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Review

A role for mRNA trafficking and localized translation in peroxisome biogenesis and function?☆

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ABSTRACT

Peroxisomes are distinct membrane-enclosed organelles involved in the β-oxidation of fatty acids and synthesis of ether phospholipids (*e.g.* plasmalogens), as well as cholesterol and its derivatives (*e.g.* bile acids). Peroxisomes comprise a distinct and highly segregated subset of cellular proteins, including those of the peroxisome membrane and the interior matrix, and while the mechanisms of protein import into peroxisomes have been extensively studied, they are not fully understood. Here we will examine the potential role of RNA trafficking and localized translation on protein import into peroxisomes and its role in peroxisome biogenesis and function. Given that RNAs encoding peroxisome biogenesis (*PEX*) and matrix proteins have been found in association with the endoplasmic reticulum and peroxisomes, it suggests that localized translation may play a significant role in the import pathways of these different peroxisomal constituents. This article is part of a Special Issue entitled: Peroxisomes.

1. Introduction

Membranes divide living cells into specialized compartments, each possessing a distinct protein composition and function. Many of these proteins possess sequence motifs or undergo modifications that allow them to localize to the relevant compartment. In eukaryotes, such sequences include those for nuclear localization (*i.e.* nuclear localization signal; NLS), mitochondrial targeting (*i.e.* mitochondrial targeting signal; MTS), endoplasmic reticulum (ER) import (*i.e.* signal peptide) and peroxisome targeting (*i.e.* peroxisome targeting signal; PTS). In addition to protein targeting, mRNA localization to sub-cellular domains, a process that is common to organisms from all domains of life, plays an important role in regulating local translation (recently reviewed in [1–4]). Since a single mRNA molecule can serve as a template to multiple rounds of translation, this is an efficient mechanism to restrict protein production in a spatial-temporal manner. In this article, we will review the available evidence for mRNA localization to peroxisomes, as well as mechanisms of translational regulation that can allow for peroxisomal protein targeting. We will then discuss the future of the field, what necessitates further investigation, and which tools are required.

1.1. Peroxisome biogenesis and protein import

Peroxisomes are small organelles surrounded by a single lipid bilayer that is found in all eukaryotes. Peroxisomes facilitate functions related to the metabolism of reactive oxygen species, the β-oxidation of fatty acids, and synthesis of ether lipids and bile acids [5,6]. There are several human heritable disorders that are related to defects in peroxisome biogenesis or function [7,8], and which serve to highlight the importance of this organelle and the need to understand its biogenesis, maintenance, and actions. For the non-expert, we recommend the peroxisome database website, a comprehensive database that includes detailed descriptions of all known peroxisomal proteins and their functions (http://www.peroxisomedb.org) [9].

1.1.1. The mechanism of peroxisomal biogenesis is complex and is a matter of some debate

Current models suggest the existence of two pathways for peroxisome biogenesis (reviewed in [10–13] and reviews in this special issue of BBA-MCR). Peroxisomes have been proposed to form *de novo* via the budding of pre-peroxisomes (*i.e.* cargo-selective vesicles) from

Abbreviations: ChIP, chromatin immunoprecipitation; CLIP, crosslinking immunoprecipitation; ER, endoplasmic reticulum; FISH, fluorescent *in situ* hybridization; GET, Golgi-ER trafficking; ISH, *in situ* hybridization; MFP, multifunctional protein; mPP, mRNA encoding peroxisomal protein; MTS, mitochondrial targeting signal; NLS, nuclear localization signal; PEX, peroxin; PMP, peroxisome membrane protein; PTS, peroxisome targeting signal; PUF, pumilio/fem-3 mRNA binding factor; RaPID, RNA purification and identification; RBP, RNA-binding protein; RNA-seq, RNA sequencing; RT-qPCR, reverse transcription-quantitative polymerase chain reaction; TMD, transmembrane domain; TOM, translocase of outer membrane; SILAC, stable isotope labeling by amino acids in cell culture; smFISH, single-molecule fluorescent *in situ* hybridization; SNARE, soluble *N*-ethylmaleimide sensitive fusion protein (NSF) attachment protein receptor; SRP, signal recognition particle; UTR, untranslated region.

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the ER, which then fuse to form mature peroxisomes that contain only newly synthesized proteins. Alternatively, the fission of pre-existing peroxisomes can produce new peroxisomes whose content is composed of both old and newly synthesized lipids and proteins. Either mechanism necessitates the import of both matrix proteins and peroxisomal membrane proteins (PMPs), however, whether import occurs directly from cytoplasm, *via* delivery from the ER, or is due to a combination thereof is not fully understood. In either case, matrix proteins are generally thought to be imported post-translationally across peroxisomal membranes, whereas the mechanism of PMP delivery to peroxisomes is far more controversial an issue, as described below. In this review it is not our intention to weigh in with regard to the veracity of the different models of PMP import or to imply that the RNA localization studies described in this review absolutely distinguish between the various possibilities.

1.1.2. Matrix protein import

The import of matrix proteins has been extensively reviewed [11,13,14], but basically is divided into four steps: 1) Matrix protein recognition in the cytosol by soluble cargo receptors; 2) association of the receptor-cargo complex with the peroxisomal membrane; 3) translocation of the cargo into the peroxisome; and 4) recycling of the cargo receptor to the cytosol. Two soluble cargo receptors exist: Pex5, which recognizes the type 1 PTS [PTS1; composed of a C-terminal SKL-like tripeptide, (S/A/C)-(K/R/H)-(L/A)] and Pex7, which recognizes a type 2 PTS [PTS2; composed of an N-terminal nonapeptide (R/K)-(L/V/I)-XXXXX-(H/Q)-(L/A/F)]. Although Pex5 is thought to associate with PTS1-containing proteins in the cytosol, it also acts as a component of a transient import channel that is composed of Pex13 and Pex14 (and Pex17 in yeast). Thus, Pex5 shuttles between two states: that as a cytosolic receptor and that as membrane-bound component of the translocation complex. Importantly, the translocation of PTS1-containing proteins does not depend upon protein unfolding or the involvement of molecular chaperones and even oligomeric protein complexes can be imported intact. After import, the Pex5 cargo receptor is ubiquitinated by peroxisome-specific E3 ligases (*e.g.* Pex2 and Pex10, and Pex4 and Pex12) and while the polyubiquitinated form is exported for degradation, the monoubiquitinated form is recycled upon export and deubiquitination. Importantly, the ubiquitin-dependent retrotranslocation of Pex5 into the cytosol has been suggested to occur in a manner reminiscent of reverse ER-associated protein degradation (ERAD), *i.e.* using a heterohexamer of the Pex1 and Pex6 AAA ATPases to perform the ATP-dependent mechanorelease of Pex5 [14]. Pex7, on the other hand, acts along with other Pex proteins (*e.g.* Pex18, 20, and 21 in yeast, and PEX5L in mammals) to recognize and translocate PTS2-containing peroxisomal cargo proteins *via* the Pex13–Pex14 import channel, in a manner independent of Pex5. Thus, two distinct and non-redundant import pathways exist for soluble proteins to access the peroxisome matrix. An abbreviated model for the import of peroxisome matrix proteins and the potential role of mPP localization in matrix protein import is shown in Fig. 1.

1.1.3. Peroxisome membrane protein import

The possible mechanisms for PMP protein import have also been extensively studied and reviewed, however, the overall mechanism is far less well understood than for matrix proteins. At least three possibilities exist for the import of PMPs: 1) A direct route whereby PMPs are imported into existing peroxisomes; 2) an indirect route whereby PMPs are imported into the ER and are segregated into a subdomain that leads to peroxisomes *via* membrane contact points; and 3) an indirect route whereby PMPs are imported into ER-derived vesicles that undergo maturation into peroxisomes either *via* the direct import of matrix proteins or due to the fusion of separate classes of pre-peroxisomal vesicles, followed by matrix protein import. PMP import into peroxisomes is generally thought to be post-translational, although ribosomal proteins may co-purify with peroxisomes [15] and any indirect import of PMPs *via* the ER is likely to imply the existence of co-translational translocation. An abbreviated model for PMP import is shown in Fig. 2.

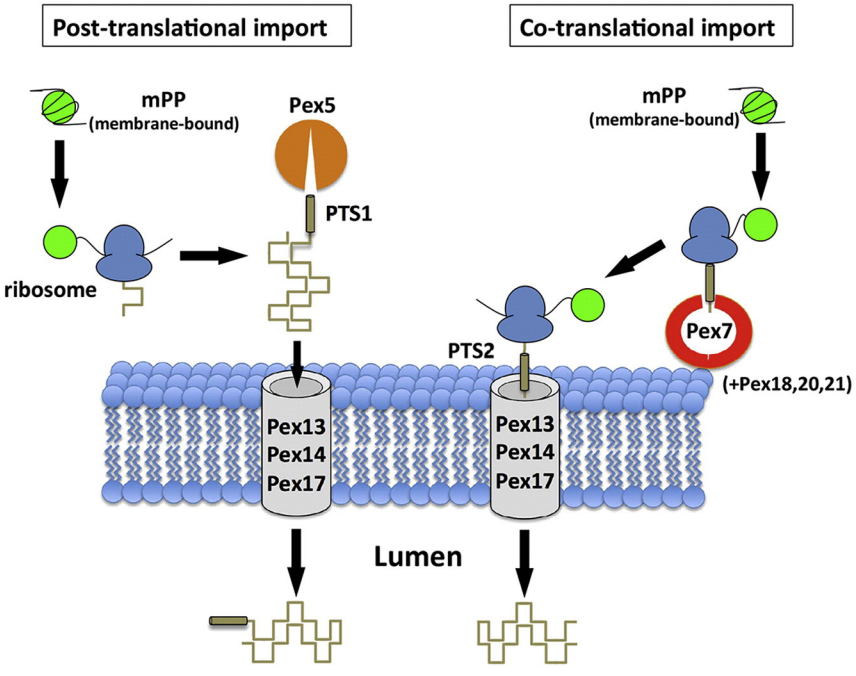

Fig. 1. Mechanisms for matrix protein import: role of mPP localization. Matrix protein import is mediated *via* two known routes, a post-translational route in the case of PTS1-containing messages and a second, perhaps, co-translational route in the case of PTS2-containing messages. In the first case, fully translated PTS1-containing proteins are recognized *via* the Pex5 cargo receptor and are imported into the lumen of peroxisomes *via* the Pex13, and 14 (and Pex17 in yeast) importomer complex. In contrast, the translation of PTS2-containing transcripts presumably allows for the nascent chain to be recognized by Pex7 import receptor and, along with other peroxins (*e.g.* Pex18, 20, and 21), allows for the co-translational import of PTS2-containing matrix proteins. In either case, the presence of mPPs in close association with the peroxisome membrane is likely to facilitate import upon translation. Thus, mPP delivery and anchoring to peroxisomal membranes may prove to be an important means to facilitate peroxisome biogenesis and function.

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