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Peroxisomal Dysfunction in Age-Related Diseases

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Abstract

Peroxisomes carry out many key functions related to lipid and reactive oxygen species (ROS) metabolism. The fundamental importance of peroxisomes for health in humans is underscored by the existence of devastating genetic disorders caused by impaired peroxisomal function or lack of peroxisomes. Emerging studies suggest that peroxisomal function may also be altered with aging and contribute to the pathogenesis of a variety of diseases, including diabetes and its related complications, neurodegenerative disorders, and cancer. With increasing evidence connecting peroxisomal dysfunction to the pathogenesis of these acquired diseases, the possibility of targeting peroxisomal function in disease prevention or treatment becomes intriguing. Here, we review recent developments in understanding the pathophysiological implications of peroxisomal dysfunctions outside the context of inherited peroxisomal disorders.

Keywords

aging; neurodegeneration; peroxisome; pexophagy; reactive oxygen species

Peroxisome: the Little Organelle that Could

Peroxisomes are ubiquitous and highly versatile cellular organelles. Although they were originally named based on their role in hydrogen peroxide production and catabolism, the functions of peroxisomes extend far beyond **ROS (see Glossary)** metabolism. Compartmentalized in these small organelles are >50 different enzymes, constituting several distinct pathways that regulate various aspects of cellular metabolism, including fatty acid (FA) oxidation and lipid synthesis. The size and appearance of peroxisomes often varies among different types of tissues, ranging from 0.1 to 1 μ m in diameter. As highly dynamic organelles, peroxisomes can modify their size, morphology, abundance, and function, depending on external stimuli or developmental stage [1,2].

As an organelle, peroxisomes are often neglected, perhaps due to the misconception that they play only ancillary or redundant roles. However, it is becoming increasingly clear that peroxisomes are essential organelles whose functions cannot be replaced by other

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organelles. Much of our understanding of the critical importance of peroxisomes for health in humans is based on the existence of devastating genetic disorders caused by impaired function or biogenesis of this organelle. Most of these disorders cause severe neurological dysfunctions, a host of other abnormalities, and death in early childhood [3,4]. What is underappreciated is the notion that peroxisomal function may also be altered with aging, contributing to disease. Recent studies support a peroxisomal role in the pathogenesis of aging-related diseases, including diabetes, neurodegenerative disorders, and cancer [5], although it is still uncertain whether these pathologies may be a cause or consequence of peroxisomal dysfunction.

Here, we briefly discuss major metabolic functions of peroxisomes and then highlight recent studies suggesting that peroxisomal function is altered with aging, emphasizing the processes involved in peroxisomal dysfunction, and the contribution to disease development.

Major Metabolic Functions of Peroxisomes

In addition to regulating ROS metabolism, peroxisomes are responsible for a variety of lipid metabolic functions, including **beta oxidation** of very long chain fatty acids (VLCFAs), **alpha oxidation** of branched-chain FAs, and synthesis of ether lipids and bile acids [2], as illustrated in Figure 1. Although peroxisomal functions can be broadly classified into two major categories, lipid metabolism and ROS metabolism; both are interconnected. These metabolic functions require cooperation of peroxisomes with other organelles including mitochondria, endoplasmic reticulum (ER), lipid droplets, and lysosomes.

Lipid Metabolism

Peroxisomes in all eukaryotic organisms have the ability to oxidize FAs. Oxidation of FAs requires activation of FAs to a fatty acyl-CoA. Fatty acyl-CoA transport across the peroxisomal membrane occurs through peroxisomal ATP binding cassette (ABC) subfamily D half transporters, that form heterodimers [6]. Beta oxidation of the fatty acyl-CoA molecule results in the removal of two carbons from its carboxyl terminus. Peroxisomal beta oxidation differs from mitochondrial beta oxidation in several key aspects, as described in Table 1. While the mechanisms of peroxisomal and mitochondrial beta oxidation are similar, the enzymes involved are unique to each organelle. The first step of mitochondrial beta oxidation produces FADH₂, which is used to generate ATP via the electron transport chain. The first step of beta oxidation in peroxisomes, by contrast, is not coupled to energy production, but instead to the reduction of O₂ to the ROS (H₂O₂) [7]. The FA specificities of each organelle differ as well. Mitochondria preferentially oxidize short-chain (<C6) and medium-chain (C6–C12) FAs, while both mitochondria and peroxisomes oxidize long-chain (C12–C20) FAs. Mitochondria are thought to have a quantitatively greater contribution to oxidation of long chain FAs, but the relative contribution of peroxisomes to this process can vary depending on physiological context [8]. Beta oxidation of VLCFAs (>C20) and dicarboxylic acids occurs exclusively in peroxisomes [9,10]. Peroxisomal beta oxidation is a chain-shortening process and is not carried to completion. Peroxisomes exhibit carnitine acyltransferase activity, reflecting the need to shuttle the breakdown products into mitochondria for further oxidation [11].

While beta oxidation is the preferential mode of FA oxidation for a variety of substrates, long chain 2-hydroxy FAs and 3-methyl branched FAs, such as phytanic acid, cannot be oxidized through beta oxidation directly, and must first undergo alpha oxidation, which occurs exclusively in peroxisomes. In alpha oxidation, FAs are first converted to their CoA ester and then α -hydroxylase adds a hydroxyl group to the α -carbon. The product is decarboxylated to form an aldehyde, which is then oxidized by an aldehyde dehydrogenase. Further catabolism proceeds through beta oxidation [12].

Peroxisomes are not only involved in catabolic reactions but also in the synthesis of a specialized class of phospholipids called **ether lipids** [13]. In contrast to the more common diacyl phospholipids, which have fatty acyl side chains linked to the sn-1 and sn-2 positions of the glycerol backbone by ester bonds, ether lipids have the sn-1 substituent attached by an ether bond. **Plasmalogens** are a subtype of ether-linked phospholipids that have a *cis* double bond adjacent to the ether bond. Peroxisomes are involved in the initial steps of ether lipid synthesis and completion occurs in the ER, as explained in Box 1. The gene encoding the enzyme that catalyzes the terminal peroxisomal step was recently identified, and the protein was named peroxisomal reductase activating peroxisome proliferator-activated receptor γ (PexRAP), based on its proposed function in adipocytes [14]. Ether lipids account for up to 20% of the total phospholipid content in humans and are particularly abundant in the brain, heart, and neutrophils [15]. Plasmalogens are important components of cellular membranes and may be involved in the organization of cholesterol-rich membrane regions known as detergent-resistant microdomains, which have been implicated in cellular signaling [16]. Besides their structural roles, plasmalogens have been associated with a wide variety of other functions including antioxidant, signaling, spermatogenic [17], neurological [18], and immunometabolic [19] functions.

Box 1

Ether Lipid Synthesis

The ether lipid synthetic pathway uses DHAP, produced by dehydrogenation of glycerol 3-phosphate (G3P), as a building block for the synthesis of phospholipids. Acyl CoA, derived from *de novo* lipogenesis is used by DHAPAT to acylate DHAP. Alkyl-DHAP synthase (also called AGPS) converts acyl-DHAP to alkyl-DHAP, which is then reduced to 1-O-alkyl glycerol-3-phosphate by the peroxisomal membrane protein acyl/alkyl DHAP reductase (also called PexRAP) [2,14]. Further steps to complete ether-linked phospholipid synthesis, including acylation of the sn-2 position of the glycerol backbone and addition of the head group, occur in the ER.

Peroxisomes are also involved in bile acid synthesis [20]. In addition, several enzymes involved in the early stages of cholesterol synthesis (pre-squalene segment of the pathway) have been reported to be present in peroxisomes [21], but the overall contribution of peroxisomes to cholesterol synthesis is unclear [22]. Cholesterol is an essential lipid accounting for 30–40% of total cellular lipid store and is involved in many cellular functions, including signal transduction, bile acid synthesis, steroid synthesis, and plasma membrane composition. Peroxisomes have also been reported to be involved in transport of

free cholesterol. A recent study showed that cholesterol can be transported from the lysosomes to the peroxisomes through lysosomal–peroxisomal membrane contact (LPMC), and knockdown of peroxisomal proteins leads to impaired cholesterol transport [23].

ROS Metabolism

Peroxisomes account for up to 20% of total cellular oxygen consumption [24]. Unlike mitochondrial respiration, which is linked to ATP synthesis, peroxisomal respiration produces H_2O_2 as the end product through the action of multiple oxidases present in the organelle. Peroxisomes can account for up to 35% of total H_2O_2 generation in mammalian tissues [25]. To counterbalance the damaging effect of this ROS, peroxisomes in many, but not all cell types, contain abundant amounts of the antioxidant enzyme catalase, which reduces H_2O_2 to water. Peroxisomes are also involved in the production of other ROS, including superoxide radicals and nitric oxide radicals, and are equipped with their associated antioxidant enzymes as well [26,27]. Oxidative stress is a major contributor to cellular senescence and pathogenesis of various age-related disorders, suggesting that the ability of peroxisomes to maintain a balance between ROS production and catabolism may be compromised with aging.

Relationship between Peroxisomal Dysfunction and Aging

The role of peroxisomal dysfunction in aging has been largely neglected, in part due to the similarities in the functions of peroxisomes and mitochondria, with much of the attention on oxidative-stress-associated aging focusing on the role of mitochondrial dysfunction [28]. Although peroxisomes play a major role in H_2O_2 production, it is difficult to isolate the contribution of peroxisomes in this process from that of mitochondria, and delineate the site of ROS origination within cells [29]. Nevertheless, accumulating evidence suggests that peroxisomal function declines with aging, and links oxidative stress caused by dysregulated peroxisomal ROS metabolism to disease [5,29].

Peroxisome-mediated ROS production is thought to have a profound effect on mitochondrial integrity. Induction of intraperoxisomal ROS production using a peroxisome-localized photosensitizer results in increased mitochondrial fragmentation; a manifestation of aging at the cellular level [30]. Moreover, genetic inactivation of catalase, a predominantly peroxisomal protein, perturbs mitochondrial redox potential in mice [31]. Reflecting the intimate link between the two organelles, these studies suggest that peroxisomal dysfunction may be a precursor for mitochondrial dysfunction.

Studies in cultured cells suggest that catalase is increasingly excluded from the peroxisomes as cells age with serial passaging, resulting in increased oxidative stress and cellular senescence. Surprisingly, the number of peroxisomes is increased in older cells, suggesting accumulation of the defective organelles with aging [24]. Recently, a quantitative mass-spectrometry-based study in *Caenorhabditis elegans* identified ~30 peroxisomal proteins whose abundance decreased with aging [32]. One such protein identified was Pex5, an import receptor for peroxisomal matrix proteins containing a conserved C-terminal tripeptide called peroxisomal targeting sequence 1 [33,34]. Pex5 is involved in peroxisomal import of catalase [35] and has been shown to be redox sensitive [36,37]. Thus, oxidative

stress could directly interfere with Pex5 import activity. Decreased abundance and/or impaired function of Pex5 could potentially explain the mechanism for aging-related mislocalization of the antioxidant enzyme. However, the *C. elegans* study indicated that proteins involved in peroxisomal FA oxidation, ether lipid synthesis, and other peroxisomal processes were also decreased [32], suggesting that aging-related peroxisomal dysfunction extends beyond dysregulated ROS metabolism.

Together, these studies suggest that peroxisomal function is compromised with aging. To avoid pathologies associated with the accumulation of defective peroxisomes, the ability to maintain peroxisomal homeostasis may be critical.

Clearance of Dysfunctional Peroxisomes through Autophagy

Peroxisomal homeostasis is maintained through coordinated regulation of biogenesis and degradation of the organelle in response to changing environmental conditions. Under basal conditions, peroxisomes have a half-life of ~2 days [38]. Old or dysfunctional peroxisomes are removed primarily by **autophagy**; a catabolic process that involves lysosomal degradation of intracellular components through formation of a double membrane autophagosome around the cargo, which then fuses with lysosomes [39,40].

In addition to the canonical autophagy pathway, which is a nonselective (bulk) degradation of cytoplasmic contents, selective autophagy exists. Selective autophagy involves adaptor proteins, such as p62 and NBR1, which recognize ubiquitinated autophagic cargo and tether it to the site of autophagosomal engulfment [41]. Selective autophagic degradation of peroxisomes is called **pexophagy**. The pexophagy pathway in yeast has been well characterized [42], but the molecular mechanism of the process in mammals is just now beginning to be understood. The identity of the receptor in mammals that undergoes ubiquitination and marks peroxisomes for autophagic degradation has long been a matter of debate. Recently, two groups independently demonstrated that pexophagy requires ubiquitination of Pex5 [43,44]. Activation of pexophagy involves Pex5-dependent translocation of the kinase ataxia–telangiectasia mutated (ATM) to peroxisomes. In response to exogenously applied H₂O₂ or clofibrate treatment, which increases peroxisomal fatty acid oxidation and leads to ROS production, ATM is activated and promotes autophagy by inhibiting signaling from the mammalian target of rapamycin complex 1 (mTORC)1. ROS-activated ATM also phosphorylates Pex5. This in turn primes Pex5 for an E3 ligase-mediated ubiquitination and p62-mediated autophagy (Figure 2) [44,45]. Together, these studies suggest that excessive ROS production may be a signal of peroxisomal dysfunction to trigger pexophagy. Hypoxia also activates pexophagy through a process dependent on hypoxia-inducible factor 2 α [46]. Recently, Pex2 was shown to be the E3 ligase that mediates Pex5 ubiquitination during starvation-induced pexophagy [47]. Whether Pex2 is a general regulator of pexophagy, including the degradation induced by ROS and hypoxia, remains unclear.

Peroxisomal Dysfunction in Disease Development

Normal physiology requires not only a balance between peroxisomal biogenesis and degradation, but also proper maintenance of peroxisomal function. Impaired or dysregulated peroxisomal function has been described as a component of a variety of age-related diseases, including diabetes, neurological disorders, and cancer, as shown in Figure 3.

Peroxisomal Dysfunction in Diabetes and Related Complications

Diabetes is characterized by abnormally high levels of glucose in the blood, which if left untreated, results in numerous complications, including end-stage renal disease, blindness, cardiovascular disease, and nontraumatic limb amputation. Diabetes is classified into two major types. Type 1 diabetes results from the autoimmune destruction of the insulin-producing beta cells of the islets of Langerhans in the pancreas and accounts for 5–10% of all cases of the disease. These patients absolutely require exogenous insulin for survival. Type 2 diabetes, which is significantly more common, is associated with obesity and insulin resistance. Beta cells compensate for insulin resistance by hypersecretion of insulin. Ultimately, beta cell failure ensues and frank diabetes develops [48].

Nonesterified fatty acids (NEFAs) have long been known to exert **lipotoxicity** in insulin-producing cells. Oxidative stress is a major mediator of lipotoxicity [49]. Conventional wisdom holds that increased mitochondrial respiration leads to H_2O_2 formation through the electron transport chain, resulting in cellular stress [50]. Using an H_2O_2 -sensitive fluorescent protein, this notion was challenged by the observation that the subcellular site of ROS production in palmitate-treated beta cells is primarily peroxisomes and not mitochondria. Moreover, overexpression of catalase in peroxisomes, but not mitochondria, reduces oxidative stress and protects beta cells from palmitate-induced lipotoxicity. This suggests that H_2O_2 production in peroxisomes rather than mitochondria is primarily responsible for NEFA-induced lipotoxicity in beta cells [51].

Peroxisomal H_2O_2 formation is not just problematic in islets, but also in the development of diabetic neuropathies and osteoarthritis [31,52,53]. Treating cultured human retinal cells or diabetic mice with peroxisome-localized catalase protein reduces oxidative stress and improves intraretinal calcium channel activity [54]. Conversely, knockout of catalase in diabetic mice increases oxidative stress and features of nephropathy as compared to wild-type diabetic mice, despite similar levels of hyperglycemia in the two groups. Furthermore, catalase inactivation results in impaired peroxisomal biogenesis and increased renal lipid accumulation. This suggests that increased oxidative stress results in peroxisomal dysfunction that exacerbates diabetic renal injury [31]. Peroxisomal dysfunction has also been implicated in the early incidence and development of osteoarthritis in diabetic patients. Peroxisomal gene expression and catalase activity were shown to be downregulated in chondrocytes isolated from diabetes-associated osteoarthritis patients [52].

Dysregulation of Peroxisomal Lipid Metabolism in Neurodegenerative Disorders

Inherited peroxisomal disorders are associated with severe neurological dysfunctions, including hypotonia, seizures, cerebellar ataxia, sensory impairments, and developmental

deficits [4]. Recent studies suggest that peroxisomal function also declines with age and may be linked to age-related neurological disorders such as Alzheimer's disease (AD). AD is characterized by β -amyloid accumulation and formation of tau tangles, resulting in inflammation and neuronal cell death. FA composition in the brains of AD patients is altered. Notably, levels of VLCFAs in cortical regions of the brain are increased in these patients, suggesting a possible defect in peroxisomal beta oxidation [55]. Consistent with this possibility, treatment of rats with a high fat diet or streptozotocin to induce diabetes impairs beta oxidation in the cerebral cortex, resulting in accumulation of β -amyloid peptide in the brain [56]. Accumulation of β amyloid is also associated with induction of ROS, and treatment of primary rat neuronal cells with peroxisomally targeted catalase protects from a soluble form of amyloid β peptide called amyloid- β -derived diffusible ligands [57].

Peroxisomal lipid synthesis is impaired in AD patients in addition to peroxisomal FA oxidation, suggesting a general defect in peroxisomal function. In the gyrus frontalis of human postmortem AD brains, reduced plasmalogen levels are observed in addition to increased amounts of VLCFAs. These phenotypes are exacerbated in brains exhibiting neurofibrillary tangles in addition to neuritic plaques, as compared to neuritic plaques alone [55]. One of the early features of AD is synaptic vesicle loss, which is likely coincident with cognitive impairment. The synaptic vesicle is enriched in ether lipids [58], and neurotransmitter release from these vesicles into the presynaptic cleft is impaired in synaptosomes isolated from the brains of mice with knockout of the ether lipid synthetic enzyme dihydroacetone phosphate acyl transferase (DHAPAT) [59]. Examination of 29 independent neurolipidomic datasets consistently revealed increased hydrolysis of ethanolamine-containing membrane plasmalogens and decreased levels of other ether-linked structural phospholipids in AD, potentially contributing to the vesicular depletion [60]. Taken together, these data indicate a role for peroxisomal dysfunction in both the pathogenesis and progressive worsening of AD.

Peroxisomal dysfunction has also been linked to other neurodegenerative disorders, including Parkinson's disease (PD). PD is characterized by accumulation of the protein α -synuclein (α S) and underproduction of the neurotransmitter dopamine. Plasmalogen levels are significantly reduced in postmortem human frontal cortex lipid rafts with PD [61]. Supplementation of plasmalogens in a mouse model of PD, using the orally bioavailable ethanolamine plasmalogen precursor PPI-1011, reverses striatal dopamine loss [62]. The mechanism through which this occurs is unknown. In this study, PPI-1011 significantly increased plasmalogen levels in serum but not in brain tissue, which the authors conjectured could have been due to challenges in assaying small quantities of brain tissue for plasmalogen species. Another possibility is that neuroprotection was provided through increases in docosahexaenoic acid or lipoic acid levels, which are also increased by PPI-1011 [62]. Peroxisomal dysfunction may contribute to the accumulation of α S in the brain. The normal function of α S is thought to be binding to presynaptic vesicles and promoting fusion with neurotransmitter vesicles. Recent studies in peroxisome-deficient (Pex3 mutant) yeast models of PD found that α S could not bind to lipid droplets in lipid-loaded peroxisome-deficient yeast cells, as it did in wild type cells [63]. More work is necessary to establish whether peroxisomal dysfunction can affect α S function in mammalian brains.

Altered Peroxisomal Metabolism in Cancer

Lipid metabolism is known to be dysregulated in cancer cells. Cancer cells typically exhibit increased **lipogenesis** in order to support membrane synthesis and generation of oncogenic lipid signaling molecules [64]. Ether lipids specifically are upregulated in a wide variety of neoplastic tissues [65,66]. Although their precise role in cancer pathogenicity is unclear, ether lipids are important for the organization of detergent-resistant membrane microdomains [2]. Ether lipids may also be required for the assembly and release of exosomes, 40–100-nm vesicles secreted by cells, which may be involved in cell–cell communication and promoting cancer metastasis [67].

Recent studies suggest a link between ether lipid synthesis and cancer progression. Overexpression of the tumor suppressor H-rev107 has been shown to result in mislocalization of various peroxisomal proteins and a marked decrease in ether lipid levels in cultured cells [68]. H-rev107 interacts with and inhibits the function of Pex19 [69], a cytosolic chaperone involved in the import of peroxisomal membrane proteins [70], including the peroxisomal lipid synthetic enzyme PexRAP [14]. H-rev107 itself is an inhibitor of the oncogene *H-ras*, and transformation of *H-ras* into moderately aggressive cell lines results in increased expression of the ether lipid synthetic enzyme alkylglycerone phosphate synthase (AGPS). AGPS expression is elevated in a variety of aggressive cancer cells. Its knockdown results in impaired metrics of cancer pathogenicity and reduced levels of oncogenic lipid signals, while its overexpression increases cancer cell aggressiveness [71,72]. A small-molecule screen to find inhibitors of AGPS identified several candidate compounds. One such compound appears to be particularly promising in lowering ether lipid levels and impairing survival and migration of cancer cells [73].

Ether lipid synthesis is not the only peroxisomal metabolic process that is upregulated in cancer. The enzyme α -methylacyl-CoA racemase (AMACR), which localizes to both mitochondria and peroxisomes and catalyzes a key chiral inversion reaction in branched-chain lipid metabolism and bile acid synthesis, is upregulated particularly in prostate cancer and in some other cancers [74,75]. Knockdown of AMACR in myxofibrosarcoma cell lines reduces expression of markers of cell proliferation and suppresses cell growth [76]. The mechanism through which AMACR expression or activity is associated with cancer is unknown, although gene amplification at 5p13.3 drives AMACR overexpression in 20% of myxofibrosarcomas [76]. It is unclear what drives overexpression of AMACR in the remainder of cases. One hypothesized role for AMACR overexpression is that it may facilitate a switch from glucose metabolism to FA metabolism during cancer [77]. Regardless of its precise role in cancer progression, AMACR has become an important diagnostic parameter for prostate cancer and a potential target for cancer treatment [75,76].

In addition to changes in the expression levels of peroxisomal proteins, altered peroxisomal compartmentalization of metabolic enzymes might also affect the metabolism of cancer cells. Cancer cells exhibit a high rate of glycolysis, followed by lactic acid fermentation, even if sufficient oxygen is present, to support mitochondrial oxidative phosphorylation. This observation is known as the **Warburg effect** [78]. Because glycolysis is an inefficient way to generate ATP as opposed to the complete oxidation of glucose, the precise role of the

high rate of aerobic glycolysis in cancer cells is unclear. Several possible explanations have been proposed, including generation of metabolic intermediates and reducing equivalents to support biomass production, acidification of the tumor microenvironment to promote invasiveness, and production of cellular signaling molecules through ROS metabolism [79]. Emerging studies suggest that isoforms of various glucose metabolism enzymes, including GAPDH, 3-phosphoglycerate kinase, and lactate dehydrogenase are partially localized in peroxisomes through a C-terminal peroxisomal targeting sequence generated by ribosomal read-through of a stop codon [80–82]. Whether the peroxisomal localization of these metabolic enzymes is a cancer-associated dysregulation related to the Warburg effect remains to be determined. However, monocarboxylate transporter (MCT)2, another peroxisome-localized metabolic enzyme that regulates pyruvate for lactate exchange (converting NADH to NAD⁺ in the process to fuel peroxisomal beta oxidation and promote ROS production) [83], is indeed involved in cancer [84]. Increased peroxisomal localization of MCT2 is associated with malignant transformation of prostate cancer cells and its knockdown attenuates growth of prostate cancer cells [85,86].

Concluding Remarks and Future Perspectives

Increasing evidence suggests that peroxisomal function is affected with aging, due to altered expression or localization of peroxisomal matrix proteins. Impaired peroxisomal function has been implicated in neurodegenerative disorders, beta cell failure, and diabetes-related complications, while dysregulated peroxisomal function is associated with cancer. The molecular mechanisms underlying the role of peroxisomal dysfunction in these diseases are not well understood (see Outstanding Questions). Moreover, it is unclear whether peroxisomal dysfunction is the cause or a response to disease. The severe phenotypes, including neurologic degeneration, associated with inherited peroxisomal disorders [3,4] suggest a causative role of peroxisomal dysfunction in disease.

Outstanding Questions

How do peroxisomes leverage their relationship with mitochondria to maintain lipid metabolism and oxidative homeostasis? What is the physiological basis for the organelle-specific differences in chain length specificity for FA oxidation?

Does disruption of peroxisomal lipid metabolism directly affect disease pathogenesis through changes in membrane structure or indirectly through oxidative imbalance?

Do cancer cells exploit peroxisomal compartmentalization of multiple metabolic pathways to more efficiently regulate their metabolism?

Do ether lipids play a structural or signaling role in promoting cancer progression?

Could peroxisomal metabolism be safely targeted to prevent or treat aging-related disorders?

Could dietary interventions be used to alter peroxisomal activities to impact the clinical course of neurologic diseases?

Based on the essential role of peroxisomes in lipid and ROS metabolism, peroxisomal dysfunction can potentially contribute to the pathogenesis of age-related diseases through impaired oxidative homeostasis, membrane lipid remodeling, and/or generation of lipid signaling molecules. For example, impaired peroxisomal function leads to abnormal ether lipid synthesis, which could interfere with insulin and/or synaptic vesicle structure and function. Future research is necessary to determine mechanistically how peroxisomal processes relate to important cellular functions like neurotransmission and insulin secretion, and whether these processes could be manipulated through dietary or pharmacological means for disease interventions. Furthermore, additional work is needed to determine whether an increased peroxisomal compartmentalization of metabolic pathways is a mechanism exploited by cancer cells to improve the efficiency of biomass production. Lending support to this notion, compartmentalization of heterologous metabolic pathways in yeast peroxisomes dramatically improves product titer, presumably due to isolation of pathways in a compact and suitable environment [87,88].

Our aim here was to bring the relationship between peroxisomal dysfunction and common age-related diseases to the forefront of the lipid metabolism field, and to encourage future investigation into this area of research still in its infancy. A better understanding of how peroxisome function is altered during aging might lead to new approaches to treat disease.

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Glossary

Alpha oxidation

process by which branched-chain FAs undergo oxidative decarboxylation to remove the terminal carboxyl group as CO₂

Autophagy

process for degradation of intracellular components through formation of a double membrane structure called autophagosome around the cargo, which then fuses with lysosomes

Beta oxidation

process of FA catabolism by which two carbons are removed from the carboxyl terminus of a fatty acyl CoA molecule. The process is named as such because the beta carbon of the FA undergoes oxidation

Ether lipid

phospholipid characterized by an ether linkage of a long-chain alkyl moiety at one or more carbons of the glycerol backbone, as opposed to the more typical ester linkage

Lipogenesis

endogenous generation of fats using carbohydrates as precursors

Lipotoxicity

accumulation of lipids in tissues other than adipose tissue, resulting in metabolic dysfunction

Pexophagy

selective autophagy of peroxisomes

Plasmalogen

ether lipid characterized by a vinyl ether linkage at the sn-1 position of the glycerol backbone

Reactive oxygen species (ROS)

chemically reactive species containing a reduced form of oxygen

Warburg effect

phenomenon characterized by a high rate of aerobic glycolysis observed in cancer cells

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Trends Box

- Peroxisomes are multifunctional organelles involved in ROS metabolism, fatty acid oxidation, ether lipid synthesis, bile acid synthesis, and cholesterol transport.
- Peroxisomal homeostasis is an important regulator of health and old or defective peroxisomes are removed through autophagy.
- Disruption of peroxisomal function can lead to mitochondrial dysfunction, reflecting the intimate link between the two organelles.
- Accumulating evidence suggests that peroxisomal function is altered with aging due to changes in the expression and/or localization of peroxisomal matrix proteins.
- Impaired peroxisomal function has been implicated in neurodegenerative disorders and diabetes, while dysregulated peroxisomal function is associated with cancer.

Figure 1. Metabolic Functions of Peroxisomes

Peroxisomes perform a variety of lipid metabolic functions. Catabolic functions include beta oxidation of VLCFAs and alpha oxidation of 3-methyl branched FAs, whereas anabolic functions include ether lipid synthesis and bile acid synthesis. Peroxisomes are also involved in the metabolism of reactive oxygen species. Abbreviations: DHAP, dihydroxyacetone phosphate; FA, fatty acid; G3P, glycerol 3-phosphate; ROS, reactive oxygen species; VLCFA, very long chain fatty acid.

Figure 2. Removal of Dysfunctional Peroxisomes by Pexophagy

ROS-activated ATM kinase both signals to mTORC1 to inhibit its suppression of autophagy and phosphorylates Pex5 to promote its ubiquitination and its subsequent binding of p62, thus targeting the peroxisome for degradation. Abbreviations: ATM, ataxia–telangiectasia mutated; LC3, microtubule-associated protein light chain 3; mTORC1, mammalian target of rapamycin complex 1; Pex5, peroxisomal biogenesis factor 5; ROS, reactive oxygen species; TSC, tuberous sclerosis complex; Ub, ubiquitinated; ULK1, Unc-51-like autophagy activating kinase 1.

Figure 3. Peroxisomal Dysfunction in Age-Related Diseases

Decreased expression or peroxisomal localization of proteins involved in ROS and lipid metabolism is observed in metabolic and neurodegenerative disorders. Increased expression or peroxisomal compartmentalization of different metabolic enzymes is observed in cancer. Abbreviations: AGPS, alkylglycerone phosphate synthase; FAO, fatty acid oxidation; MCT2, monocarboxylate transporter 2; ROS, reactive oxygen species; VLCFA, very long chain fatty acid.

Table 1

Comparison between Mitochondrial and Peroxisomal FA oxidation

Parameter	Mitochondrial pathway	Peroxisomal pathway	Refs
Substrate specificity	Short (<C6), medium (C6–C12), and long (C12–C20) chain fatty acids	Long and very long (C>20) chain fatty acids, dicarboxylic acids	[9,10]
Transport mechanism	Diffusion (short and medium chain), carnitine shuttle (long chain)	ABCD subfamily half-transporters	[6]
Enzymes	1 Acyl CoA dehydrogenase 2 MTP ^a <ul style="list-style-type: none"> • Enoyl-CoA hydratase • 3-Hydroxyacyl-CoA dehydrogenase • 3-Ketoacyl-CoA thiolase 	1 Acyl CoA oxidase 2 MFE1/MFE2 ^b <ul style="list-style-type: none"> • Enoyl-CoA hydratase • 3-Hydroxyacyl-CoA dehydrogenase 3 3-Ketoacyl-CoA thiolase	[7]
Side products	ATP	H ₂ O ₂ , heat	[7]
Products	Acetyl-CoA	Shortened chain fatty acyl-CoAs, acetyl-CoA	[7]

^aMitochondrial trifunctional protein that catalyzes Steps 2–4 of long chain FA oxidation. Mitochondria also possess separate individual enzymes that catalyze these steps for chain-shortened FAs.

^bPeroxisomal multifunctional enzymes (Types 1 and 2) that possess the two indicated activities.

MFE.,; MTP.,