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Peroxisome homeostasis: Mechanisms of division and selective degradation of peroxisomes in mammals

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ABSTRACT

Peroxisome number and quality are maintained by its biogenesis and turnover and are important for the homeostasis of peroxisomes. Peroxisomes are increased in number by division with dynamic morphological changes including elongation, constriction, and fission. In the course of peroxisomal division, peroxisomal morphogenesis is orchestrated by Pex11β, dynamin-like protein 1 (DLP1), and mitochondrial fission factor (Mff). Conversely, peroxisome number is reduced by its degradation. Peroxisomes are mainly degraded by pexophagy, a type of autophagy specific for peroxisomes. Upon pexophagy, an adaptor protein translocates on peroxisomal membrane and connects peroxisomes to autophagic machineries. Molecular mechanisms of pexophagy are well studied in yeast systems where several specific adaptor proteins are identified. Pexophagy in mammals also proceeds in a manner dependent on adaptor proteins. In this review, we address the recent progress in studies on peroxisome morphogenesis and pexophagy.

1. Introduction

Peroxisomes are single membrane-bounded organelles that function in numerous metabolic pathways, including β-oxidation of very long chain fatty acids, detoxification of hydrogen peroxide, and synthesis of ether phospholipids and bile acids [1–3]. Impairment of peroxisome biogenesis causes peroxisome biogenesis disorders (PBD), termed Zellweger spectrum, including Zellweger syndrome, neonatal adrenoleukodystrophy, infantile Refsum disease, and rhizomelic chondrodysplasia punctata [4,5]. Several hundreds of peroxisomes present in mammalian cells are maintained by a balance between biogenesis and breakdown [6]. The maintenance of peroxisome number and quality is important for the homeostasis of peroxisomes.

Peroxisomes are generated by either division from pre-existing peroxisomes [7–12] and/or *de novo* formation from the endoplasmic reticulum (ER) [1,13,14]. The "growth and division" model of peroxisome biogenesis where peroxisomes grow and multiply by taking up newly synthesized proteins from the cytosol is generally accepted. The regulatory mechanisms of peroxisomal growth and division have attracted considerable attention due to a new disorder defective in peroxisome morphology [15].

Peroxisome abundance can be induced by the expression of *PEX11β* in a manner independent of extracellular stimuli [16] and peroxisomal metabolism [17]. Analyses of the morphological changes of peroxisomes upon induction by the *PEX11β* expression suggest that peroxisome proliferation involves a set of multiple processes including elongation, constriction, and fission of peroxisomes. Such processes are also confirmed in animal models [18]. Given these data, a view of peroxisomal growth and division model comprising elongation, constriction, and fission of peroxisomes is now generally accepted [7,18–21].

Peroxisomes proliferate in response to administration of fibrate derivatives to rodent [22]. Upon withdrawal of the peroxisome proliferators, excess peroxisomes are degraded by pexophagy, a type of autophagy specific for peroxisomes [23,24]. Autophagy is a catabolic process that degrades cytoplasmic components including proteins and organelles in lysosomes (vacuoles in yeast) and is highly conserved in eukaryotes. In the course of autophagy, a cup-shaped membrane sac, termed isolation membrane, engulfs cytoplasmic components, giving rise to double-membrane bound vesicular structure, termed autophagosome. Autophagosomes then fuse with lysosomes/vacuoles to degrade their components [25,26]. Generally, autophagy is drastically induced under starvation conditions. Upon starvation, autophagy degrades cellular components in a non-selective manner and generates nutrients and energy for survival [27]. In addition to non-selective

Abbreviations: A11-BS, Atg11-binding site; ACBD, acyl-CoA binding domain containing; AIM, Atg8-interacting motif; CC, coiled-coil; CHO, Chinese hamster ovary; DHA, docosahexaenoic acid; DLP1, dynamin-like protein 1; ER, endoplasmic reticulum; Fis1, Fission 1; GDAP1, ganglioside-induced differentiation associated protein 1; J-UBA, juxta-UBA; LIR, LC3-interacting region; Mff, mitochondrial fission factor; NBR1, neighbor of BRCA1 gene 1; PB1, phox/bem1; PMP, peroxisomal membrane protein; PTS, peroxisome targeting signal; Ub, ubiquitin; UBA, ubiquitin associated.

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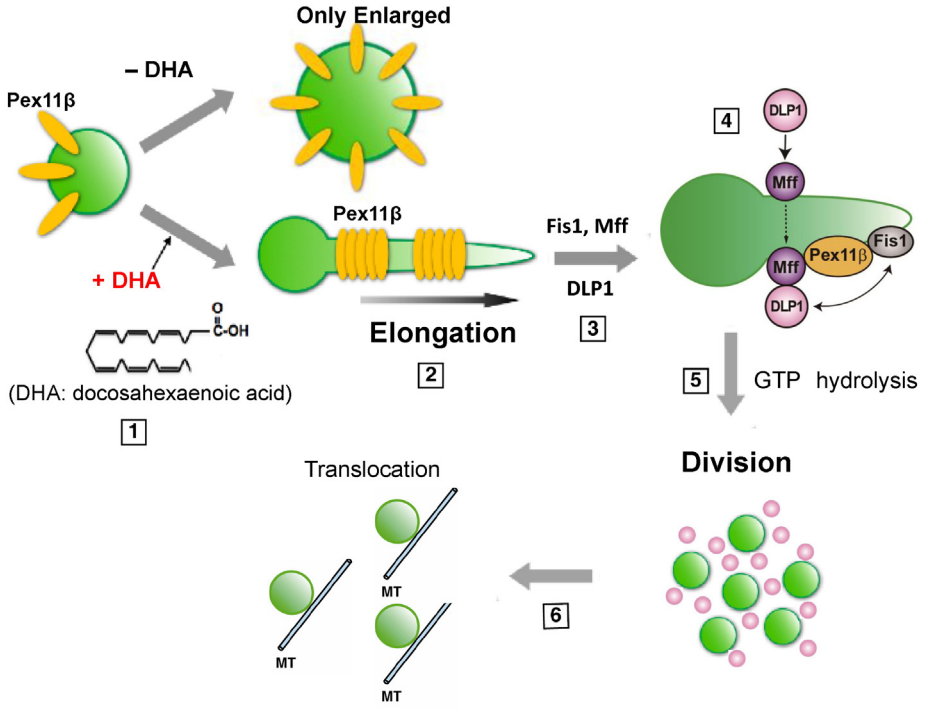

Fig. 1. Model of peroxisome division in mammalian cells. DHA facilitates the oligomerization of Pex11β, which leads to the formation of Pex11β-rich regions and initiates peroxisome elongation (step 1). Peroxisomes elongate there in one direction (step 2). Mff and Fis1 are localized to peroxisomes (step 3), where Mff then recruits DLP1 and the Mff–DLP1 complex translocates to the membrane-constricted regions of elongated peroxisomes. The functional complex comprising Pex11β, Mff, and DLP1 promotes Mff-mediated fission during peroxisomal division (step 4). The complex may include Fis1 that also interacts with DLP1. The activated DLP1 hydrolyzes GTP, by which peroxisomal membranes are cleaved, thereby giving rise to peroxisomal fission (step 5), followed by translocation of daughter peroxisomes via microtubules (MT) (step 6). See the text for details.

type of autophagy, cellular components including damaged organelles, invading bacteria, and aggregated proteins are degraded by selective-autophagy [28]. Thus, peroxisomes, mitochondria, ribosomes, endoplasmic reticulum (ER), lipid droplets, and bacteria are degraded by autophagy, which were respectively called pexophagy [29,30], mitophagy [31–33], ribophagy [34,35], ERphagy [36–38], lipophagy [39–41], and xenophagy [42–44]. Such selective types of autophagy utilize specific adaptor proteins at the surface of substrates for their recognition, while they utilize common general autophagic machineries in an autophagosome formation and subsequent degradation in the lysosome/vacuole system.

Molecular mechanisms underlying the pexophagy are well studied in yeast because the inducing and detection system of pexophagy is established. However, mechanism of pexophagy in mammals was not defined because pexophagy was hardly induced in cultured mammalian cells. Investigation using the cell culture system has an advantage at a molecular level as compared to that with a mouse model. Such a bottleneck has recently been overcome by investigation using several specialized culture conditions or overexpression of pexophagy-related proteins.

In this review, we focus on the molecular mechanisms of peroxisome division and pexophagy in yeast and mammals that are essential for the homeostasis of peroxisomes.

2. Division of peroxisomes

Peroxisomal division comprises three stages: elongation, constriction, and fission (Fig. 1). According to the growth and division model of peroxisomes, it is conceivable that dysfunction of factor(s) required for peroxisome division may induce aberrant peroxisome morphology. Potential candidates thus far studied for the factors involved in such stages include Pex11β, dynamin-like protein 1 (DLP1), mitochondrial fission factor (Mff), and Fission 1 (Fis1).

2.1. Fission machinery of peroxisome

The *PEX11β* knockout (*PEX11β*$^{-/-}$) in mouse [45] and dysfunction of human Pex11β reduce peroxisome abundance and increase elongation of peroxisomes [15]. In addition, aberrant morphology of peroxisomes is reported in a CHO cell mutant [46] and human fibroblasts [47] defective in DLP1, a member of the large GTPase family, and cells knocked-down of *DLP1* [48,49]. The elongated peroxisomes are shown in human fibroblasts defective in Mff [50] and cells in which Mff or Fis1 is knocked-down [51–55]. Similarly, knock-down of ganglioside-induced differentiation associated protein 1 (GDAP1) causes elongation of peroxisomes [56]. It is noteworthy that most of these morphogenesis factors, except for Pex11, are shared with the mitochondria [53,56–58], thereby the loss of functions of these factors also gives rise to mitochondrial elongation.

In mammals, three *PEX11* isoforms, namely *PEX11α*, *PEX11β*, and *PEX11γ* have been identified basically by the homology search for the expressed sequence tag database using yeast *PEX* genes [16,59–62]. All of the isoform gene products are localized to peroxisomes [16,59–61, 63]. *PEX11β* is constitutively expressed, whereas *PEX11α* and *PEX11γ* are expressed in a tissue-specific manner [16,62]. Ectopic expression of *PEX11β* prominently induces peroxisome proliferation via elongation of peroxisomal membrane [16,55]. In contrast, ectopic expression of *PEX11α* shows very limited proliferation-promoting activity [16] and *PEX11γ* expression forms large peroxisomal membrane stacks [58,64]. Accordingly, Pex11β most likely plays a pivotal role in the process of growth and elongation step during the peroxisome division, although the individual functions of mammalian Pex11 family are not fully defined.

DLP1, Fis1, and Mff that are involved in peroxisomal division are originally identified as fission factors in mitochondrial morphogenesis. Recent studies on these factors led to the findings that endogenous DLP1 [46,48], Fis1 [55], and Mff [53] are also localized to peroxisomes.

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