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Minireview

Protein translocation machineries of peroxisomes

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Abstract Targeting of peroxisomal matrix and membrane proteins is performed by distinct transport machineries and requires the concerted action of at least 23 peroxins. Cargo recognition takes place in the cytosol and the multiple binding sites for peroxisomal signal sequence receptors at the peroxisomal membrane reflect the existence of an import cascade where the cargo-loaded receptors successively interact with different components of the import machinery. These interactions are likely to trigger conformational changes of the proteins within the import cascade which are required for the consecutive steps of peroxisomal protein import: docking, translocation, cargo release and receptor recycling.

Key words: Peroxisome biogenesis; Protein targeting; Peroxin

1. Introduction

Peroxisomes are almost ubiquitously found in eukaryotic cells and belong to the microbody family of organelles along with glyoxysomes of plants and glycosomes of trypanosomes. They are single-membrane bound and spherical subcellular compartments which differ in size (0.1–1 μm in diameter), number and protein composition between cell types. Defects in the structure and/or function of peroxisomes have profound clinical consequences and lead to mostly fatal inborn errors, the peroxisomal disorders (for a review see [1]). The peroxisomal matrix houses enzymes involved in for example H_2O_2 metabolism, β-oxidation of fatty acids, synthesis of cholesterol, bile acids and plasmalogens in mammals, the glyoxylate cycle in plants and methanol oxidation in yeasts [2].

The biogenesis of peroxisomes conceptually consists of (i) the formation of the peroxisome membrane including the acquisition of peroxisomal membrane proteins (PMPs), (ii) the import of peroxisomal matrix proteins, and (iii) the proliferation of peroxisomes. Peroxisome generation is a conserved process from yeast to man. At present, 23 *PEX* genes have been identified which encode proteins that are essential for the biogenesis of peroxisomes, collectively called peroxins [3–5]. Different models for the formation of peroxisomes have been favored over the years. Originally, it was assumed that peroxisomes form by budding from the endoplasmic reticulum (ER) [6]. Since 1985, the 'growth and division' model of Lazarow and Fujiki [7] has been broadly accepted, and it is supported by experimental evidence. It suggests that new peroxisomes form by division and fission of pre-existing ones after the import of newly synthesized proteins from the cytosol. In recent years, however, accumulating evidence suggests that vesicles which originate from the ER or other kinds of endomembranes might be involved in the formation of the peroxisomal membrane and, thus, de novo formation of peroxisomes might be possible. The intriguing questions on the cellular origin of peroxisomes have been reviewed recently in detail by others (reviewed in e.g. [8,9]).

The aim of this review is to summarize the recent progress in our understanding of the cellular machineries required for the topogenesis of peroxisomal proteins. Most interestingly, in contrast to what is known from the majority of other cellular organelles, peroxisomes can import folded, even oligomeric proteins (e.g. [10,11]). And, as outlined in Fig. 1, targeting and import/insertion of the peroxisomal matrix and membrane proteins is performed by distinct transport machineries [12,13]. Thus, the elucidation of the peroxisomal protein import is expected to add new principles to the paradigms of organelle biogenesis and protein translocation.

2. Import of peroxisomal matrix proteins

2.1. Cargo recognition and peroxisomal targeting

Peroxisomes acquire their matrix proteins by post-translational import from the cytosol via two pathways that rely on two conserved peroxisomal targeting signals (PTS). The vast majority of peroxisomal matrix proteins possesses a PTS1 at the extreme C-terminus consisting of the tripeptide SKL sequence or species-specific variants [14,15]. The PTS2 is found near the N-terminus of only a few matrix proteins and has the consensus sequence (R/K)(L/V/I)X_5(H/Q)(L/A) [15,16]. PTS2-containing proteins are recognized by the WD40 protein Pex7p [17,18]. Surprisingly, the PTS2 pathway for matrix protein import is completely lost in the nematode *Caenorhabditis elegans* [19]. The worm has compensated this otherwise fatal disadvantage by switching from PTS2 solely to PTS1 recognition of matrix proteins.

Pex5p, the receptor for PTS1 [20], interacts with the signal via six tetratricopeptide repeats (TPRs) within its C-terminal half. The crystal structure of the C-terminal domain of human

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Abbreviations: PTS, peroxisomal targeting signal; PMP, peroxisomal membrane protein; TPR, tetratricopeptide repeats; SH3, Src homology 3; ER, endoplasmic reticulum

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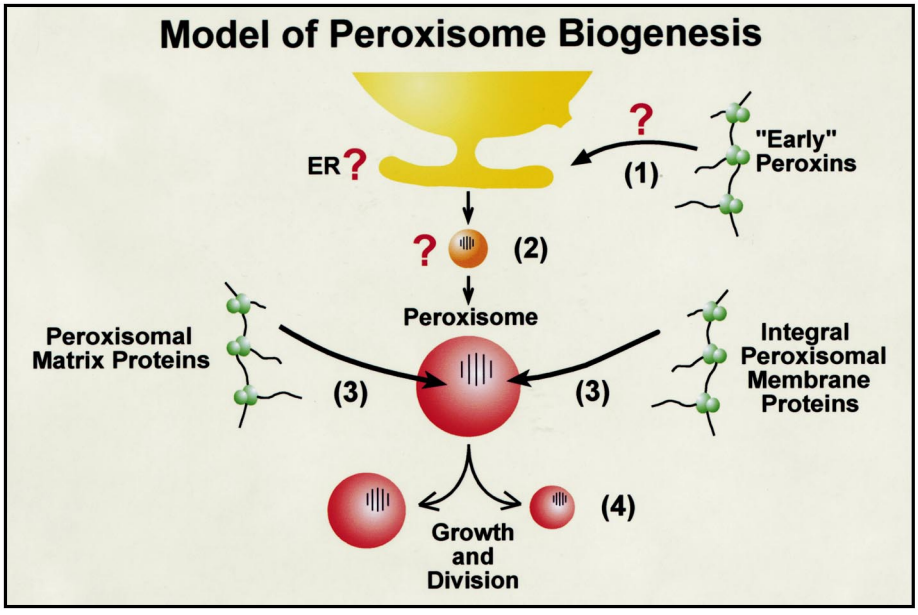

Fig. 1. Model of peroxisome biogenesis. The topogenesis of peroxisomal matrix and membrane proteins is performed by distinct transport machineries. (1) A subset of PMPs, likely peroxins involved in the early stages of peroxisome biogenesis ('early' peroxins), are supposed to insert into endomembranes, presumably the ER. (2) Vesicles harboring these PMPs bud from the ER and fuse with peroxisomes. (3) Peroxisomal matrix proteins and other PMPs are synthesized on free ribosomes in the cytosol and imported post-translationally into peroxisomes. (4) Peroxisomes grow and undergo fission to form new peroxisomes.

Pex5p in complex with a PTS1 revealed that two clusters of three TPRs almost completely surround the peptide [21]. Certain chaperones or auxiliary targeting factors have been identified which might act in tandem with the peroxisomal import receptors in cargo recognition and/or peroxisomal targeting. These are Hsp70, the DnaJ-like protein Djp1p, as well as the two related peroxins Pex18p and Pex21p that specifically bind to Pex7p [22–24].

A remarkable finding concerning the early stages of matrix protein import comes from the studies on Pex5p in mammalian cells. In CHO cells as well as in human fibroblasts, a short and a long isoform of Pex5p have been identified, termed Pex5pS and Pex5pL. These proteins differ only by an insertion of 37 amino acids in Pex5pL [25,26]. It has been shown for mammalian cells that protein targeting to peroxisomes via the PTS2 pathway requires the interaction of the Pex7p–PTS2 protein complex with Pex5pL [26,27]. In yeast, the import routes for PTS1 and PTS2 proteins meet at the peroxisomal docking complex (see below). In mammals, however, both PTS pathways might converge already in the cytosol at the level of the PTS1 receptor Pex5pL.

Taken together, these new results indicate that although the general principles of peroxisome matrix protein targeting are conserved, species-specific differences and variations have emerged.

2.2. Docking

The original 'hypothesis of shuttling receptors' assumes that the PTS receptors cycle between the cytosol and the peroxisomal membrane. They recognize and bind their cargo proteins in the cytosol and deliver them to a docking and translocation machinery at the peroxisomal membrane. After the release of the cargo proteins to the translocation machinery, the receptors shuttle back to the cytosol [17,28].

The import receptors Pex5p and Pex7p are predominantly localized in the cytosol and at the peroxisomal membrane (e.g. [28]). However, a fraction of Pex5p is even found in the lumen of peroxisomes (e.g. [29]) which gave rise to the 'extended shuttle hypothesis' of peroxisomal protein import [30]. This model suggests that the PTS receptors do not release the cargo proteins after the docking step but instead enter the peroxisomal matrix together with the cargo proteins. The receptors release their cargo in the peroxisomal lumen and are subsequently recycled to the cytosol.

The docking complex of the peroxisomal import machinery for matrix proteins comprises the three peroxins Pex13p, Pex14p and Pex17p. Pex17p is a peripheral PMP which associates with the peroxisomal membrane via Pex14p [31]. Pex13p is an integral PMP with both its C- and N-termini extending into the cytosol. The C-terminal region contains a Src homology 3 (SH3) domain which directly binds Pex5p as well as Pex14p (for review see [8]) whereas the N-terminal region is required for direct or indirect interaction with Pex7p [32]. It has been suggested that Pex5p and Pex14p bind to the SH3 domain at distinct sites [32–34]. Binding of Pex14p to the SH3 domain is mediated by a typical proline-rich SH3 ligand motif [32,34] while binding of Pex5p to Pex13p shows a novel mode of SH3 interaction which depends on a 25 amino acid α-helical element within the Pex5p sequence [33]. Cargo binding seems to alter the affinity of Pex5p to Pex14p and Pex13p [35]. As outlined in Fig. 2, both Pex13p and Pex14p could provide the initial binding sites for Pex5p and Pex7p. However, in pex14Δ mutants of *Hansenula polymorpha*, the import defect for PTS1 proteins could be complemented by overexpression of Pex5p [36]. Moreover, overexpression of Pex14p but not Pex10p, Pex12p or Pex13p caused accumulation of Pex5p in peroxisomes of mammalian cells [26]. These data support the notion that Pex14p might function at the earliest step in docking of Pex5p at the peroxisomal membrane.

2.3. Translocation, receptor recycling and evidence for an import cascade

The mechanism of translocation and the components of the translocon have not yet been identified. It could well be that the docking proteins themselves are part of the translocon. The multiple binding sites for Pex5p at the peroxisomal membrane might reflect the existence of an import cascade where the cargo-loaded receptor successively interacts with the different components of the import machinery [8]. This import cascade might either lead to a vectorial transport of the PTS1 receptor across the peroxisomal membrane and/or trigger conformational changes in the involved components which are required for docking, translocation, cargo release and recycling of the receptor. In support of the existence of an import cascade, further binding sites for Pex5p among components of the import machinery have been reported. Pex5p has recently been shown to also interact with Pex8p [37], a peroxin associated with the matrix side of the peroxisomal membrane as well as with Pex12p (see below).

In cells lacking Pex8p, the PTS1 receptor still associates with membrane-bound components of the import machinery, suggesting that the Pex8p function follows the docking event [37]. Pex8p of *Yarrowia lipolytica* also forms a complex with Pex20p, a predominantly cytosolic protein which has been shown to function in PTS2-dependent protein import [38]. The function of Pex20p has not yet been elucidated in great detail but it is likely that it contributes to cargo recognition and/or peroxisomal targeting of newly synthesized PTS2 proteins. Remarkably, in mutants deficient in Pex8p, Pex20p is associated with peroxisomes in a protease-protected manner [39]. This finding supports the notion that Pex8p might function in the dissociation of the cargo–receptor complexes and/or recycling of the PTS receptors to the cytosol and supports the 'extended shuttle' model of peroxisomal protein import.

The RING finger peroxins Pex2p, Pex10p and Pex12p are integral PMPs which are likely to form a heteromeric complex that is thought to act downstream of receptor docking. Pex12p and Pex10p interact with each other via their C-terminal zinc RING domains and Pex12p binds Pex5p through the zinc RING domain, too [40,41]. The loss of Pex12p and Pex10p does not reduce the amount of Pex5p associated with peroxisomes, indicating that these proteins are not required for receptor docking [40]. The defined function of the RING finger peroxins has not yet been elucidated. Recent data suggest that Pex12p might also be associated with components of the docking complex, indicating that the RING finger complex and the docking complex might be physically associated in vivo [42].

An epistasis analysis of Gould and coworkers recently suggested that the peroxins Pex1p and Pex6p as well as Pex4p and Pex22p function in a step after the cargo proteins have reached the peroxisomal lumen [43]. Consistent with this assumption, *pex1*, *pex6*, *pex4* and *pex22* mutants possess peroxisomes that still import detectable amounts of matrix proteins. Pex22p was identified as an integral PMP that interacts with the E2-type ubiquitin-conjugating enzyme Pex4p and anchors it to the cytosolic face of peroxisomes [44,45]. In *H. polymorpha*, the deficiency in Pex4p can be suppressed by overexpression of Pex5p [46] and under this condition, the overexpressed Pex5p specifically accumulates at the lumenal side of the peroxisomal membrane. The PTS1 receptor has also been shown to accumulate inside peroxisomes in a patient with a mutation in *PEX10* [28]. These data suggest that the RING finger peroxins and Pex4p/Pex22p play an essential role in the normal functioning of Pex5p, possibly in mediating recycling of Pex5p from the peroxisome to the cytosol.

How might a ubiquitin-conjugating enzyme like Pex4p perform its function in this cellular process? It is interesting to

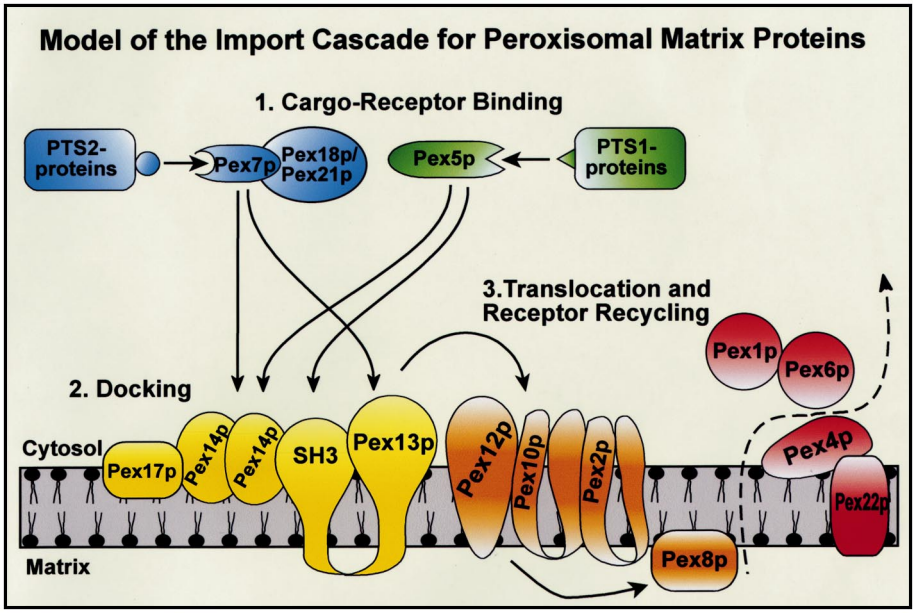

Fig. 2. Peroxisomal matrix protein import cascade. Proteins harboring one of the two PTSs, PTS1 or PTS2, are recognized in the cytosol by specific signal sequence receptors (Pex5p and Pex7p). The multiple binding sites for peroxisomal signal sequence receptors at the peroxisomal membrane reflect the existence of an import cascade where the cargo-loaded receptors successively interact with different components of the import machinery. These interactions are likely to trigger conformational changes of the proteins within the import cascade which are required for the consecutive steps of peroxisomal protein import: docking, translocation, cargo release and receptor recycling. How protein translocation proceeds through the peroxisomal membrane has not yet been resolved.

note that RING finger proteins have been implicated as mediators of ubiquitin ligase activity (for review see [47]). This opens the possibility that the peroxisomal RING finger complex might act in tandem with the Pex22p/Pex4p ubiquitin-conjugating enzyme complex in catalyzing a protein modification which leads to the translocation or recycling of the PTS receptors.

Pex1p and Pex6p are two membrane-associated ATPases of the AAA family [48–50]. This type of ATPase is known to function in all types of membrane fusion events discovered so far by binding to and disrupting specific oligomeric protein complexes formed at the membrane [51]. In line with these findings, Pex1p and Pex6p have been reported to play a role early in peroxisome assembly in the fusion reaction of small peroxisomal vesicles in *Y. lipolytica* (reviewed in [9]). According to Collins et al. [43] Pex1p and Pex6p act upstream of Pex4p and Pex22p but downstream of receptor docking and translocation. Therefore, the ATPases could function in the release of the receptors from the translocation machinery thereby allowing its transfer to the Pex4p–Pex22p complex and further recycling. However, these findings observed in *Pichia pastoris* are in clear discrepancy to the proposed function of Pex1p and Pex6p in early peroxisome fusion in *Y. lipolytica* [9]. It will be interesting to find out which of the two proposed roles for the AAA peroxins will turn out to be true. The various interactions among peroxins within the proposed import cascade for peroxisomal matrix proteins are illustrated in Fig. 2.

3. Insertion of PMPs

Genetic studies revealed that the post-translational sorting of PMPs from the cytosol to the peroxisomal membrane occurs independently of the import of matrix proteins and, thus, is performed by a distinct transport machinery. This was demonstrated by the observation that the targeting and insertion of PMPs is not affected in cells lacking essential components of the import machinery for peroxisomal matrix proteins [12,13]. The peroxisomal membrane targeting signals (mPTS) characterized thus far are clearly distinct from PTS1 and PTS2 and mostly comprise at least parts of a transmembrane segment [52–56].

Our knowledge of the mechanism of PMP targeting and insertion is still rather scarce. Most *pex* mutants show a matrix protein import defect but are characterized by PMP-containing peroxisomal ghosts, suggesting that targeting of PMPs is still functional [57]. However, cells deficient in Pex3p, Pex16p or Pex19p lack these peroxisomal remnants and mislocalize the PMPs to the cytosol where they are rapidly degraded [58,59]. Thus, Pex3p, Pex16p and Pex19p play essential roles in the biogenesis of the peroxisomal membrane and are likely to be components of the import machinery for PMPs. Small vesicular remnants distinct from the typical peroxisomal membrane ghosts have been observed in the *pex19* mutant [60]. These vesicle remnants still contain Pex3p, suggesting that Pex3p might play a role in the very early steps of peroxisome biogenesis.

Remarkably, Pex19p is distributed between the cytosol and the peroxisomal membrane and has been shown to bind multiple PMPs, including Pex3p [61,62]. These properties would be consistent with Pex19p being a mobile mPTS receptor and Pex3p being part of the corresponding docking site at the peroxisomal membrane. In this scenario, Pex19p would cycle between the peroxisomal membrane and the cytosol in analogy to the function of the PTS receptors for matrix protein import. This, however, requires that Pex19p specifically recognizes the mPTS of PMPs, a presumption which has not yet been convincingly demonstrated. In contrast, it has been shown that the binding regions for Pex19p and mPTSs are clearly distinct in at least three (Pex3p, Pex13p and Pex22p) of the PMPs tested [53,63]. Nevertheless, it may well be that distinct mPTSs exist for PMPs with different functions. We still have to consider that some PMPs, especially peroxins, might contain mPTSs which direct them to peroxisomes in a distinct way, possibly via the ER. It may turn out that different mPTS pathways for PMPs exist with one of them being mediated by Pex19p.

4. Concluding remarks

Twenty-three peroxins are known to date which are all required for the biogenesis of peroxisomes. We have identified many interactions between these peroxins and we have categorized them into groups which are likely to perform certain aspects of the assembly of these organelles. However, our knowledge of the molecular principles of these cellular processes is still scarce. A major challenge will be to find out how folded and oligomeric matrix proteins traverse the peroxisomal membrane. Structures like nuclear pores have not been detected in the peroxisomal membrane. A recent report, however, described that the peroxisome-associated Pex5p fraction behaves as a transmembrane protein with domains exposed on both sides of the peroxisomal membrane [64]. Moreover, the peroxisomal Pex5p was found in a stable, high molecular weight complex with Pex14p with an estimated Pex5p:Pex14p ratio of 1:5. Thus, such a membrane-spanning complex could be the long sought-after candidate to form pores in the peroxisomal membrane for matrix protein import. An alternative pathway for the import of folded proteins might include an invagination process of the peroxisomal membrane [10]. Proteins destined for import might be directed to a certain site at the surface of peroxisomes, which upon binding invaginates to form a vesicle which buds into the peroxisomal lumen. Degradation of the vesicle membranes or redistribution of the lipids to the peroxisomal membrane would result in the release of the cargo proteins into the peroxisomal lumen.

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