Biochimica et Biophysica Acta xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamcr

Review

No peroxisome is an island — Peroxisome contact sites☆

Nadav Shai, Maya Schuldiner, Einat Zalckvar *

Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 7610001, Israel

ARTICLE INFO

Article history:
Received 2 July 2015
Received in revised form 10 September 2015
Accepted 11 September 2015
Available online xxxx

Keywords:
Peroxisome
Membrane contact site
Mitochondria
Endoplasmic reticulum
Lipid droplet
Chloroplast

ABSTRACT

In order to optimize their multiple cellular functions, peroxisomes must collaborate and communicate with the surrounding organelles. A common way of communication between organelles is through physical membrane contact sites where membranes of two organelles are tethered, facilitating exchange of small molecules and intracellular signaling. In addition contact sites are important for controlling processes such as metabolism, organelle trafficking, inheritance and division. How peroxisomes rely on contact sites for their various cellular activities is only recently starting to be appreciated and explored and the extent of peroxisomal communication, their contact sites and their functions are less characterized. In this review we summarize the identified peroxisomal contact sites, their tethering complexes and their potential physiological roles. Additionally, we highlight some of the preliminary evidence that exists in the field for unexplored peroxisomal contact sites.
This article is part of a Special Issue entitled: Peroxisomes.

1. Organelle communication through contact sites

The hallmark of eukaryotic cells is compartmentalization of cellular domains into membrane-bound organelles. Organelles allow the segregation and regulation of multiple parallel processes that require unique conditions; however they cannot function in isolation. In order to promote the well-being of the cell, organelles must work in harmony with each other, exchanging information and products to coordinate cellular functions.

Numerous mechanisms have evolved to enable cross-talk between organelles including signal transduction pathways and vesicular trafficking. However, in the past few years it is becoming apparent that a common way of communication between organelles is through membrane contact sites where membranes of two organelles are tethered, facilitating close-range interactions such as transport of small molecules [1,2].

Importantly, not all membranes that come into close proximity form contact sites. True contacts are established and maintained in durable or transient states by tethering structures, which keep the two membranes in proximity while disenabling fusion. Tethering structures can form by proteins on the opposing membranes or by protein–lipid interactions. Moreover, contact sites form unique domains that harbor a defined membrane composition and are enriched with specific proteins to optimize their function [3].

2. Cellular functions of contact sites

What are the functions of contact sites? A diversity of processes has been demonstrated to rely on the formation of contact sites — some of which have been studied more extensively than others:

2.1. Arrangement of the cellular landscape

Contact sites may promote an organization such that organelles are tethered to each other, creating a dynamic but controlled map of the cell. This architecture may enable efficient targeting of molecules to organelles as well as optimize many biosynthetic pathways and responses that utilize more than one organelle to function.

2.2. Exchange of molecules

One advantage of close proximity between two organelles is the ability to exchange various molecules without relying on time-consuming extensive diffusion distances through a chaotic cytosol. Indeed, the two most studied functions of contact sites are the exchange of lipids and Ca^{2+} (reviewed in [2,4]). Notably, a recent study revealed that channels for ions other than Ca^{2+} and additional small molecules are enriched in a contact site formed between mitochondria and vacuoles (yeast lysosome) suggesting that the transfer of many additional molecules may benefit from direct contact between organelles [5].

2.3. Organelle inheritance and trafficking

Most organelles cannot form *de novo* and hence inheritance of organelles is an essential and regulated process in which contact sites

☆ This article is part of a Special Issue entitled: Peroxisomes.
* Corresponding author.
E-mail address: einat.zalckvar@weizmann.ac.il (E. Zalckvar).

http://dx.doi.org/10.1016/j.bbamcr.2015.09.016
0167-4889/

seem to play a major role [6–10]. Dynamics of organelle movements, for other needs than inheritance, may also rely on contact sites.

2.4. Organelle fission and division

A new and unexpected role for contact sites between the endoplasmic reticulum (ER) and other organelles was recently demonstrated: The site of contact between the ER tubules and mitochondria or endosomes [11,12] marks the point in which fission of the organelles will occur. It would be intriguing to discover whether other fission events are also regulated by contacts with ER tubules.

3. Mapping peroxisome contact sites

Despite the growing body of work on contact sites and their obvious importance in coordinating organelle functions, there is still little known about even the most well-studied contacts. Some contacts have been poorly studied and some contacts have yet to be identified. Most contacts studied to date focus on those that involve one of the two biggest organelles — the ER and mitochondria. However, this review will focus on contacts formed by the peroxisome — a highly diverse and important organelle.

Peroxisomes are single-membrane-enclosed organelles that are found in almost all eukaryotes and participate in central pathways of cellular metabolism such as β-oxidation of fatty acids, amino acid catabolism and detoxification of reactive oxygen species (ROS). Peroxisomes are remarkably diverse in size, number, and the enzymes that they contain. This diversity depends on the cell type and environment and can be rapidly regulated in response to metabolic signals [13]. Like any other organelle peroxisomes must collaborate with their surroundings. Unraveling the communication of peroxisomes with the rest of the cell will enable a new level of understanding of the biogenesis, division and function of peroxisomes.

For many years electron microscopy (EM) images of peroxisomes from fungi, plants and mammals, have demonstrated that peroxisomal membranes are juxtaposed to other organelles, mainly the ER, plasma membrane (PM), lipid droplets (LDs), chloroplasts and mitochondria (reviewed in [14]) suggesting that contact sites form between these organelles. Indeed, in recent years several contact sites of peroxisomes were identified in different organisms and their functions have started to be explored. In this review we will present the known contact sites of peroxisomes, and when known, discuss their tethering proteins and functions. Additionally, we will discuss new possibilities of the cross-talk between peroxisomes and the rest of the cell.

4. Peroxisome — ER contact sites

For many years it has been known that peroxisomes can be found in close proximity to the ER. In fact EM images not only showed that these organelles are adjacent to each other, but also demonstrated that the ER membrane can wrap around peroxisomes [15–18]. Over the years several functions have been suggested for the close proximity between the two organelles including peroxisome maturation, proliferation, inheritance, dynamics and transfer of molecules.

4.1. Function

4.1.1. Maturation and proliferation

Peroxisomes can either be formed *de novo* from the ER or by fission of pre-existing peroxisomes [19–22]. Despite the fact that ER contacts have been shown to play an important role in fission of other organelles, currently for neither pathway is there evidence for a role of contact sites. Regardless of the mechanism of biogenesis, young peroxisomes, as well as pre-fission peroxisomes, would require a maturation step in which they are supplied with vital proteins and lipids as peroxisomes are lacking the enzymes that synthesize membrane lipids [23]. One way by which such molecules can be provided may be through vesicles demonstrated to arrive from the ER [24,25]. However, a non-vesicular transfer of ER-derived phospholipids to peroxisomes has also been described [26]. This pathway was suggested to be bidirectional and therefore is likely to provide a mechanism for the cell to rapidly regulate the amount and composition of lipids in peroxisomal membranes. Such alterations may modify the organelle's physical properties thereby supporting membrane bending or elongation during peroxisome growth and division. The fact that this transport is rapid and efficient reinforces the conjecture that it is occurring in peroxisome-ER contacts, despite the fact that specific proteins that transfer lipids to peroxisomes have not been described thus far [3,27,28].

Peroxisome-ER contact sites were suggested to have a role in controlling peroxisome proliferation in the yeast *Saccharomyces cerevisiae*. During peroxisome proliferation, Pex30 is localized primarily to ER-peroxisome contacts [29,30] where it becomes part of a complex with the ER reticulons, Rtn1, Rtn2 and Yop1, which maintain the tubular morphology of the ER (Fig. 1B). Interestingly, in cells lacking the ER reticulons or Pex30 the formation of peroxisomes is accelerated suggesting that this complex negatively regulates proliferation. Studies in the yeast *Pichia pastoris* support these findings by demonstrating that Pex30 is localized mostly to the ER interface [30]. Despite these studies suggesting that Pex30 facilitates the connection between peroxisomes and the ER, its role as a tether has not yet been proven.

4.1.2. Inheritance

During *S. cerevisiae* budding some peroxisomes remain in the mother cell while others segregate to the newly formed daughter bud. This regulated inheritance is mediated by two complexes acting at ER-peroxisome interfaces: One that allows retention of peroxisomes to the mother cell and another that promotes their segregation to the bud.

The tethering complex that is suggested to control peroxisome inheritance consists of Pex3, an integral membrane protein that resides in both peroxisomes and the ER, and the peroxisome inheritance factor, Inp1. While Pex3 provides a membrane anchor for the tether, Inp1 bridges the two compartments by acting as a molecular hinge between ER-bound Pex3 and peroxisomal Pex3. It was suggested that this tethering keeps specific peroxisomes in mother cells. Indeed, in cells lacking the ER-peroxisome tether, peroxisomes accumulate in daughter cells. Conversely, peroxisomes that are enriched in Inp2, an adaptor that connects peroxisomes to microtubules via Myo2 (class V myosin motor protein 2), are actively recruited to the daughter cell (Fig. 1A). Thus, tethering to the ER plays a critical role in selective inheritance and control of the peroxisomal population [10].

4.1.3. Dynamics

A correlation between the dynamic behavior of peroxisomes and the neighboring ER has been demonstrated as peroxisomes align with and follow the dynamic movement of adjacent ER tubules. This suggests that the two organelles are indeed connected, possibly through contact sites [31]. An example of such a contact was demonstrated to enable dynamics of peroxisomes in *Arabidopsis thaliana* plants specifically under oxidative stress [32].

4.1.4. Transfer of molecules

The peroxisome-ER cross-talk is vital for many lipid-related metabolic pathways, including the biosynthesis of ether-phospholipids, production of polyunsaturated fatty acids, cholesterol, bile acids and isoprenoids (Reviewed in [14]). For these products to be biosynthesized efficiently the ER and peroxisomes must exchange key enzymes and metabolites. Although it is not yet clear if the two organelles must be tethered together, or even adjacent, for this to occur, the existence of a contact site would definitely facilitate the efficient exchange of molecules.

In summary, although several tethering complexes have already been studied, the variety of functions that require contacts between

Please cite this article as: N. Shai, et al., No peroxisome is an island — Peroxisome contact sites, Biochim. Biophys. Acta (2015), http://dx.doi.org/10.1016/j.bbamcr.2015.09.016