Evolving models for peroxisome biogenesis

Ewald H Hettema¹, Ralf Erdmann², Ida van der Klei³ and Marten Veenhuis³

Significant progress has been made towards our understanding of the mechanism of peroxisome formation, in particular concerning sorting of peroxisomal membrane proteins, matrix protein import and organelle multiplication. Here we evaluate the progress made in recent years. We focus mainly on progress made in yeasts. We indicate the gaps in our knowledge and discuss conflicting models.

Addresses
¹ Department of Molecular Biology and Biotechnology, University of Sheffield, Western Bank, Sheffield S10 2TN, UK
² System Bioch, Ruhr Universitat Bochum, Universitatstr. 150, D-44780, Bochum, Germany
³ Molecular Cell Biology, Groningen Biomolecular Sciences and Biotechnology institute, University of Groningen, 11 103, 9700CC, Groningen, The Netherlands

Corresponding author: Hettema, Ewald H (e.hettema@sheffield.ac.uk)

Introduction

Peroxisomes are eukaryotic organelles bound by a single membrane. Their abundance and functions vary between organisms, cell types and environmental conditions. In a seminal review, Lazarow and Fujiki [1] proposed that peroxisomal membrane and matrix proteins are synthesized on free polyribosomes and imported postranslationally into preexisting peroxisomes. The endoplasmic reticulum was presumed to synthesize the membrane phospholipids of peroxisomes. Thus, they were considered autonomous organelles like mitochondria and chloroplasts. Lazarow and Fujiki stated that one of the implications of this model is that peroxisomes never form de novo [1].

Genetic screens in the late 80s and 90s identified many factors required for import of peroxisomal matrix proteins. The growth and division model was challenged by the discovery that mutants that appear to lack peroxisomal membranes can form peroxisomes de novo from the ER upon complementation. Since then the ER has been central to studies on peroxisome biogenesis. Below we assess the recent literature on peroxisomal matrix protein import and membrane formation.

Posttranslational import of matrix proteins

Protein import into peroxisomes differs from protein import into most other organelles as (1) peroxisomes import folded and even oligomeric proteins and (2) peroxisomal import receptors cycle between a soluble, free form in the cytosol and a cargo-loaded form at the peroxisomal membrane, which is associated with the translocon, and at the end of the cycle is ubiquitinated and released from the membrane in an ATP-dependent process [2]. Peroxisomal matrix proteins contain specific peroxisomal targeting signals (PTS1 or PTS2) that are post-translationally recognized in the cytosol by the import receptors Pex5 and Pex7, respectively [3–7,8**].

Receptor-cargo complexes are directed to a docking complex at the peroxisomal membrane (see Figure 1). The PTS1 receptor mediates cargo binding as well as association with the import machinery, whereas the PTS2 receptor binds cargo but requires auxiliary proteins such as PEX5L in mammals and plants, or proteins of the Pex18 family in fungi for membrane association and cargo translocation [2]. The crystal structure of Pex7 in complex with the Pex18 paralog Pex21 and a PTS2 peptide visualizes the cooperative binding mode of the PTS2 pre-import complex [8**].

The cargo-loaded receptor is thought to assemble with components of the docking complex to form the translocon, which allows translocation of folded proteins across the peroxisomal membrane into the matrix. The current opinion is based on the concept of a transient pore that assembles at the peroxisomal membrane and is disassembled after import, with its components being recycled for further rounds of protein import [9]. The major constituents of the dynamic pore for PTS1 import are the PTS1 receptor and the PMP Pex14: this constitutes the minimal functional unit for translocation of matrix proteins in vivo [10], and in electrophysiological studies it displays features of a regulated pore [11]. A major question is whether PTS1 and PTS2 proteins are imported via common or distinct import pores. Also currently debated is whether the cargo-loaded receptor remains associated with the pore (shuttle hypothesis) or whether it is released as a soluble receptor-cargo complex.
Mono-ubiquitination of receptors is performed by the peroxisomal ubiquitin-conjugating enzyme Pex4 [17]. Mono-ubiquitination is thought to prime the receptor for recognition by a complex of the AAA-type ATPases Pex1 and Pex6, which functions as dislocase to release the modified receptor from the membrane to the cytosol [18,19]. AWP1 has been identified as a cofactor of mammalian Pex6 that binds mono-ubiquitinated Pex5 and is involved in the regulation of Pex5 export [20]. During or shortly after export, the PTS1 receptor is deubiquitinated and thus made available for another round of import [21,22].

The mechanism of how folded proteins are translocated through the peroxisomal pore and also the driving force for this process remain elusive. The tagging of a substrate by monoubiquitylation or polyubiquitylation and its subsequent recognition and ATP-dependent removal from a membrane by ATPases of the AAA-family of proteins, resembles the mechanism of the membrane release of proteins for ER-associated degradation (ERAD) [23,24]. As the ATP-dependent release of the ubiquitinated peroxisomal receptor from the membrane is the energy-requiring step of the matrix protein import cascade, the
peroxisomal AAA peroxins might induce conformational changes of the receptor in an ATP-dependent manner that allows receptor release and cargo translocation. This link of receptor export and protein import is described by the export-driven import model [23].

**Different mechanisms of PMP sorting**

Until recently, two classes of PMPs were distinguished based on their Pex19 dependence for targeting to peroxisomes [25]. Class 1 PMPs contain targeting information that is recognized by Pex19, which binds newly synthesized PMPs in the cytosol and acts as a chaperone/targeting receptor, thus (1) preventing them from aggregating and (2) delivering them to the peroxisomal membrane for docking on Pex3 [26–28]. Although posttranslational targeting of PMPs to peroxisomes *in vivo* and *in vitro* is well documented [25,28–31,32**], the mechanism of insertion remains unclear. The central role of Pex3 and Pex19 in PMP biogenesis is evident from the phenotype of *pec3* and *pex19* mutants, in which peroxisomal membranes are undetectable and class I PMPs are unstable or mislocalized [33]. On the basis of these observations we propose that these mutants lack any peroxisomal structures.

Class 2 PMPs, the best-studied example of which is Pex3, contain targeting signals that are not recognized by Pex19. Upon *de novo* formation of peroxisomes by induction of Pex3 expression in *S. cerevisiae* *pex3* cells, most data support a model whereby Pex3 enters the ER and forms preperoxisomes that develop into peroxisomes [34–36]. Its targeting and subsequent sorting signals have been described [37,38], and the ER translocon has been implicated in this process [37]. *In vitro* budding reactions release vesicles containing Pex3, dependent on Pex19, cytosol and ATP [39,40]. Budding occurs independently of the machinery required for ER exit of secretory proteins. These vesicles therefore might represent transport vesicles that fuse with pre-existing peroxisomes, thereby delivering Pex3 and lipids to peroxisomes (Figure 2).

![Figure 2](https://www.sciencedirect.com)
As Pex3 is not observed in the ER of WT cells, one has to propose that its transit through the ER is fast. Thus far, Pex3 has been visualized in the ER only after overexpression, or by using mutant versions appended with large tags in cells blocked in peroxisome formation (pex19 or pex3 cells). It is therefore possible that yeast Pex3 bypasses the ER in wild type cells and is inserted directly into the peroxisomal membrane as has been reported for human Pex3 [41]. In line with this is the study by Knoops et al. [42]. They could detect no ER pool of Pex3 after its reintroduction into pex3 cells and propose that H. polymorpha Pex3 bypasses the ER altogether (see also below). This is an issue that needs further investigation.

Recently, detailed microscopy studies challenged the view that pex3 and pex19 cells are devoid of peroxisomal structures with the finding that the H. polymorpha pex3 and pex19 cells contain pre-peroxisomes to which Pex13 and Pex14 localise [42]. This suggests that Pex13 and Pex14 represent a third class of PMPs that also sort independent of Pex3 and Pex19. Pex13-containing membrane structures have been found in Pichia pastoris pex3 cells [43], and in S. cerevisiae pex3 and pex19 cells [44]. Furthermore, mammalian Pex13 inserts into membranes independent of Pex19 [45]. Also, Pex13 is required for Pex14 sorting [46], underlining that these PMPs behave differently from class I and II PMPs.

**Peroxisome multiplication and the contribution of the ER**

In wild type yeast cells, peroxisomes receive newly synthesized membrane and matrix proteins and lipids (growth) and multiply by fission [38,47,48,49,50]. Peroxisome fission is mediated by dynamin-related proteins and Pex11 (for recent review see [51]). Most peroxisomal membrane lipids are synthesized in the ER. They may be directly transferred from the ER to peroxisomes [59] or reach peroxisomes via vesicular transport. However, it has also been proposed that peroxisomal membranes derive from the ER via budding of vesicles containing PMPs. Tabak and coworkers recently reported that all newly synthesized S. cerevisiae PMPs insert into the ER, and that the Pex13/14 docking complex and the RING-finger complex exit the ER in distinct vesicles [44,52]. These ‘half importer’ complexes were proposed to be brought together by heterotypic vesicle fusion dependent on Pex1 and Pex6, forming a pre-peroxisomal membrane structure able to import matrix proteins. Subsequent fission would produce peroxisomes of final size and membrane composition (Figure 2). Besides being responsible for de novo formation of peroxisomes in peroxisome-deficient mutant cells, Tabak and coworkers claim that this mechanism also provides a ‘continuous stream’ of de novo formed peroxisomes in wild type cells [52,53]. Although elegant, this model is irreconcilable with many of the independent studies described above. This model disregards for instance the well established role of Pex19-dependent posttranslational insertion of newly synthesized PMPs directly into peroxisomes [25–31,32**, the mislocalisation of many S. cerevisiae PMPs to the cytosol in pex3 and pex19 cells [33], and that new peroxisomes are derived from preexisting peroxisomes [47–50]. Furthermore, Pex25 is required for de novo peroxisome formation, but most pex25 cells contain peroxisomes, which suggests the de novo pathway is not essential for peroxisome maintenance [54**,55]. Additionally, the studies by Knoops et al. [42] indicated that not the ER, but the Pex13/Pex14-containing structures present in H. polymorpha pex3 cells are the target for reintroduced Pex3. Although the origin of the Pex13/Pex14 preperoxisomal structures is unclear, their formation is independent of Pex3.

The shape of the ER appears to affect peroxisome multiplication. Pex30 is a Class 2 PMP [56] that localises to both peroxisomes and an ER subdomain found in close association with peroxisomes [57,58**]. It has been postulated that new peroxisomes can form from these ER subdomains. Interestingly, COPI components were found in complex with Pex30, although the functional significance of this is unclear. The ER reticulons Rtn1, Rtn2 and Ypo1 were identified as core components of Pex30 complexes. ER reticulons are important for maintaining the morphology of tubular ER by stabilizing the strongly curved membranes. Interestingly, in cells lacking the ER reticulons or Pex30, de novo formation of peroxisomes is accelerated [58**]. Whether these mutants form peroxisomes de novo all the time is not known.

**A multi-step model for peroxisome biogenesis**

There is overwhelming evidence in favor of a growth and division model, whereby the insertion machinery for Class1 PMPs is central. As Pex3 is present at steady-state on peroxisomes in wild type cells, Pex19 bound to newly synthesized Class1 PMPs may dock here to deliver them. Class 2 PMPs, including Pex3, traffic via the ER and vesicular transport to peroxisomes. This route may provide sufficient membrane constituents for continuing growth and division of peroxisomes, although a non-vesicular membrane transfer may contribute as well [59]. In cells forming peroxisomes de novo, Pex3 first inserts in the ER and sorts to preperoxisomes, where it facilitates Class 1 PMP insertion, allowing these membrane structures to import matrix proteins and mature into peroxisomes. Pex13 and Pex14 may follow the Pex3 route in cells synthesizing peroxisomes de novo, or they may bypass the ER and insert directly into preperoxisomes that can form independently of Pex3. Whether Pex13 and Pex14 follow this route in wild type cells is an important question and remains to be determined.

**Concluding remarks**

The global mechanisms of peroxisome membrane biogenesis and matrix protein import are becoming clear, but
many questions remain. To mention but a few: how are ER-inserted PMPs sorted away from the secretory pathway? How do PMPs leave the ER, and how are they delivered specifically to peroxisomes? Do Class1 PMPs insert spontaneously into peroxisomal membranes after targeting, or is a specialised machinery required? How is peroxisome size and number regulated? Which proteins make up the pores for matrix protein import, and how is matrix protein translocation mediated? New approaches will need to be developed to shed light on these questions.

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