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Mini Review

Redox regulated peroxisome homeostasis

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ABSTRACT

Peroxisomes are ubiquitous organelles present in nearly all eukaryotic cells. Conserved functions of peroxisomes encompass beta-oxidation of fatty acids and scavenging of reactive oxygen species generated from diverse peroxisomal metabolic pathways. Peroxisome content, number, and size can change quickly in response to environmental and/or developmental cues. To achieve efficient peroxisome homeostasis, peroxisome biogenesis and degradation must be orchestrated. We review the current knowledge on redox regulated peroxisome biogenesis and degradation with an emphasis on yeasts and plants.

Contents

Introduction

Peroxisomes are multifunctional organelles harboring at least two conserved metabolic pathways: fatty acid beta-oxidation and detoxification of hydrogen peroxide [1,2]. Moreover, peroxisomal metabolism varies tremendously within different organisms, encompassing glycolysis in Trypanosome, the glyoxylate cycle in seedlings, and photorespiration in leaves [1,3]. Peroxisome number and size adapt rapidly to environmental and developmental cues. Recent data suggest that redox plays an important role in peroxisome homeostasis by coordinating peroxisome biogenesis and degradation [4,5]. Here, we discuss how redox regulates peroxisome homeostasis, focusing on yeasts and plants.

Antioxidant system in peroxisomes

In addition to fatty acid beta-oxidation, in lower eukaryotic cells, peroxisomes are crucial compartments for secondary metabolism, including the catabolism of oleic acid, methanol, polyamines, purine bases, n-alkanes, and D-amino acids [2,6]. These reactions result in the production of high levels of hydrogen peroxide, which needs to be scavenged to maintain functional peroxisomes. Catalase, peroxidase, and small molecule thiol such as glutathione are major players of the peroxisomal antioxidant system [7–9]. Hydrogen peroxide produced in the peroxisome

Abbreviations: APX, ascorbate peroxidase; DHAR, dehydroascorbate reductase; GR, glutathione reductase; Grx, glutaredoxins; GSSG, oxidized glutathione; MAPK, mitogen-activated protein kinase; MDAR, monodehydroascorbate peroxidase; PAS, phagophore assembly site; PexAD, peroxisome-associated protein degradation; RADAR, receptor accumulation and degradation pathway; ROS, reactive oxygen species; UPS, ubiquitin-proteasome system.

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lumen is mainly scavenged by peroxisomal catalase and glutathione peroxidase, encoded by PMP20 in *Candida boidini* and GPX1 in *Saccharomyces cerevisiae*[7,10]. Removal of hydrogen peroxide by catalases, but not glutathione peroxidases, is independent of cellular reducing cofactors, such as glutathione or thioredoxin, as they catalyze a dismutation reaction converting H_2O_2 to water and O_2. However, peroxisomal glutathione peroxidase requires glutathione as a cellular reductant to reduce H_2O_2 to water [10]. Glutathione has been found to be present in yeast peroxisomes [7]. However, how glutathione is imported into peroxisomes is not clear. It has been suggested that the peroxisomal membrane is freely permeable to small metabolites; therefore, cytosolic glutathione is presumably delivered to the peroxisome lumen by diffusing across the peroxisomal membrane [11]. Oxidized glutathione (GSSG) is thought to be exported to the cytosol through Opt2, a peroxisomal glutathione transporter, wherein it is reduced to GSH by cytosolic glutathione reductase in an NADPH-dependent manner [12].

Besides glutathione peroxidase, glutaredoxins (Grx) also utilize glutathione as a cofactor to reduce disulfide bridges of oxidized proteins. A small family of glutaredoxins exists in *S. cerevisiae*[13]. However, it remains unclear whether any of them reside within the peroxisome lumen. It has been shown recently that *S. cerevisiae* Gto1, one of the three omega-class glutathione transferases whose function is related to the dithiol glutaredoxins, Grx1 and Grx2, is targeted to the peroxisome lumen through the PTS1 pathway [14].

Moreover, fatty acid beta-oxidation in germinating seeds and photorespiration in leaves are important sources of hydrogen peroxide generation in plant peroxisomes [1]. The antioxidant defense system in plant peroxisomes is much more sophisticated than what has been found in lower eukaryotic cells (Table 1). In addition to catalases and glutathione peroxidases, an ascorbate–glutathione cycle is involved in decomposing hydrogen peroxide [15–17]. In *Arabidopsis thaliana*, the ascorbate–glutathione cycle is composed of four types of peroxisomal enzymes: ascorbate peroxidase 3 (APX3), monodehydroascorbate peroxidase 1 and 4 (MDAR1/4), dehydroascorbate reductase 1 (DHAR1), and glutathione reductase 1 (GR1) as well as two reductants, ascorbate and glutathione [18–21]. Other antioxidative enzymes, including Cu/Zn SOD and glutathione S-transferases, participate in removing superoxide radicals and hydroperoxides, respectively [20,22,23].

Table 1
Peroxisomal antioxidatant enzymes in *Saccharomyces cerevisiae* and *Arabidopsis thaliana*.

Gene locus	Acronym	Annotation	Localization	Reference
YDR256C	ScCta1	Catalase	Matrix	[9]
YKL026C	ScGpx1	Glutathione peroxidase	Matrix	[10]
YPR194C	ScOpt2	Glutathione transporter	Peroxisomal membrane	[12]
AT4G35000	AtAPX3	Ascorbate peroxidase	Peroxisomal membrane	[18]
AT1G20630	AtCAT1	Catalase	Matrix	[20]
AT4G35090	AtCAT2	Catalase	Matrix	[20]
AT1G20620	AtCAT3	Catalase	Matrix	[20]
AT5G18100	AtCSD3	Copper/Zinc superoxide dismutase	Matrix	[20,22]
AT1G19570	AtDHAR1	Dehydroascorbate reductase	Matrix	[21]
AT3G24170	AtGR1	Glutathione reductase	Matrix	[20]
AT5G41210	AtGSTT1	Glutathione transferase	Matrix	[20,23]
AT5G41240	AtGSTT2	Glutathione transferase	Matrix	[23]
AT5G41220	AtGSTT3	Glutathione transferase	Matrix	[23]
AT3G52880	AtMDAR1	Monodehydroascorbate reductase	Matrix	[19]
AT3G27820	AtMDAR4	Monodehydroascorbate reductase	Peroxisomal membrane	[19]

Reactive oxygen species (ROS) are not solely by-products of peroxisomal metabolism. As signaling molecules, peroxisomal ROS can affect peroxisome homeostasis, e.g. the biogenesis and degradation of peroxisomes [4,5]. The latter is also named pexophagy, the selective degradation of peroxisomes in the vacuole [24,25].

Repression of peroxisome biogenesis under oxidative stress

Besides oxidative damage of peroxisomal proteins, peroxisomal matrix protein import and peroxisome proliferation are impaired when the peroxisomal antioxidant system breaks down, such as in the absence of antioxidative enzymes or severe abiotic stresses [4,5]. Therefore, maintenance of the peroxisomal redox balance is crucial for preventing peroxisomal proteins from oxidative damage and sustaining functional peroxisomes.

The subcellular localization and activities of several peroxisomal matrix proteins are known to be regulated by redox. Upon exposure to osmotic stress, *S. cerevisiae* Gpd1, a NAD^+-dependent glycerol 3-phosphate dehydrogenase, changes its subcellular localization from the peroxisome lumen to the cytosol and nucleus [26]. Moreover, it has been shown recently that redox switches confer the alternative targeting of *Arabidopsis* plastidic glucose-6-phosphate dehydrogenase to peroxisomes [27]. Furthermore, the activity of *Arabidopsis* 3-ketoacyl-CoA thiolase, an essential enzyme in the beta-oxidation pathway, is controlled by a redox sensitive switch in the peroxisome within a physiological range [28,29].

Although it is quite clear that peroxisome biogenesis could be damaged under oxidative stress, the underlying mechanism is still elusive. It is speculated that the peroxisomal protein import machinery is damaged under oxidative stress. This hypothesis is supported by evidence that few peroxins, proteins involved in peroxisome biogenesis, are known to be modified or impaired by an imbalance of cellular ROS [30–32].

The minimal peroxisomal translocon is composed of Pex5 and Pex14 [33,34]. Pex5 is the receptor of PTS1 proteins and shuttles between the cytosol and peroxisome lumen. This process relies on a conserved cysteine at the N-terminus of Pex5. After unloading peroxisomal cargo in the matrix, the recycling of Pex5 is initiated by monoubiquitination on this conserved N-terminal cysteine [35,36]. Cys 10 of *Pichia pastoris* Pex5 plays a critical role in cargo binding and release since disulfide bond-linked and reduced Pex5 show differential cargo binding affinity [30]. Dissipation of the redox balance between the cytosol and the peroxisome matrix activates the receptor accumulation and degradation pathway (RADAR), resulting in an import defect. Cys 11 in human Pex5 functions as a redox sensitive residue as well, although a different model of regulation of PTS1 import was proposed [37]. Also, one of the two major components of the peroxisomal translocon, Pex14, is degraded in the absence of PMP20, probably by the ubiquitin-proteasome system (UPS) [31]. Therefore, under oxidative stress, the import of peroxisomal proteins would be shut down immediately as the peroxisomal translocon is disassembled. A third redox sensitive peroxin is Pex11, whose homodimerization via intermolecular disulfide bonds, along with the increasing oxidative metabolism within old peroxisomes, inhibits peroxisomal division [32].

In contrast to peroxisomal membrane protein quality control by the UPS, three modes of clearance of damaged peroxisomal matrix proteins have been proposed: (I) Degradation in the peroxisome lumen by the peroxisomal Lon protease [38,39]; (II) export from the peroxisomal matrix and degraded by the proteasome, a process called peroxisome-associated protein degradation (PexAD) in plants [40,41]; and (III) sequestering in daughter cells and removal

through coordinated fission and degradation by autophagy [42]. The first mode has been found in both yeasts and plants, while modes 2 and 3 were observed in *Arabidopsis* seedlings and *Hansenula polymorpha*, respectively. Pexophagy may be triggered when oxidative damage is unmanageable by peroxisomal quality control mechanisms resulting in complete loss of the whole organelle.

Nutrient adaption triggered pexophagy

Pexophagy has been best studied in methylotrophic yeasts, especially *P. pastoris* and *H. polymorpha*[24,25]. Two types of pexophagy, macropexophagy and micropexophagy, have been characterized extensively in *P. pastoris*. Macropexophagy is activated by moving *P. pastoris* cells from methanol to ethanol or from oleate to glucose. Thus, proliferated peroxisomes produced in methanol or oleate become superfluous organelles under peroxisome biogenesis repressed conditions and are engulfed individually by pexophagosomes (Fig. 1A). The process of macropexophagy is completed by fusing pexophagosomes with the vacuole to deliver peroxisomes into the vacuole lumen for degradation. A remarkable feature of methanol-induced peroxisomes is the formation of peroxisome clusters. How individual peroxisomes are separated from a cluster and engulfed by pexophagosomes is not known, although macropexophagy in *P. pastoris* has been firmly proven by fluorescence microscopy. Mao et al. showed that Dnm1 and Vps1 mediated peroxisomal fission is critical for the efficient degradation of the organelle [43]. Whether this is also true for macropexophagy needs further investigation. In contrast, micropexophagy is triggered by transferring cells from methanol to glucose, wherein a cluster of peroxisomes is directly delivered to the vacuole through fusion of the vacuolar sequestering membranes with the micropexophagy specific apparatus. Regarding the signaling events, the Subramani laboratory screened the *S. cerevisiae* kinase/phosphatase knockout strain collection for pexophagy defects and found that a mitogen-activated protein kinase (MAPK), Slt2, and its upstream components are essential for the pexophagy pathway [44]. Furthermore, the Klionsky group found that *S. cerevisiae* Slt2 is required not only for pexophagy, but also for mitophagy [45].

Pexophagy shares core autophagic machinery with general autophagy, including the Atg1 kinase complex (a basic scaffold for assembling of the phagophore assembly site, PAS), the Atg9 cycling system (essential for phagophore elongation), the PI3K complexes for PtdIns3P generation, and the ubiqutin-like conjugation systems for autophagosome formation [24,25]. But in addition, pexophagy recruits unique components for its selectivity, such as Atg11, Atg26, Atg30/Atg36, and Atg37 [46–49]. Atg30 and Atg36 are the pexophagy-specific receptors identified in *P. pastoris* and *S. cerevisiae*, respectively [46,48]. *P. pastoris* Atg30 serves as a bridge between the peroxisomes to be degraded and the phagophore assembly site. Atg30 interacts with two peroxisomal membrane proteins, Pex14 and Pex3, under pexophagy conditions, a process regulated by phosphorylation [46]. Furthermore, in mammalian systems, Pex14 and Pex3 also have a role in peroxisome degradation, although the underlying molecular details differ. When starved Chinese Hamster Ovary cells are transferred to nutrient-rich medium, Pex14 binds to

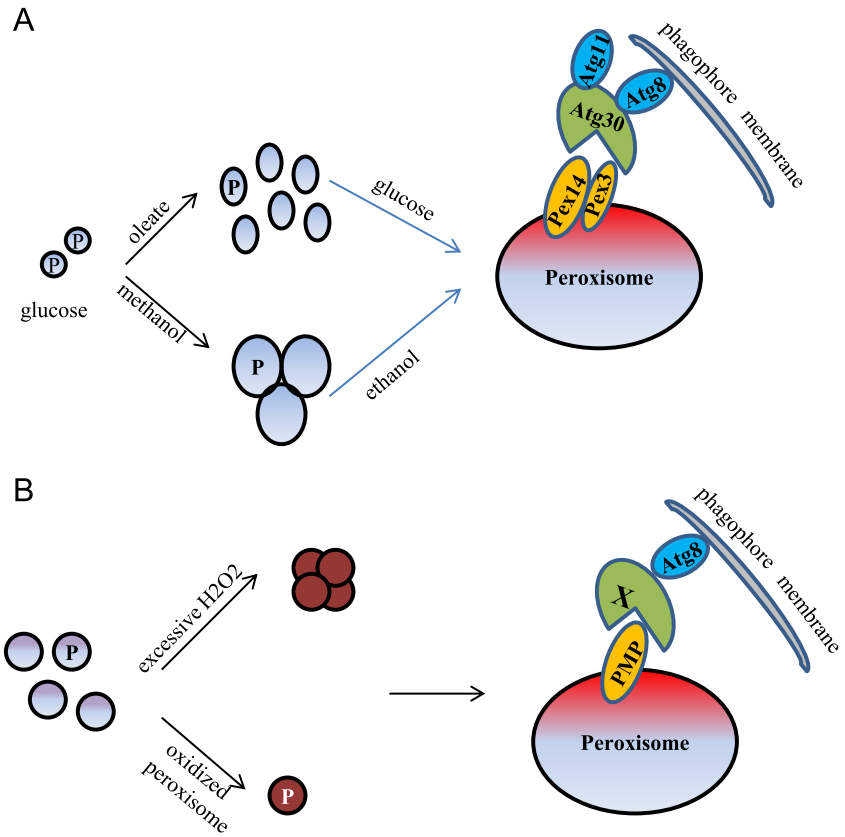

Fig. 1. Mechanistic views of pexophagy in yeasts and plants. (A) Peroxisome proliferation is induced when *P. pastoris* cells are grown in methanol or oleate medium. Macropexophagy is triggered by shifting cells from methanol to ethanol or from oleate to glucose. Atg30 is the pexophagy receptor and interacts with Pex14 and Pex3 on the peroxisomal membrane. Moreover, it binds the autophagy adaptor protein Atg11 and the ubiquitin-like protein Atg8 at the pexophagy-specific PAS. Phosphorylation of Atg30 coordinates its interaction with Atg8 and Atg11. (B) In plants, peroxisomes become oxidatively damaged when the redox status in the peroxisomal lumen is unmanageable. Oxidized peroxisomes are degraded by pexophagy. However, the plant pexophagy-specific receptor (designated as X), a homolog of Atg30 or Atg36, has not been characterized. And it is also not known how the plant pexophagy-specific receptor is associated with the damaged peroxisomes, but it may interact with a PMP.

the processed and lipidated form of LC3, an animal ortholog of yeast Atg8 [50,51]. Moreover, mammalian pexophagy may be triggered by monoubiquitination of Pex3 or PMP34 [52]. On the other hand, Atg30 or Atg36 interacts with the ubiquitin-like protein Atg8 and the scaffold protein Atg11, which requires phosphoregulation as well [53]. In *S. cerevisiae*, it has been recently shown that Hrr25-mediated phosphorylation of Atg36 enhances its interactions with the common adaptor Atg11 [54].

Activation of pexophagy by oxidative stress

In the past decade, efforts have been mainly focused on how superfluous peroxisomes are degraded by pexophagy. However, in contrast to lower eukaryotic cells, peroxisome number in plants is constant during the entire lifecycle. Therefore, the major role of pexophagy in plants is to remove oxidatively damaged peroxisomes, rather than the clear superfluous peroxisomes. Only recently large progress has been achieved on how oxidized peroxisomes are removed by pexophagy in plants (Fig. 1B) [55,56]. Shibata et al. showed that in the leaves of *Arabidopsis atg2* , *atg7*, and *atg18a* mutants, peroxisomes form large aggregates and separate from chloroplasts and mitochondria, organelles generally clustered together with peroxisomes to facilitate the shuttling of metabolites generated during photorespiration [55]. The aggregated peroxisomes in these *atg* mutants accumulate inactive catalases, suggesting that the peroxisome aggregates result from peroxisomes that were oxidized and damaged by excessive hydrogen peroxide. This hypothesis is supported by the observation of high concentrations of hydrogen peroxide in the *atg2* mutant and a more oxidized intraperoxisomal state in *atg2* and *atg5* mutants compared to wild-type. Furthermore, the *cat2* mutant also contained peroxisome aggregates. In addition, Atg8 was found to frequently colocalize with aggregated peroxisomes, suggesting oxidatively damaged, dysfunctional peroxisomes are selectively degraded by autophagy. Interestingly, Yoshimoto et al. found that in the *atg5* mutant a proportion of peroxisome-containing protein aggregates, mainly composed of inactive catalase, is segregated or "torn off" from the whole organelle by unknown mechanisms and degraded through pexophagy [56]. A similar phenomenon has been observed in *H. polymorpha*. The Van der Klei group demonstrated that peroxisomal matrix protein aggregates were removed by concerted peroxisomal fission and autophagy [42]. Whether this is also true in plants requires further investigation.

In addition to pexophagy found in *Arabidopsis* leaves, peroxisomes are selectively degraded during the functional transition of seedling glyoxysomes to leaf peroxisomes [40]. Seedling glyoxysomes play a pivotal role in lipid metabolism, producing acetyl-CoA used by the glyoxylate cycle to form organic acids, which are converted into sugars by gluconeogenesis [1]. Glyoxysomes can transform into leaf glyoxysomes by specifically removing malate synthase and isocitrate lyase, two peroxisomal enzymes of the glyoxylate cycle, through PexAD, concomitant with the import of enzymes required for photorespiration [40]. Furthermore, several groups have recently shown that this organelle remodeling process can be accelerated by selectively degrading oxidized glyoxysomes when the LON2 protease is disabled [39,57]. However, it is still unknown whether LON2 regulates pexophagy directly or indirectly. It is estimated that in mice liver 20–30% of excess peroxisomes are destroyed by peroxisomal Lon protease mediated degradation [58]. Kim et al. showed that pexophagy preferably happens in hypocotyls, while it is less obvious at the whole-seedling level [59]. Therefore, it seems that pexophagy plays a crucial role in preventing the accumulation of damaged peroxisomes in plants at different developmental stages.

Although in plants, oxidized peroxisomes have been demonstrated to be degraded by pexophagy, neither the plant pexophagy-specific receptor, a functional homolog of Atg30, nor the signaling events of the plant pexophagy pathway have been characterized. ATG genes required for general autophagy are conserved among different organisms [60]. However, it seems that genes needed for the selective autophagy pathways are organism-specific. For example, Atg30 and Atg36 are conserved only among a few yeast species [46,48]. Therefore, identifying these plant specific ATG proteins will shed more light on the molecular mechanisms of pexophagy in higher eukaryotic cells.

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