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Review

Fission and proliferation of peroxisomes ☆

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ABSTRACT

Peroxisomes are remarkably dynamic, multifunctional organelles, which react to physiological changes in their cellular environment and adopt their morphology, number, enzyme content and metabolic functions accordingly. At the organelle level, the key molecular machinery controlling peroxisomal membrane elongation and remodeling as well as membrane fission is becoming increasingly established and defined. Key players in peroxisome division are conserved in animals, plants and fungi, and key fission components are shared with mitochondria. However, the physiological stimuli and corresponding signal transduction pathways regulating and modulating peroxisome maintenance and proliferation are, despite a few exceptions, largely unexplored. There is emerging evidence that peroxisomal dynamics and proper regulation of peroxisome number and morphology are crucial for the physiology of the cell, as well as for the pathology of the organism. Here, we discuss several key aspects of peroxisomal fission and proliferation and highlight their association with certain diseases. We address signaling and transcriptional events resulting in peroxisome proliferation, and focus on novel findings concerning the key division components and their interplay. Finally, we present an updated model of peroxisomal growth and division. This article is part of a Special Issue entitled: Metabolic Functions and Biogenesis of Peroxisomes in Health and Disease.

1. Introduction

Peroxisomes are dynamic, multifunctional organelles that contribute to numerous anabolic and catabolic pathways and are thus essential for human health and development. Common functions include the metabolism of hydrogen peroxide and the oxidation of fatty acids. However, several specialized functions have been acquired such as plasmalogen biosynthesis in mammals, photorespiration and glyoxylate cycle in plants, penicillin biosynthesis in fungi, and glycolysis in trypanosomes. In animals, peroxisomes are as well involved in the synthesis of bile acids, mediators of inflammation (e.g. leukotrienes) and docosahexaenoic acid, a modulator of neuronal function [1]. A new biological function for peroxisomes in anti-viral innate immunity and anti-viral (MAVS) signaling was recently discovered [2]. To adapt to the changing physiological requirements of a cell or organism, peroxisomes have to constantly adjust their morphology, number, enzyme content and metabolic functions accordingly. This requires dynamic processes which modulate peroxisome abundance, e.g. by peroxisome formation (biogenesis), degradation (pexophagy), or inheritance (cell division or budding) [3,4]. Peroxisomes can form by growth and division (fission) from pre-existing ones [5,6]. Alternatively, they can also arise from the ER [7–9]. This *de novo* formation was first discovered in mutant cells completely lacking peroxisomes after reintroduction of the deficient gene (PEX19, PEX3, or PEX16, which are thought to mediate peroxisome membrane biogenesis) (see Chapter 2, this issue). Recent publications indicate, that this process may also occur under normal conditions [10,11] involving the formation of vesicles containing a subset of peroxisomal membrane proteins (PMPs) budding from specialized ER sites [12,13]. Currently, however, the proportional contribution of both biogenesis pathways to the maintenance and abundance of peroxisomes is largely unknown and may vary considerably among different organisms. Here, we will focus mainly on peroxisome formation by growth and division and highlight recent advancements in the field. It is evident now, that an imbalance in peroxisome abundance, e.g. by impairment of regulatory pathways or defects in key division components can contribute to disorders displaying phenotypes, which often differ from those of classical peroxisome biogenesis disorders (see Chapter 3, this issue).

The terms “peroxisome proliferation” or “peroxisome multiplication” are commonly used to define the mode of peroxisome generation. Whereas “multiplication” refers to the maintenance of peroxisome numbers, peroxisome proliferation generally describes a pronounced increase in peroxisome number (usually after external

Abbreviations: ER, endoplasmic reticulum; Pex, peroxin; PGC-1α, peroxisome proliferator activated receptor γ coactivator-1α; PMP, peroxisomal membrane protein; PPAR, peroxisome proliferator activated receptor; PPRE, peroxisome proliferator response element; ROS, reactive oxygen species

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stimulation). In this review, the terms "multiplication" and "proliferation" will be used interchangeably, as both processes likely require the same machinery at the organelle level. Peroxisome proliferation has to be controlled by coordinated signaling events in the nucleus thus enhancing transcription of proliferation-relevant genes and concerted actions of biogenesis proteins at the cellular sites of peroxisome formation. Despite a few exceptions, the extracellular and intracellular signaling cascades involved in peroxisome proliferation are largely unknown. Key players in peroxisome division have, however, been identified during the last years and found to be conserved in animals, plants and fungi. Division of peroxisomes is preceded by elongation of the organelle membrane involving the conserved membrane protein Pex11p. Final fission requires dynamin-like proteins with GTPase activity and associated receptor and adaptor proteins (e.g. DLP1/Drp1 and its receptors Fis1 and Mff in mammals). Notably, these key components are shared with mitochondria which is a common strategy used by mammals, fungi and plants. Peroxisome formation from either the ER or by growth and division appears to follow a maturation process involving the recruitment of new membrane and matrix proteins.

In summary, peroxisome abundance is controlled at various stages and sites. On the one hand, it is regulated by controlled transcription of biogenesis- and division-related genes. On the other hand, peroxisome division requires a timely and spatially coordinated series of interactions between the various components involved. In the following, we will provide a comprehensive overview of our current knowledge on fission and proliferation of peroxisomes. We will first address signaling and transcriptional events resulting in peroxisome proliferation, and will afterwards focus on novel findings concerning the key components of the peroxisomal fission machinery and their interplay. The most recent findings have been incorporated in an updated model of peroxisomal growth and division.

2. Regulation of peroxisome proliferation

2.1. PPARα-controlled peroxisome proliferation — the classical scheme in mammals

The capability of peroxisomes to proliferate in response to exogenous stimuli has been described soon after their initial characterization in 1965 by Hess and coworkers [14], who treated rats with the hypolipidemic drug ethyl-chlorophenoxy-isobutyrate. However, it took another 10 years to link the hypolipidemic effect of the further on so-called "peroxisome proliferators" to peroxisomal fatty acid β-oxidation [15] (see Chapter 4, this issue). Treatment of rodents with classic peroxisome proliferators does not only result in a significant increase in organelle number, but also in changes in the peroxisomal protein composition. Whereas enzymes involved in fatty acid β-oxidation show an increase in both amounts and activities in response to the stimulation, proteins involved in other tasks – e.g., the H_2O_2 detoxifying enzyme catalase – are irresponsive or even decreased. Importantly, different species respond with variable intensities to synthetic peroxisome proliferators: potent hypolipidemic drugs such as fibrates, induce peroxisome proliferation [14] and expression of β-oxidation enzymes [15], but also the formation of liver tumors in rodent species [16]. Further studies showed that a massive peroxisome proliferation upon treatment with peroxisome proliferators is only observed in Muridae, whereas other organisms, including humans, are much more refractory [17] (see Section 2.2). Prolonged treatment with peroxisome proliferators has a carcinogenic effect in rodents leading to liver tumors [18–20] but apparently not in humans [21]. After the nuclear receptor Peroxisome Proliferator Activated Receptor α (PPARα), which belongs to the superfamily of steroid/thyroid/retinoid receptors, was identified as the responsible mediator for changing the expression of peroxisomal genes [22–24], it was possible to unveil that unsaturated long chain fatty acids are natural ligands of this receptor and thus transmit signals for the requirement of enhanced lipid catabolism [25] (Fig. 1). Later on, two related nuclear receptors, PPARγ and PPARβ/δ, were identified, which have partially overlapping substrate specificity but are not transmitting the signals of classical peroxisome proliferators [23,24]. Notably, constitutive expression of peroxisomal genes is not dependent on PPARα since the corresponding knockout mice proved to be viable, fertile and exhibit normal peroxisomes but are more susceptible to obesity [26,27]. Synthetic compounds triggering peroxisome proliferation via activation of PPARα are structurally remarkably different including fibrates, phthalate esters, polycyclic aromatic hydrocarbons, perfluorooctanoate and related compounds or dehydroepiandrosterone. Activation of PPARα does not only enhance the transcription of peroxisomal genes implicated in fatty acid β-oxidation but also those involved in peroxisome division, e.g. Pex11α (see Section 3.1, Table 1). However, PPARα-dependent peroxisome proliferators are capable of inducing peroxisome proliferation in a Pex11α knockout mouse model thus pointing to a potential functional compensation by the remaining Pex11 isoforms or to other, hitherto undetected factors [28]. Like all nuclear receptors, PPARs have to form dimers to attach to their correspondent DNA-binding sites (Fig. 1). For PPARα, ligand-binding induces conformational changes which permit an interaction with Retinoid X Receptor-α (RXRα), thus building the activated heterodimer capable of recognizing PPARα-responsive elements (PPREs) (Fig. 1). PPREs have been reported for all peroxisomal β-oxidation enzymes but also for several microsomal cytochrome P-450 subtypes and for apolipoproteins types I and II [29]. Thus, besides ligands for PPARα, full activation of the peroxisomal response depends as well on binding of 9-cis-retinoic acid to RXRα [30]. Further, it was shown that PPARα requires fatty acid-binding protein (FABP) for a full response to peroxisome proliferators [31], which may act as a mediator for nuclear transport of fatty acids.

2.2. Rats and mice are special — molecular background for species differences

Concerning the species differences in peroxisome proliferation, the affinities of endogenous or exogenous ligands to PPARα were not found to be responsible as was shown by experiments with species-specific PPARαs and reporter constructs based on the rat PPAR response element [32–34]. However, rats and mice exhibited a one-magnitude higher expression level of PPARα in liver than humans or guinea pigs [35,36], which would therefore allow a more frequent interaction between receptor and ligand. Moreover, primates exhibit significant sequence differences in both PPARα response elements and the corresponding DNA binding domain of the receptor, possibly leading to differential activation of PPAR-controlled genes. Indeed, insertion of murine response elements into human cell lines result in a comparable activation of the peroxisomal ACOX1 gene, encoding for acyl CoA oxidase 1, a key enzyme of peroxisomal β-oxidation [37]. PPARα-humanized mice (the human PPARα was introduced into the background of a PPARα knockout mouse line), however, still show a mouse-like activation of β-oxidation activities, but do not develop the proliferation-related tumors found in wild-type strains [38]. Thus, species differences in peroxisome proliferation appear to be caused by a species-specific coevolution of PPARα and its DNA-binding site elements allowing to adapt to individual physiological needs which are at the moment still not completely understood.

2.3. PPARα and then? — new regulating factors emerge

Physiologically, PPARα appears to regulate peroxisome number according to the requirements of increased lipolysis, e.g. in different tissues from fasting or hibernating animals, where peroxisome number and PPARα expression are up-regulated in parallel [39–41]. In brown adipose tissue, however, also PPARγ was suggested to