The impact of peroxisomes on cellular aging and death

Selvambigai Manivannan†, Christian Quintus Scheckhuber†, Marten Veenhuis and Ida Johanna van der Klei *

Molecular Cell Biology, Groningen Biomolecular Sciences and Biotechnology Institute, Kluyver Centre for Genomics of Industrial Fermentation, University of Groningen, Groningen, Netherlands

INTRODUCTION

The production and accumulation of reactive oxygen species (ROS) is a profound stress factor in living cells due to the fact that ROS can oxidize and therefore damage vital macromolecules such as nucleic acids, proteins, and lipids. Intracellular accumulation of these damaged components leads to aging – a process defined as the deterioration of cells in time which is accompanied by gradual loss of cell viability. Until recently, mitochondria were considered as the main players in ROS production and hence in aging of eukaryotic cells. However, recent reports proposed that peroxisomes also produce significant amounts of ROS. Therefore, like mitochondrial dysfunction, peroxisomal dysfunction may also contribute to cell death and aging. The role of mitochondria in cell death pathways such as apoptosis and necrosis is well established. However, the importance of peroxisomes in these processes is much less understood. In this contribution we summarize findings on the role of peroxisomes in aging and cell death processes. We focus on data obtained in yeast and discuss the relevance of these findings for higher eukaryotes including man.

PEROXISOMES: STRUCTURE AND FUNCTION

Peroxisomes are ubiquitous eukaryotic organelles, which perform a plethora of functions including hydrogen peroxide metabolism and β-oxidation of fatty acids. Reactive oxygen species produced by peroxisomes are a major contributing factor to cellular oxidative stress, which is supposed to significantly accelerate aging and cell death according to the free radical theory of aging. However, relative to mitochondria, the role of the other oxidative organelles, the peroxisomes, in these degenerative pathways has not been extensively investigated. In this contribution we discuss our current knowledge on the role of peroxisomes in aging and cell death, with focus on studies performed in yeast.

Keywords: aging, autophagy, cell death, peroxisome, yeast

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*Correspondence: Ida Johanna van der Klei, Molecular Cell Biology, Groningen Biomolecular Sciences and Biotechnology Institute, Kluyver Centre for Genomics of Industrial Fermentation, University of Groningen, Groningen, Netherlands
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†Selvambigai Manivannan and Christian Quintus Scheckhuber have contributed equally to this work.
chronological aging in baker’s yeast (Palermo et al., 2007). These beneficial effects might be based on improved content mixing of mitochondria so that molecular damage to proteins, lipids, and mtDNA can be ameliorated more efficiently. However, it has to be stressed that the effect of DNM1 deletion on peroxisome fission was not investigated in these studies. Hence, the observed effects may also be partially due to defects in peroxisomal fission.

Several data suggest that peroxisomes divide asymmetrically, resulting in larger mature organelles and small, nascent ones (Koch et al., 2003, 2010; Cepinska et al., 2011; Huber et al., 2012). As a consequence cells contain a heterologous population of peroxisomes, ranging from relatively young and vital nascent organelles to relatively old, mature ones, in which dysfunctional components accumulate in time due to damage caused by products of peroxisomal metabolism.

In addition to fission, peroxisomes can also be formed de novo, a process that is most prominent in yeast pex3 or pex mutants that lack pre-existing peroxisomes, upon reintroduction of the corresponding genes. Several data suggested that these new organelles originate from the endoplasmic reticulum (ER; Hoepfner et al., 2005; Zipor et al., 2009).

Data in yeast, data in yeast indicate that the major pathway of peroxisome proliferation is fission. However, possibly in other species the formation of peroxisomes from the ER is a more prominent process (Geuze et al., 2003; Tabak et al., 2003; Kim et al., 2006; Yonekawa et al., 2011).

Autophagy can result in a reduction in the number of peroxisomes per cell. Autophagy is the pivotal cellular housekeeping process that can eliminate redundant or unwanted components or entire organelles from the cell. Selective degradation of peroxisomes by autophagy is designated “pexophagy,” a phenomenon mainly studied in the methylotrophic yeast species H. polymorpha and Pichia pastoris.

In H. polymorpha, macropexophagy is induced when methanol-grown cells are shifted to glucose (Figure 1). Under these conditions, the key peroxisomal enzymes of methanol metabolism become redundant for growth. The surplus in organelles is then selectively degraded by macropexophagy (Monastyrskaya et al., 2004), a process that involves sequestration of individual peroxisomes from the cytosol and subsequent fusion with the vacuole for degradation (Veenhuis et al., 1983).

When methanol-grown cells of P. pastoris are shifted to glucose, peroxisomes are degraded by micropexophagy, which involves the formation of finger-like protrusions by the vacuole and subsequent engulfment of clusters of peroxisomes from the cytosol with ultimate degradation in the vacuole. Before this takes place, a double membrane flattened sac-like structure termed micropexophagy-specific membrane apparatus (MIPA) is synthesized at the peroxisome surface to complete the sequestration process (Tuttle and Dunn, 1995; Mukaiyama et al., 2004).

In addition, data obtained with H. polymorpha revealed a constant removal of peroxisomes by autophagy (Aksam et al., 2007). This process most likely prevents the accumulation of damaged peroxisomal components, which would be potentially hazardous for the cells. Hence, at peroxisome-inducing conditions, organelle proliferation and degradation occur simultaneously to maintain
tightly controlled organelle homeostasis. This mechanism is consistent with the view that timely rejuvenation of peroxisomes is vital for cell viability and survival. Most likely the oldest, mature organelles are most susceptible for autophagic degradation. A central question that offers interesting perspectives for future research is how these peroxisomes are recognized by the pexophagy machinery. The peroxisomal membrane proteins Pex3p and Pex14p have been shown to play a role in the early stage of pexophagy (Bellu et al., 2001, 2002; van Zutphen et al., 2008) and may play a role in this recognition process. Indeed Pex3p was shown to interact with Atg30p, a phosphoprotein that is necessary for the presentation of the compromised peroxisome to the vacuole for its subsequent degradation (Farre et al., 2008).

PEROXISOMAL DAMAGE AND REPAIR MECHANISMS
PEROXISOMAL ROS AND ANTIOXIDANT ENZYMES
Peroxisomes counteract the compromising effects of ROS by antioxidant enzymes. Among these are peroxisomal catalase, glutathione peroxidase, peroxiredoxin I and Pmp20p to degrade hydrogen peroxide and CuZnSOD and MnSOD to detoxify superoxide anions (Bonekamp et al., 2009).

Saccharomyces cerevisiae contains two catalases, namely peroxisomal Cta1p and cytosolic Ctt1p. Unexpectedly, inactivation of both catalases in this yeast was shown to result in an increase of the chronological lifespan (Mesquita et al., 2010). This surprising finding could be explained by the activation of superoxide dismutases by the elevated hydrogen peroxide levels. In this view elevated levels of hydrogen peroxide in catalase-deficient cells cells prolong chronological lifespan.

However, earlier studies indicated that deletion of the gene encoding the peroxisomal catalase in S. cerevisiae resulted in a shortened lifespan (Petriv and Rachubinski, 2004). These seemingly contradictory results may be possibly related to differences in the experimental procedures to determine the chronological lifespan (i.e., use of different cultivation conditions such as media composition and growth temperatures; Mesquita et al., 2010; SC medium, 26˚C; Petriv and Rachubinski, 2004; YNBD medium, 30˚C). The same authors also reported that in Caenorhabditis elegans the deletion of peroxisomal catalase (Ct-2) in the genetic background of the long lived clk-1 mutant shortens the maximum lifespan as well. The shortened lifespan was accompanied by altered peroxisome morphology that might point to compromised peroxisomal function with increased production of ROS (Petriv and Rachubinski, 2004).

Similar to catalase, the peroxisomal peroxidoredoxin Pmp20p is also involved in degradation of H₂O₂. Peroxiredoxins are thiol-specific evolutionary conserved antioxidant enzymes. In addition to H₂O₂ breakdown they are also involved in degradation of organic hydroperoxides (ROOH) and therefore important for maintaining the integrity of lipid membranes (Yamashita et al., 1999).

Studies in the methylotrophic yeasts H. polymorpha and C. boidinii demonstrated that Pmp20p is important for cell viability during growth on methanol due to its capability to repair ROS generated damages (i.e., lipid peroxidation) at the peroxisomal membrane surface (Horiguchi et al., 2001; Aksam et al., 2007). In the fission yeast Schizosaccharomyces pombe it was shown that Pmp20p (in addition to thioredoxin peroxidase and glutathione peroxidase) inhibited thermal aggregation of citrate synthase at a high temperature (43˚C) in vitro. This suggests that at least in S. pombe peroxisomal Pmp20p may have a second function as a molecular chaperone which could be important for organelle quality control (Kim et al., 2010).

In man catalase gene mutations have been identified and linked to detrimental conditions like diabetes, hypertension, macular degeneration, cataracts, cancer, and skin pigmentation disorders (Goth et al., 2004). A severe decrease of catalase activity is found in clinical cases of hypo- or acatalasemia and has been predominantly identified in Japan and certain European countries (e.g., Hungary, Switzerland). Clinical symptoms are severe (among them hemolytic anemia), illustrating the importance of functional catalase for health. Re-direction of functional catalase to peroxisomes in catalase-deficient cell lines led to increased detoxification of H₂O₂ and also restoration of cellular plasmalogen and fatty acid levels (Sheikh et al., 1998).

Reactive oxygen species are usually associated with their potent damaging capabilities but they are also involved in crucial cellular signaling processes. With regard to aging, low levels of ROS might induce a hormesis response which increases chances of cellular survival by up-regulating pathways dedicated to high-stress adaptation like the retrograde response (Jazwinski, 2012) and the target of rapamycin (TOR) and adenosine mono phosphate kinase (AMPK) pathways (Gems and Partridge, 2008). Although it is clear that mitochondria are supposedly the main players in this regard, it is likely that also peroxisomes integrate into the signaling network as important mediators of aging processes.

PEROXISOMAL LON PROTEASE
So far one conserved peroxisomal protease is known that plays a role in peroxisomal protein quality control, namely the peroxisomal Lon protease, Pln (Kikuchi et al., 2004; Aksam et al., 2007). Pln belongs to the ATPases associated with diverse cellular activities (AAA) protein family which is supposed to be involved in degradation of unfolded and non-assembled peroxisomal matrix proteins (Aksam et al., 2007; Ngo and Davies, 2007). Studies in H. polymorpha showed that the deletion of the gene encoding Pln leads to a pronounced decrease in cell viability accompanied by enhanced ROS production (Aksam et al., 2009). One possible explanation could be that the accumulation of unfolded proteins leads to the formation of protein aggregates, resulting in a disturbance of ROS homeostasis which ultimately leads to cell death. Indeed, electron dense aggregates are often observed in peroxisomes of H. polymorpha cells lacking Pln (Aksam et al., 2007). However, the precise molecular mechanism and interplay between protein aggregation, ROS production, and cell death still remains unclear and needs to be studied in more detail.

Several studies have investigated the function of Pln in mammalian cells after the identification of this enzyme in rat liver peroxisomes (Kikuchi et al., 2004). In mammals Pln also seems to play a role in peroxisomal matrix protein import as catalase import is compromised when Pln is overproduced (Omi et al., 2008).
THE ROLE OF PEROXISOMES IN YEAST AGING

Mechanistic insights into the role of peroxisomes in aging have been gained mainly from studies conducted in *S. cerevisiae*. When this yeast is grown in glucose rich media, neutral lipids (e.g., triacylglycerols) are produced in the ER and incorporated in lipid bodies (Olofsson et al., 2009). When these storage lipids need to be mobilized, peroxisomes and lipid bodies come into close contact to allow uptake of the neutral lipids for subsequent oxidation of the non-esterified fatty acids (free fatty acids; Binns et al., 2006). An intriguing model has been put forward linking life span determination and the synthesis and degradation of lipids in the ER, lipid bodies, and peroxisomes (Goldberg et al., 2009a,b; Titorenko and Terlecky, 2011). According to this model, repression of essential components of fatty acid β-oxidation by ethanol (produced as a side-product of glucose fermentation) leads to the accumulation of free fatty acids. This challenges the cell with detrimental effects, i.e., stimulation of necrotic cell death (Aksam et al., 2008; Jungwirth et al., 2008) and lipoapoptosis (shown in the fission yeast *S. pombe*; Low et al., 2005). Moreover, as a result of impaired β-oxidation in peroxisomes diacylglycerol accumulates in the ER and mediates the induction of protein kinase C-dependent signaling which ultimately affects cellular pathways involved in various stress responses (as demonstrated in the nematode *C. elegans*; Feng et al., 2007).

Peroxisomes and peroxisomal enzymes also play a vital role in the phenomenon of retrograde response (RTG) in baker’s yeast (Butow and Avadhani, 2004; Jazwinski, 2012). RTG is activated in yeast cells that are confronted with mitochondrial respiratory dysfunction. Interestingly, induction of RTG leads to an increased replicative lifespan (Kirchman et al., 1999). The more pronounced RTG induction leads to the induction of transcription of several nuclear genes that help to promote the survival of the cell despite mitochondrial dysfunction (Table 1). Genes encoding Cit1p, Aco1p, Idh1/2p (first enzymes of the citric acid cycle), Ald4p and Acs1p (enzymes for cytosolic biosynthesis of acetyl-CoA), Crc1p, Ctp1p, Dic1p, and Odc2p (membrane transporters for shuttling metabolites between mitochondria, peroxisomes, and the cytosol), and Pex11p, Pxa1p,

### Table 1 | Overview of genes mentioned in this article.

| Name of gene | *S. cerevisiae* | *H. polymorpha* | Mammals | Description of protein | Pathway |
|--------------|----------------|----------------|---------|-----------------------|---------|
| ACO1         | ++            | +              | +       | Aconitase             | Krebs cycle/RTG in *S. cerevisiae* |
| ACS1         | +             | +              | +       | Acetyl-CoA synthetase  | Acetate utilization/RTG in *S. cerevisiae* |
| ALD4         | +             | +              | +       | Aldehyde dehydrogenase | Glucose fermentation/RTG in *S. cerevisiae* |
| ATG30        | –             | +              | –       | Peroxisomal receptor  | Pexophagy |
| CIT1         | +             | +              | –       | Citrate synthase 1 (mito.) | Krebs cycle/RTG in *S. cerevisiae* |
| CIT2         | +             | –              | –       | Citrate synthase 2 (peroxi.) | RTG in *S. cerevisiae* |
| CRC1         | +             | +              | –       | Carnitine carrier     | Fatty acid metabolism/RTG in *S. cerevisiae* |
| CTA1         | +             | +              | +       | Peroxisomal catalase  | ROS detoxification |
| CTP1         | +             | +              | +       | Citrate transport protein | Mitochondr. transporter/RTG in *S. cerevisiae* |
| CTT1         | +             | –              | –       | Cytosolic catalase     | ROS detoxification |
| DIC1         | +             | +              | –       | Dicarboxylate carrier  | Mitochondr. transporter/RTG in *S. cerevisiae* |
| DNM1/Drp1    | +             | +              | +       | Dynamin-related protein (DRP) 1 | Mitochondrial/peroxisomal division |
| Ephx2        | +             | +              | +       | Epoxide hydrolase      | Detoxification of epoxides |
| FIS1/hFis1   | +             | +              | +       | Binding partner for DRP 1 | Mitochondrial/peroxisomal division |
| FOX1/2       | +             | +              | +       | Enzymes involved in β-oxidation of fatty acids | Fatty acid oxidation/RTG in *S. cerevisiae* |
| IDH1/2       | +             | +              | +       | Isocitrate dehydrogenase | Krebs cycle/RTG in *S. cerevisiae* |
| ODC2         | +             | +              | +       | Oxodicarboxylate carrier | Amino acid metabolism/RTG in *S. cerevisiae* |
| PEX3         | +             | +              | +       | Peroxisomal membrane protein | Peroxisome biogenesis/inheritance |
| PEX6         | +             | +              | +       | AAA-peroxin            | Recycling of peroxisomal signal receptor Pex5p |
| PEX11        | +             | +              | +       | Peroxisomal membrane protein | Peroxisome proliferation |
| PEX14        | +             | +              | +       | Peroxisomal membrane protein | Peroxisomal protein import |
| PLN          | –             | +              | +       | Peroxisomal LON protease | Protein degradation |
| PMP20        | –             | +              | +       | Peroxisomal peroxiredoxin | ROS detoxification |
| POT1/Acaa1a  | +             | +              | +       | 3-ketoacyl-thiolase     | Fatty acid oxidation/RTG in *S. cerevisiae* |
| PXA1         | +             | +              | +       | Peroxisomal ABC transporter | Fatty acid transport/RTG in *S. cerevisiae* |
| VPS1         | +             | +              | –       | Vacuolar protein sorting 1 | Vacuolar sorting/peroxisomal division (S. cerevisiae) |

+, homolog present; −, homolog not present; RTG, retrograde response.
Cit2p, Fox1p, Fox2p, Pot1p (peroxisomal proteins) belong to this group. Collectively, these (and further) proteins enable yeast cells to enhance oxidation of fatty acids and to synthesize essential metabolic intermediates of the Krebs cycle that otherwise would not be available.

THE ROLE OF PEROXISOMES IN AGING IN MAMMALS

In rat hepatocytes subject to conditions of hyperinsulinemia leads to an inhibition of β-oxidation and a concomitant acceleration of aging in these animals (Xu et al., 1995). Clearly, the activity of the peroxisomal marker enzyme catalase decreases by 30–40% in liver samples isolated from old mice and rats (Haining and Legan, 1973; Sensei et al., 1989; Perichon and Bourre, 1995, 1996; Xia et al., 1995). Decreased levels/activity of this H₂O₂-decomposing protein is contributing to the phenomenon of peroxisome senescence. This process leads to diminished regulation of organelle maturation and division, protein import and overall dysfunction (Legakis et al., 2002; Koepeke et al., 2008). A comparative study with the goal to identify differences between liver subproteomes from young and old mice revealed several up-regulated peroxisomal proteins. One of the up-regulated enzymes was epoxide hydrolase 2 (Ephx2), which detoxifies epoxides and converts these to excretable dihydrodiols (Amelina et al., 2011). This may constitute a counteracting mechanism in old animals. Another up-regulated enzyme, peroxisomal 3-ketoacyl-thiolase A [Acaa1a, Pot1p (Fox3p) in baker’s yeast] was epoxide hydrolase 2 (Ephx2), which detoxifies epoxides and converts these to excretable dihydrodiols (Amelina et al., 2011). This may constitute a counteracting mechanism in old animals. Another up-regulated enzyme, peroxisomal 3-ketoacyl-thiolase A [Acaa1a, Pot1p (Fox3p) in baker’s yeast], was correlated to another up-regulated enzyme, peroxisomal 3-ketoacyl-thiolase Aksam, E. B., Jungwirth, H., Kohlwein, S. D., Ring, J., Madeo, F., Veenhuis, M., and van der Klei, I. J. (2008). Absence of the peroxide-doxin Pmp20 causes peroxisomal protein leakage and necrotic cell death. Free Radic. Biol. Med. 45, 1115–1124.

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Cellular death has many different faces. Two of the most common ones, apoptosis and necrosis, have been studied in much detail over the past few years (Golstein and Kroemer, 2007; Taylor et al., 2008). Apoptosis is a ubiquitous mode of programmed cell death, strictly regulated and conserved in eukaryotes (Madeo et al., 2004). This highly organized process is manifested by condensation and cleavage of nuclear DNA, release of pro-apoptotic proteins from mitochondria and, at later stages, “blebbing” of the plasma membrane. Mitochondria are key factors when it comes to the execution of apoptosis. Necrosis, on the other hand, is accompanied by rupture of organelles and the plasma membrane. Recent evidence demonstrates that necrosis can be also tightly controlled, similar to apoptosis (Golstein and Kroemer, 2007). Peroxisomes are involved in regulation of necrosis. For example, S. cerevisiae PEX6 deletion cells display hallmarks of necrosis and strongly elevated formation of ROS (Jungwirth et al., 2008). Moreover, in the methylotrophic yeast H. polymorpha deletion of PMP20 leads to pronounced induction of necrosis when the cells are grown on methanol-containing medium (Aksam et al., 2008). Interestingly, matrix proteins of the peroxisomes were found to be leaking into the cytosol of PMP20 deletion cells during necrosis. This is reminiscent of protein release by mitochondria during apoptosis and constitutes an interesting parallel between mitochondria and apoptosis on the one hand and peroxisomes and necrosis on the other hand (Eisenberg et al., 2010).

PERSPECTIVES

Research on the role peroxisomes play during cellular degeneration is supposed to unravel exciting new mechanisms and will likely integrate these fascinating organelles into the network of cellular pathways mediating aging. Some of the interesting lines of research that will yield promising insights into the role of peroxisomes might comprise (i) identification and characterization of a peroxisomal unfolded protein response (UPR) as a mechanism to signal organelle dysfunction (and subsequent degradation), (ii) studying selective inheritance of peroxisomes during replicative aging so that the daughter cells receive “healthy” peroxisomes (Cepinska et al., 2011), and (iii) investigating the role of de novo formation of peroxisomes vs. fission in maintaining a functional peroxisomal population during chronological and replicative aging.

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