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Review

De novo peroxisome biogenesis: Evolving concepts and conundrums☆

Gaurav Agrawal, Suresh Subramani *

Section of Molecular Biology, Division of Biological Sciences, University of California, San Diego, 9500 Gilman Drive, UC San Diego, La Jolla, CA 92093-0322, USA

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ABSTRACT

Peroxisomes proliferate by growth and division of pre-existing peroxisomes or could arise *de novo*. Though the *de novo* pathway of peroxisome biogenesis is a more recent discovery, several studies have highlighted key mechanistic details of the pathway. The endoplasmic reticulum (ER) is the primary source of lipids and proteins for the newly-formed peroxisomes. More recently, an intricate sorting process functioning at the ER has been proposed, that segregates specific PMPs first to peroxisome-specific ER domains (pER) and then assembles PMPs selectively into distinct pre-peroxisomal vesicles (ppVs) that later fuse to form import-competent peroxisomes. In addition, plausible roles of the three key peroxins Pex3, Pex16 and Pex19, which are also central to the growth and division pathway, have been suggested in the *de novo* process. In this review, we discuss key developments and highlight the unexplored avenues in *de novo* peroxisome biogenesis. This article is part of a Special Issue entitled: Peroxisomes edited by Ralf Erdmann.

1. An introduction to peroxisomes

Early enzyme distribution studies in 1950s with animal cells led to the discovery of peroxisomes. Based on their appearance in liver parenchymal cells as an organelle with a single membrane surrounding a dense and granular matrix, peroxisomes were first named microbodies [1,2]. Later in 1960s, a thorough analysis of their enzymatic content revealed a unique sequestering of a variety of oxidases with catalase, an enzyme critical for the disposal of oxidase-generated hydrogen peroxide, and hence the term 'peroxisome' was proposed [3,4].

Today peroxisomes are known as essential subcellular organelles that are ubiquitously present in all eukaryotes and with glycosomes (protozoan peroxisome) and glyoxysomes (plant peroxisomes) constitute the microbody family. Microbodies share their basic properties and are very adaptable organelles and often exhibit extraordinary specializations. Depending on the species, peroxisomes sequester specific enzymes for metabolizing distinct substrates, which often provide the organism vital adaptability, enabling it to survive in unique environments. For example, in methylotropic yeasts, peroxisomes are essential for utilizing methanol as a carbon source [5]. In animal cells, peroxisomes are essential for the biosynthesis of cholesterol, dolichol, bile acids and most importantly in the β-oxidation of branched chain and very long-chain fatty acids and catabolism of polyamines and D-amino acids [6,7]. Peroxisomes are also essential for the biosynthesis of the glycerophospholipids: plasmalogens, which are highly abundant in the myelin sheath of neurons. Evidently, several peroxisomal biogenesis disorders (PBDs) are associated with the nervous system [8]. In plants, peroxisomes are essential for the glyoxylate cycle and photorespiration [9]. Interestingly, plant peroxisomal proteins are essential for synthesis and delivery of antifungal compounds outside the cell at the site of fungal infections [10,11].

2. Alternate pathways of peroxisome biogenesis

2.1. Growth and division model

Prevailing paradigms of peroxisome biogenesis continue to be actively debated [12]. Early characterization suggested that peroxisomes

Abbreviations: aa, amino acids; ARF1, ADP-ribosylation-factor 1; APX, ascorbate peroxidase; BFA, brefeldin A; BY-2, bright yellow-2; COP, coatomer protein; ER, endoplasmic reticulum; ERES, endoplasmic reticulum exit sites; ERPIC, ER-peroxisome intermediate compartment; ERGIC, ER-Golgi intermediate compartment; GFP, green fluorescent protein; HA, hemagglutinin; p33, 33-kDa replication protein; Pex, peroxin; PBD, peroxisome biogenesis disorder; PMP, Peroxisomal membrane protein; pER, pre-peroxisomal ER; pMVBs, peroxisomal multivesicular bodies; PTS, peroxisome targeting signal; TA proteins, Tail anchored proteins; TBSV, tomato bushy stunt virus; TMD, transmembrane domain.

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* Corresponding author at: Room 3326 Bonner Hall, 9500 Gilman Drive, University California, San Diego, CA 92093-0322, USA.
E-mail address: ssubramani@ucsd.edu (S. Subramani).

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are like mitochondria and chloroplasts in functioning as autonomous organelles of endosymbiont origin that divide by growth and division of pre-existing organelles [13–15]. Supporting this view, cell fractionation experiments depicted several peroxisomal proteins in the soluble fractions, and some of the PMPs tested were synthesized on free ribosomes [14,16–18]. Peroxisomes divide and segregate between the dividing cells like other autonomous organelles. Moreover, peroxisomes have unique peroxisome targeting signals for matrix (PTS1 and PTS2) and membrane proteins (mPTS) and a unique membrane translocation machinery [19,20]. In mammalian cells, the peroxin (proteins involved in peroxisome biogenesis), Pex19, stabilizes newly-synthesized PMPs in the cytosol by binding them through their mPTS sequences [20,21]. Pex19, with its N-terminal Pex3-binding site [22–24], interacts with Pex3 on the peroxisomal membrane, thereby inserting the PMPs into the membrane [25]. However, the growth and division pathway does not account for the source of membrane lipids required for the growth of dividing peroxisomes or the precise mechanism for membrane insertion of Pex3 or even other PMPs (Fig. 1).

2.2. De novo peroxisome biogenesis

Novikoff and colleagues were the first to demonstrate a connection between peroxisomes and the ER [26]. They identified stalk-like structures attaching peroxisomes to certain specialized areas of the smooth ER in the kidney tubule cells of guinea pig. Later in 1990s, the genetic studies identifying the essential genes for peroxisome biogenesis discovered two peroxins Pex3 and Pex19. Although, *pex3*Δ and *pex19*Δ cells were devoid of any detectable peroxisomes,

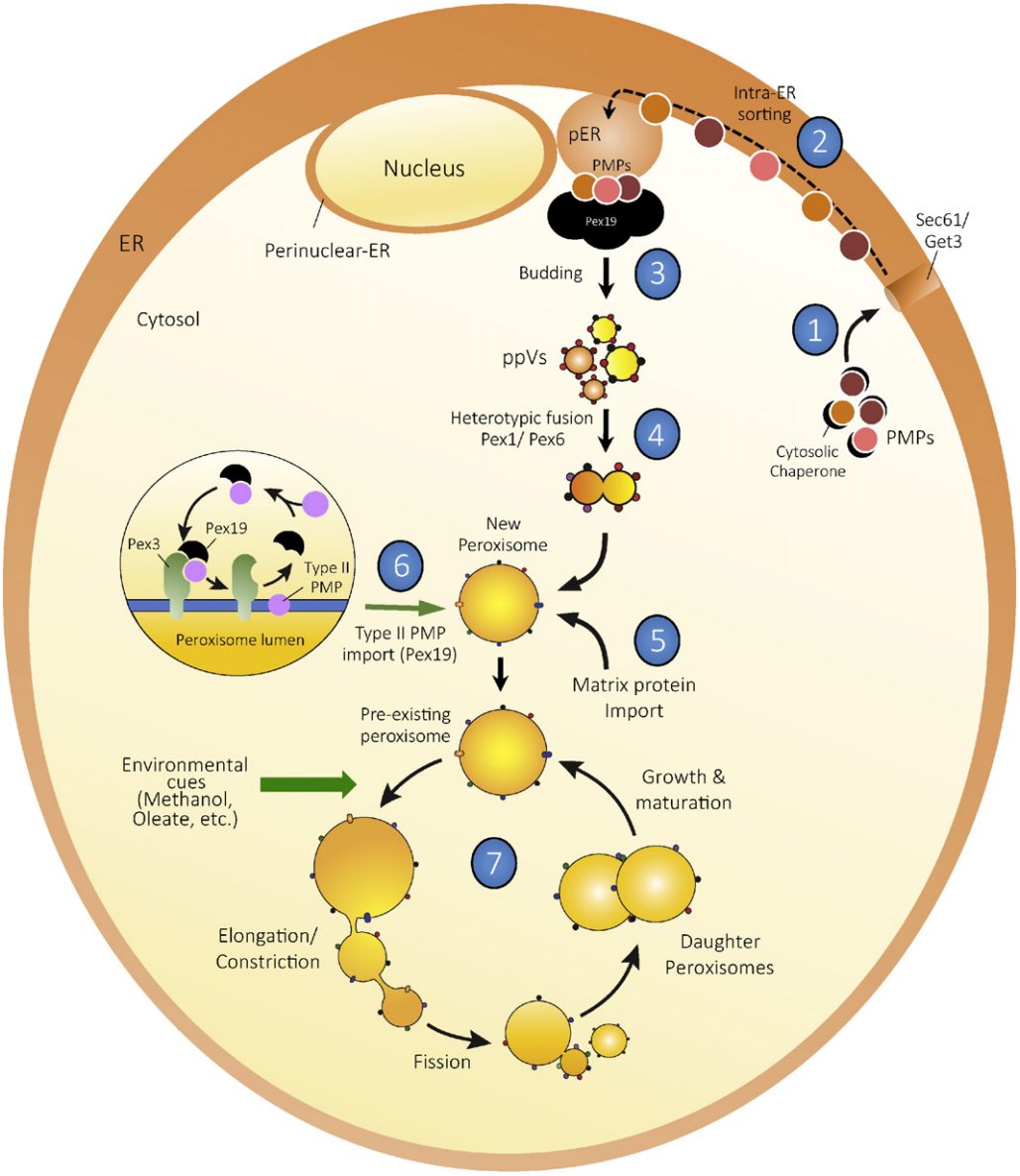

Fig. 1. Schematic representation of peroxisome biogenesis pathways.
1] PMPs are both translated in the cytosol on free ribosomes or on the ER-associated ribosomes and incorporated post-translationally or cotranslationally in the ER-membrane. The ER-translocon, Sec61, is important for the PMP incorporation process. Similarly, TA-proteins are imported into the ER-membrane *via* the GET pathway. 2] Subsequently, an intra-ER sorting process targets the PMPs to respective pER domains. 3] The PMPs are exported from the ER in vesicular carriers and require Pex19. Pex16 is also important for the exit of Pex3 and other PMPs from the ER in mammalian cells. 4] The vesicular carriers containing complementary sets of PMPs fuse to assemble the importomer complex. The fusion process requires peroxins Pex1 and Pex6. 5] This assembly enables the nascent peroxisome to import matrix proteins and become a metabolically active organelle. 6] Type II PMPs are imported directly into the peroxisome membrane with the assistance of Pex3 and Pex19 (inset). 7] The *de novo* route involving the ER also contributes to the cellular peroxisome population, thus sustaining the growth and division pathway and substituting for it when it is blocked or impaired. Using this backup pathway, in mutant cells (such as *pex3*Δ and *pex19*Δ cells) lacking functional pre-existing peroxisomes, reintroduction of the missing gene will form peroxisomes *de novo* and the new peroxisomes that are generated will restart growth and division pathway.