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Novel Peroxisome–Vacuole Contacts in Yeast

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Abstract

Peroxisomes are important organelles and present in almost all eukaryotic cells. Close associations between peroxisomes and other cell compartments are known for several decades. The first molecular details of physical contacts between peroxisomes and various other organelles are now beginning to emerge. We recently described a novel contact between peroxisomes and vacuoles in the yeast *Hansenula polymorpha*, which develops during conditions of strong peroxisome proliferation. At such conditions, Pex3-GFP forms focal patches at the peroxisome–vacuole contacts, while overproduction of Pex3 promotes their formation. These results reveal a novel function for Pex3 in the formation of these contacts, where it might act as a tethering protein. We speculate that the peroxisome–vacuole contact is important for membrane lipid transfer at conditions of strong organellar expansion.

Keywords

peroxisome, vacuole, membrane contact site, Pex3, yeast

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On their discovery in 1954, peroxisomes were initially assumed to be unimportant because of their small size and low abundance and thus largely ignored. However, now we know that they are crucial for proper cell function and involved in many metabolic pathways. In addition to their common functions in lipid metabolism and degradation of hydrogen peroxide, highly specialized metabolic roles have been described, such as bile acid and penicillin biosynthesis. Also, the list of nonmetabolic peroxisome functions is rapidly expanding and includes among others antiviral signaling and innate immune response. This has placed the analysis of peroxisome biology again at the heart of modern cell biology research (reviewed by Islinger et al., 2018).

Yeast peroxisomes lack lipid biosynthesis enzymes and thus acquire all membrane lipids from other membranes. This property makes these organisms ideal models to study membrane lipid transport. Several reports support the occurrence of vesicular lipid transport from the endoplasmic reticulum (ER) to peroxisomes. However, other data indicate that nonvesicular lipid transport can occur as well (for a recent review, see Akşit & van der Klei, 2018). Nonvesicular lipid transport typically occurs at regions where two membranes come into close proximity. Recently, the first peroxisome–ER contact site involved in lipid transport and peroxisomal expansion has been identified in mammals (Costello et al., 2017; Hua et al., 2017). This contact requires the peroxisomal membrane protein acyl-coenzyme A-binding domain protein 5 (ACBD5) as a binding partner for the ER protein vesicle-associated membrane protein-associated protein B (VAPB) and functions not only in peroxisomal membrane growth but also in the synthesis of plasmalogens and the maintenance of cellular cholesterol levels (Costello et al., 2017; Hua et al., 2017).

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In our recent paper (Wu et al., 2019), we analyzed the presence of peroxisomal contact sites in the yeast *Hansenula polymorpha*. Detailed electron microscopy studies revealed that at peroxisome-inducing growth conditions (methanol medium) peroxisomes form close contacts with many different membranes including the ER, mitochondria, vacuoles, and plasma membrane. Remarkably, the vacuole–peroxisome contact sites were fully absent in cells grown at peroxisome-repressing growth conditions (glucose medium) but were formed on shifting these cells to methanol medium conditions that lead to a rapid increase in the total peroxisome membrane surface (i.e., a 100-fold increase within the first 6 to 8 hours after the shift; Figure 1). These data suggest that the vacuole may serve as an additional membrane lipid donor at conditions of strong, substrate-induced expansion of the peroxisomal membrane, whereas at peroxisome-repressing conditions, the lipids may derive only from the ER.

Our data indicate that Pex3 plays a direct role in this process, as this peroxisomal membrane protein is observed to accumulate in patches at the sites of vacuole–peroxisome contacts. Moreover, these contacts also appeared on artificial overproduction of Pex3 in glucose-grown cells, growth conditions where such contacts are invariably completely absent in wild-type cells.

Pex3 is a peroxisomal membrane protein that consists of a membrane spanning region and a large cytosolic domain. Pex3 was initially described as peroxin involved in peroxisome biogenesis, which functions together with the soluble protein Pex19 in sorting of peroxisomal membrane proteins. Later studies revealed that Pex3 also functions in organelle inheritance and pexophagy for which it associates with Inp1 and Atg30 or Atg36, respectively (Burnett, Farré, Nazarko, & Subramani, 2015; Motley, Nuttall, & Hettema, 2012). Together with our current observation, we propose that a general function of Pex3 may be recruiting other proteins or structures to the peroxisomal membrane. If correct, Pex3 may function in tethering peroxisomes to vacuoles by binding to a yet unknown protein in the vacuolar membrane. Alternatively, Pex3 may bind directly to vacuolar membrane lipids.

For now, we speculate that peroxisome–vacuole contacts are involved in lipid transfer similar as described for yeast vCLAMP (vacuole and mitochondria patch) that is involved in lipid transfer from vacuoles to mitochondria and redundant with the ER–mitochondrial contact site ER-mitochondria encounter structure (ERMES) (Elbaz-Alon et al., 2014; Hönscher et al., 2014). Indeed, also in yeast, ER–peroxisome contacts have been described. ER proteins that localize to these contact sites (for instance, Pex29 and Pex30) are proposed to play a role vesicle budding from the ER as part of the de novo peroxisome formation pathway (David et al., 2013; Joshi et al., 2016; Mast et al., 2016; Wang et al., 2018). However, it cannot be excluded that these peroxisome–ER contact sites also play a role in nonvesicular lipid transport. Importantly, our electron microscopy studies revealed that in glucose- and in methanol-grown *H. polymorpha* cells peroxisomes tightly associate with the ER as well (Wu et al., 2019). Possibly, multiple pathways exist that can mediate membrane lipid transfer to cell organelles and become operative dependent on specific cellular demands.

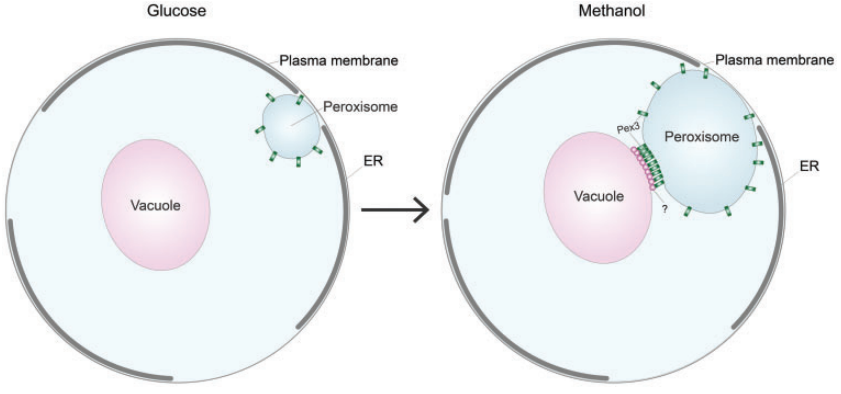

Figure 1. Pex3-dependent formation of peroxisome–vacuole contact sites. Schematic representation of Pex3-dependent formation of peroxisome–vacuole contact sites in yeast. At peroxisome-repressing conditions (glucose), the relatively small, single peroxisome associates with the plasma membrane and ER. Pex3 is present at the membrane of these organelles. On a shift to methanol medium, the single small organelle rapidly expands during the first hours after the shift. At these conditions, the level of Pex3 is rapidly increasing, which is paralleled by the formation of patches, where Pex3 is enriched, at peroxisome–vacuole contact sites. The molecules at the vacuolar membrane to which Pex3 associates at these contact sites (indicated by a question mark) are still unknown. ER = endoplasmic reticulum.

Declaration of Conflicting Interests

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