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Peroxisomal Biogenesis: Genetic Disorders Reveal the Mechanisms

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1. Introduction

Peroxisomes are small and abundant membrane-bound organelles that contain enzymes for a variety of metabolic functions, including ß-oxidation of fatty acids, synthesis of plasmalogens and bile acids, and H_2O_2 production (1, 2). A group of human genetic diseases involves peroxisomal disorders (3) derived from two type of alterations: i) defects in a single peroxisomal enzyme, as found in X-Linked Adrenoleukodystrophy and Acatalasemia; and ii) Peroxisome Biogenesis Disorders (PBDs), which include the Zellweger's Syndrome (ZS). Intense research has been devoted for decades to understand the mechanisms of biogenesis and maintenance of peroxisomes. Despite the paramount progress, there are still enigmatic aspects, specially regarding the pathways followed by peroxisomal membrane proteins and the origin of peroxisomal membrane precursors (2). Here we give an overview of the evidence that involves the endoplasmic reticulum (ER) from the most important genetic tools in the field: fibroblast cultures derived from Zellweger patients and yeast mutants.

2. Peroxisome biogenesis: challenging the paradigm

2.1 Zellweger's Syndrome (ZS) as the prototypic Peroxisome Biogenesis Disorder (PBD)

ZS is characterized by craniofacial dysmorphia, neurological impairment, severe metabolic disturbances and neonatal death, caused either by complete absence of peroxisomes or by defects in protein importation into peroxisomal membrane precursors (1, 4-8). From the clinical point of view, a severity spectrum of these disorders has been established (SZ spectrum), including Neonatal Adrenoleukodystrophy (NALD; MIM 202370), Infantile Refsum disease (IRD; MIM] 266510) and SZ (ZS; MIM 214100) as the most severe (8). Initial studies in liver biopsies of ZS patients failed to find evidence of peroxisomal components and thus led to the notion that ZS patients lack peroxisomes (9). Later studies in Zellweger fibroblasts detected membranes containing peroxisomal membrane proteins (PMPs) but that lack most of the matrix proteins and were called "peroxisomal membrane ghosts" (10-12). Since then, a defect in the peroxisomal importing machinery for matrix proteins became

apparent as a crucial cause of ZS. The fibroblasts from these patients provided a genetic model system for studying the mechanisms of peroxisomal biogenesis (1), while the incorporation of genetic tools in yeast allowed complementary and more detailed approaches (13-15).

2.2 Peroxisome growth and division versus *de novo* synthesis

In 1985, Lazarow and Fujiki postulated that peroxisomes are autonomous organelles, like mitochondria and chloroplasts, that form by growth and division (16). This assumption was based on the findings that peroxisomal matrix and membrane proteins are synthesized on free ribosomes and are imported post-translationaly into pre-existing parenteral organelles. Kinetics assays measuring the peroxisomal incorporation of newly synthesized proteins (17), as well as the discovery of specific targeting sequences recognized by soluble receptors that direct import into the organelle, gave further support to this hypothesis (18). Furthermore, most of the complementation groups exhibit only peroxisomal ghosts as the result of defects in the importing machinery for peroxisomal matrix proteins (10, 11). However, the observation that *de novo* peroxisomal synthesis is possible, first demonstrated in yeast (13) and then in mammalian cells (19), challenges the "growth and division" model..

2.3 The biogenesis of new peroxisomes is orchestrated by Pex3p, Pex16p and Pex19p peroxins

The analysis of the genetic heterogeneity in ZS and disorders of peroxisome biogenesis in mammalian cells led to discover the peroxins and their encoding genes (PEX) as the source of alterations causing several phenotypes (20). To date 32 PEX genes encoding the peroxisomal biogenetic machinery have been identified and at least 12 different complementation groups have been described among ZS patients, most of them displaying peroxisomal ghosts (7, 8, 18, 20). However, three of these complementation groups, groups 9 (PEX16 gene defect), 12 (PEX3 gene defect) and 14 (PEX19 gene defect) lack peroxisomes, peroxisome ghosts and any peroxisomal membrane (5, 7, 14, 19-26). This phenotype is reproduced in yeast by PEX3 and PEX19 mutations (13, 27). Strikingly, the expression of exogenous wild type PEX genes in ZS cells and mutant yeasts reestablish the generation of functional peroxisomes (13, 14, 19, 22, 26-31), demonstrating that new peroxisomes can be generated without requiring a preexisting organelle.

These observations also indicate that early stages of peroxisome biogenesis are driven by peroxins Pex3p, Pex16p and Pex19p, respectively encoded by PEX3, PEX16 and PEX19 genes (18). Therefore, it became clear that elucidating the function of these peroxins should help to understand the biogenetic mechanisms of peroxisomes, from preexisting organelles or/and from newly made precursor membranes.

Both matrix and PMPs are synthesized on free polysomes and captured in the cytosol by soluble receptors that direct them to peroxisomes. However, the importing machinery for PMPs involving Pex3p, Pex16p and Pex19p is different from the importing machinery for matrix proteins, both in sorting signals and importing peroxins (15, 32-35). Matrix proteins contain at least two distinct sorting signals: a tripeptide Peroxisomal Targeting Signal type I (PTS-1) and a nonapeptide Peroxisomal Targeting Signal type 2 (PTS-2), which are recognized by their respective cytosolic receptors Pex5p and Pex7p. These complexes are translocated by membrane importers involving Pex14p and RING peroxins (18, 36, 37). Instead, import of most PMPs depends on Pex19p that recognizes peroxisomal membrane-

targeting signals (mPTS) and acts as a cytoplasmic chaperone for nascent PMPs, stabilizing and targeting them to the peroxisomal membrane (18). Recent evidence indicates that Pex3p, which is an integral membrane protein initially considered the only PMP imported independently of Pex19p (33, 34), actually also interacts with Pex19p and is imported through a mechanism involving Pex16p as docking element (35). Pex16p is also an integral membrane protein and seems to act as a Pex3p receptor or as a membrane translocator component (34). In turn, Pex3p once integrated into the peroxisomal membrane constitutes a Pex19p docking element and recruits complexes of Pex19p and PMPs as part of the PMPs incoming mechanisms (18, 34).

Recent experiments using a peroxisome-targeting assay in semi-intact CHO-K1 cells strengthened the notion that PMPs are directly imported into the peroxisomal membranes (35). This work also proposed a new classification of the import pathways. Previous work suggested the existence of two distinct PMPs import pathways (33, 34): *(i)* a Pex19p and Pex3p-dependent class I pathway followed by most PMPs including Pex16p, and; *(ii)* a Pex19p- and Pex3p-independent class II pathway, which so far had included Pex3p as the only PMP cargo yet identified. However, the most recent work found that Pex3p follows a novel import pathway involving a complex with Pex19p in the cytosol and a subsequent docking at Pex16p in the peroxisomal membrane (35). Based on these observations, it was suggested that pathways that depend on Pex19p-mediated membrane docking be classified as follows: *(i)* a class I pathway involving Pex3p as the membrane receptor, and; *(ii)* a class II pathway where Pex16p provides the docking site.

Under this new scenery a problem arises regarding the initial stages of peroxisome membrane biogenesis. Pex16p is known to be imported by the Pex19p-dependent pathway mediated by Pex3p as membrane receptor for the Pex16p/Pex19p complex (33, 34, 38, 39). At the same time, in the new pathway the import of Pex3p is mediated by Pex16p acting as receptor of the Pex3p/Pex19p complex (35). This apparent "chicken-and egg" problem can be solved by considering an ER pathway in which Pex16p would use another membrane insertion mechanism than Pex3p (26, 30).

3. The endoplasmic reticulum in peroxisomal biogenesis

The absence or non-sense mutations of any of the PEX3; PEX19 and PEX16 genes preclude the generation of peroxisomes, which as mentioned above can be re-established by reintroducing the respective wild type genes (18). In yeast, the endoplasmic reticulum clearly emerged as the source of membrane involved in the initial biosynthetic event (40). Plants also contributed with evidence of an ER-to- peroxisome pathway (41-43). Although in mammalian cells such possibility has been more controversial, accumulated evidence (26, 30) prompts reconsidering its validity.

3.1 Experiments in yeast involve the endoplasmic reticulum as the origin of newly formed peroxisomes

Yeast model systems provided the first evidence involving the ER in peroxisome biogenesis (44-46). In *Yarrowa lipolytica*, the finding of N-glycosylation in Px16p and Pex2p indirectly revealed trafficking through the ER to peroxisomes (40, 44). In *Hansenula polymorpha*, Pex3p, Pex8p and Pex14p accumulate in the ER in the presence of presence of Brefeldin (BFA) and become targeted to peroxisomes after BFA removal (47). In *Saccharomyces cerevisiae*,

Hoepfner *et al*., (14) showed direct evidence that Pex3p and Pex19p are synthesized in the ER and then move to peroxisomes. Complementation experiments in yeast lacking Pex3p, and thus lacking peroxisomes, demonstrated that certain structures growing out from the ER, and containing Pex3p-GFP, constitute peroxisomal precursors that delineate a subdomain of the ER (14, 31). Also in yeast, recombinant Pex3p bearing an attached signal sequence and, therefore, unequivocally addressed to the ER, ends up integrated into peroxisomes (22). More recently, work on *Saccaromyces* reported ER targeting of 16 PMPs mediated by Sec61p and Get13, both in proliferating wild-type cells and in mutant cells lacking peroxisomes (48). This work also showed that PMPs leave the ER in a Pex3-Pex19p-dependent manner, implying a new functional role for Pex3p and Pex19p, i.e. promoting exit from the ER. The recent isolation of vesicular carriers that buds from the ER through a mechanism requiring Pex19p and carrying Pex3p and Pex15p provided compelling evidence for the existence of an ER-to- peroxisome pathway, which is independent of the COPII mediated pathway characteristic of the exocytic route (49).

3.2 The ER-to-peroxisome pathway in plants

Plants have also provided evidence of an ER-to-peroxisome pathway. In germinating castor beans, early pulse chase experiments showed peroxisomal proteins appearing first in the ER while en route to glyoxisomes that are specialized peroxisomes (41, 42). Pex16p has been reported in the ER as well as in peroxisomes (43) and its distribution suggested that specific domains might exist in the ER, defined by the concentration of certain peroxisomal proteins.

3.3 The ER-to-peroxisome pathway in mammalian cells

The ER-to-peroxisome pathway has been more difficult to disclose in mammalian cells. Several observations initially argued against the possibility that such a pathway might even exist or play a physiologically relevant function. For instance, kinetics studies have shown that Pex3p is rapidly imported into preexisting peroxisomes in wild type cells, one or two order of magnitude faster than the process of *de novo* peroxisome biogenesis (28). Thus, the chance to mediating *de novo* peroxisome biogenesis while most Pex3p is being consumed by importation into preexisting organelles seemed remote. On the other hand, attempts to follow up the newly synthesized Pex3p *in vivo* failed to find evidence of traffic through the ER to peroxisomes, both in wild type cells and in cells that lack peroxisomes (28, 34). This failure suggested that previous observations in yeast might not be extensible to mammalian cells. Until recently, the lack of direct evidence involving the ER in peroxisomal biogenesis in mammalian cells contributed to maintain the original notion of fission of pre-existing peroxisomes as the only source of the organelles (17).

Early electron-microscopic observations revealed close associations of peroxisomes and the ER in intestinal cells (50). The functional relevance of such observations remained for a long time enigmatic. Suggestive evidence of an ER involvement in peroxisomal biogenesis includes the finding of synthesis of PMP50 in ER-bound ribosomes in rat liver (51) and lamellar structures containing Pex13 and PMP70 that are continuous with both the ER and peroxisomes in dendritic cells (52). The role of the ER so clearly shown in yeast, as a platform for the outgrowth of new peroxisomes, had to wait in mammalian cells for new experimental approaches. The most direct evidence of the ER in peroxisome biogenesis came from live cell imaging in synchronized transport systems. First, it was shown that Pex16p is addressed to the ER before its sorting to peroxisomes (30). Afterwards, a similar

route was revealed for Pex3p in ZS fibroblasts (26), thus providing the elusive evidence of previous studies.

In wild type mammalian cells (Cos7 cells), experiments with a photoactivable Pex16p-GFP revealed a trafficking pathway initiated at the ER and leading to peroxisomes (30). These studies also showed that incorporation of Pex16p into the ER is independent of Pex19p and occurs cotranslationally (30), thus contrasting with the direct post-translational pathway that requires both Pex19p and Pex3p for import of Pex16p into the peroxisomal membrane (33, 34, 38, 39). Furthermore, overexpression of Pex16p in cells lacking peroxisomes due to a nonsense mutation of the PEX16 gene relocates Pex3p from mitochondria to the ER (30), suggesting that Pex16p is a Pex3p recruiting receptor at the ER, perhaps mimicking its recently proposed role in pre-existing peroxisomes (35). The evidence suggested that most peroxisomes derive from the ER pathway rather than from preexisting organelles.

Prompted by the refreshing results on Pex16p traffic in living mammalian cells (30) and the contrasting observations regarding Pex3p trafficking in yeast (14, 22, 31) and mammalian cells (28, 34), we decided to study the sorting behavior of Pex3p and Pex16p in a fibroblast cell line (called MR) derived from a Chilean patient with ZS (26). In this new MR cell line we found complete lack of peroxisomes, including peroxisomal membrane ghosts, due to nonsense mutation in the PEX3 gene. An inactivating nonsense mutation generated a stop codon at position 53, previously reported in PEX3 deficient human cells (28). Cell fractionation and immunofluorescence showed peroxisomal matrix enzymes such as catalase and thiolase in the cytosol of these cells. Exogenous expression of Pex3p (tagged with GFP) restored the peroxisomal biogenesis. The newly generated peroxisomes imported catalase and thiolase. Therefore, the MR cells show the expected phenotype for the lack of function of Pex3p and for the reestablishment of Pex3p expression.

Unexpectedly, we detected an important phenotypic feature previously unnoticed in ZS. Cells with PEX3 or PEX19 mutations usually mistarget endogenous PMPs to mitochondria, perhaps due to the presence of a cryptic and weak mitochondrial signal (24, 53). In congruency, by using a reported serum that specifically recognizes several human PMPs (11), we detected the majority of PMPs distributed in mitochondrial membranes in both MR and GM6231 cell lines (26). However, we also detected a small pool of endogenous PMPs distributed in ER membranes and small cytoplasmic vesicles (26). An early study in rat liver using cell fractionation methods described data suggesting the presence of PMP50 and PMP36 in ER membrane fractions (51). Only very recently a targeting of a variety of PMPs to the ER has been reported in yeast (48). However, this is a previously unknown feature of ZS cells, which not only entails great interest regarding the role of the ER in peroxisomal biogenesis but also suggests a new role of Pex3p and Pex16p dealing with the traffic of PMPs from the ER to peroxisomes.

The interrelated functions of Pex16p and Pex3p (34, 35) suggest that these peroxins should act in concert. Thus, we analyzed the sorting behaviour of newly synthesized Pex3p and Pex16p in their respective mutant ZS as well as in the counterpart mutations. Microinjection expression experiments of GFP-coupled versions of these peroxins allowed the study of early stages of their transport. Previous studies in mammalian cells lacking PEX3 have shown that nuclear microinjection of PEX3 gene re-establishes peroxisomes within 3 h (28), but did not report an analysis of Pex3p distribution at shorter time periods. Strikingly, we found Pex3p-GFP localizing first to the ER and subsequently to peroxisomes in MR cells. Within the first hour of expression we detected almost 70% of the Pex3p-GFP mainly in the

ER. After 4 h Pex3p-GFP became clearly detectable in newly formed peroxisomes. These results contrast with those that failed to detect Pex3p sorted into an ER-to- peroxisome pathway in mammalian cells (28, 34). Our evidence that Pex3p follows the same pathway of Pex16p (26), strengthen the notion that mammalian cells share with yeast an ER involvement in peroxisomal biogenesis.

In agreement with previous studies (30), we also found that Pex16p-GFP exogenously expressed in ZS cells GM6231, which carry a well characterized mutation of PEX16 and lack peroxisomes, follows an ER-to- peroxisome pathway and reestablishes peroxisomal biogenesis. In these GM6231 cells, Pex16p-GFP expressed by microinjection distributed in bright dots or vesicles likely corresponding to peroxisome precursors (26). Interestingly, we observed that MR fibroblasts lacking Pex3p distributed Pex16p-GFP mainly to the ER (26). Previous studies in mammalian cells lacking Pex19p have shown that exogenously expressed Pex16p-GFP is targeted to the ER and accumulates there without promoting newly synthesis of peroxisomes (30). There are also studies in yeast lacking Pex3p or Pex19p that show PMPs arrested in the ER (48), and more recently, that Pex19p is part of the mechanism which produces membrane carriers containing Pex3p from the ER (49). Taken together with our results, the overall evidence indicates that Pex16p does not require Pex3p for its insertion into the ER membrane, in agreement with its previously reported cotranslational incorporation (30), but seemingly does require Pex3p and Pex19p for exiting the ER in peroxisomal membrane precursors. Because Pex3p is a docking factor for Pex19p in peroxisomes (34), a likely explanation is that a Pex3p/Pex19p complex formed at the ER membrane promotes the formation of membrane carriers for Pex16p and presumably other PMPs.

With regard to the role of Pex16p, GM6231 cells lacking Pex16p distributed Pex3p-GFP to mitochondria, indicating that Pex16p is crucial for the ER incorporation of Pex3p (26). Pex16p seems to act at earlier stages of peroxisomal membrane biogenesis than Pex3p (25). Actually, there is evidence that Pex16p is cotranslationally inserted into the ER and its overexpression leads to Pex3p recruitment to the ER (30). It is very likely that Pex16p once inserted into the ER membranes acts as receptor for Pex3p in the process leading to ER derived peroxisomal precursors. A requirement of Pex16p for ER targeting of Pex3p marks a big difference with most yeast strains, which do not express Pex16p. On the other hand, Pex3p could provide a docking site for Pex19p coupled to PMPs, as described in pre-existing peroxisomes (54). Pex19p-dependent recruitment of PMPs could then drive further progression of peroxisomal biogenesis.

The mechanism of Pex3p incorporation into the ER remains unknown, but likely involves Pex16p cotranslationally inserted in the ER membrane (30). Other PMPs might be inserted into the ER following a Sec61-translocon mediated mechanism similar to that described for a number of PMPs in yeast (48). The process might include maturation of incipient peroxisomal membrane at certain regions of the ER or homotypic fusion with other peroxisomal precursor vesicles.

Evidence in yeast indicates that new peroxisomes form by budding from ER in a COPI- and COPII- independent manner using a new branch of the secretory pathway (45). Definitive evidence of a COPII independent pathway has been recently reported in a reconstituted *in vitro* transport system in yeast (49). These observations in yeast agree with previous observations in mammalian cells (28, 55, 56) and with our recent results in MR and GM6231 cells (26). Inhibition of either the COPI vesicular pathway with Brefaldin A or the COPII

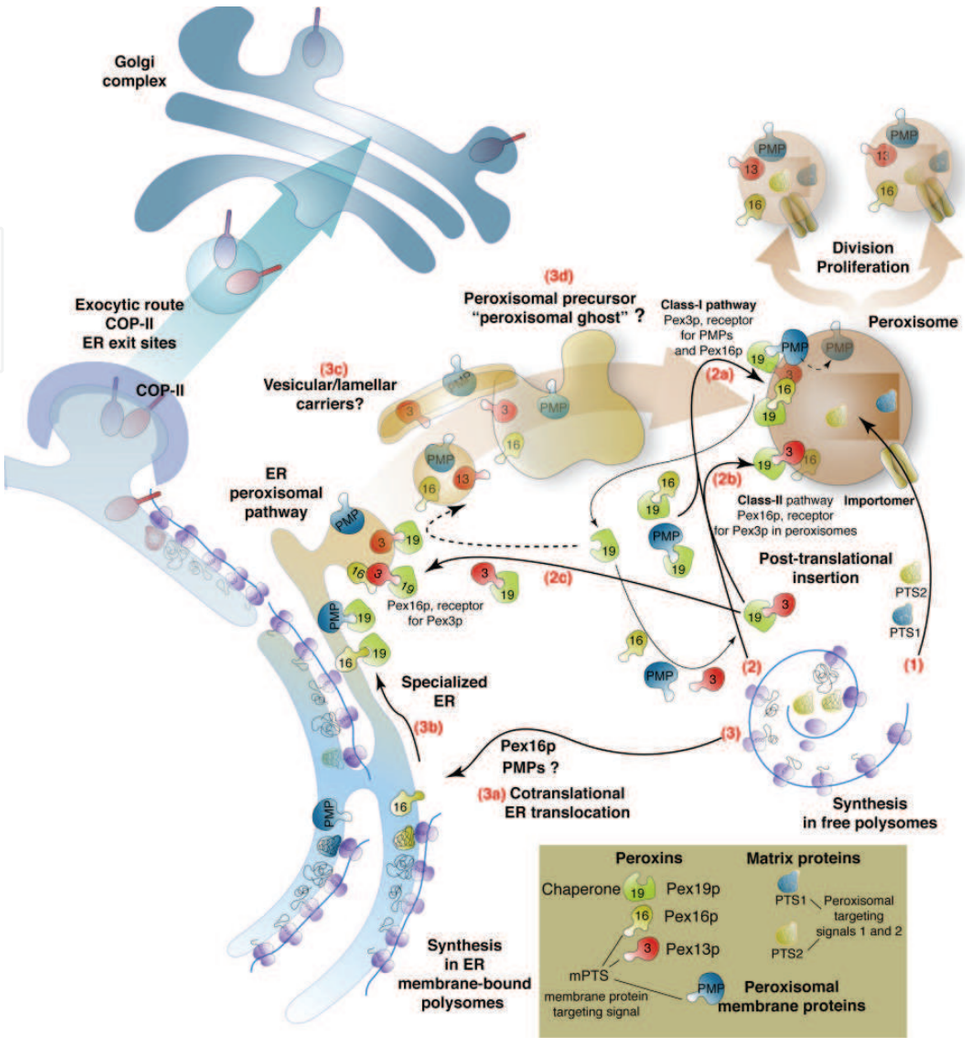

Fig. 1. Integrated model of peroxisome biogenesis pathways. As previous models established, matrix and PMPs are synthesized in free polysomes and are post-translationally imported into pre-existent peroxisomes. Routes followed by these proteins are depicted as routes: (1) for matrix proteins bearing PTS1 or PTS2 that are incorporated into mature peroxisomes by importomer complex (18, 36, 37); (2) PMPs, including Pex16p and Pex3p, forming a complex with Pex19p follow either a subroute (2a) in which Pex3p acts as a docking site for Pex19p-PMPs complexes (18, 34), or subroute (2b) mediated by Pex16p acting as docking site for Pex3p (34, 35). An additional subroute (2c) is followed by Pex3p targeted to the ER, presumably also in complex with Pex19p and requiring Pex16p as docking site (26). The ER-to-peroxisome route (3) includes the following steps: (3a) direct co-translational insertion of Pex16p (30), and likely other PMPs, as described in yeast (48); (3b) segregation of these proteins into specialized ER areas lacking ribosomes and other ER components, as suggested by the studies in dendritic cells (53); (3c) generation of hypothetical vesicular carriers, similar to those described in yeast (49), and/or lamellar carriers based on observations in dendritic cells (50). The ER-to-peroxisome transport requires Pex19p (30, 49); (3d) formation of peroxisomal precursors, still lacking matrix proteins, which might be equivalent to the peroxisomal ghosts described in most ZS cells (10-12). Mature peroxisomes proliferate by growth and division (16)

vesicular pathway by a Sar1 mutant in PEX3 or PEX16 mutant fibroblasts do not affect the recovery of peroxisome biogenesis (28). Our experiments in PEX3 and PEX16 mutant fibroblasts (MR and GM6231) indicates that PMPs are incapable of leaving the ER, causing an enlargement of ER cisternae (26), while the biosynthetic traffic of the temperature sensitive VSVG-tsO45 seem to function normally (unpublished results). At the non-permissive temperature of 40ºC, VSVG-tsO45 accumulates at the ER, but after shifting to the permissive temperature it becomes transported to the Golgi apparatus and then to the cell surface in both MR and GM6231 cells, at similar kinetics as in wild type cells. This observation provides the first evidence of a normal traffic between the ER, Golgi apparatus and plasma membrane in ZS lines.

4. Summary and integrative model of peroxisome biogenesis

We reviewed here the evidence supporting a role of the ER as a platform for the function of PMPs (Pex3p and Pex16p) in the initial stages of peroxisomal biogenesis and integrated all data in the model depicted in Figure 1. Our recently published data suggested that other PMPs are addressed to the ER and accumulate there in the absence of Pex3p or P16p (26), in agreement with the most recent results in yeast (48). There is no doubt that peroxisomes can be originated *de novo* and that peroxins crucially involved in the initial steps of peroxisome biogenesis can be sorted first to the ER and from there to nascent peroxisomes following a COP-II-independent route (45, 49). However, in mammalian cells there is also strong evidence of a direct pathway from the cytosol to pre-existing peroxisomes, which under normal circumstances seems to be a mayor route (28, 35). Even though only a small fraction of Pex3p might be targeted to the ER, this could be enough for providing new peroxisomal membrane precursors as required for sustaining a continuous peroxisomal growth and proliferation. Peroxisomes possess a machinery for direct import of Pex3 in a Pex19p- and Pex16p dependent manner (35). On the other hand, peroxisomal targeting of Pex16p depends on Pex19p and Pex3p (33, 34). This apparent "chicken-and-egg" problem (35) can be solved considering a Pex3p-independent source of Pex16p in peroxisomal precursors, generated after cotranslational insertion into ER membranes (26, 30). ER targeting of Pex16p would conform the platform for *de novo* peroxisome biogenesis, offering a docking site for Pex3p at the ER, as it does at the peroxisomal membrane. Once inserted in the ER membrane, Pex3p would offer a docking site for Pex19p complexes with other PMPs. This pathway would generate pre-peroxisomes that mature towards complete and functional entities in concert with the direct import route. Co-existing with the ER-to- peroxisome pathway, both Pex16p and Pex3p peroxins would become directly targeted to pre-existing peroxisomes in the described ''mutual-dependent targeting'' manner (35). In this way, the classical ''growth and division'' model of peroxisome biogenesis is complemented with an ER-dependent mechanism responsible for *de novo* renewal of peroxisomal membranes. These cellular mechanisms are important to consider when evaluating the pathogenesis of Human Peroxisomal Genetic Disorders.

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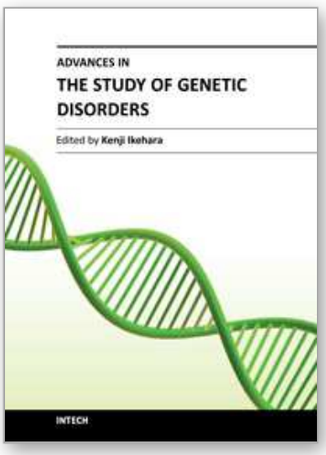

Advances in the Study of Genetic Disorders

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The studies on genetic disorders have been rapidly advancing in recent years as to be able to understand the reasons why genetic disorders are caused. The first Section of this volume provides readers with background and several methodologies for understanding genetic disorders. Genetic defects, diagnoses and treatments of the respective unifactorial and multifactorial genetic disorders are reviewed in the second and third Sections. Certainly, it is quite difficult or almost impossible to cure a genetic disorder fundamentally at the present time. However, our knowledge of genetic functions has rapidly accumulated since the double-stranded structure of DNA was discovered by Watson and Crick in 1956. Therefore, nowadays it is possible to understand the reasons why genetic disorders are caused. It is probable that the knowledge of genetic disorders described in this book will lead to the discovery of an epoch of new medical treatment and relieve human beings from the genetic disorders of the future.

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