Redox Biology 4 (2015) 104–108

Contents lists available at ScienceDirect

Redox Biology

journal homepage: www.elsevier.com/locate/redox

Mini Review

Redox regulated peroxisome homeostasis

Xiaofeng Wang, Shuo Li, Yu Liu, Changle Ma*

College of Life Sciences, Shandong Normal University, Wenhua East Road 88, Jinan, Shandong 250014, China

ARTICLE INFO

Article history:
Received 10 November 2014
Received in revised form
13 December 2014
Accepted 15 December 2014
Available online 18 December 2014

Keywords:
Peroxisome
Pexophagy
Redox
Catalase
Oxidative stress

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.

* Corresponding author.
E-mail address: changlema@yahoo.com (C. Ma).

http://dx.doi.org/10.1016/j.redox.2014.12.006

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