The novel peroxin Pex37: the Pxmp2 family joins the peroxisomal fission machinery

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Peroxisomes can undergo fission during cell division, followed by their segregation between mother and daughter cells. Despite species-specific variations in the molecular composition of the fission machinery, the central mechanistic factors can be assigned to two groups: the Pex11 family and the dynamin-related protein family. In a recent study, Singh et al. describe the involvement of a member of the Pxmp2-related protein family in peroxisome fission: the novel peroxin Pex37.

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The division of eukaryotic cells is accompanied by the distribution of the different organelles between mother and daughter cells. In the case of peroxisomes, this segregation is preceded by division of the organelles. Despite species-specific variations in the molecular composition of the fission machinery, the central mechanistic factors can be assigned to two groups: the Pex11 family and the dynamin-related protein (DRP) family. In a recent study, Singh et al. [1] describe the involvement of a member of the Pxmp2-related protein family in peroxisome fission: the novel peroxin Pex37.

Peroxisomal fission is an important cellular process, and its dysfunction leads to severe disorders in humans [2]. It is assumed that peroxisomes divide mainly during two scenarios: (a) either upon induction of peroxisomal proliferation via upregulation of the gene expression of peroxisomal biogenesis factors under peroxisome-inducing conditions, or (b) as part of a concerted mechanism of organelle distribution between mother and daughter cell, during cell budding. In the second scenario, the mother peroxisome is retained in the mother cell via its binding to the cortical endoplasmic reticulum (cER), mediated by Inp1 and Pex3, while the daughter peroxisome is transported to the daughter cell via the motor protein Myo2 bound to its peroxisomal adaptor Inp2. The current model for the

Abbreviations

DRP, dynamin-related protein; cER, cortical endoplasmic reticulum.
peroxisomal fission process itself (reviewed in Ref. [3]) defines three separate steps, consisting of (a) elongation, (b) constriction and (c) scission of the organelle. The elongation step depends on the highly abundant peroxisomal membrane protein Pex11, which forms a small protein family together with Pex25 and Pex27 in *Saccharomyces cerevisiae*. Similarly, Pex11β and the related proteins Pex11α and Pex11γ were identified in mammals. The functional role of Pex11 in the elongation step is thought to be mediated by the extreme N-terminal domain of Pex11, which is able to adopt an amphipathic α-helical structure that induces membrane curvature and finally organelle tubulation. The molecular mechanism underlying the second step, peroxisome constriction, is only poorly understood and it is assumed that it could represent the starting point of the final scission process, which is carried out by DRPs. These large GTPases execute scission of the membrane by forming ring-like structures that tighten upon GTP hydrolysis until the membrane finally severs. Mammalian cells contain Drp1 (Dlp1) as DRP, which, together with its membrane-bound cofactors Fis1 and Mff, is also involved in the fission of mitochondria. The corresponding *S. cerevisiae* DRP is Dnm1, which is mainly required for peroxisomal proliferation under peroxisome-inducing conditions. *S. cerevisiae* exhibits with Vps1, a second DRP involved in peroxisome fission, which seems to be more required under glucose conditions. However, for peroxisome fission both DRPs are still partially redundant in their function [3].

Direct evidence for the existence of a clearly condition-selective fission machinery component in addition to the Pex11 family and DRP family was presented in a recent study by Singh *et al.* [1] in the methylotrophic yeast *Hansenula polymorpha*. In this organism, Dnm1 is the only DLP required for the scission step both under peroxisome-inducing conditions (methanol medium) and under peroxisome-repressing conditions (glucose medium) [4]. Moreover, Pex11 was demonstrated to have a central role in peroxisome fission under both conditions. It is not only required for the elongation step due to its membrane remodelling abilities [5,6], but it also contributes to the scission step by functioning as a GTPase-activating protein for the GTPase Dnm1 [7].

Glucose-grown *H. polymorpha* cells usually contain one peroxisome, which divides during cell budding in order to inherit the newly formed peroxisome to the daughter cell (Fig. 1A). The *pex11Δ* cells contain one enlarged peroxisome, which does not undergo elongation and which is transported to the daughter cell, resulting in a peroxisome-deficient mother cell in glucose-grown cells [5]. The *inp1Δ* strain shows a similar distribution behaviour, indicating a role of Pex11 also in the functional integrity of Inp1 [5]. Because Dnm1 acts at a later time point in the fission process, *dnm1Δ* cells display an elongated peroxisome, whose protrusion reaches into the bud. This protrusion is cut by cytokinesis, resulting in the presence of peroxisomes in both mother and daughter cells [4].

The novel peroxin Pex37 (Hp32g403) affects peroxisome abundance only in glucose-grown but not in methanol-grown cells [1]. The fission and segregation phenotype of *pex37Δ* cells differs from the other mutant strains in that the single peroxisome is either present in the mother cell or in the daughter cell. The finding that overexpression of Pex37 results in an increase in the number of small peroxisomes in a Dnm1-dependent manner indicates that Pex37 acts upstream of the Dnm1-mediated scission step. Moreover, the absence of Pex37 blocks the formation of the peroxisomal protrusion, suggesting that it also acts upstream of the Pex11-mediated elongation step. In contrast, the absence of Pex37 had no effect on the association of peroxisomes with the cortical ER, suggesting that it might act downstream of the Inp1-mediated anchoring of the organelle to the cell periphery (Fig. 1B).

The combination of this epistasis analysis as well as the peculiar phenotype of peroxisome distribution between mother and daughter cells suggests a potential role of Pex37 in the balancing of the Inp1/Pex3-mediated retention force and the Inp2/Myo2-mediated pulling force acting on the peroxisome during fission and segregation. The exact mechanistic role of Pex37 in these processes remains to be elucidated.

Besides these still to solve mechanistic aspects, the intriguing question remains why Pex37 is only required in glucose-grown cells and not in methanol-grown cells. Because each *H. polymorpha* cell normally contains only one peroxisome under glucose conditions, the coordination of peroxisome fission and distribution between the mother and the daughter cells is of crucial importance and has to be regulated tightly. Even though peroxisomal fission in *H. polymorpha* seems to depend only on Pex11 and Dnm1, there is additional need for condition-specific factors. As reported earlier by the discoverers of Pex27, *pex11Δ* mother cells lost their peroxisome to the daughter cell under glucose conditions [5], while the *pex11Δ* mother cells could retain their peroxisome under methanol conditions. Under these conditions, only a peroxisomal membrane fragment is inherited to the daughter cell, which then is capable to form a new peroxisome [8]. Therefore, it is conceivable that selective factors such as Pex37 are especially relevant under glucose conditions.
Another interesting aspect of Pex37 is that it has been identified as a *H. polymorpha* homolog of the human Pxmp2, which is one of the founding members of the Pxmp2-related protein family [1,9]. These proteins share a common consensus sequence and four hydrophobic motifs that might represent transmembrane domains. This fits to the finding that the Pxmp2-related proteins localize to the membranes of different organelles. Members of this protein family are present in all analysed eukaryotic cells. A common function for them has not yet been described. However, it is interesting to note that several members have been demonstrated to function as nonselective ion channels, like the human Mpv17 [9] and its *S. cerevisiae* homolog Sym1 [10] at the inner mitochondrial membrane or the human Pxmp2 at the peroxisomal membrane [11].

The idea that the Pxmp2 homolog Pex37 might potentially also have pore-forming abilities is even more striking as also the other membrane protein
factor required for peroxisomal fission, namely Pex11, can function as a nonselective channel as well in *S. cerevisiae* [12]. Moreover, it has been assumed that Pxmp2 and Pex11β contribute to H₂O₂ transport together with a yet unidentified channel in mammalian cells [13].

The question that arises is whether these functions of Pex11 and Pex37 as peroxisome fission factors as well as potential membrane pores can be categorized as independent tasks and therefore might represent moonlighting functions, or whether these activities are functionally connected. Along this line, it could be of importance to investigate whether Pex11 and Pex37 play a transceptor-related role. Certain plasma membrane nutrient transporters additionally function as signalling receptors. Thus, they do not just transport the corresponding nutrient but can also induce downstream signalling cascades that regulate the further handling of the nutrient [14]. It would be interesting to find out whether the yet not well-known translocated cargoes of Pex11 and Pex37 might signal the physiological situation concerning, for example, beta-oxidation or H₂O₂ detoxification that might trigger peroxisome fission.

In summary, even if the Pex11 proteins might have been categorized as multifunctional factors involved in peroxisomal fission [5], the formation of peroxisome–mitochondria contact sites [15], possibly the correct targeting of the peroxisomal import machinery [13] and the solute transport across the peroxisomal membrane [12], the discovery of the Pxmp2-family member Pex37 in peroxisome fission and segregation could hold the key to the understanding of how these disparate roles of peroxisomal fission factors might be functionally connected.

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**Conflict of interest**

The authors declare no conflict of interest.

**Author contributions**

HWP and RE wrote the manuscript. HWP prepared the figure.

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