Chapter 3

Aging, Age-Related Diseases and Peroxisomes

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Abstract

Human aging is considered as one of the biggest risk factors for the development of multiple diseases such as cancer, type-2 diabetes, and neurodegeneration. In addition, it is widely accepted that these age-related diseases result from a combination of various genetic, lifestyle, and environmental factors. As biological aging is a complex and multifactorial phenomenon, the molecular mechanisms underlying disease initiation and progression are not yet fully understood. However, a significant amount of evidence supports the theory that oxidative stress may act as a primary etiologic factor. Indeed, many signaling components like kinases, phosphatases, and transcription factors are exquisitely sensitive to the cellular redox status, and a chronic or severe disturbance in redox homeostasis can promote cell proliferation or trigger cell death. Now, almost 50 years after their discovery, there is a wealth of evidence that peroxisomes can function as a subcellular source, sink, or target of reactive oxygen and nitrogen molecules. Yet, the possibility that these organelles may act as a signaling platform for a variety of age-related processes has so far been underestimated and largely neglected. In this review, we will critically discuss the possible role of peroxisomes in the human aging process in light of the available data.

Keywords

Peroxisomes • interorganellar crosstalk • catalase • oxidative stress • redox signaling

3.1 Aging and Organelle Dysfunction: the Inextricable Link

Over the years, mammalian aging has been linked to a wide range of cellular changes, such as telomere shortening, DNA methylation, organelle dysfunction, a decline in autophagic and proteasomal proteolysis, incorrect protein folding, and alterations in membrane lipid composition (Hamanaka et al. 2010; Boya 2012). Considerable efforts have already been made to integrate this information into a unifying model (Terman et al. 2010; Sahin and DePinho 2012). However, although the general consensus is that progressive DNA damage and mitochondrial decline may act as prime instigators of natural aging, it remains to be established how all these factors are interconnected and drive this process (Sahin and DePinho 2012). In the context of this chapter, we will briefly discuss the intricate relationship between organelle (dys)function and aging (Fig. 3.1).

Currently, there is good evidence that the process of physiological aging is associated with changes in organelle composition, morphology and function (Soltow et al. 2010). For example, it has repeatedly been reported that both mitochondrial respiratory function and lysosomal activity decline with age (Gómez and Hagen 2012; Rajawat et al. 2009). These findings, among others, have led to the mitochondrial-lysosomal axis theory of aging (Terman et al. 2010). This theory proposes that defective and enlarged mitochondria, which produce less ATP and generate increased amounts of reactive oxygen species (ROS), progressively accumulate with age as a result of imperfect autophagocytosis. On the other hand, there is also abundant evidence that organelles themselves can contribute to the pathophysiology of age-related diseases (Hamanaka et al. 2010; Schon and Przedborski 2011; Boya 2012). This may occur through their normal functions or as a result of damage (e.g. by exposure to harmful substances such as oxygen radicals). For example, changes in nuclear envelope composition that result in more deformable nuclei may contribute to cancer progression (Zwerger et al. 2011), and protein misfolding in the endoplasmic reticulum (ER) may activate the unfolded protein response (UPR), which – in case stress is too severe – can initiate apoptosis via ER-mitochondrial Ca^{2+} -signaling (Decuypere et al. 2011). These examples also nicely illustrate that the reciprocal interplay between organelle activity and aging depends on dynamic and highly interconnected signaling networks. However, the identity of the interorganellar signaling pathways and messenger molecules remain largely to be determined. Nevertheless, it has recently been postulated that aging-associated functional losses are primarily caused by a progressive disruption of redox-regulated signaling mechanisms (Sohal and Orr 2012), and that at least several of these mechanisms may intersect and converge on mitochondria (Sahin and DePinho 2012).

3.2 Peroxisomes and Cellular Aging

During the last decade, mounting evidence has been collected suggesting that peroxisomes may actively contribute to the maintenance of the cellular redox balance (del Rio 2011; Fransen et al. 2012). In addition, strong arguments have been presented that peroxisomal metabolism and cellular aging are closely intertwined (Titorenko and Terlecky 2011), and that these organelles closely cooperate with mitochondria to fulfill their functions (Islinger et al. 2012). Each of these aspects is discussed in more detail below (Fig. 3.2). Note that, as these sections are mainly focused on the possible role of peroxisomal ROS in the mammalian aging process, we refer to other informative reviews for pioneering research on this topic in other model organisms such as plants (del Rio et al., 1998; del Rio et al., 2006) and yeasts (Mannivannan et al., 2012).

3.2.1 Peroxisomal Metabolism and Oxidative Stress

Mammalian peroxisomes are highly dynamic, multifunctional organelles that play a key role in various metabolic pathways, including fatty acid α - and β -oxidation, amino acid catabolism, and the biosynthesis of docosahexaenoic acid (DHA or 22:6 n-3), bile acids, and

plasmalogens (Wanders and Waterham 2006). Many of the enzymes involved in these pathways produce ROS or reactive nitrogen species (RNS) as part of their normal catalytic cycle (see Chapters 13 and 15). These species include hydrogen peroxide (H_2O_2), superoxide ($\text{O}_2^{\cdot-}$), and nitric oxide ($\text{NO}^{\cdot}$). In addition, inside peroxisomes, H_2O_2 can decompose into the highly reactive hydroxyl radical ($\cdot\text{OH}$) via the transition metal-catalyzed Fenton reaction, and $\text{O}_2^{\cdot-}$ and $\text{NO}^{\cdot}$ may rapidly combine to form peroxynitrite ($\text{ONOO}^{\cdot}$). To combat the destructive effects of these molecules, peroxisomes also contain various antioxidant enzymes such as catalase (CAT), peroxiredoxin 5 (PRDX5), and Cu/Zn-superoxide dismutase (SOD1) (Antonenkova et al. 2010). For a detailed description of enzymes involved in peroxisomal ROS metabolism, we refer to other excellent reviews (Bonekamp et al. 2009; Antonenkova et al. 2010).

Given that mammalian peroxisomes contain copious amounts of H_2O_2 -producing flavin-containing oxidases and the H_2O_2 -decomposing enzyme catalase, these organelles can be considered as potentially significant sources or sinks of H_2O_2 , a key molecule in cellular redox signaling. This has been nicely illustrated in a number of studies, which showed that (i) in rat liver, peroxisomes may be responsible for as much as 35% of the total H_2O_2 production (Boveris et al. 1972), (ii) overexpression of the peroxisomal H_2O_2 -producing enzyme acyl-CoA oxidase 1 (ACOX1) leads to activation of NF κ B1, a pleiotropic redox-sensitive transcription factor that is involved in many biological processes, including cell growth and differentiation, inflammation, tumorigenesis, and apoptosis (Li et al. 2000), and (iii) inhibition of catalase activity by 3-aminotriazole increases the cellular protein disulfide content by 20% (Yang et al. 2007). Moreover, as peroxisomes play an essential role in cellular lipid metabolism (Van Veldhoven 2010), they may also protect cells against adverse effects of oxidative stress by actively maintaining the optimal membrane lipid composition (Périchon et al. 1998). For example, a decrease in peroxisomal β -oxidation will influence the ability of the cell to shorten very-long-chain fatty acids (VLCFAs) and to synthesize sufficient amounts of DHA (Van Veldhoven 2010). As these VLCFAs may overaccumulate in cellular membranes and DHA is an important membrane phospholipid component, changes in peroxisomal β -oxidation are likely to alter membrane composition, structure, fluidity, and function. In addition, as the first two steps in the biosynthesis of plasmalogens occur exclusively in peroxisomes, a decrease in peroxisome activity will also affect the cell's ability to synthesize sufficient amounts of this class of glycerophospholipids, which normally constitutes up to 18% of the total phospholipid mass in humans (Bravermann and Moser 2012). Importantly, plasmalogens are characterized by the presence of a vinyl ether linkage at the *sn*-1 position, and it has been suggested that this functionality may serve as sacrificial trap for free radicals and singlet oxygen (Wallner and Schmitz 2011). The finding that plasmalogen-deficient cells from patients with peroxisome biogenesis disorders (PBDs) display an increased sensitivity to UV-induced oxidative stress is in line with this hypothesis (Hoeftler et al. 1991). Furthermore, plasmalogens are targets of hypochlorous (HOCl) and hypobromous (HOBr) acids, oxidants produced by myeloperoxidase, an enzyme released by activated leukocytes during inflammation (Pattison and Davies 2006). The generated 2-chloroaldehydes can in turn inhibit nitric oxide biosynthesis (Marsche et al. 2004).

In summary, these data clearly show that peroxisomes can participate, directly or indirectly, in the maintenance of cellular redox homeostasis. Nonetheless, the extent to which these organelles contribute to cellular oxidative stress and redox signaling remain to be established, and – over the years – this topic has generated some controversy. For example, while some studies state that peroxisome proliferation induces oxidative stress (Reddy et al. 1980), others claim that this process may prevent ROS production (Santos et al. 2005; Diano et al. 2011). However, one should always keep in mind that different physiological and environmental variables may predispose whether peroxisomes act as net sources or sinks of ROS within a cell (Fransen et al. 2012).

3.2.2 Peroxisomal Metabolism and Cellular Aging

Over the years, several studies have presented compelling evidence that peroxisomal metabolism and aging are closely intertwined (Titorenko and Terlecky 2011; and references therein). For example, peroxisomal β -oxidation, plasmalogen biosynthesis, and catalase activity have been reported to gradually decrease with age (Périchon et al. 1998; Braverman and Moser 2012). In addition, there are indications that the activities of at least some peroxisomal H_2O_2 -producing enzymes (e.g. D-amino acid oxidase) increase with age (Périchon et al. 1998). Furthermore, proteomic analysis studies of peroxisome-enriched fractions from young and old mouse liver and kidney have identified a select set of age-dependent alterations (Mi et al. 2007; Amelina et al. 2011). Finally, it is also known that some peroxisomal enzymes – including catalase – progressively mislocalize to the cytosol as cells age, despite the fact that the volume density of these organelles gradually increases (Beier et al. 1993; Legakis et al. 2002). Whether this increase in peroxisome number is due to increased proliferation or reduced degradation remains to be investigated. However, as the autophagy-lysosomal system is the major degradation pathway for peroxisomes (Ezaki et al. 2011), it sounds reasonable that an age-related decline in lysosome activity may also result in an accumulation of peroxisomes when cells age (Fransen et al. 2012). In this context, it is also interesting to note that a pharmacological inhibition of autophagy raises the percentage of peroxisomes with an abnormally high redox state over time (Ivashchenko et al. 2011). In summary, these findings strongly indicate that cellular aging is likely to have a major impact on peroxisomal lipid and ROS metabolism.

At the moment, it is difficult to provide a definitive assessment of how alterations in peroxisomal pro- and antioxidant enzyme activities may influence the cellular aging process. However, in the light of the available evidence, the self-sustaining peroxisome deterioration spiral model is currently most likely the best working hypothesis (Terlecky et al. 2006). This model places catalase, the most abundant and efficient H_2O_2 -metabolizing enzyme, in the centre of an aging spiral and is mainly based on two observations. Firstly, chronically reducing peroxisomal catalase activity induces multiple characteristics of cellular aging, including elevated H_2O_2 -associated ROS levels, oxidative protein and DNA damage, the up-regulation of matrix metalloproteases secretion, a slow-down of cell proliferation, and mitochondrial impairment (Wood et al. 2006). Secondly, (extracellular) H_2O_2 causes Pex5p, the import receptor for peroxisomal matrix proteins containing a C-terminal peroxisomal targeting signal (PTS1), to amass on the organelle thereby reducing PTS1 protein import (Legakis et al. 2002). As such, a decrease in peroxisomal catalase activity may result in increased cellular concentrations of H_2O_2 , and this may in turn further decrease the efficiency of peroxisomal matrix protein import and result in a self-perpetuating negative spiral. Indeed, as catalase contains a weak PTS1 that interacts poorly with Pex5p, this enzyme will most likely be particularly affected (Legakis et al. 2002). Importantly, the potential validity of this hypothesis has more recently been reinforced by studies showing that catalase-SKL, a molecule which contains a high affinity binding signal for Pex5p, delays the appearance of senescence markers in aging cells (Koepke et al. 2008).

Catalase is known to be one of the most efficient biocatalysts in our cells. Despite this, it has been shown that the enzyme can not completely prevent H_2O_2 release from intact peroxisomes (Mueller et al. 2002). This release most likely occurs through a porin-like channel (Rokka et al. 2009). As H_2O_2 , depending on the cell type and its concentration, can have both positive (signaling) and negative (damaging) effects (Veal et al. 2007), it has been postulated that peroxisomal ROS production can play a dual role in determining cell fate: at low levels, peroxisomal ROS may mediate the communication between peroxisomes and other cell compartments and govern anti-aging processes; above a certain threshold, peroxisomal ROS may trigger diverse signaling cascades involved in cell proliferation and apoptosis or even act as a DNA damaging agent (Titorenko and Terlecky 2011). In this context, it is interesting to note that several studies have shown that catalase-overexpressing cells (or animals) are more sensitive to certain types of stressors compared to control cells (or animals) (Chen et al. 2004;

Carter et al. 2004). These findings indicate that high levels of catalase activity can dampen H₂O₂-mediated signaling pathways.

3.2.3 The Peroxisome-Mitochondria Connection

Peroxisomes closely cooperate with mitochondria to fulfill their physiological functions (see Chapter 1). The best-known example is perhaps the oxidative metabolism of specific fatty acids, which are initially processed in peroxisomes and then trafficked to mitochondria where their catabolism is completed (Van Veldhoven 2010). Further evidence that peroxisomes and mitochondria are metabolically linked can be (indirectly) inferred from the observations that both organelles share a redox-sensitive relationship (for more details, see next paragraph) and are linked by division (Islinger et al. 2012). The latter finding reflects the view that the sharing of division proteins may allow the cell to strictly coordinate the number and morphology (and thus activity) of both organelles (Islinger et al. 2012). Finally, peroxisomes and mitochondria have also been reported to cooperate in anti-viral signaling and defense (Dixit et al. 2010).

It is already known for a long time that mitochondrial size, shape, number and functionality is aberrant in human patients and mice with peroxisome biogenesis disorders (Goldfischer et al. 1973; Baes et al. 1997). Although the molecular mechanisms underlying these changes remain unclear, there is considerable evidence that a disturbance in peroxisomal redox homeostasis may affect mitochondrial redox balance, structure and function. For example, it has been shown that brain mitochondria exhibit a decreased respiratory capacity in a catalase-deficient mouse model (Ho et al. 2004). In the meantime, this finding has been indirectly confirmed and extended by others who have shown that a complete or even partial inhibition of catalase activity in intact cells rapidly impairs the mitochondrial redox state, inner membrane potential, and function (Koepke et al. 2008; Ivashchenko et al. 2011; Walton and Pizzitelli 2012; Hwang et al. 2012). In addition, there are data showing that the inner mitochondrial membrane potential is affected in peroxisome-deficient mouse hepatocytes (Dirkx et al. 2005), and that the mitochondrial redox balance is perturbed in peroxisome-deficient fibroblasts (Fransen M. and Apanasets O., unpublished data) and upon generation of excess ROS inside peroxisomes (Ivashchenko et al. 2011). In summary, these findings – among others – suggest that a disturbance in peroxisome function may trigger signaling events that ultimately result in increased mitochondrial stress.

An intriguing question is how peroxisomes and mitochondria can communicate with each other. Potential mechanisms include (i) anaplerotic metabolism, (ii) diffusion of ROS, (iii) transport by vesicular carriers, and (iv) direct physical connections. Regarding the first possibility, one can envisage that – as peroxisomal metabolism slows down – critical metabolic intermediates are not properly produced and trafficked to mitochondria. This in turn may affect mitochondrial metabolism and result in an increase in uncoupled reactions and ROS production (Titorenko and Terlecky 2011). Concerning the second possibility, we have indications that the type of ROS generated inside peroxisomes can differ from the type of ROS causing oxidative stress inside mitochondria (Wang B. and Fransen M., unpublished data). This finding suggests that, at least under the conditions employed, a simple diffusion of ROS from peroxisomes through the cytosol to mitochondria is unlikely. As to the third possibility, it should be noted that – although there is evidence for the existence of a vesicular transport pathway from mitochondria to peroxisomes (Neuspiel et al. 2008) – no data currently exist for such a pathway in the opposite direction. Finally, regarding the last possibility, it is of relevance to point out that a recent confocal microscopy study has visualized a mitochondrial-associated membrane (MAM) that physically connects peroxisomes to mitochondria (Horner et al. 2011). Whether or not these contact sites provide an axis through which stress stimuli and metabolites are transmitted from peroxisomes to mitochondria remains to be investigated.

3.3 Peroxisomes and Age-Related Diseases

Until about a decade ago, defects in peroxisome function were virtually solely linked with severe congenital neurodevelopmental disorders. Since then, many things have changed, and – from an experimental point of view – there is now abundant evidence for the involvement of these organelles in the etiology and progression of aging and age-related diseases (Fransen et al. 2012). Indeed, as already pointed out above, peroxisomes play an indispensable role in cellular lipid and ROS metabolism, and alterations in these processes have been associated with an age-related decline in cellular, tissue, and organismal function. In this context, it is interesting to note that cellular senescence, a process that can be delayed by restoring the peroxisomal redox balance (see above), has recently been causally implicated in generating age-related phenotypes (Baker et al. 2011). The observation that a compromised catalase activity can be directly correlated with the early onset of some age-related human pathologies, such as psoriasis, hypertension, schizophrenia, type 2-diabetes and cancer (Góth et al. 2004), is in line with these findings. In the following sections, we will focus on the potential role of peroxisomal (dys)function in the age-related pathogenesis of neurodegeneration, cancer, and diabetes (Fig. 3.3).

3.3.1 Peroxisomes and Neurodegenerative Diseases

Plasmalogens and DHA represent essential constituents of neuronal myelin sheaths, which surround and protect nerve fibers. As (i) the synthesis of plasmalogens is critically dependent on peroxisomes, and (ii) the levels of these lipids fall during aging, it is tempting to speculate that alterations in peroxisomal metabolism contribute to the development of neurodegenerative diseases (Lizard et al. 2012). One of the strongest indirect arguments in favor of this hypothesis is that most peroxisomal disorders cause severe neurological dysfunction due to myelin abnormalities, neuronal migration defects, neuroinflammatory reactions, and axonal damage (Wanders and Waterham 2006; Bottelberghs et al. 2012).

One of the proposed causative factors for axonal degeneration in conditions of peroxisome deficiency is oxidative stress. This assumption is mainly based on the observations that (i) excessive levels of oxidative stress can be observed in the spinal cord of a mouse model of X-linked adrenoleukodystrophy (X-ALD; this is the most common single-enzyme defect of the peroxisomal disorders), even long before disease onset (Fourcade et al. 2008), (ii) an *in vivo* antioxidant treatment of these animals prevents oxidation of proteins, axonal damage, and motor disability (López-Erauskin et al. 2011), and (iii) a complete inactivation of peroxisome function in the brain of Nestin-Cre/Pex13-LoxP mice leads to mitochondria-mediated oxidative stress, neuronal cell death, and impairment of cerebellar development (Müller et al. 2011). However, another study which employed Nestin-Cre/Pex5-LoxP mice could not confirm the role of oxidative stress in neuronal degeneration caused by peroxisome inactivation (Bottelberghs et al. 2012). The reasons for these apparently conflicting data remain unclear.

Another causative factor for axonal degeneration may be neuroinflammation. This postulate is mainly based on the observation that the absence of functional peroxisomes in oligodendrocytes causes a strong proinflammatory environment and the infiltration of B and activated CD8⁺ T cells into brain lesions (Kassmann et al. 2007). In this context, it should be noted that peroxisomal β -oxidation is also involved in the breakdown of eicosanoids, a class of bioactive lipid mediators that can elicit a broad range of inflammatory reactions (Van Veldhoven 2010; Terlecky et al. 2012). As (i) a decrease in peroxisomal β -oxidation may lead to an accumulation of VLCFAs (Van Veldhoven 2010), (ii) high concentrations of VLCFAs can stimulate the expression of inflammatory mediators (Singh et al. 2009), and (iii) such molecules are also reported to downregulate peroxisome function (Paintlia et al. 2008), this may eventually result in the activation of a self-perpetuating inflammatory cascade.

Over the years, a vast array of age-related diseases has been associated with changes in lipid metabolism, a disturbance of ROS homeostasis, and chronic neuroinflammation. Somewhat surprisingly, despite the fact that peroxisomes play a critical role in all these processes, the potential involvement of this organelle in the initiation and progression of neurodegenerative disorders has been overlooked for a long time. In the following three paragraphs, we will discuss the data currently available for the potential involvement of peroxisomes in Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis.

Alzheimer's disease (AD) is one of the most common neurological disorders affecting the elderly. It is characterized by progressive impairments in memory and cognition, synaptic loss, and the presence of intracellular neurofibrillary tangles (NFTs) and extracellular neuritic plaques containing, respectively, hyperphosphorylated tau proteins and the amyloid- β peptide (A β) (Lizard et al. 2012). Another hallmark of AD is mitochondrial dysfunction (Schon and Przedborski 2011). A β has been shown to progressively accumulate in mitochondria of brains from AD patients, and – as this is thought to result in a faulty mitochondrial energy metabolism – this may increase mitochondrial ROS production and lead to cellular oxidative stress. Interestingly, on one hand, it has been reported that peroxisome proliferation protects hippocampal neurons from A β -induced oxidative stress, neurotoxicity, and cell death (Santos et al. 2005). However, on the other hand, there is also evidence that peroxisomes represent a cellular target for A β . This is illustrated by the observation that A β -induced ROS production lowers the activity levels of alkylglycerone phosphate synthase (AGPS), a peroxisomal enzyme required for plasmalogen synthesis (Grimm et al. 2011). Intriguingly, a recent longitudinal community-based cohort study focusing on peroxisomes in well-defined autopsy material also revealed substantial peroxisome-related changes in AD brains (Kou et al. 2011). Specifically, this study showed that (i) AD brains contain a marked reduction in plasmalogen content and a significant increase in VLCFA (C22:0, C24:0, and C26:0) levels, and (ii) at advanced AD stages, peroxisomal volume density is strongly increased and decreased, respectively, in the somata and neurites of neurons in gyrus frontalis. Note that, although the plasmalogen data are in concordance with the findings reported by Grimm et al. (2011), it remains to be investigated whether the observed increase in VLCFA content is due to reduced peroxisomal β -oxidation or enhanced fatty acid elongation (Kou et al. 2011). In addition, as it has already been shown that overexpression of Tau inhibits the kinesin-dependent transport of peroxisomes into neurites (Stamer et al. 2002), the increase in somatic peroxisome density most likely results from abnormally phosphorylated Tau impairing peroxisome trafficking.

Parkinson's disease is a degenerative disorder of the central nervous system which is characterized by the presence of α -synuclein (α S) protein inclusions in the brain and an ongoing loss of dopaminergic neurons in the substantia nigra. Although the etiology and pathogenesis of PD are still elusive, a large body of evidence suggests a prominent role of oxidative stress, inflammation, and mitochondrial dysfunction (Chaturvedi and Beal 2008). Interestingly, it has also been reported that neurons and glia of X-ALD and PBD patients contain increased depositions of α S (Suzuki et al. 2007; Yakunin et al. 2010). In addition, these α S abnormalities are not due to induced oxidative stress and do not correlate with mitochondrial dysfunction; however, they associate with elevated levels of n-6 polyunsaturated fatty acids (PUFAs), a condition associated with PBD mouse models (Yakunin et al. 2010). These findings are in line with other studies showing that peroxisome proliferation abrogates α S toxicity leading to PD (Chaturvedi and Beal 2008).

Amyotrophic lateral sclerosis (ALS) is one of the most common neuromuscular diseases worldwide. The disease is characterized by progressive motor neuron degeneration, skeletal muscle atrophy, paralysis, and death from respiratory failure (Mitchell et al. 2010). The precise molecular mechanisms underlying motor neuron loss remain uncertain. However, several etiological hypotheses have been proposed, including mitochondrial dysfunction and motoneuronal vulnerability to excitotoxicity (Higgins et al. 2003; Sasabe et al. 2012).

Interestingly, approximately 5% of all ALS cases have a family history of ALS (familial ALS; FALS), and two ALS-linked genes have been directly or indirectly linked to peroxisomal dysfunction (Higgins et al. 2003; Mitchell et al. 2010). One of these genes encodes SOD1, an antioxidant enzyme that catalyzes the conversion of $O_2^{\cdot -}$ into O_2 and H_2O_2 and has been found in different cell compartments, including peroxisomes (Islinger et al. 2009). Approximately 20% of all FALS cases are caused by mutations in SOD1. SOD1_{G93A}, the most intensely studied mutant form of SOD1, has been shown to cause mitochondrial vacuolation by expansion of the intermembrane space (Higgins et al. 2003). The same study also reported that peroxisomes actively migrate to or proliferate in the vicinity of abnormal mitochondria and participate in the vacuolation process. Unfortunately, the exact function of these organelles in mitochondrial vacuolation remains to be fully determined. The second ALS-linked gene encodes D-amino acid oxidase (DAO), an exclusively peroxisomal flavoprotein that catalyzes the oxidative deamination of neutral and polar D-amino acids into the corresponding α -keto acids, ammonia, and H_2O_2 . Approximately 0.3% of FALS cases have been shown to be associated with a rare mutation (R199W) in the gene coding for human DAO (Mitchell et al. 2010). This mutation causes almost total loss of enzyme activity, and cell lines expressing DAO_{R199W} show decreased viability and increased levels of ubiquitinated aggregates compared with cells expressing the wild-type protein (Mitchell et al. 2010). Finally, the importance of dysfunctional DAO in FALS has been unequivocally established by studies in DAO knockout mice, which clearly show that loss of DAO activity triggers motor neuron degeneration (Sasabe et al. 2012).

3.3.2 Peroxisomes and Cancer

Over the years, mounting evidence has been collected that peroxisomes are involved, either directly or indirectly, in cancer cell metabolism (see Chapter 5). A classic example is the observation that a prolonged treatment of rodents with peroxisome proliferators causes hepatocellular carcinomas (Reddy et al. 1980). Along the same lines, it has been reported that mice lacking ACOX1, a peroxisomal enzyme which is associated with the degradation of putative endogenous ligands of peroxisome proliferator activated receptor- α (PPAR α), develop hepatic adenomas and carcinomas (Fan et al. 1998). Another line of evidence is that the activity of catalase, the most abundant protein in mammalian peroxisomes, has been inversely associated with cancer. Indeed, it has been shown that (i) the activity of catalase is strongly decreased in breast, colon, liver, and skin cancers (Lauer et al. 1999; Frederiks et al. 2010; Seyed and Mukhtar, 2012), (ii) hypocatalasemic mice, with approximately ten-fold less catalase than normal mice, display a higher susceptibility to spontaneous and induced tumorigenesis (Ishii et al. 1996), and (iii) women with a higher catalase activity appear to have a reduced risk of breast cancer and non-melanoma skin cancers (Ahn et al. 2005; Seyed and Mukhtar 2012). As a last example, we would like to mention the selective upregulation of peroxisomal branched chain fatty acid β -oxidation in prostate cancers (Zha et al. 2005). Importantly, this finding suggests that a disturbed peroxisomal β -oxidation may elicit metabolic features that would give unique metabolic advantage for prostate transformation (Zha et al. 2005).

The exact mechanisms of how peroxisomal enzymes are up- or downregulated in cancer cells are not yet well understood. One factor that may account for at least some of these changes is tumor necrosis factor- α (TNF- α), a pleiotropic inflammatory cytokine that – among other functions – has been shown to downregulate PPAR- α and the mRNAs encoding peroxisomal proteins (Beier et al. 1997). In addition, it is also unknown how a disturbance in peroxisomal metabolism may promote tumor formation. Our leading hypothesis is that alterations in peroxisomal redox metabolism may cause severe imbalances in the cellular redox proteome (see below).

3.3.3 Peroxisomes and Type 2-Diabetes

Type 2-diabetes is a complex age-related metabolic disorder with a continuously growing prevalence worldwide. The disease is characterized by progressive β -cell failure and peripheral insulin resistance. Long-term complications of diabetes include – among others – retinopathy, nephropathy, neuropathy, and cardiomyopathy. Mounting evidence has strengthened the view that oxidative stress may function as the primary component of diabetes pathology. One potential explanation may be that pancreatic β -cells are particularly susceptible to oxidative damage (Lenzen et al. 1996). This is most likely due to the fact that these cells contain virtually no catalase, since the catalase gene is – together with a handful of other genes – tissue-specifically repressed in islets of Langerhans (Thorrez et al. 2011).

It is already known for some time that elevated levels of long-chain and very-long-chain saturated non-esterified fatty acids (NEFA) exhibit a strong cytotoxic effect on insulin-producing β -cells (Poitout and Robertson 2002). Recently, it has been shown that this cytotoxic effect is mediated by H_2O_2 derived from peroxisomal β -oxidation, and that overexpression of catalase in the peroxisomes and the cytosol – but not in the mitochondria – can protect the cells against palmitic acid-induced toxicity (Elsner et al. 2011). Others have shown β -cell protection upon exposure to peroxisome proliferators (Hellemans et al. 2007). On the other hand, it has also been reported that catalase overexpression in pancreatic β -cells sensitizes non-obese diabetic mice to autoimmune diabetes and islet cell death (Li et al. 2006). Combined, these findings suggest that a tight regulation of peroxisomal redox metabolism is crucial for pancreatic β -cell function and viability.

The importance of peroxisomes for diabetes progression was recently further exemplified by a study with catalase-knockout mice (Hwang et al. 2012). This study showed that catalase plays an important role in protecting the kidney from NEFA-induced diabetic stress through maintaining peroxisomal and mitochondrial fitness. Finally, it should be noted that both insulin action and islet inflammation have been reported to have a negative impact on peroxisome function: insulin inhibits peroxisomal fatty acid β -oxidation by a yet unclear mechanism requiring insulin degrading enzyme, a protein found in multiple cell compartments, including peroxisomes (Hamel et al. 2001); and the onset of insulinitis results in a significantly reduced activity of glyceronephosphate O-acyltransferase (GNPAT) (Lindfors et al. 2009), a peroxisomal enzyme required for plasmalogen synthesis.

3.4. Open Questions and Perspectives

As reviewed here, a growing body of evidence links peroxisomal dysfunction to aging and age-related diseases. Peroxisomes are intimately involved in cellular lipid and ROS metabolism, and alterations in these processes have been invoked in diverse complex diseases such as AD, PD, ALS, type 2-diabetes, and cancer. However, as peroxisomal metabolism both influences and is influenced by the aging process, it is speculative to what extent these organelles are the causal factor for disease initiation and progression. Nevertheless, despite the multifaceted nature of this bidirectional crosstalk, there is now sufficient information available to warrant the conclusion that peroxisomal metabolism and cellular aging are closely intertwined.

There is still a large gap in our understanding of how peroxisomes contribute to stress responses and metabolic signaling pathways that regulate the aging process. A hypothesis gaining prominence is that low concentrations of peroxisomal ROS can exert important physiological roles in cellular signaling and proliferation (= concept of 'peroxihormesis'), and that a disturbance of peroxisomal redox homeostasis may trigger signaling/communication events that ultimately result in increased mitochondrial stress and the activation of mitochondrial stress pathways (= the peroxisome/mitochondria axis of aging) (Titorenko et al. 2011; Ivashchenko et al. 2011). Experimental evidence in line with the concept of

peroxihormesis includes the observations that (i) inhibition of catalase activity by 3-aminotriazole increases the cellular protein disulfide content by 20% (Yang et al. 2007), (ii) the intracellular localization and activity of many proteins (e.g. kinases, phosphatases, transcription factors, ...) are reversibly controlled by the oxidation status of redox-sensitive cysteine residues (Hekimi et al. 2011), and (iii) peroxisomal H₂O₂ can function as an important modulator of NFκB1, a pleiotropic transcription factor involved in many biological processes, including cell growth and differentiation, inflammation, tumorigenesis, and apoptosis (Li et al. 2000). Unfortunately, virtually nothing else is known about how peroxisomal ROS may effect the cellular redox proteome, neither in physiological nor in pathological conditions. In addition, albeit it is clear that peroxisomes and mitochondria share a redox-sensitive relationship, it is not known how these organelles communicate with each other. Nevertheless, the idea that peroxisomes may act as upstream initiators of mitochondrial ROS signaling pathways may change much of the way we think about aging and how to manipulate it.

A challenging question is whether peroxisomes represent an interesting therapeutic target to mitigate or even stop age-related neurodegenerative diseases. In this context, it is interesting to note that it has been reported that substances able to activate PPAR-α and/or induce peroxisome proliferation may constitute attractive therapeutic tools against neurodegenerative diseases, such as AD and PD (Santos et al. 2005; Mutez et al. 2009; Cimini et al. 2009). However, as many of these compounds also induce non-peroxisomal responses, it is not always clear whether or not clinical improvements are related to an increase in peroxisomal metabolism.

In summary, this review discusses the potential role of peroxisomes in aging and age-related diseases. From all these data, it is clear that peroxisomes can act as a redox signaling platform. However, as the proximal targets of peroxisomal ROS and the signaling pathways that drive mitochondrial degeneration are not yet known, further work is needed to elucidate the mechanisms of how these organelles are incorporated into (intra)cellular communication networks. This in turn is essential to gain a better insight into the importance of peroxisomes in the pathogenesis of age-related diseases.

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Abbreviations

α S, α -synuclein; A β , amyloid- β peptide; ACOX1, acyl-CoA oxidase 1; AD, Alzheimer's disease; AGPS, alkylglycerone phosphate synthase; AOX, antioxidants; CAT, catalase; DAO, D-amino acid oxidase; DHA, docosahexaenoic acid; ER, endoplasmic reticulum; (F)ALS, (familial) amyotrophic lateral sclerosis; GNPAT, glyceronephosphate O-acyltransferase; MAM, mitochondrial-associated membrane; NEFAs, non-esterified fatty acids; NFTs, neurofibrillary tangles; PBDs, peroxisome biogenesis disorders; PD, Parkinson's disease; PPAR- α , peroxisome proliferator activated receptor-alpha; PRDX5, peroxiredoxin 5; PTS1, C-terminal peroxisomal targeting signal; PUFAs, polyunsaturated fatty acids; RNS, reactive oxygen species; ROS, reactive oxygen species; SOD1, Cu/Zn superoxide dismutase; TNF- α , tumor necrosis factor-alpha; UPR, unfolded protein response; VLCFAs, very-long-chain fatty acids; X-ALD, X-linked adrenoleukodystrophy.

Legends to figures

Fig. 3.1 Aging and organelle dysfunction. AOX, antioxidants; ER, endoplasmic reticulum; LY, lysosomes; MT, mitochondria; NU, nucleus; PO, peroxisomes; ROS, reactive oxygen species; UPR, unfolded protein response. See text for details.

Fig. 3.2 Peroxisomes and cellular aging. AOX, antioxidants; DAO, D-amino acid oxidase; NOS2, inducible nitric oxide synthase; PO, peroxisomes; PRDX5, peroxiredoxin 5; PXMP2, porin-like peroxisomal membrane protein; RNA, reactive nitrogen species; ROS, reactive oxygen species; SOD1, Cu/Zn superoxide dismutase; VLCFAs, very-long-chain fatty acids; XDH, xanthine dehydrogenase. See text for details.

Fig. 3.3 Peroxisomes and age-related diseases. α S, α -synuclein; A β , amyloid- β peptide; AD, Alzheimer's disease; AGPS, alkylglycerone phosphate synthase; DAO, D-amino acid oxidase; FALS, familial amyotrophic lateral sclerosis; GNPAT, glyceronephosphate O-acyltransferase; PD, Parkinson's disease; PUFAs, polyunsaturated fatty acids; ROS, reactive oxygen species; SOD1, Cu/Zn superoxide dismutase; VLCFAs, very-long-chain fatty acids. See text for details.

Fig. 1

Fig. 2

Fig. 3