Available online at www.sciencedirect.com
ScienceDirect
Biochimica et Biophysica Acta 1763 (2006) 1755–1766
BIOCHIMICA ET BIOPHYSICA ACTA
BBA
www.elsevier.com/locate/bbamcr

Review

Peroxisomes and oxidative stress

Michael Schrader [a,*], H. Dariush Fahimi [a,b]

[a] Department of Cell Biology and Cell Pathology, University of Marburg, Robert Koch Str. 6, 35037 Marburg, Germany
[b] Department of Anatomy and Cell Biology, Division of Medical Cell Biology, University of Heidelberg, Im Neuenheimer Feld 307, 69120 Heidelberg, Germany

Received 5 May 2006; received in revised form 5 September 2006; accepted 6 September 2006
Available online 14 September 2006

Abstract

The discovery of the colocalization of catalase with H_2O_2-generating oxidases in peroxisomes was the first indication of their involvement in the metabolism of oxygen metabolites. In past decades it has been revealed that peroxisomes participate not only in the generation of reactive oxygen species (ROS) with grave consequences for cell fate such as malignant degeneration but also in cell rescue from the damaging effects of such radicals. In this review the role of peroxisomes in a variety of physiological and pathological processes involving ROS mainly in animal cells is presented. At the outset the enzymes generating and scavenging H_2O_2 and other oxygen metabolites are reviewed. The exposure of cultured cells to UV light and different oxidizing agents induces peroxisome proliferation with formation of tubular peroxisomes and apparent upregulation of PEX genes. Significant reduction of peroxisomal volume density and several of their enzymes is observed in inflammatory processes such as infections, ischemia–reperfusion injury and hepatic allograft rejection. The latter response is related to the suppressive effects of TNFα on peroxisomal function and on PPARα. Their massive proliferation induced by a variety of xenobiotics and the subsequent tumor formation in rodents is evidently due to an imbalance in the formation and scavenging of ROS, and is mediated by PPARα. In PEX5$^{-/-}$ mice with the absence of functional peroxisomes severe abnormalities of mitochondria in different organs are observed which resemble closely those in respiratory chain disorders associated with oxidative stress. Interestingly, no evidence of oxidative damage to proteins or lipids, nor of increased peroxide production has been found in that mouse model. In this respect the role of PPARα, which is highly activated in those mice, in prevention of oxidative stress deserves further investigation.

Keywords: ROS; Peroxisome proliferation; Oxygen; Antioxidant enzymes; PEX5$^{-/-}$ mice; Oxidative injury

1. Oxidative stress and peroxisomes in brief

1.1. The "good" and the "evil" of ROS

Oxidative stress arises from a significant increase in the concentration of reactive oxygen species (ROS) and reactive nitrogen species (RNS), and/or a decrease in their detoxification mechanisms. There are many natural sources of oxidative stress, for example exposure to environmental oxidants, toxins like heavy metals, ionizing and UV irradiation, heat shock, and inflammation [1]. High levels of ROS exert a toxic effect on biomolecules such as DNA, proteins, and lipids (e. g., non-enzymatic lipoperoxidation), thus leading to the accumulation of oxidative damage in diverse cellular locations, to the deregulation of redox-sensitive metabolic and signalling pathways, and to pathological conditions. Much interest in oxidative stress comes from human pathologies, for example ischemia–reperfusion injury, atherosclerosis, hypertension, inflammation, cystic fibrosis, cancer, type-2 diabetes, or neurodegenerative diseases such as Parkinson's or Alzheimer's disease. Furthermore, oxidative stress has been linked to aging [2]. Besides their harmful role in clinical conditions, the importance of ROS (RNS) as mediators in various vital cellular processes and cell signalling pathways became apparent (reviewed in [3,4]). A typical example is their function in apoptosis.

Abbreviations: ER, endoplasmic reticulum; iNOS, inducible nitric oxide synthase; MnSOD, manganese superoxide dismutase; PBD, peroxisome biogenesis disorder; PEX, peroxin; PMP, peroxisomal membrane protein; PPAR, peroxisome proliferator activated receptor; PTS, peroxisomal targeting signal; ROS, reactive oxygen species; TNF, tumor necrosis factor

* Corresponding author. Tel.: +49 6421 2863857; fax: +6421 2866414.
E-mail address: schrader@mailer.uni-marburg.de (M. Schrader).

0167-4889/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbamcr.2006.09.006

ROS include radical species (containing free, i. e. unpaired, electrons), such as the *superoxide anion* ($O_2^{\bullet-}$), which is formed through one-electron reduction of O_2 ($O_2 + e^- \rightarrow O_2^{\bullet-}$). *Hydrogen peroxide* ($H_2O_2$) is also ascribed to ROS, although it has no unpaired electrons, and thus is not a radical. It can, for example, be formed by the dismutation reaction of $O_2^{\bullet-}$ (catalyzed by superoxide dismutases) via the hydroperoxyl radical ($O_2^{\bullet-} + H^+ \rightarrow HO_2^{\bullet-}$; $2HO_2^{\bullet-} \rightarrow H_2O_2 + O_2$). Probably the most highly reactive and toxic form of oxygen, the *hydroxyl radical* ($^{\bullet}OH$), can be formed by the metal ion (e. g., iron or copper)-catalyzed decomposition of H_2O_2 ($H_2O_2 + O_2^{\bullet-} \rightarrow O_2 + OH^- + {}^{\bullet}OH$). Similarly, RNS include radical species such as primary *nitric oxide* ($^{\bullet}NO$). $^{\bullet}NO$ and H_2O_2 are membrane permeable, diffusible molecules, which are less-reactive and longer-lived than $^{\bullet}OH$, thus being best suited for intra- and even intercellular signalling. In particular H_2O_2, which is not harmful until converted to more reactive ROS, acts on cellular thiol-disulfide redox buffer systems such as glutathione, thioredoxin and peroxiredoxin (for review see [5,6]).

1.2. Peroxisomes and ROS

Oxygen is consumed in various metabolic reactions in different cellular locations, with mitochondria, the ER, and peroxisomes being the major sites (Fig. 1A). De Duve and Baudhuin [7] first described a respiratory pathway in peroxisomes, in which electrons removed from various metabolites reduce O_2 to H_2O_2, which is further reduced to H_2O. The respiratory pathway in peroxisomes is not coupled to oxidative phosphorylation, and does not lead to the production of ATP. Free energy is released in the form of heat.

The high peroxisomal consumption of O_2, the demonstration of the production of H_2O_2, $O_2^{\bullet-}$, $^{\bullet}OH$, and recently of $^{\bullet}NO$ in peroxisomes [7–10], as well as the discovery of several ROS-metabolizing enzymes in peroxisomes (see Tables 1 and 2) has supported the notion that these ubiquitous organelles play a key role in both the production *and* scavening of ROS in the cell, in particular H_2O_2 (Fig. 2).

Initially, it was assumed that the main function of peroxisomes was the decomposition of H_2O_2 generated by different peroxisomal oxidases (mainly flavoproteins) via catalase, the classical peroxisomal marker enzyme. However, it is now clear that peroxisomes are involved in a variety of important cellular functions in almost all eukaryotic cells (for details see articles about peroxisomal metabolism, this issue). The main metabolic processes contributing to the generation of H_2O_2 in peroxisomes are the β-oxidation of fatty acids, the enzymatic reactions of the flavin oxidases, the disproportionation of superoxide radicals, and in plant peroxisomes, the photorespiratory glycolate oxidase reaction. It has been estimated that about 35% of all H_2O_2 formed in rat liver derives from peroxisomal oxidases [11]. To degrade the ROS, which are produced due to their metabolic activity, and to maintain the equilibrium between production and scavenging of ROS, peroxisomes harbour several powerful defense mechanisms and antioxidant enzymes in addition to catalase (Table 2, Fig. 2).

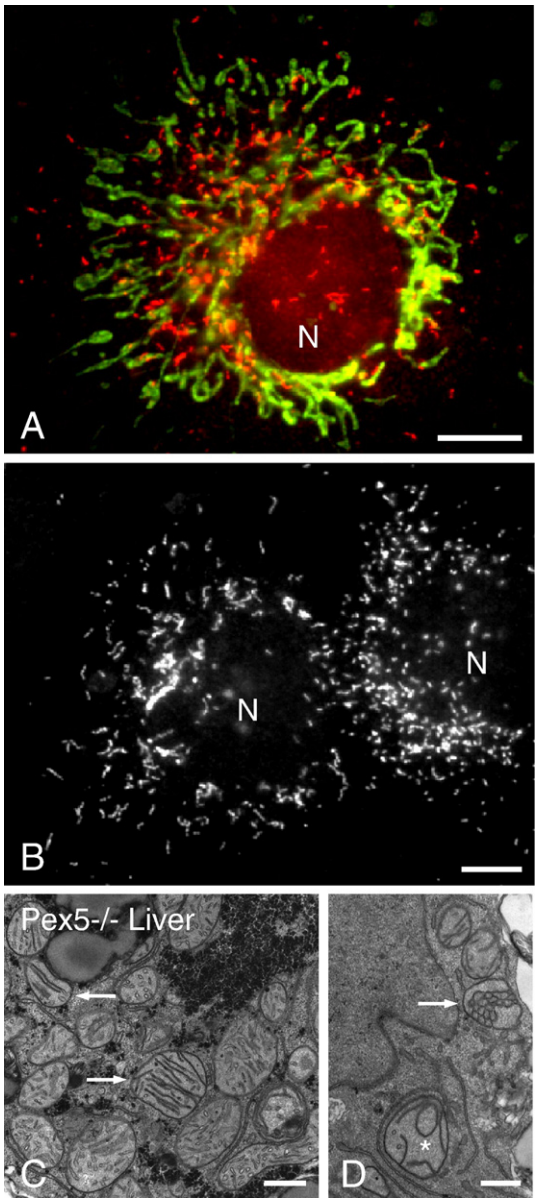

Fig. 1. (A) Fluorescence microscopy of peroxisomes and mitochondria, two major subcellular organelles involved in the metabolism of ROS, in COS-7 cells, a green monkey kidney cell line. Cells were stained with antibodies to peroxisomal catalase (red) and to mitochondrial MnSOD (green). (B) Mammalian cells can exhibit different peroxisomal morphologies under normal culture conditions. Peroxisomes in COS-7 cells were visualized by immunofluorescence using specific antibodies directed to PMP70, a peroxisomal membrane protein. Note the spherical shape of peroxisomes in the cell at the left, in contrast to their elongated, tubular morphology in the cell at right. The formation of elongated peroxisomes is induced after UV irradiation or exposure to H_2O_2 (see Section 4.2). (C, D) Electron micrographs of altered mitochondria in hepatocytes of $PEX5^{-/-}$ mice (reprinted from [91] with permission from Springer-Verlag) (C) Pleomorphic mitochondria with altered cristae. Some of the round, large mitochondria exhibit stacks of parallel cristae (arrows). (D) Mitochondria with circular cristae (asterisks) or mitochondrial ghosts (arrow). Scale bars, 10 μm (A, B), 500 nm (C, D).

An interesting feature of peroxisomes is their ability to proliferate and multiply, or be degraded in response to nutritional and environmental stimuli. In rodents, for example, the number and size of peroxisomes as well as the expression of peroxisomal