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Review

Peroxisome and pexophagy in neurological diseases

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ABSTRACT

Peroxisomes and pexophagy have gained increasing attention in their role within the central nervous system (CNS) in recent years. In this review, we comprehensively discussed the physiological and pathological mechanisms of peroxisomes and pexophagy in neurological diseases. Peroxisomes communicate with mitochondria, endoplasmic reticulum, and lipid bodies. Their types, sizes, and shapes vary in different regions of the brain. Moreover, peroxisomes play an important role in oxidative homeostasis, lipid synthesis, and degradation in the CNS, whereas its dysfunction causes various neurological diseases. Therefore, selective removal of dysfunctional or superfluous peroxisomes (pexophagy) provides neuroprotective effects, which indicate a promising therapeutic target. However, pexophagy largely remains unexplored in neurological disorders. More studies are needed to explore the pexophagy's crosstalk mechanisms in neurological pathology.

1. Introduction

Peroxisomes are small, single-membrane-bound organelles, which were first discovered by Christian De Duve in the 1960s [1,2]. They are dynamic and ubiquitous. Besides, the peroxisomes directly interact with other organelles, such as endoplasmic reticulum (ER), mitochondria, or lysosomes [3]. Peroxisomes exert different functions in various cells through both the catabolic and anabolic pathways. The main functions of peroxisomes can be categorized as reactive oxygen species (ROS) metabolism, lipid metabolism, and ether-phospholipid biosynthesis. Moreover, peroxisomes also play important roles in inflammatory signaling and the innate immune response [4,5].

In the central nervous system (CNS), peroxisomes are important in the synthesis of myelin sheaths and cellular membranes. Besides, ether phospholipids, synthesized by peroxisomes, are essential in keeping the normal functions of neurons and glia [6,7]. Unsurprisingly, peroxisome dysfunction reportedly caused devastating damage to the neural cells, and is associated with neurological diseases, such as peroxisome biogenesis disorders (PBDs), stroke, PD, etc. [8,9]. Peroxisomes are essential organelles in maintaining cellular homeostasis, especially in the CNS.

Peroxisomes maintain their normal functions by developing a set of sophisticated mechanisms to control their quality and quantity [10,11]. Novel peroxisomes are generated through the growth and division of pre-existing peroxisomes or through de novo synthesis from mitochondria and ER. Abundant or dysfunctional peroxisomes are degraded via selective autophagy (pexophagy) [12]. All the generation and degradation processes are mediated by peroxisome biogenesis factors, known as peroxisomal membrane proteins (PMPs) and peroxins (PEXs) [13]. Selective autophagy of cellular organelles is an important process that maintains homeostasis during various internal and external stress responses. Pexophagy, the selective autophagy of peroxisomes, is important in maintaining peroxisome homeostasis [14,15], and a growing number of studies have demonstrated that pexophagy plays an important role in the pathology of neurological diseases [16].

Peroxisomes are quite important in maintaining cellular redox homeostasis and lipid metabolism in the CNS. However, the physiologic and pathologic roles of peroxisomes in CNS remain poorly understood when compared with other organelles. Therefore, we extensively reviewed the current understanding of peroxisomal metabolism in neurological diseases.

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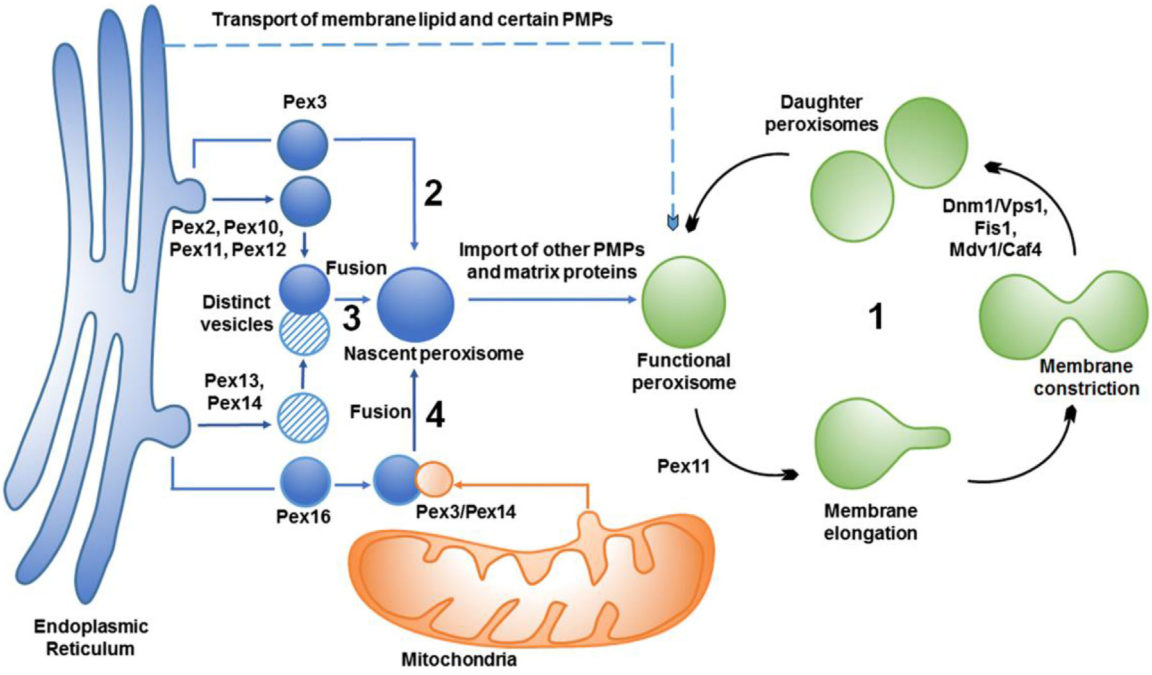

Fig. 1. Peroxisomes originate from ERs or mitochondria with the help of PEXs via class I and class II pathways. Moreover, the PEX11 and other fission related proteins (Mdv/Caf4, Fis1 and Dnm/Vps1) involved in the division of peroxisomes. Reproduced with permission [19].

2. Biogenesis and physiology of peroxisome

The biogenesis of peroxisomes involved formation of peroxisomal membrane, import of matrix proteins, and peroxisomal growth, division, and proliferation [17,18] (Fig. 1). Numerous proteins involved in these various processes have been found through studies using yeasts, animal models, and human cells. The majority of the proteins, which are called peroxins or PEX proteins due to their function in peroxisome formation, are involved in the biogenesis of peroxisomes. The current theory of human peroxisome biogenesis is briefly discussed here.

2.1. Development of peroxisomal membranes and import of peroxisomal proteins

The endoplasmic reticulum is where the phospholipids that comprise the peroxisomal membrane are most likely to originate [17,18,20–22]. Three peroxins, PEX3, PEX16, and PEX19, have been identified as having a specialized role in the synthesis of peroxisomal membranes. As an import receptor for freshly generated PMPs, PEX19, a protein that is mostly found in the cytosol, possesses chaperone-like properties to stabilize PMPs in the cytoplasm [23,24]. PEX19 binds to Pex3, an integral membrane protein that is part of the Class I pathway, and forms stable complexes with PMPs in the cytosol that are directed to the peroxisomal membrane [25–27].

PEX16, also known as the Class II pathway, serves as the membrane receptor in mammalian cells for PEX19 complexes with freshly generated PEX3 [26]. In the Class I pathway, PEX19 docks with Pex3 on the peroxisomal membrane to unload the cargo PMP before moving back to the cytosol for further PMP transport. In the absence of ATP, integration of the released PMP into the peroxisomal membrane occurs [28–30]. Coordination between PEX19 and PEX3 makes the insertion of hydrophobic transmembrane regions easier [31,32]. It is still necessary to improve the molecular processes behind the cargo PMPs' incorporation into the membrane.

2.2. Import of peroxisomal matrix proteins

Peroxisome-specific proteins are produced on free cytosolic polyribosomes after being encoded by nuclear genes, then transported to peroxisomes. The cytosolic receptor proteins, PEX5S, PEX5L [33], and PEX7, bind freshly produced proteins in the cytosol and then route them to the peroxisomal membrane. Differential splicing of the PEX5 gene's main transcript results in PEX5S and PEX5L. To be directed to the peroxisomal membrane, PEX7 is required to interact with PEX5L [33,34]. The peroxisomal docking complex, which is made up of the peroxisomal membrane proteins, PEX14 and PEX13, is where the receptor proteins are loaded with matrix proteins dock [35,36].

2.3. Peroxisome development, division, and proliferation

Peroxisomes divide concurrently with a number of events, such as elongation, constriction, and fission, after membrane construction and import of matrix proteins. A membrane peroxin known as PEX11 is essential for peroxisomal morphogenesis and division. Additionally, mitochondrial fission factor (Mff) [37,38], fission 1 (Fis1) [39,40], and dynamin-like protein 1 (DLP1) [41,42] in mammals are necessary for peroxisomal division. Peroxisome proliferation is induced by ectopic PEX11 expression [43,44], whereas PEX11 knockout in mice [45] and genetic defects in human PEX11 reduce peroxisome abundance [46,47]. It is hypothesized that PEX11′s homo-oligomerization through its N-terminal region is what drives the protein's morphogenic function [40]. Additionally, amphipathic helixes in the N-terminal region of PEX11 are necessary for the homo-oligomerization of PEX11 and their interaction with membrane phospholipids, which results in peroxisomal membrane deformation [48–50]. Surprisingly, DHA, a polyunsaturated fatty acid found in peroxisomal -oxidation metabolites, causes membranes rich in PEX11 to extend, as well as peroxisomes to lengthen [38]. These findings show that PEX11 is essential for the peroxisome elongation process, and that its function necessitates controlled oligomerization of PEX11 via interaction with phospholipids containing DHA in its N-terminal amphipathic region [51]. By moving to the locations of membrane constriction, DLP1, a member of the dynamin GTPase family, is crucial for the membrane fission of peroxisomes and mitochondria [42,52]. Large multimeric spirals created by DLP1 are thought to mediate the fission step [53,54]. A growing body of research indicates that PEX11 promotes fission during peroxisome division by forming a ternary fission machinery complex with Mff and DLP1 in the constricted membrane region of elon-

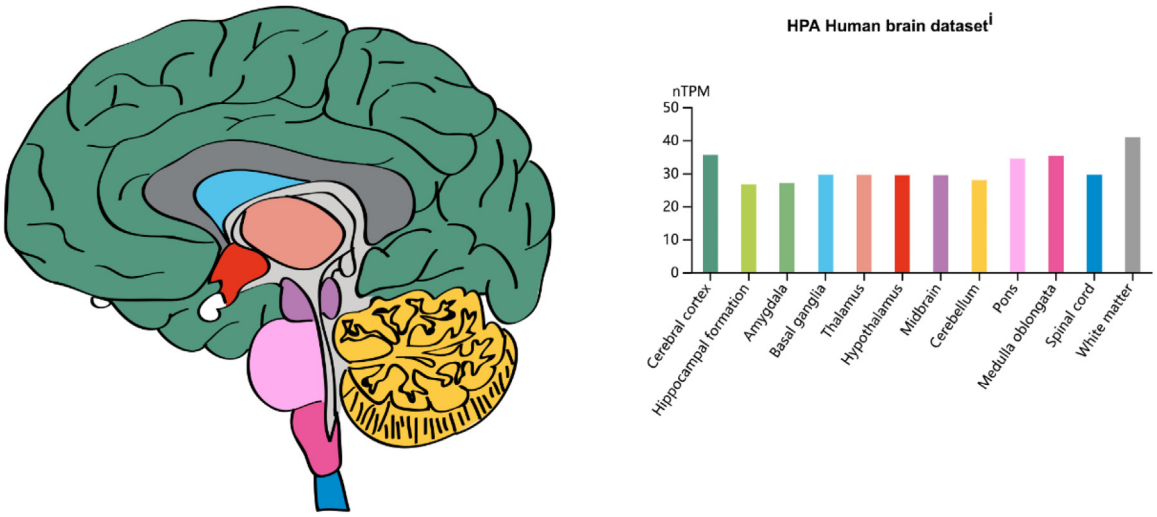

Fig. 2. The different distributions and activities of peroxisomes (catalase) in human brain (referenced from the human protein atlas: https://www.proteinatlas.org/ENSG00000121691-CAT/brain).

gated peroxisomes [51]. PEX11 increases DLP1's GTPase activity [55], demonstrating the numerous roles played during peroxisome division processes.

3. Peroxisome and central nervous system

In the CNS, nearly all cell types contain peroxisomes, including neurons [19,56,57], oligodendrocytes [58], astrocytes [57], and ependymal cells [59] (Fig. 2). The peroxisomes in the brain are smaller (0.1–0.2 μm) than peroxisomes in other tissues, and are consequentially referred to as microperoxisomes [60,61]. Peroxisomes were first found in the brain of a newborn mouse and the dorsal root ganglia of guinea pig spinal cord [62]. After that, various techniques have been applied to explore the distribution of peroxisomes in CNS [63]. In 1995, a complete peroxisome map of the CNS was first completed by Moreno and his colleagues with the help of a catalase antibody [64].

A moderate number of peroxisomes were observed in nearly all neurons of rat brains, whereas numerous peroxisomes were identified in ependymal cells around the ventral hypothalamus [59]. In addition, both in the brain and spinal cord, many more peroxisomes were found in oligodendrocytes. However, compared with neurons, very few peroxisomes were observed in astrocytes [59]. In addition, moderate numbers of peroxisomes were reported in the satellite and Schwann cells of the peripheral nervous system (marked by catalase staining) [58]. Singh and his colleagues also found that the activity of peroxisomal catalase was higher in oligodendrocytes than astrocytes of the rat brain [65]. In human brains, with the help of PEX14 antibody, a distinct number of neuronal peroxisomes were shown in each part of the brain (cerebellum, hippocampus, and thalamus) [66].

In addition, the distribution and activity of brain peroxisomes were altered during development [61]. For example, the number of neuronal peroxisomes was decreased in mature neurons when compared with differentiating cells. Another study found that the number of peroxisomes was decreased in both cerebrum and cerebellum. Purkinje cells of the cerebellum showed the greatest change in peroxisome distribution, which increased from 4 to 8 per unit area between postnatal and adult animals [58]. Similarly, neurons of the pons (locus coeruleus) and spinal cord had different numbers of neuronal peroxisomes between early neonatal and postnatal periods, respectively [58]. Besides, during myelination of the rat brain, peroxisomes increased in oligodendrocytes [58]. Studies of immunohistochemistry using catalase antibody showed that peroxisomes appeared early in evolution (about 27–28 weeks after conception) in ancient structures like the basal ganglia, thalamus, and cerebellum [67]. Moreover, with increasing age, peroxisomes in the glial cells gradually shifted from deep to superficial white matter [67].

In the brain, peroxisomes play an important role in degrading saturated very-long-chain fatty acids (VLCFA) like C24:0 and C26:0, as well as in maintaining their equilibrium in the myelin [68] (Fig. 3). Additionally, DHA, the most prevalent polyunsaturated fatty acid (PUFA) in brain tissues, is synthesized through b-oxidation of C24:6 n-3 [69]. A variety of functions are performed by DHA in the brain, including calcium concentration homeostasis, neurotransmission, synaptic plasticity, and gene expression [70,71]. Peroxisomes also play an important role in plasmalogen synthesis in the brain, as the first two steps of this pathway take place there [72]. The major predicted roles of plasmalogens are to contribute to membrane fluidity, buffer oxidative stress, and serve as reservoirs for second messengers [73]. Moreover, The peroxisomal enzymes play an essential role in maintaining ROS homeostasis in a cell, and the loss of that homeostasis can cause neurological disorders, such as X-linked adrenoleukodystrophy (X-ALD), ischemic stroke, etc. [4].

4. Dysfunction of peroxisome and neurological diseases

4.1. Alzheimer's disease (AD)

AD is one of the most common neurodegenerative diseases characterized by extracellular amyloid β (Aβ) peptides and intracellular neurofibrillary tangles [74,75] (Table 1). Many studies have shown the changes of oxidative stress level, antioxidant enzymes such as catalase and peroxisomal-related proteins among patients with Alzheimer's disease [76]. For example, symptoms of dementia were correlated with the dramatic decrease in plasmalogen levels in white and gray matter in different regions of human brain tissue, as well as the gyrus frontalis [77,78]. PtdEtn and PtdCho levels were significantly decreased in the postmortem brains of AD subjects and transgenic mice with AD [79,80]. In all cortical regions of AD patients, there was an increase in short- and long-chain fatty acids (C22:0, C24:0, and C26:0), which suggests that functional peroxisomes were lost [77]. Additionally, AD patients' brain sections were found to have a higher density of peroxisomes [77]. Furthermore, increasing peroxisome proliferation and catalase activity can reduce ROS production, which plays a crucial role in AD pathogenesis, and first established a direct link between peroxisomes and AD. A number of peroxisomal proteins (PMP70, CAT, PEX5, GPX1) were significantly altered in the neocortex and hippocampus of three-month-old Tg2576 mice model of AD [75,77]. It is interesting that supplementation with acetyl-L-carnitine (ALC), a metabolite synthesized in peroxisomes,

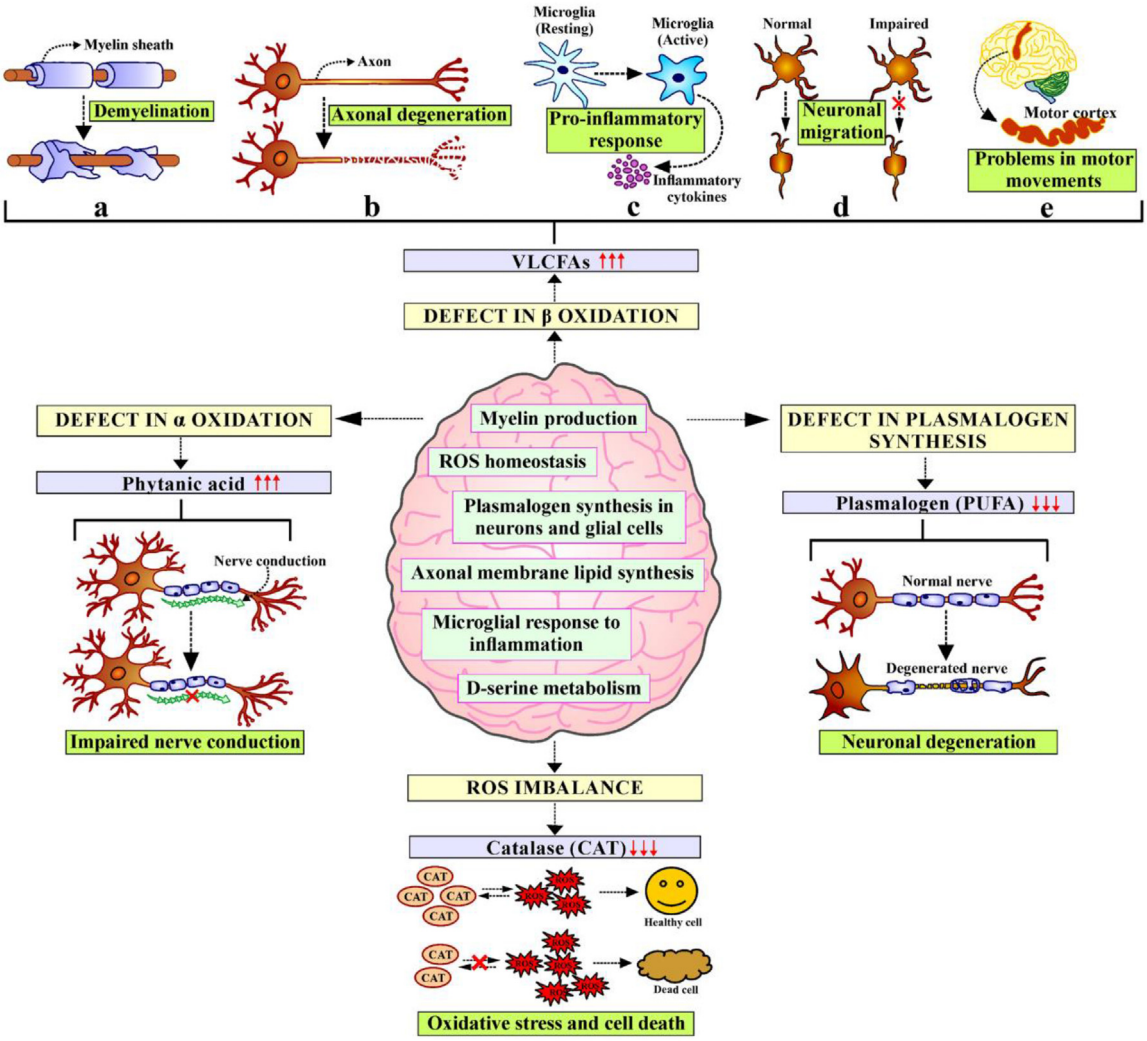

Fig. 3. The specialized functions of peroxisomes and neurological disorders rising due to peroxisomal dysfunction in the brain. Reproduced with permission [68].

Table 1
Disruption of peroxisomal metabolisms in neurological diseases.

Neurological disorder	Hallmark	Peroxisomal protein/function affected
Alzheimer's disease	extracellular amyloid β (Aβ) peptides and intracellular neurofibrillary tangles	PtdEtn and PtdCho, PMP70, catalase, PEX5, GPX1
Parkinson's Disease	accumulation of α-synuclein, the main components of Lewy bodies (LBs)	PEX2, PUFA, Plasmalogens
Multiple Sclerosis	axonal degeneration and progressive demyelination	VLCFAs; PtdEtn
Amyotrophic Lateral Sclerosis	Demyelination of motor neurons causing muscle weakness	cholesterol; D-AAO
Stroke	brain is not supplied with enough blood	Peroxisome biogenesis; catalase, PPAR
Peroxisome Biogenesis Disorders (Zellweger syndrome)	mutations in the PEX genes involved in peroxisome biogenesis	PEX16, VLCFA, catalase, fatty acids

Abbreviations: PEX, peroxisome; PUFA, Polyunsaturated fatty acid; VLCFA, Very long chain fatty acid; D-AAO, D-amino acid oxidase; PPAR, peroxisome proliferator-activated receptor.

significantly reduced Aβ accumulation and tau hyperphosphorylation in a rat AD model [81].

4.2. Parkinson's disease (PD)

The ROS and peroxisomal related proteins were also reported to be dramatically changed in PD patients, which was characterized with accumulation of α-synuclein, the main components of Lewy bodies [82,83]. Interestingly, a reduced level of catalase was observed in α-synuclein expressing cells of mice brain [84]. As Willingham and coworkers demonstrated, yeast cells lacking PEX2 exhibited growth defects compared with yeast cells with PEX2, emphasizing the protective roles of peroxisomes in α-synuclein-induced cellular toxicity [85]. Additionally, many studies focused on the roles of peroxisomes in lipid metabolism [3]. The levels of lipids such as oxysterols and cholesterol were demonstrated to contribute to the development of PD [86].

Besides, the levels of fatty acids, such as PUFA, were also shown to be downregulated in patients with PD [87]. Deficiencies in peroxisomes shorten the acyl chains in these cells, affecting the composition of lipid droplets, which in turn affects synuclein binding. Plasmalogens were found to be reduced in PD patients' frontal cortex postmortem [88]. Peroxisomal enzyme glycerone-phosphate O-acyltransferase (GNPAT) synthesizes plasmalogens in the brain by phosphorylating glycerone phosphate [89]. Compared to wild-type mice, GNAPT knockout mice displayed rapid declines in mean dopamine levels [90]. When mice with Parkinson's disease were supplemented with the highly bioavailable plasmalogen precursor, PPI-1011, the striatal dopamine loss was reversed [91].

4.3. Multiple sclerosis (MS)

MS is characterized by progressive loss of axonal function caused by demyelination in the central nervous system. An axonal degeneration and progressive demyelination were observed in the PEX5 knockout mice lacking functional peroxisomes in oligodendrocytes [92]. Besides, in MS brain tissues, PMP70 expression was reduced overall. As a result, the gray matter neurons produced elevated levels of VLCFAs (C26:0) [93]. In MS patients, DHA containing PlsEtn was found to be reduced, supporting the role of peroxisomes in MS [94].

4.4. Amyotrophic lateral sclerosis (ALS)

The progressive disease, ALS, primarily affects motor neurons that control voluntary muscle movement. An analysis of genome-wide expression identified genes and pathways associated with ALS, including peroxisome-related genes [95]. Furthermore, ALS patients have reportedly had defects in cholesterol metabolism, which requires functional peroxisomes [96]. In the brain and spinal cord, D-proline, D-serine, and D-alanine are oxidized by the peroxisomal enzyme D-amino acid oxidase (D-AAO) [97], while impairment in the clearance of D-serine greatly contribute to the pathogenesis of ALS [98]. Patients with familial ALS have also been found to carry a mutation in D-AAO (R199W D-AAO)[98]. When mutant D-AAO is overexpressed in motor neurons, autophagy is activated and cell death occurs [99].

4.5. Stroke

In mouse models with ischemic brains, ROS metabolism is directly related to brain development. During brain ischemia, the brain is not supplied with enough blood, resulting in cell death within neurons [100,101]. The study found that neurons improve their antioxidant abilities in response to ischemic injury in mouse models of ischemic injury. A study found that ischemic injury in neurons increased peroxisome biogenesis, resulting in increased expression and number of peroxisomes [102]. Peroxisome proliferator-activated receptor (PPAR)-activation reduces expression of NOS and COX2 as well as proinflammatory cytokines, making it a potent therapeutic target for treating ischemic stroke [103]. By using WY14643, oxidative damage resulting from ischemic stroke in rats was remarkably reduced [104]. In one of our own studies, we found that the functions of peroxisomes were compromised in the animal model of subarachnoid hemorrhage, which reversely exacerbated cerebral white matter injury via thioredoxin-binding protein (TXNIP) and GNPAT pathways [44].

4.6. Peroxisome biogenesis disorders (Zellweger syndrome)

A group of autosomal recessive inherited disorders involved in peroxisome biogenesis are known as PBDs. Cerebro-hepato syndrome (CHS) or Zellweger syndrome (ZS) is caused by mutations in the PEX genes involved in peroxisome biogenesis [105]. In Zellweger patients, accumulation of branched and very long chains of fatty acids leads to brain dysfunction [106]. Neuronal migration defects led to cerebellar malformations and abnormal Purkinje cell positioning in ZS patients' postnatal cerebellums [107]. A disordered neuronal migration has also been associated with abnormalities in the cerebral hemispheres and cerebellum [108]. Hypotonia and craniofacial dysmorphism are common in newborns with ZS [2]. The ZS abnormalities were studied in mice with knockouts of PEX2, PEX5, and PEX13 [109–111]. The study reported abnormalities in cerebellum development and subsequently in brain formation, as well as hypotonia, growth retardation, and impairment of granule cell migration. As a result, there is an increase in cell death within days of birth [109–111]. In ZS patients with a PEX16 mutation, VLCFA levels were elevated and catalase levels were decreased, suggesting that the peroxisomal functions were abnormal [112].

5. Pexophagy: molecular and cellular mechanisms

In 1997, Klionsky described pexophagy for the first time [113]. The macropexophagy and micropexophagy modes of pexophagy were later discovered by researchers [114–116]. The macropexophagy of mammals is defined as single peroxisomes being engulfed by autophagosomes to form pexophagosomes, which are then fused with lysosomes and degraded for recycling. As a result of micropexophagy, vacuolar sequestering membranes (VSMs) and micropexophagy-specific apparatus (MIPA) engulf the peroxisome [117], in which the peroxisomes are cradled by cup-shaped VSMs [118].

In addition to the proteins that form the core of autophagy machinery, pexophagy reportedly involves a number of specific proteins. One is autophagy receptors. NBR1 and SQSTM1/p62 reportedly act as autophagy receptors in mammalian cells [119]. Two functional domains are shared by these receptors. One is LIR, which binds to LC3, delivering peroxisomes to autophagosomes, and the other is ubiquitin-associated domain. The other domains are ubiquitin-associated, which interact with ubiquitinated residues on peroxisomes [120]. In spite of SQSTM1's contribution to pexophagy, it is not required for pexophagy when NBR1 is sufficient. Despite this, SQSTM1 can raise NBR1-mediated pexophagy's efficiency by binding to NBR1 [121]. Moreover, these two receptors have also been reported to participate in mitophagy, lysophagy, and ER-phagy as well [122–124]. PEX14 also reportedly interacts directly with LC3-II under conditions of nutrient deprivation to facilitate pexophagy [125]. Moreover, NBR1 and/or SQSTM1/p62 facilitate interactions between PEX14 and LC3-II by altering its conformation, enabling LC3-II to interact with transmembrane domains of PEX14 [126]. It has been found that PEX5 ubiquitination is one of the mechanisms that initiate pexophagy when some stresses occur, such as dysfunctional peroxisomes or oxidative stress. Furthermore, ataxia-telangiectasia mutated (ATM) kinase is another significant factor. Activation of ATM could phosphorylate and activate PEX5, which leads to PEX5 self-ubiquitination and finally promotes pexophagy [127,128] (Fig. 4).

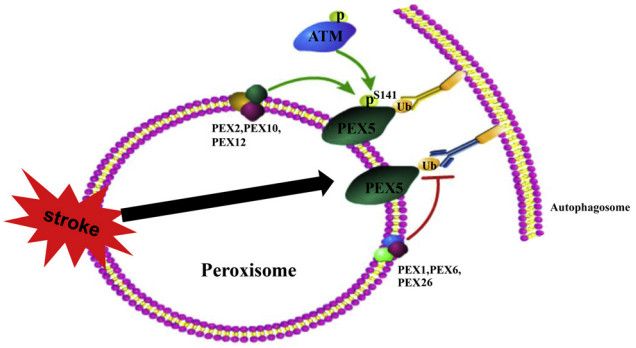

Fig. 4. The underlying mechanisms of pexophagy in mammals.

5.1. Ubiquitination-mediated pexophagy

In recent years, evidence has accumulated that ubiquitination of some proteins is one of the prerequisites for selective autophagy [129–131]. Pexophagy is associated with PEX5 ubiquitination. Peroxisome-localized ATM is phosphorylated and activated by oxidative stress, which in turn activates PEX5. PEX5 is then subsequently phosphorylated by PEX2. PEX10, or PEX12, which ubiquitinates it at K209, allowing PEX5 to be targeted by SQSTM1/p62 for pexophagic degradation [127].

5.2. Adaptor-mediated pexophagy

The SQSTM1/p62 protein serves as an autophagy adaptor and possesses two functional domains: the LIR of the motif and the UBA domain at its C-terminus [123,132]. This autophagy adaptor is a key regulator of autophagic signaling pathways, and has always been used as a biomarker for monitoring autophagy levels [123,133,134]. Pexophagy occurs when SQSTM1/p62 engages LC3II through the LC3-interacting region (LIR). And Ubiquitin-Associated (UBA) domains interact with ubiquitinated peroxisome regions, followed by engulfment of peroxisome [135,136].

NBR1 is another mediator for pexophagy, which also possesses an LIR and a UBA domain [137,138]. The NBR1 helps to transport peroxisome to the lysosomes, and activates pexophagy [121]. Additionally, although p62 cannot initiate pexophagy due to a lack of juxta-UBA (JUBA) domain, its interaction with NBR1 can increase the efficiency of NBR1-induced pexophagy [121].

6. Pexophagy and neurological diseases

6.1. Pexophagy in mammals

The roles of pexophagy in mammal cells has recently been studied and its physiological and pathological functions have also been explored. There have been links demonstrated between pexophagy and cellular aging [100,101], inflammation [44], cancer development [43,102], and apoptosis [7,98,99]. For example, one study showed that dysfunctional peroxisomes were cleared via pexophagy, which in turn reduced the oxidative stress and renal damage in vascular endothelial cells under exposure to lipopolysaccharides [107,108]. Furthermore, cone cell retinal dystrophy may be caused by a mutation of the pexophagy-specific protein, ACBD5 [109]. Besides, the role of pexophagy in CNS has been reviewed in recent years. Peroxisomes are important in maintaining redox hemostasis of CNS. Peroxisomal dysfunction or excessive accumulation of peroxisomes contribute greatly to the pathogenesis of neurological diseases. Selective removal of dysfunctional or superfluous peroxisomes provides neuroprotective effects, which has been firmly proven in animal models [139]. Moreover, there are several signs of neurodegeneration caused by pexophagy gene knockouts, including growth retardation, abnormal reflexes, premature death, and progressive motor deficits [140–142].

6.2. Neuroprotection of pexophagy in neurological diseases

Unlike other cell types, neurons rely heavily on basal autophagy, since they are post-mitotic and suffer from aggregation of toxic proteins, as well as structural damage [143–145]. Growing evidence indicates that pharmacologically inducing pexophagy can help treat neurological disorders. For example, in a middle cerebral artery occlusion (MCAO) animal model, Zhu and his colleagues found that pexophagy flux was decreased in TSC1 knockout mice, which showed that there were sustained larger infarcts than WT mice [16]. Furthermore, doxorubicin-based chemotherapy decreases peroxisome production and pexophagy in neurons [146]. However, Hydroxypropyl-β-cyclodextrin (HPβCD), a regulator of autophagy and lysosome functions, can decrease oxidative stress and pexophagy-related damage caused by doxorubicin. Several studies have suggested that most peroxisome biogenesis disorders, such as Zellweger syndrome, do not result from a failure to produce peroxisomes, but rather from dysfunction of pexophagy. However, more studies are needed to study the functions of pexophagy in PBDs.

The ACBD5, a human ortholog of Atg37, is localized to peroxisomes and participates in pexophagy [147]. According to a recent study, mutant ACBD5 is associated with impaired very long-chain fatty acid oxidation and leads to the white matter diseases [148]. What's more, the biogenesis and degradation of peroxisomes are also impaired in PD and AD. A dysfunctional peroxisome can produce ROS that contribute to cellular degeneration, including neurodegeneration and aging. Therefore, degrading dysfunctional peroxisomes is very important, and recent studies indicate pexophagy is important for neurodegenerative diseases [149]. In addition, a lack of HSPA9 increased peroxisomal ROS, resulting in dysfunctional peroxisomes and pexophagy [150]. The PD-associated mutants of HSPA9 (R126W, A476T, and P509S) failed to inhibit pexophagy in HSPA9-deficient neuronal cells when overexpressed, whereas WT HSPA9 reversed the loss of peroxisomes [150]. However, much remains unknown about how pexophagy is affected by these diseases and more studies should be conducted.

6.3. Potential clinical values of pexophagy in neurological diseases

Pexophagy is reportedly involved in several neurological diseases, including stroke, Zellweger Syndrome, and PBDs, suggesting that pexophagy can be a promising target of treatment. In one clinical trial (NCT03856866), the effects of hydroxychloroquine (HCQ) are evaluated for treating peroxisomal biogenesis disorders (PBD-ZSD). They hypothesized that HCQ will reduce pexophagy, which will arrest ongoing injury in Zellweger Syndrome and PBDs caused by PEX1, PEX6, or PEX26. However, no results have been reached currently. The study of pexophagy in the central nervous system is still largely unexplored and most evidence is based on preclinical animal studies. There are currently several limitations for the clinical study of pexophagy. Clinical translation of the drugs is still in its infancy, which is limited by drug development. Most of the drugs have not been introduced into clinical practice. Additionally, we are unable to dynamically evaluate autophagy in living cells. The importance of this limitation is evident since it determines the diagnosis and monitoring of the effectiveness of any autophagy-based therapy. Several experimental studies have reported that pairing the macroautophagy reporter, mRFP-GFP-LC3, and intraventricular delivery of an adeno-associated virus can be effective in monitoring autophagy [151]. However, there are currently no clinically applicable autophagy reporters. Therefore, for clinical translation of autophagy-based drugs, it will be essential to develop methods for monitoring autophagy.

7. Conclusion and perspectives

In this review, we comprehensively discussed the physiological and pathological mechanisms of peroxisomes and pexophagy in neurological diseases. Several types of cells and tissues use peroxisomes, and they collaborate extensively with mitochondria, ERs, and lipid bodies. There are a variety of types, sizes, and shapes of peroxisomes in different tissues and cells. However, the exact impact of these differences on the function of peroxisomes in various cell types is unclear.

There is a high degree of diversity in the nervous system and brain, especially in terms of morphology, number, and function. As described above, several brain-related disorders are now known to be caused by peroxisomes. Peroxisomes play an important role in oxidative homeostasis, lipid synthesis, and degradation. The neurological diseases are linked to altered peroxisome activities as well as decreased peroxisome function. However, a thorough investigation of the molecular details, as well as the implications, is needed.

Moreover, pexophagy was also discussed in relation to neurological diseases, which is a promising therapeutic target. However, pexophagy remains largely unexplored in neurological disorders despite its crucial role in cell physiology. Accumulating studies have identified the functions of adaptors, such as p62 and NBR1, in mediating pexophagy. However, these adaptors do not exclusively play a role in pexophagy, and are involved in other selective autophagic processes, including xenophagy and mitophagy. Elucidating the roles of pexophagy adaptors and peroxisomal proteins will help to enable a better understanding of the molecular mechanisms of pexophagy in neurological diseases. Moreover, we do not have any clinical evidence that pexophagy is involved in neurological diseases as most of the evidence is based on preclinical animal studies. It is necessary to develop a broad range of reagents and therapeutic targets for manipulating pexophagy and to further elucidate pexophagy's crosstalk mechanisms in the neurological pathology.

Declaration of competing interest

The authors declare that they have no conflicts of interest in this work.

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Supplementary materials

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References

[1] C. De Duve, P. Baudhuin, Peroxisomes (microbodies and related particles), Physiol. Rev. 46 (2) (1966) 323–357.
[2] N.E. Braverman, M.D. D'Agostino, G.E. Maclean, Peroxisome biogenesis disorders: Biological, clinical and pathophysiological perspectives, Dev. Disabil. Res. Rev. 17 (3) (2013) 187–196.
[3] D.S. Jo, D.H. Cho, Peroxisomal dysfunction in neurodegenerative diseases, Arch. Pharm. Res. 42 (5) (2019) 393–406.
[4] M. Fransen, et al., Role of peroxisomes in ROS/RNS-metabolism: Implications for human disease, Biochim. Biophys. Acta 1822 (9) (2012) 1363–1373.
[5] E. Dixit, et al., Peroxisomes are signaling platforms for antiviral innate immunity, Cell 141 (4) (2010) 668–681.
[6] J.M. Powers, Normal and defective neuronal membranes: Structure and function: Neuronal lesions in peroxisomal disorders, J. Mol. Neurosci. 16 (2–3) (2001) 317–321 285-7; discussion.
[7] A.A. Farooqui, L.A. Horrocks, Plasmalogens: Workhorse lipids of membranes in normal and injured neurons and glia, Neuroscientist 7 (3) (2001) 232–245.
[8] C.M. Kassmann, Myelin peroxisomes - essential organelles for the maintenance of white matter in the nervous system, Biochimie 98 (2014) 111–118.
[9] A. Bottelbergs, et al., Axonal integrity in the absence of functional peroxisomes from projection neurons and astrocytes, Glia 58 (13) (2010) 1532–1543.
[10] D.H. Cho, et al., Pexophagy: Molecular mechanisms and implications for health and diseases, Mol. Cells 41 (1) (2018) 55–64.
[11] M. Oku, Y. Sakai, Peroxisomes as dynamic organelles: Autophagic degradation, FEBS J. 277 (16) (2010) 3289–3294.
[12] A. Sugiura, et al., Newly born peroxisomes are a hybrid of mitochondrial and ER-derived pre-peroxisomes, Nature 542 (7640) (2017) 251–254.
[13] G. Agrawal, S. Subramani, De novo peroxisome biogenesis: Evolving concepts and conundrums, Biochim. Biophys. Acta 1863 (5) (2016) 892–901.
[14] K.M. Walter, et al., Hif-2alpha promotes degradation of mammalian peroxisomes by selective autophagy, Cell Metab. 20 (5) (2014) 882–897.
[15] S.Y. Eun, et al., PEX5 regulates autophagy via the mTORC1-TFEB axis during starvation, Exp. Mol. Med. 50 (4) (2018) 1–12.
[16] Wenbin Zhu, W. Z, Jennifer Young, Anthony P Barnes, Nabil J Alkayed, Pexophagy is neuroprotective in ischemic brain, Stroke 48 (ATP96) (2017).
[17] Y. Fujiki, K. Okumoto, S. Mukai, et al., Peroxisome biogenesis in mammalian cells, Front. Physiol. 5 (2014) 307.
[18] J.J. Smith, J.D. Aitchison, Peroxisomes take shape, Nat. Rev. Mol. Cell Biol. 14 (12) (2013) 803–817.
[19] R. Deb, N. Joshi, S. Nagotu, Peroxisomes of the brain: Distribution, functions, and associated diseases, Neurotox. Res. 39 (3) (2021) 986–1006.
[20] L. Dimitrov, S.K. Lam, R. Schekman, The role of the endoplasmic reticulum in peroxisome biogenesis, Cold Spring Harb. Perspect. Biol. 5 (5) (2013) a013243.
[21] C. Ma, G. Agrawal, S. Subramani, Peroxisome assembly: Matrix and membrane protein biogenesis, J. Cell Biol. 193 (1) (2011) 7–16.
[22] G. Agrawal, S. Subramani, Emerging role of the endoplasmic reticulum in peroxisome biogenesis, Front. Physiol. 4 (2013) 286.
[23] J.M. Jones, J.C. Morrell, S.J. Gould, PEX19 is a predominantly cytosolic chaperone and import receptor for class 1 peroxisomal membrane proteins, J. Cell Biol. 164 (1) (2004) 57–67.
[24] Y. Matsuzono, T. Matsuzaki, Y. Fujiki, Functional domain mapping of peroxin Pex19p: Interaction with Pex3p is essential for function and translocation, J. Cell Sci. 119 (17) (2006) 3539–3550 Pt.
[25] Y. Fang, J.C. Morrell, J.M. Jones, et al., PEX3 functions as a PEX19 docking factor in the import of class I peroxisomal membrane proteins, J. Cell Biol. 164 (6) (2004) 863–875.
[26] T. Matsuzaki, Y. Fujiki, The peroxisomal membrane protein import receptor Pex3p is directly transported to peroxisomes by a novel Pex19p- and Pex16p-dependent pathway, J. Cell Biol. 183 (7) (2008) 1275–1286.
[27] Y. Liu, Y. Yagita, Y. Fujiki, Assembly of peroxisomal membrane proteins via the direct Pex19p-Pex3p pathway, Traffic 17 (4) (2016) 433–455.
[28] Y. Yagita, T. Hiromasa, Y. Fujiki, Tail-anchored PEX26 targets peroxisomes via a PEX19-dependent and TRC40-independent class I pathway, J. Cell Biol. 200 (5) (2013) 651–666.
[29] P. Diestelkötter, W.W. Just, In vitro insertion of the 22-kD peroxisomal membrane protein into isolated rat liver peroxisomes, J. Cell Biol. 123 (6) (1993) 1717–1725 Pt 2.
[30] M.P. Pinto, C.P. Grou, I.S. Alencastre, et al., The import competence of a peroxisomal membrane protein is determined by Pex19p before the docking step, J. Biol. Chem. 281 (45) (2006) 34492–34502.
[31] Y. Chen, L. Pieuchot, R.A. Loh, et al., Hydrophobic handoff for direct delivery of peroxisome tail-anchored proteins, Nat. Commun. 5 (2014) 5790.
[32] F. Schmidt, et al., The role of conserved PEX3 regions in PEX19-binding and peroxisome biogenesis, Traffic 13 (9) (2012) 1244–1260.
[33] N. Braverman, et al., An isoform of pex5p, the human PTS1 receptor, is required for the import of PTS2 proteins into peroxisomes, Hum. Mol. Genet. 7 (8) (1998) 1195–1205.
[34] G. Dodt, D. Warren, E. Becker, et al., Domain mapping of human PEX5 reveals functional and structural similarities to Saccharomyces cerevisiae Pex18p and Pex21p, J. Biol. Chem. 276 (45) (2001) 41769–41781.
[35] V. Dammai, S. Subramani, The human peroxisomal targeting signal receptor, Pex5p, is translocated into the peroxisomal matrix and recycled to the cytosol, Cell 105 (2) (2001) 187–196.
[36] G. Dodt, S.J. Gould, Multiple PEX genes are required for proper subcellular distribution and stability of Pex5p, the PTS1 receptor: Evidence that PTS1 protein import is mediated by a cycling receptor, J. Cell Biol. 135 (6) (1996) 1763–1774 Pt 2.
[37] S. Gandre-Babbe, A.M. van der Bliek, The novel tail-anchored membrane protein Mff controls mitochondrial and peroxisomal fission in mammalian cells, Mol. Biol. Cell 19 (6) (2008) 2402–2412.
[38] A. Itoyama, et al., Docosahexaenoic acid mediates peroxisomal elongation, a prerequisite for peroxisome division, J. Cell Sci. 125 (Pt 3) (2012) 589–602.
[39] A. Koch, et al., A role for Fis1 in both mitochondrial and peroxisomal fission in mammalian cells, Mol. Biol. Cell 16 (11) (2005) 5077–5086.
[40] S. Kobayashi, A. Tanaka, Y. Fujiki, Fis1, DLP1, and Pex11p coordinately regulate peroxisome morphogenesis, Exp. Cell. Res. 313 (8) (2007) 1675–1686.
[41] X. Li, S.J. Gould, The dynamin-like GTPase DLP1 is essential for peroxisome division and is recruited to peroxisomes in part by PEX11, J. Biol. Chem. 278 (19) (2003) 17012–17020.
[42] A. Tanaka, S. Kobayashi, Y. Fujiki, Peroxisome division is impaired in a CHO cell mutant with an inactivating point-mutation in dynamin-like protein 1 gene, Exp. Cell. Res. 312 (9) (2006) 1671–1684.
[43] M. Schrader, B.E. Reuber, J.C. Morrell, et al., Expression of PEX11beta mediates peroxisome proliferation in the absence of extracellular stimuli, J. Biol. Chem. 273 (45) (1998) 29607–29614.
[44] W. Xu, J. Yan, S. Chen, et al., Peroxisomal dysfunction contributes to white matter injury following subarachnoid hemorrhage in rats via thioredoxin-interacting protein-dependent manner, Front. Cell Dev. Biol. 8 (2020) 576482.
[45] X. Li, E. Baumgart, J.C. Morrell, et al., PEX11 beta deficiency is lethal and impairs neuronal migration but does not abrogate peroxisome function, Mol. Cell. Biol. 22 (12) (2002) 4358–4365.
[46] M.S. Ebberink, et al., A novel defect of peroxisome division due to a homozygous non-sense mutation in the PEX11β gene, J. Med. Genet. 49 (5) (2012) 307–313.
[47] S. Thoms, J. Gärtner, First PEX11β patient extends spectrum of peroxisomal biogenesis disorder phenotypes, J. Med. Genet. 49 (5) (2012) 314–316.
[48] Ł. Opaliński, et al., Membrane curvature during peroxisome fission requires Pex11, EMBO J. 30 (1) (2011) 5–16.
[49] Y. Yoshida, H. Niwa, M. Honsho, et al., Pex11mediates peroxisomal proliferation by promoting deformation of the lipid membrane, Biol. Open 4 (6) (2015) 710–721.
[50] J. Su, A.S. Thomas, T. Grabietz, et al., The N-terminal amphipathic helix of Pex11p self-interacts to induce membrane remodelling during peroxisome fission, Biochim. Biophys. Acta Biomembr. 1860 (6) (2018) 1292–1300.
[51] M. Islinger, et al., The peroxisome: An update on mysteries 2.0, Histochem. Cell Biol. 150 (5) (2018) 443–471.
[52] N. Ishihara, M. Nomura, A. Jofuku, et al., Mitochondrial fission factor Drp1 is es-

sential for embryonic development and synapse formation in mice, Nat. Cell Biol. 11 (8) (2009) 958–966.
[53] C. Fröhlich, G. Grabiger, D. Schwefel, et al., Structural insights into oligomerization and mitochondrial remodelling of dynamin 1-like protein, EMBO J. 32 (9) (2013) 1280–1292.
[54] H.T. Bui, J.M. Shaw, Dynamin assembly strategies and adaptor proteins in mitochondrial fission, Curr. Biol. 23 (19) (2013) R891–R899.
[55] C. Williams, L. Opalinski, C. Landgraf, et al., The membrane remodeling protein Pex11p activates the GTPase Dnm1p during peroxisomal fission, Proc. Natl. Acad. Sci. U. S. A. 112 (20) (2015) 6377–6382.
[56] E. Holtzman, S. Teichberg, S.J. Abrahams, et al., Notes on synaptic vesicles and related structures, endoplasmic reticulum, lysosomes and peroxisomes in nervous tissue and the adrenal medulla, J. Histochem. Cytochem. 21 (4) (1973) 349–385.
[57] G. Arnold, L. Liscum, E. Holtzman, Ultrastructural localization of D-amino acid oxidase in microperoxisomes of the rat nervous system, J. Histochem. Cytochem. 27 (3) (1979) 735–745.
[58] G. Arnold, E. Holtzman, Microperoxisomes in the central nervous system of the postnatal rat, Brain Res. 155 (1) (1978) 1–17.
[59] O. McKenna, G. Arnold, E. Holtzman, Microperoxisome distribution in the central nervous system of the rat, Brain Res. 117 (2) (1976) 181–194.
[60] A.B. Novikoff, et al., Studies on microperoxisomes. II. A cytochemical method for light and electron microscopy, J. Histochem. Cytochem. 20 (12) (1972) 1006–1023.
[61] J. Berger, F. Dorninger, S. Forss-Petter, et al., Peroxisomes in brain development and function, Biochim. Biophys. Acta 1863 (5) (2016) 934–955.
[62] Z. Hruban, et al., Microbodies: Constituent organelles of animal cells, Lab. Invest. 27 (2) (1972) 184–191.
[63] M.J. Schonenberger, W.J. Kovacs, Isolation of Peroxisomes from mouse brain using a continuous nycodenz gradient: A comparison to the isolation of liver and kidney peroxisomes, Methods Mol. Biol. 1595 (2017) 13–26.
[64] S. Moreno, E. Mugnaini, M.P. Ceru, Immunocytochemical localization of catalase in the central nervous system of the rat, J. Histochem. Cytochem. 43 (12) (1995) 1253–1267.
[65] I. Singh, O. Carillo, A. Namboodiri, Isolation and biochemical characterization of peroxisomes from cultured rat glial cells, Neurochem. Res. 25 (2) (2000) 197–203.
[66] P. Grant, B. Ahlemeyer, S. Karnati, et al., The biogenesis protein PEX14 is an optimal marker for the identification and localization of peroxisomes in different cell types, tissues, and species in morphological studies, Histochem. Cell Biol. 140 (4) (2013) 423–442.
[67] S. Houdou, H. Kuruta 1, M. Hasegawa, et al., Developmental immunohistochemistry of catalase in the human brain, Brain Res. 556 (2) (1991) 267–270.
[68] N.M. Deori, A. Kale, P.K. Maurya, et al., Peroxisomes: Role in cellular ageing and age related disorders, Biogerontology 19 (5) (2018) 303–324.
[69] S. Ferdinandusse, et al., Identification of the peroxisomal beta-oxidation enzymes involved in the biosynthesis of docosahexaenoic acid, J. Lipid Res. 42 (12) (2001) 1987–1995.
[70] N., Jr. Salem, B. Litman, H.-Y. Kim, et al., Mechanisms of action of docosahexaenoic acid in the nervous system, Lipids 36 (9) (2001) 945–959.
[71] R.S. Chapkin, W. Kim, J.R. Lupton, et al., Dietary docosahexaenoic and eicosapentaenoic acid: Emerging mediators of inflammation, Prostaglandins Leukot. Essent. Fatty Acids 81 (2–3) (2009) 187–191.
[72] P. Brites, H.R. Waterham, R.J. Wanders, Functions and biosynthesis of plasmalogens in health and disease, Biochim. Biophys. Acta 1636 (2–3) (2004) 219–231.
[73] N.E. Braverman, A.B. Moser, Functions of plasmalogen lipids in health and disease, Biochim. Biophys. Acta 1822 (9) (2012) 1442–1452.
[74] D.J. Selkoe, Cell biology of protein misfolding: The examples of Alzheimer's and Parkinson's diseases, Nat. Cell Biol. 6 (11) (2004) 1054–1061.
[75] A. Cimini, S. Moreno, M. D'Amelio, et al., Early biochemical and morphological modifications in the brain of a transgenic mouse model of Alzheimer's disease: A role for peroxisomes, J. Alzheimers Dis. 18 (4) (2009) 935–952.
[76] D.L. Marcus, C. Thomas, C. Rodriguez, et al., Increased peroxidation and reduced antioxidant enzyme activity in Alzheimer's disease, Exp. Neurol. 150 (1) (1998) 40–44.
[77] J. Kou, G.G. Kovacs, R. Höftberger, et al., Peroxisomal alterations in Alzheimer's disease, Acta Neuropathol. 122 (3) (2011) 271–283.
[78] X.Q. Su, J. Wang, A.J. Sinclair, Plasmalogens and Alzheimer's disease: A review, Lipids Health Dis. 18 (1) (2019) 100.
[79] M. Igarashi, K. Ma, F. Gao, et al., Disturbed choline plasmalogen and phospholipid fatty acid concentrations in Alzheimer's disease prefrontal cortex, J. Alzheimers Dis. 24 (3) (2011) 507–517.
[80] G. Lizard, O. Rouaudb, J. Demarquoy, et al., Potential roles of peroxisomes in Alzheimer's disease and in dementia of the Alzheimer's type, J. Alzheimers Dis. 29 (2) (2012) 241–254.
[81] P. Zhou, Z. Chen, N. Zhao, et al., Acetyl- L-carnitine attenuates homocysteine-induced Alzheimer-like histopathological and behavioral abnormalities, Rejuvenation Res. 14 (6) (2011) 669–679.
[82] L. Sironi, L.M. Restelli, M. Tolnay, et al., Dysregulated interorganellar crosstalk of mitochondria in the pathogenesis of Parkinson's disease, Cells 9 (1) (2020).
[83] K. Wakabayashi, K. Tanji, F. Mori, et al., The Lewy body in Parkinson's disease: Molecules implicated in the formation and degradation of alpha-synuclein aggregates, Neuropathology 27 (5) (2007) 494–506.
[84] E. Yakunin, H. Kisos, W. Kulik, et al., The regulation of catalase activity by PPAR gamma is affected by alpha-synuclein, Ann. Clin. Transl. Neurol. 1 (3) (2014) 145–159.
[85] S. Willingham, T.F. Outeiro, M.J. DeVit, et al., Yeast genes that enhance the toxicity of a mutant huntingtin fragment or alpha-synuclein, Science 302 (5651) (2003) 1769–1772.
[86] M. Doria, L. Maugest, T. Moreau, et al., Contribution of cholesterol and oxysterols to the pathophysiology of Parkinson's disease, Free Radic. Biol. Med. 101 (2016) 393–400.
[87] M.G. Martin, F. Pfrieger, C.G. Dotti, Cholesterol in brain disease: Sometimes determinant and frequently implicated, EMBO Rep. 15 (10) (2014) 1036–1052.
[88] N. Fabelo, V. Martin, G. Santpere, et al., Severe alterations in lipid composition of frontal cortex lipid rafts from Parkinson's disease and incidental Parkinson's disease, Mol. Med. 17 (9–10) (2011) 1107–1118.
[89] D. Liu, N. Nagan, W.W. Just, et al., Role of dihydroxyacetonephosphate acyltransferase in the biosynthesis of plasmalogens and nonether glycerolipids, J. Lipid Res. 46 (4) (2005) 727–735.
[90] F. Dorninger, T. König, P. Scholze, et al., Disturbed neurotransmitter homeostasis in ether lipid deficiency, Hum. Mol. Genet. 28 (12) (2019) 2046–2061.
[91] E. Miville-Godbout, et al., Plasmalogen augmentation reverses striatal dopamine loss in MPTP mice, PLoS One 11 (3) (2016) e0151020.
[92] C.M. Kassmann, C. Lappe-Siefke, M. Baes, et al., Axonal loss and neuroinflammation caused by peroxisome-deficient oligodendrocytes, Nat. Genet. 39 (8) (2007) 969–976.
[93] E. Gray, C. Rice, K. Hares, et al., Reductions in neuronal peroxisomes in multiple sclerosis grey matter, Mult. Scler. 20 (6) (2014) 651–659.
[94] V.K. Senanayake, et al., Metabolic dysfunctions in multiple sclerosis: Implications as to causation, early detection, and treatment, a case control study, BMC Neurol. 15 (2015) 154.
[95] Y. Du, Y. Wen, X. Guo, et al., A genome-wide expression association analysis identifies genes and pathways associated with amyotrophic lateral sclerosis, Cell. Mol. Neurobiol. 38 (3) (2018) 635–639.
[96] J. Abdel-Khalik, E. Yutuc, P.J. Crick, et al., Defective cholesterol metabolism in amyotrophic lateral sclerosis, J. Lipid Res. 58 (1) (2017) 267–278.
[97] N.R. Kondori, P. Paul, J.P. Robbins, et al., Focus on the role of D-serine and D-amino acid oxidase in amyotrophic lateral sclerosis/motor neuron disease (ALS), Front. Mol. Biosci. 5 (2018) 8.
[98] J. Sasabe, M. Suzuki, N. Imanishi, et al., Activity of D-amino acid oxidase is widespread in the human central nervous system, Front. Synaptic Neurosci. 6 (2014) 14.
[99] J. Mitchell, P. Paul, H.-J. Chen, et al., Familial amyotrophic lateral sclerosis is associated with a mutation in D-amino acid oxidase, Proc. Natl. Acad. Sci. U. S. A. 107 (16) (2010) 7556–7561.
[100] V. Janardhan, A.I. Qureshi, Mechanisms of ischemic brain injury, Curr. Cardiol. Rep. 6 (2) (2004) 117–123.
[101] R.H.C. Lee, et al., Cerebral ischemia and neuroregeneration, Neural Regen. Res. 13 (3) (2018) 373–385.
[102] J.M. Young, et al., Peroxisomal biogenesis in ischemic brain, Antioxid. Redox. Signal. 22 (2) (2015) 109–120.
[103] S.H. Liu, et al., IL-13 downregulates PPAR-gamma/heme oxygenase-1 via ER stress-stimulated calpain activation: Aggravation of activated microglia death, Cell. Mol. Life Sci. 67 (9) (2010) 1465–1476.
[104] M. Collino, et al., Oxidative stress and inflammatory response evoked by transient cerebral ischemia/reperfusion: Effects of the PPAR-alpha agonist WY14643, Free Radic. Biol. Med. 41 (4) (2006) 579–589.
[105] M. Warren, et al., Histologic and ultrastructural features in early and advanced phases of Zellweger spectrum disorder (infantile Refsum disease), Ultrastruct. Pathol. 42 (3) (2018) 220–227.
[106] H.R. Waterham, S. Ferdinandusse, R.J. Wanders, Human disorders of peroxisome metabolism and biogenesis, Biochim. Biophys. Acta 1863 (5) (2016) 922–933.
[107] S. Weller, H. Rosewich, J. Gartner, Cerebral MRI as a valuable diagnostic tool in Zellweger spectrum patients, J. Inherit. Metab. Dis. 31 (2) (2008) 270–280.
[108] P. Evrard, et al., The mechanism of arrest of neuronal migration in the Zellweger malformation: An hypothesis bases upon cytoarchitectonic analysis, Acta Neuropathol. 41 (2) (1978) 109–117.
[109] M. Baes, P.P. Van Veldhoven, Generalised and conditional inactivation of Pex genes in mice, Biochim. Biophys. Acta 1763 (12) (2006) 1785–1793.
[110] O. Krysko, et al., Neocortical and cerebellar developmental abnormalities in conditions of selective elimination of peroxisomes from brain or from liver, J. Neurosci. Res. 85 (1) (2007) 58–72.
[111] C.C. Muller, et al., PEX13 deficiency in mouse brain as a model of Zellweger syndrome: Abnormal cerebellum formation, reactive gliosis and oxidative stress, Dis. Model Mech. 4 (1) (2011) 104–119.
[112] N.A. Zaabi, et al., Atypical PEX16 peroxisome biogenesis disorder with mild biochemical disruptions and long survival, Brain Dev. 41 (1) (2019) 57–65.
[113] S.V. Scott, D.J. Klionsky, Delivery of proteins and organelles to the vacuole from the cytoplasm, Curr. Opin. Cell Biol. 10 (4) (1998) 523–529.
[114] Y. Sakai, et al., Peroxisome degradation by microautophagy in Pichia pastoris: Identification of specific steps and morphological intermediates, J. Cell Biol. 141 (3) (1998) 625–636.
[115] M. Veenhuis, et al., Degradation and turnover of peroxisomes in the yeast Hansenula polymorpha induced by selective inactivation of peroxisomal enzymes, Arch. Microbiol. 134 (3) (1983) 193–203.
[116] D.L. Tuttle, W.A. Dunn, Jr, Divergent modes of autophagy in the methylotrophic yeast Pichia pastoris, J. Cell Sci. 108 (1) (1995) 25–35.
[117] H. Mukaiyama, et al., Modification of a ubiquitin-like protein Paz2 conducted micropexophagy through formation of a novel membrane structure, Mol. Biol. Cell 15 (1) (2004) 58–70.
[118] J.C. Farre, et al., Turnover of organelles by autophagy in yeast, Curr. Opin. Cell Biol. 21 (4) (2009) 522–530.
[119] J.D. Mancias, A.C. Kimmelman, Mechanisms of selective autophagy in normal physiology and cancer, J. Mol. Biol. 428 (9) (2016) 1659–1680 Pt A.

[120] V. Kirkin, et al., A role for ubiquitin in selective autophagy, Mol. Cell 34 (3) (2009) 259–269.
[121] E. Deosaran, et al., NBR1 acts as an autophagy receptor for peroxisomes, J. Cell Sci. 126 (4) (2013) 939–952 Pt.
[122] A.L. Anding, E.H. Baehrecke, Cleaning house: Selective autophagy of organelles, Dev. Cell 41 (1) (2017) 10–22.
[123] Y. Katsuragi, Y. Ichimura, M. Komatsu, p62/SQSTM1 functions as a signaling hub and an autophagy adaptor, FEBS J. 282 (24) (2015) 4672–4678.
[124] S.W. Ryter, S.M. Cloonan, A.M. Choi, Autophagy: A critical regulator of cellular metabolism and homeostasis, Mol. Cells 36 (1) (2013) 7–16.
[125] S. Hara-Kuge, Y. Fujiki, The peroxin Pex14p is involved in LC3-dependent degradation of mammalian peroxisomes, Exp. Cell. Res. 314 (19) (2008) 3531–3541.
[126] L. Jiang, et al., Peroxin Pex14p is the key component for coordinated autophagic degradation of mammalian peroxisomes by direct binding to LC3-II, Genes Cells 20 (1) (2015) 36–49.
[127] J. Zhang, et al., ATM functions at the peroxisome to induce pexophagy in response to ROS, Nat. Cell Biol. 17 (10) (2015) 1259–1269.
[128] A. Alexander, et al., ATM signals to TSC2 in the cytoplasm to regulate mTORC1 in response to ROS, Proc. Natl. Acad. Sci. U.S.A. 107 (9) (2010) 4153–4158.
[129] L. Feng, et al., Ubiquitin ligase SYVN1/HRD1 facilitates degradation of the SERPINA1 Z variant/alpha-1-antitrypsin Z variant via SQSTM1/p62-dependent selective autophagy, Autophagy 13 (4) (2017) 686–702.
[130] C. Vives-Bauza, et al., PINK1-dependent recruitment of Parkin to mitochondria in mitophagy, Proc. Natl. Acad. Sci. U.S.A. 107 (1) (2010) 378–383.
[131] S. Yamashita, et al., The membrane peroxin PEX3 induces peroxisome-ubiquitination-linked pexophagy, Autophagy 10 (9) (2014) 1549–1564.
[132] R.K. Vadlamudi, et al., p62, a phosphotyrosine-independent ligand of the SH2 domain of p56lck, belongs to a new class of ubiquitin-binding proteins, J. Biol. Chem. 271 (34) (1996) 20235–20237.
[133] G. Bjorkoy, et al., p62/SQSTM1 forms protein aggregates degraded by autophagy and has a protective effect on huntingtin-induced cell death, J. Cell Biol. 171 (4) (2005) 603–614.
[134] M. Komatsu, et al., Homeostatic levels of p62 control cytoplasmic inclusion body formation in autophagy-deficient mice, Cell 131 (6) (2007) 1149–1163.
[135] Y. Ichimura, et al., Structural basis for sorting mechanism of p62 in selective autophagy, J. Biol. Chem. 283 (33) (2008) 22847–22857.
[136] V. Kirkin, et al., A role for NBR1 in autophagosomal degradation of ubiquitinated substrates, Mol. Cell 33 (4) (2009) 505–516.
[137] F.K. Mardakheh, et al., Nbr1 is a novel inhibitor of ligand-mediated receptor tyrosine kinase degradation, Mol. Cell. Biol. 30 (24) (2010) 5672–5685.
[138] K. Zientara-Rytter, S. Subramani, Autophagic degradation of peroxisomes in mammals, Biochem. Soc. Trans. 44 (2) (2016) 431–440.
[139] J. Nishiyama, et al., Aberrant membranes and double-membrane structures accumulate in the axons of Atg5-null Purkinje cells before neuronal death, Autophagy 3 (6) (2007) 591–596.
[140] T. Hara, et al., Suppression of basal autophagy in neural cells causes neurodegenerative disease in mice, Nature 441 (7095) (2006) 885–889.
[141] M. Komatsu, et al., Loss of autophagy in the central nervous system causes neurodegeneration in mice, Nature 441 (7095) (2006) 880–884.
[142] M. Komatsu, et al., Essential role for autophagy protein Atg7 in the maintenance of axonal homeostasis and the prevention of axonal degeneration, Proc. Natl. Acad. Sci. U.S.A. 104 (36) (2007) 14489–14494.
[143] S.A. Tooze, G. Schiavo, Liaisons dangereuses: Autophagy, neuronal survival and neurodegeneration, Curr. Opin. Neurobiol. 18 (5) (2008) 504–515.
[144] J.H. Son, et al., Neuronal autophagy and neurodegenerative diseases, Exp. Mol. Med. 44 (2) (2012) 89–98.
[145] N. Mizushima, et al., Autophagy fights disease through cellular self-digestion, Nature 451 (7182) (2008) 1069–1075.
[146] J.F. Moruno-Manchon, et al., Peroxisomes contribute to oxidative stress in neurons during doxorubicin-based chemotherapy, Mol. Cell. Neurosci. 86 (2018) 65–71.
[147] T.Y. Nazarko, Atg37 regulates the assembly of the pexophagic receptor protein complex, Autophagy 10 (7) (2014) 1348–1349.
[148] S. Ferdinandusse, et al., ACBD5 deficiency causes a defect in peroxisomal very long-chain fatty acid metabolism, J. Med. Genet. 54 (5) (2017) 330–337.
[149] N.E. Uzor, L.D. McCullough, A.S. Tsvetkov, Peroxisomal dysfunction in neurological diseases and brain aging, Front. Cell Neurosci. 14 (2020) 44.
[150] D.S. Jo, et al., Loss of HSPA9 induces peroxisomal degradation by increasing pexophagy, Autophagy 16 (11) (2020) 1989–2003.
[151] K. Castillo, et al., Measurement of autophagy flux in the nervous system in vivo, Cell Death. Dis. 4 (2013) e917.

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