Biochimie xxx (2013) 1–7

Contents lists available at ScienceDirect

Biochimie

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

Mini-review

Peroxisomal metabolism and oxidative stress

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ARTICLE INFO

Article history:
Received 29 May 2013
Accepted 25 July 2013
Available online xxx

Keywords:
Peroxisome
Hydrogen peroxide
Lipid second messenger
Mitochondrial dysfunction
Age-related diseases

ABSTRACT

Peroxisomes are ubiquitous and multifunctional organelles that are primarily known for their role in cellular lipid metabolism. As many peroxisomal enzymes catalyze redox reactions as part of their normal function, these organelles are also increasingly recognized as potential regulators of oxidative stress-related signaling pathways. This in turn suggests that peroxisome dysfunction is not only associated with rare inborn errors of peroxisomal metabolism, but also with more common age-related diseases such as neurodegeneration, type 2 diabetes, and cancer. This review intends to provide a comprehensive picture of the complex role of mammalian peroxisomes in cellular redox metabolism. We highlight how peroxisomal metabolism may contribute to the bioavailability of important mediators of oxidative stress, with particular emphasis on reactive oxygen species. In addition, we review the biological properties of peroxisome-derived signaling messengers and discuss how these molecules may mediate various biological responses. Furthermore, we explore the emerging concepts that peroxisomes and mitochondria share an intricate redox-sensitive relationship and cooperate in cell fate decisions. This is particularly relevant to the observed demise of peroxisome function which accompanies cellular senescence, organismal aging, and age-related diseases.

1. Introduction

Today, it is widely accepted that the cellular redox state is an important metabolic variable that influences many aspects of cell function, including cell survival, proliferation, and differentiation [1]. A derangement in redox homeostasis may render cells more vulnerable to oxidative stress, a condition in which the production of reactive oxygen and/or nitrogen species (ROS/RNS) overwhelms the capacity of the antioxidant defense and repair mechanisms [2]. Major cellular sources of ROS/RNS encompass the electron transport chain in mitochondria, the Ero1 and cytochrome P-450 enzymes in the endoplasmic reticulum (ER), the NADPH oxidases at the plasma membrane, the flavin oxidases inside peroxisomes, and the nitric oxide synthases (NOSs) which show different subcellular localizations [3]. Natural antioxidant systems include various enzymes (e.g. superoxide dismutase, glutathione peroxidase, and catalase) and non-enzymatic metabolites (e.g. glutathione and ascorbic acid) [3]. Depending on the type of ROS/RNS, their concentration and localization, and their kinetics of production and elimination, these small reactive molecules may propagate downstream signaling events or cause oxidative damage to biomolecules [4]. As such, it is not surprising that both acute and sustained alterations in the redox state can contribute to the mechanisms of cellular aging and age-related diseases [4]. In the following sections of this review, we focus on the role of peroxisomes in oxidative stress- and antioxidant defense-related pathways in mammals (Fig. 1).

2. Peroxisomes are important sites of ROS production and degradation

As indicated by their name, peroxisomes play a central role in the cellular metabolism of hydrogen peroxide (H_2O_2) [5]. This is perhaps best illustrated by the fact that these organelles harbor copious amounts of enzymes that can produce or degrade this molecule. The best known ones are the H_2O_2-producing flavin-containing oxidases and catalase, a H_2O_2-decomposing enzyme [6]. Peroxisomes also contain enzymes that generate superoxide ($O_2^{\bullet-}$) (e.g. xanthine oxidase) or nitric oxide ($NO^{\bullet}$) (e.g. xanthine oxidase and NOS2, the inducible form of nitric oxide synthase) as

Abbreviations: AA, arachidonic acid; DHA, docosahexaenoic acid; ER, endoplasmic reticulum; GSH, reduced glutathione; GSSH, oxidized glutathione; LONP2, peroxisomal Lon protease; NOSs, nitric oxide synthases; PUFAs, polyunsaturated fatty acids; RNS, reactive nitrogen species; ROS, reactive oxygen species; UOX, urate Q1 oxidase; VLCFAs, very-long-chain fatty acids; X-ALD, X-linked adrenoleukodystrophy

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0300-9084/$ – see front matter © 2013 Published by Elsevier Masson SAS.
http://dx.doi.org/10.1016/j.biochi.2013.07.026

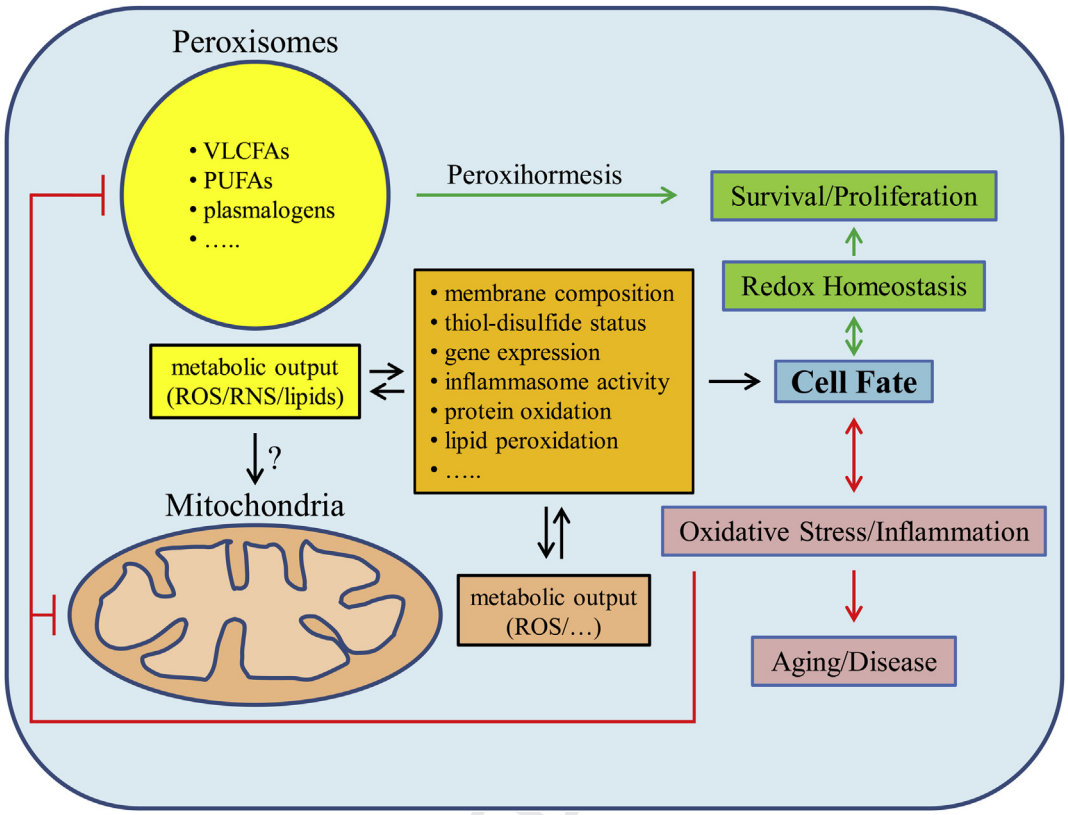

Fig. 1. Hypothetical model depicting the role of peroxisomes in cell fate decisions. Peroxisomes play a central role in cellular lipid and ROS/RNS metabolism. As such, the metabolic output of these organelles can affect mitochondrial function and modulate the bioavailability of lipid- and redox-related factors involved in diverse cellular signaling pathways. Depending on the specific pathways affected, these changes exert either cytoprotective or cytotoxic actions. The phenomenon in which peroxisome function is adapted to exert beneficial effects (e.g. to protect cells against oxidative insults, to promote cell survival and proliferation pathways, …), is called 'peroxihormesis'. Disturbances in peroxisome function (e.g. upon acute or chronic inflammation and/or exposure to oxidative stress) can evoke oxidative stress-mediated signaling mechanisms associated with cellular aging and age-related diseases. PUFAs, polyunsaturated fatty acids; RNS, reactive nitrogen species; ROS, reactive oxygen species; VLCFAs, very-long-chain fatty acids.

part of their normal catalytic activity [6]. In addition, as $NO^{\bullet}$ may rapidly combine with $O_2^{\bullet-}$ to form peroxynitrite ($ONOO^-$) [7], and H_2O_2 may give rise to hydroxyl radicals ($^{\bullet}OH$) through the Fenton reaction [8], it is very likely that these organelles also have the potential to act as a source of these ROS/RNS species. Importantly, since $ONOO^-$ and $^{\bullet}OH$ are highly unstable, they can cause direct oxidative biomolecular damage, such as lipid peroxidation [9]. In this context, it is essential to mention that peroxisomes also contain antioxidant enzymes that can degrade $O_2^{\bullet-}$ (e.g. superoxide dismutase 1), $ONOO^-$ (e.g. peroxiredoxin 5), epoxides (e.g. epoxide hydrolase 2), and lipid peroxides (e.g. peroxiredoxin 5 and glutathione S-transferase kappa). For a detailed description of these and other peroxisomal pro- and antioxidant enzymes, we refer the reader to other comprehensive reviews covering this topic [6,10,11].

As already mentioned in Introduction, the major non-enzymatic cellular redox buffer systems rely on the antioxidants glutathione and ascorbic acid. Glutathione (γ-glutamyl-cysteinyl-glycine) is a tripeptide that, within cells, can exist in reduced (GSH) and oxidized (GSSG) states [3]. Ascorbic acid, also known as vitamin C, is an essential nutrient in human diets that functions as cofactor for a number of enzymes and is capable of scavenging various ROS/RNS. Although it is well documented that plant peroxisomes contain a functional ascorbate–glutathione cycle [12], relatively little is known about the network of non-enzymatic antioxidants inside mammalian peroxisomes. Nonetheless, there is some indirect evidence that GSH may freely diffuse from the cytosol into peroxisomes via PXMP2, a non-selective pore-forming peroxisomal membrane protein with an upper molecular size limit of 300–600 Da [13]. However, it remains to be determined how GSSG can be reduced inside the peroxisomal matrix or exported back into the cytosol. In addition, although it has been demonstrated that ascorbic acid functions as a cofactor for phytanoyl-CoA 2-hydroxylase in the peroxisomal matrix [14], it remains unclear whether or not this vitamin also displays antioxidant properties in this subcellular compartment. Indeed, a recent study from our laboratory has shown that the cultivation of mouse embryonic fibroblasts in media containing ascorbic acid actually led to an increased redox state of the peroxisomal matrix [15]. This may be explained by the facts that (i) peroxisomes contain relatively large amounts of heme- and non-heme iron-containing enzymes [16], and (ii) ascorbic acid can generate hydroxyl and alkoxyl radicals in the presence of free transition metals [17].

Finally, peroxisomes also harbor several proteases whose functions may be linked to peroxisomal ROS-production. One such enzyme is peroxisomal Lon peptidase (LONP2), an enzyme that – among other functions – is implicated in the degradation of dysfunctional and/or excessive matrix proteins [18,19]. Indeed, in a recent study in *Penicillium chrysogenum*, it was shown that LONP2 selectively degrades oxidatively damaged proteins in the peroxisomal matrix, and that an inactivation of this protein enhances cellular oxidative stress [20]. In addition, it has been demonstrated that this protease is involved in the removal of excess peroxisomal β-oxidation enzymes upon removal of proliferation stimuli [18]. This observation is in line with a recent study showing that LONP2 proteolytically regulates peroxisomal fatty acid β-oxidation [19]. Taken together, these findings indicate that LONP2 may act as a

Please cite this article in press as: M. Nordgren, M. Fransen, Peroxisomal metabolism and oxidative stress, Biochimie (2013), http://dx.doi.org/10.1016/j.biochi.2013.07.026