplasmic and peroxisomal NADP(+)-dependent isocitrate dehydrogenase. *J Biol Chem* 274: 30527–30533, 1999.
42. George J, Struthers AD. Role of urate, xanthine oxidase and the effects of allopurinol in vascular oxidative stress. *Vasc Health Risk Manag* 5: 265–272, 2009.
43. Gong XQ, Frandsen A, Lu WY, Wan Y, Zabek RL, Pickering DS, and Bai D. D-aspartate and NMDA, but not L-aspartate, block AMPA receptors in rat hippocampal neurons. *Br J Pharmacol* 145: 449–459, 2005.
44. Góth L and Vitai M. The effects of hydrogen peroxide promoted by homocysteine and inherited catalase deficiency on human hypocatalasemic patients. *Free Radic Biol Med* 35: 882–888, 2003.
45. Graham IA. Seed storage oil mobilization. *Annu Rev Plant Biol* 59: 115–142, 2008.
46. Harrison R. Structure and function of xanthine oxidoreductase: Where are we now? *Free Radic Biol Med* 33: 774–797, 2002.
47. Hiltunen JK and Qin Y. Beta-oxidation—Strategies for the metabolism of a wide variety of acyl-CoA esters. *Biochim Biophys Acta* 1484: 117–128, 2000.
48. Ho YS, Xiong Y, Ma W, Spector A, and Ho DS. Mice lacking catalase develop normally but show differential sensitivity to oxidant tissue injury. *J Biol Chem* 279: 32804–32812, 2004.
49. Hooper DC, Scott GS, Zborek A, Mikheeva T, Kean RB, Koprowski H, and Spitsin SV. Uric acid, a peroxynitrite scavenger, inhibits CNS inflammation, blood–CNS barrier permeability changes, and tissue damage in a mouse model of multiple sclerosis. *FASEB J* 14: 691–698, 2000.
50. Iida R, Yasuda T, Tsubota E, Takatsuka H, Masuyama M, Matsuki T, and Kishi K. M-LP, Mpv17-like protein, has a peroxisomal membrane targeting signal comprising a transmembrane domain and a positively charged loop and upregulates expression of the manganese superoxide dismutase gene. *J Biol Chem* 278: 6301–6306, 2003.
51. Immenschuh S, Baumgart–Vogt E, Tan M, Iwahara S, Ramadori G, and Fahimi HD. Differential cellular and subcellular localization of heme-binding protein 23/peroxiredoxin I and heme oxygenase-1 in rat liver. *J Histochem Cytochem* 51: 1621–1631, 2003.
52. Islinger M, Li KW, Seitz J, Völkl A, Lüers GH. Hitchhiking of Cu/Zn superoxide dismutase to peroxisomes—Evidence for a natural piggyback import mechanism in mammals. *Traffic* 10: 1711–1721, 2009.
53. Islinger M, Lüers GH, Zischka H, Ueffing M, and Völkl A. Insights into the membrane proteome of rat liver peroxisomes: Microsomal glutathione-S-transferase is shared by both subcellular compartments. *Proteomics* 6: 804–816, 2006.
54. Janssen A, Gressens P, Grabenbauer M, Baumgart E, Schad A, Vanhorebeek I, Brouwers A, Declercq PE, Fahimi D, Evrard P, Schoonjans L, Collen D, Carmeliet P, Mannaerts G, Van Veldhoven P, and Baes M. Neuronal migration depends on intact peroxisomal function in brain and in extraneuronal tissues. *J Neurosci* 23: 9732–9741, 2003.
55. Kasai H, Okada Y, Nishimura S, Rao MS, and Reddy JK. Formation of 8-hydroxydeoxyguanosine in liver DNA of rats following long-term exposure to a peroxisome proliferator. *Cancer Res* 49:2603-2605, 1989.
56. Kassmann CM, Lappe–Siefke C, Baes M, Brügger B, Mildner A, Werner HB, Natt O, Michaelis T, Prinz M, Frahm J, and Nave KA. Axonal loss and neuroinflammation caused by peroxisome-deficient oligodendrocytes. *Nat Genet* 39: 969–976, 2007.
57. Keller GA, Warner TG, Steimer KS, and Hallewell RA. Cu,Zn superoxide dismutase is a peroxisomal enzyme in human fibroblasts and hepatoma cells. *Proc Natl Acad Sci USA* 88: 7381–7385, 1991.
58. Khan Z, Michalopoulos GK, and Stolz DB. Peroxisomal localization of hypoxia-inducible factors and hypoxia-inducible factor regulatory hydroxylases in primary rat hepatocytes exposed to hypoxia-reoxygenation. *Am J Pathol* 169: 1251–1269, 2006.
59. Kikuchi M, Hatano N, Yokota S, Shimozawa N, Imanaka T, and Taniguchi H. Proteomic analysis of rat liver peroxisome: Presence of peroxisome-specific isozyme of Lon protease. *J Biol Chem* 279: 421–428, 2004.
60. Kino M. Chronic effects of ethanol under partial inhibition of catalase activity in the rat heart: Light and electron microscopic observations. *J Mol Cell Cardiol* 13: 5–21, 1981.
61. Kirkman HN, Rolfo M, Ferraris AM, and Gaetani GF. Mechanisms of protection of catalase by NADPH. Kinetics and stoichiometry. *J Biol Chem* 274: 13908–13914, 1999.
62. Knoops B, Clippe A, Bogard C, Arsalane K, Wattiez R, Hermans C, Duconseille E, Falmagne P, and Bernard A. Cloning and characterization of AOEB166, a novel mammalian antioxidant enzyme of the peroxiredoxin family. *J Biol Chem* 274: 30451–30458, 1999.
63. Koepke JI, Wood CS, Terlecky LJ, Walton PA, Terlecky SR. Progeric effects of catalase inactivation in human cells. *Toxicol Appl Pharmacol* 232: 99–108, 2008.
64. Kohler SA, Menotti E, and Kühn LC. Molecular cloning of mouse glycolate oxidase. High evolutionary conservation and presence of an iron-responsive element-like sequence in the mRNA. *J Biol Chem* 274: 2401–2407, 1999.
65. Kondo T, Hirose M, Kageyama K. Roles of oxidative stress and redox regulation in atherosclerosis. *J Atheroscler Thromb* 16: 88–96, 2009.
66. Krick S, Shi S, Ju W, Faul C, Tsai SY, Mundel P, and Böttinger EP. Mpv17l protects against mitochondrial oxidative stress and apoptosis by activation of Omi/HtrA2 protease. *Proc Natl Acad Sci USA* 105: 14106–14111, 2008.

67. Jones JM, Morrell JC, and Gould SJ. Identification and characterization of HAOX1, HAOX2, and HAOX3, three human peroxisomal 2-hydroxy acid oxidases. *J Biol Chem* 275: 12590–12597, 2000.
68. Legakis JE, Koepke JI, Jedeszko C, Barlaskar F, Terlecky LJ, Edwards HJ, Walton PA, and Terlecky SR. Peroxisome senescence in human fibroblasts. *Mol Biol Cell* 13: 4243–4255, 2002.
69. Liochev SI and Fridovich I. The effects of superoxide dismutase on H2O2 formation. *Free Radic Biol Med* 42: 1465–1469, 2007.
70. Liu F, Ng SK, Lu Y, Low W, Lai J, and Jedd G. Making two organelles from one: Woronin body biogenesis by peroxisomal protein sorting. *J Cell Biol* 180: 325–339, 2008.
71. Liu M, Zhou L, Xu A, Lam KS, Wetzel MD, Xiang R, Zhang J, Xin X, Dong LQ, and Liu F. A disulfide-bond A oxidoreductase-like protein (DsbA-L) regulates adiponectin multimerization. *Proc Natl Acad Sci USA* 105: 18302–18307, 2008.
72. Loughran PA, Stolz DB, Vodovotz Y, Watkins SC, Simmons RL, and Billiar TR. Monomeric inducible nitric oxide synthase localizes to peroxisomes in hepatocytes. *Proc Natl Acad Sci USA* 102: 13837–13842, 2005.
73. Ma C and Subramani S. Peroxisome matrix and membrane protein biogenesis. *IUBMB Life* 61: 713–722, 2009.
74. Makino N, Mochizuki Y, Bannai S, and Sugita Y. Kinetic studies on the removal of extracellular hydrogen peroxide by cultured fibroblasts. *J Biol Chem* 269: 1020–1025, 1994.
75. Meyer K, Lee JS, Dyck PA, Cao WQ, Rao MS, Thorgeirsson SS, and Reddy JK. Molecular profiling of hepatocellular carcinomas developing spontaneously in acyl-CoA oxidase deficient mice: Comparison with liver tumors induced in wild-type mice by a peroxisome proliferator and a genotoxic carcinogen. *Carcinogenesis* 24: 975–984, 2003.
76. Moinard C, Cynober L, and de Bandt JP. Polyamines: Metabolism and implications in human diseases. *Clin Nutr* 24: 184–197, 2005.
77. Morel F, Rauch C, Petit E, Piton A, Theret N, Coles B, and Guillouzo A. Gene and protein characterization of the human glutathione S-transferase kappa and evidence for a peroxisomal localization. *J Biol Chem* 279: 16246–16253, 2004.
78. Neuspiel M, Schauss AC, Braschi E, Zunino R, Rippstein P, Rachubinski RA, Andrade-Navarro MA, and McBride HM. Cargo-selected transport from the mitochondria to peroxisomes is mediated by vesicular carriers. *Curr Biol* 18: 102–108, 2008.
79. Opperdoes FR and Szikora JP. In silico prediction of the glycosomal enzymes of Leishmania major and trypanosomes. *Mol Biochem Parasitol* 147: 193–206, 2006.
80. Pahan K, Smith BT, and Singh I. Epoxide hydrolase in human and rat peroxisomes: implication for disorders of peroxisomal biogenesis. *J Lipid Res* 37: 159–167, 1996.
81. Palmieri L, Rottensteiner H, Girzalsky W, Scarcia P, Palmieri F, and Erdmann R. Identification and functional reconstitution of the yeast peroxisomal adenine nucleotide transporter. *EMBO J* 20: 5049–5059, 2001.
82. Panchenko LF, Pirozhkov SV, Popova SV, and Antonenkov VD. Effect of chronic ethanol treatment on peroxisomal acyl-CoA oxidase activity and lipid peroxidation in rat liver and heart. *Experientia* 43: 580–581, 1987.
83. Périchon R, Bourre JM, Kelly JF, and Roth GS. The role of peroxisomes in aging. *Cell Mol Life Sci* 54: 641–652, 1998.
84. Petriv OI and Rachubinski RA. Lack of peroxisomal catalase causes a progeric phenotype in *Caenorhabditis elegans*. *J Biol Chem* 279: 19996–20001, 2004.
85. Poirier Y, Antonenkov VD, Glumoff T, and Hiltunen JK. Peroxisomal beta-oxidation—A metabolic pathway with multiple functions. *Biochim Biophys Acta* 1763: 1413–1426, 2006.
86. Qu B, Li QT, Wong KP, Ong CN, and Halliwell B. Mitochondrial damage by the "pro-oxidant" peroxisomal proliferator clofibrate. *Free Radic Biol Med* 27: 1095–1102, 1999.
87. Rao MS and Reddy JK. Hepatocarcinogenesis of peroxisome proliferators. *Ann NY Acad Sci* 804: 573–587, 1996.
88. Rao MS and Reddy JK. Peroxisome proliferation and hepatocarcinogenesis. *Carcinogenesis* 8: 631–636, 1987.
89. Reddy JK, Hashimoto T. Peroxisomal beta-oxidation and peroxisome proliferator-activated receptor alpha: An adaptive metabolic system. *Annu Rev Nutr* 21: 193–230, 2001.
90. Reddy JK, Lalwani ND, Reddy MK, and Qureshi SA. Excessive accumulation of autofluorescent lipofuscin in the liver during hepatocarcinogenesis by methyl clofenapate and other hypolipidemic peroxisome proliferators. *Cancer Res* 42: 259–266, 1982.
91. Reuber BE, Karl C, Reimann SA, Mihalik SJ, and Dodt G. Cloning and functional expression of a mammalian gene for a peroxisomal sarcosine oxidase. *J Biol Chem* 272: 6766–6776, 1997.
92. Rokka A, Antonenkov VD, Soininen R, Immonen HL, Pirilä PL, Bergmann U, Sormunen RT, Weckström M, Benz R, and Hiltunen JK. Pxmp2 is a channel-forming protein in mammalian peroxisomal membrane. *PLoS One* 4: e5090, 2009.
93. Schrader M and Fahimi HD. Peroxisomes and oxidative stress. *Biochim Biophys Acta* 1763: 1755–1766, 2006.
94. Schrader M and Yoon Y. Mitochondria and peroxisomes: Are the 'big brother' and the 'little sister' closer than assumed? *Bioessays* 29: 1105–1114, 2007.
95. Schriner SE, Linford NJ, Martin GM, Treuting P, Ogburn CE, Emond M, Coskun PE, Ladiges W, Wolf N, Van Remmen H, Wallace DC, and Rabinovitch PS. Extension of murine life span by overexpression of catalase targeted to mitochondria. *Science* 308: 1909–1911, 2005.
96. Schroeder F, Atshaves BP, McIntosh AL, Gallegos AM, Storey SM, Parr RD, Jefferson JR, Ball JM, and Kier AB. Sterol carrier protein-2: New roles in regulating lipid rafts and signaling. *Biochim Biophys Acta* 1771: 700–718, 2007.
97. Seo MS, Kang SW, Kim K, Baines IC, Lee TH, and Rhee SG. Identification of a new type of mammalian peroxiredoxin that forms an intramolecular disulfide as a reaction intermediate. *J Biol Chem* 275: 20346–20354, 2000.
98. Singh AK, Dhaunsi GS, Gupta MP, Orak JK, Asayama K, and Singh I. Demonstration of glutathione peroxidase in rat liver peroxisomes and its intraorganellar distribution. *Arch Biochem Biophys* 315: 331–338, 1994.
99. Singh AK, Dobashi K, Gupta MP, Asayama K, Singh I, and Orak JK. Manganese superoxide dismutase in rat liver peroxisomes: Biochemical and immunochemical evidence. *Mol Cell Biochem* 197: 7–12, 1999.
100. Spinazzola A, Viscomi C, Fernandez–Vizarra E, Carrara F, D'Adamo P, Calvo S, Marsano RM, Donnini C, Weiher H, Strisciuglio P, Parini R, Sarzi E, Chan A, DiMauro S, Rötig A, Gasparini P, Ferrero I, Mootha VK, Tiranti V, and Zeviani M. MPV17 encodes an inner mitochondrial membrane protein and is mutated in infantile hepatic mitochondrial DNA depletion. *Nat Genet* 38: 570–575, 2006.

101. Steinberg SJ, Dodt G, Raymond GV, Braverman NE, Moser AB, and Moser HW. Peroxisome biogenesis disorders. *Biochim Biophys Acta* 1763: 1733–1748, 2006.
102. Stolz DB, Zamora R, Vodovotz Y, Loughran PA, Billiar TR, Kim YM, Simmons RL, and Watkins SC. Peroxisomal localization of inducible nitric oxide synthase in hepatocytes. *Hepatology* 36: 81–93, 2002.
103. Suga T. Hepatocarcinogenesis by peroxisome proliferators. *J Toxicol Sci* 29: 1–12, 2004.
104. Van Veldhoven PP, Vanhove G, Assselberghs S, Eyssen HJ, and Mannaerts GP. 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, 1992.
105. Viscomi C, Spinazzola A, Maggioni M, Fernandez–Vizarra E, Massa V, Pagano C, Vettor R, Mora M, and Zeviani M. Early-onset liver mtDNA depletion and late-onset proteinuric nephropathy in Mpv17 knockout mice. *Hum Mol Genet* 18: 12–26, 2009.
106. Visser WF, van Roermund CW, Ijlst L, Waterham HR, and Wanders RJ. Metabolite transport across the peroxisomal membrane. *Biochem J* 401: 365–375, 2007.
107. Wanders RJ and Waterham HR. Biochemistry of mammalian peroxisomes revisited. *Annu Rev Biochem* 75: 295–332, 2006.
108. Wanders RJ and Waterham HR. Peroxisomal disorders: The single peroxisomal enzyme deficiencies. *Biochim Biophys Acta* 1763: 1707–1720, 2006.
109. Wang G, Gong Y, Anderson J, Sun D, Minuk G, Roberts MS, and Burczynski FJ. Antioxidative function of L-FABP in L-FABP stably transfected Chang liver cells. *Hepatology* 42: 871–879, 2005.
110. Willekens H, Chamnongpol S, Davey M, Schraudner M, Langebartels C, Van Montagu M, Inzé D, and Van Camp W. Catalase is a sink for H2O2 and is indispensable for stress defence in C3 plants. *EMBO J* 16:4806–4816, 1997.
111. Wu T, Yankovskaya V, and McIntire WS. Cloning, sequencing, and heterologous expression of the murine peroxisomal flavoprotein, N1-acetylated polyamine oxidase. *J Biol Chem* 278: 20514–20525, 2003.
112. Wu X, Wakamiya M, Vaishnav S, Geske R, Montgomery C Jr, Jones P, Bradley A, and Caskey CT. Hyperuricemia and urate nephropathy in urate oxidase-deficient mice. *Proc Natl Acad Sci USA* 91: 742–746, 1994.
113. Yamashita H, Avraham S, Jiang S, London R, Van Veldhoven PP, Subramani S, Rogers RA, and Avraham H. Characterization of human and murine PMP20 peroxisomal proteins that exhibit antioxidant activity *in vitro*. *J Biol Chem* 274: 29897–29904, 1999.
114. Yeldandi AV, Yeldandi V, Kumar S, Murthy CV, Wang XD, Alvares K, Rao MS, and Reddy JK. Molecular evolution of the urate oxidase-encoding gene in hominoid primates: Nonsense mutations. *Gene* 109: 281–284, 1991.
115. Zaar K, Köst HP, Schad A, Völkl A, Baumgart E, and Fahimi HD. Cellular and subcellular distribution of D-aspartate oxidase in human and rat brain. *J Comp Neurol* 450: 272–282, 2002.
116. Zaar K, Völkl A, and Fahimi HD. D-aspartate oxidase in rat, bovine and sheep kidney cortex is localized in peroxisomes. *Biochem J* 261: 233–238, 1989.
117. Zha S, Ferdinandusse S, Hicks JL, Denis S, Dunn TA, Wanders RJ, Luo J, De Marzo AM, and Isaacs WB. Peroxisomal branched chain fatty acid beta-oxidation pathway is upregulated in prostate cancer. *Prostate* 63: 316–323, 2005.
118. Zhang X, Klein AL, Alberle NS, Norby FL, Ren BH, Duan J, and Ren J. Cardiac-specific overexpression of catalase rescues ventricular myocytes from ethanol-induced cardiac contractile defect. *J Mol Cell Cardiol* 35: 645–652, 2003.
119. Zwacka RM, Reuter A, Pfaff E, Moll J, Gorgas K, Karasawa M, and Weiher H. The glomerulosclerosis gene Mpv17 encodes a peroxisomal protein producing reactive oxygen species. *EMBO J* 13: 5129–5134, 1994.

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Abbreviations Used

ACOX = acyl-CoA oxidase
DAB = 3,3′-diaminobenzidine
DsbA = disulfide-bond A oxidoreductase
FABP = fatty acid binding protein
FALDH = fatty aldehyde dehydrogenase
GSH = reduced glutathione
GSSG = oxidized glutathione
GST = glutathione S-transferase
mGST = membrane-bound glutathione S-transferase
NO = nitric oxide
NOS = nitric oxide synthase
PTS = peroxisomal targeting signal
ROS = reactive oxygen species
SCP2 = sterol carrier protein 2
SOD = superoxide dismutase
SPD = spermidine
SPM = spermine

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2. Mary C. Hunt, Marina I. Siponen, Stefan E.H. Alexson. 2012. The emerging role of acyl-CoA thioesterases and acyltransferases in regulating peroxisomal lipid metabolism. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease* **1822**:9, 1397-1410. [CrossRef]
3. Marc Fransen, Marcus Nordgren, Bo Wang, Oksana Apanasets. 2012. Role of peroxisomes in ROS/RNS-metabolism: Implications for human disease. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease* **1822**:9, 1363-1373. [CrossRef]
4. Courtney R. Giordano, Stanley R. Terlecky. 2012. Peroxisomes, cell senescence, and rates of aging. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease* **1822**:9, 1358-1362. [CrossRef]
5. Stuart G. Jarrett, Michael E. Boulton. 2012. Consequences of oxidative stress in age-related macular degeneration. *Molecular Aspects of Medicine* . [CrossRef]
6. Stuart G. Jarrett, Michael E. Boulton. 2012. Consequences of oxidative stress in age-related macular degeneration. *Molecular Aspects of Medicine* . [CrossRef]
7. Courtney R. Giordano, Stanley R. Terlecky. 2012. Peroxisomes, cell senescence, and rates of aging. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease* . [CrossRef]
8. Stephan Kemp, Frederica L Theodoulou, Ronald JA Wanders. 2011. Mammalian peroxisomal ABC transporters: from endogenous substrates to pathology and clinical significance. *British Journal of Pharmacology* **164**:7, 1753-1766. [CrossRef]
9. Johannes Koch, Cécile Brocard. 2011. Membrane elongation factors in organelle maintenance: the case of peroxisome proliferation. *BioMolecular Concepts* ---. [CrossRef]
10. S Mehdi Belgnaoui, Suzanne Paz, John Hiscott. 2011. Orchestrating the interferon antiviral response through the mitochondrial antiviral signaling (MAVS) adapter. *Current Opinion in Immunology* . [CrossRef]
11. Murugesan Velayutham, Craig Hemann, Jay L. Zweier. 2011. Removal of H2O2 and generation of superoxide radical: Role of cytochrome c and NADH. *Free Radical Biology and Medicine* **51**:1, 160-170. [CrossRef]
12. Ju Huang , Grace Y. Lam , John H. Brumell . 2011. Autophagy Signaling Through Reactive Oxygen Species. *Antioxidants & Redox Signaling* **14**:11, 2215-2231. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
13. Jianqiu Kou, Gabor G. Kovacs, Romana Höftberger, Willem Kulik, Alexander Brodde, Sonja Forss-Petter, Selma Hönigschnabl, Andreas Gleiss, Britta Brügger, Ronald Wanders, Wilhelm Just, Herbert Budka, Susanne Jungwirth, Peter Fischer, Johannes Berger. 2011. Peroxisomal alterations in Alzheimer's disease. *Acta Neuropathologica* . [CrossRef]
14. Yu Ru Kou, Kevin Kwong, Lu-Yuan Lee. 2011. Airway inflammation and hypersensitivity induced by chronic smoking. *Respiratory Physiology & Neurobiology* . [CrossRef]
15. Grace Y. Lam, Ju Huang, John H. Brumell. 2010. The many roles of NOX2 NADPH oxidase-derived ROS in immunity. *Seminars in Immunopathology* **32**:4, 415-430. [CrossRef]
16. Thomas Kietzmann . 2010. Intracellular Redox Compartments: Mechanisms and Significances. *Antioxidants & Redox Signaling* **13**:4, 395-398. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]