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Organellar crosstalk as a potential therapeutic target for rare neurodegenerative diseases

Josephine J. Lam[#], Chenxu Li[#], Marcia R. Terluk, Reena V. Kartha

Center for Orphan Drug Research, Department of Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, Minneapolis, MN 55455, USA.
[#]Authors contributed equally.

Correspondence to: Dr. Reena V. Kartha, Center for Orphan Drug Research, Department of Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, Room 4-214, McGuire Translational Research Facility, 2001 6th St. SE, Minneapolis, MN 55455, USA. E-mail: rvkartha@umn.edu

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Abstract

Organellar crosstalk has gained significant interest due to its essential role in maintaining cellular homeostasis and normal function. Conversely, disruptions in organelles and their interactions are increasingly recognized as key contributors to the pathogenesis of numerous diseases. Rare neurodegenerative diseases, such as Gaucher disease (GD) and X-linked adrenoleukodystrophy (ALD), are caused by inherited mutations that disrupt critical metabolic pathways. Genetic variants encoding key proteins involved in these pathways result in the excessive accumulation of corresponding substrates, which subsequently trigger organellar crosstalk dysfunction, often involving mitochondria, lysosomes, endoplasmic reticulum (ER), or peroxisomes. To date, the specific mechanisms underlying organellar interactions and their roles in the pathophysiology of these respective diseases are not fully elucidated, an area that continues to be actively studied. Understanding these mechanisms could reveal novel pathways or targets for future therapeutic development. Furthermore, the severity of these rare neurodegenerative diseases and the lack of effective treatments for patients underscore the urgency for thorough investigations into organellar crosstalk. This review provides an overview of the crosstalk between mitochondria, lysosomes, the ER, and peroxisomes in lysosomal diseases, such as GD, and peroxisomal disorders, including ALD. Additionally, we explore potential therapeutic strategies targeting these interconnected pathways.

Keywords: Organellar crosstalk, lysosomal impairment, mitochondrial dysfunction, peroxisome, Gaucher disease, adrenoleukodystrophy

INTRODUCTION

Cellular organelles in eukaryotes are widely known to possess a diverse range of highly specialized and individualized functions in separate membrane-enclosed compartments. The compartmentalization of these organelles is highly beneficial in both allowing cells to perform their respective roles without the interference of other organelles, as well as creating local environments for the facilitation of metabolic functions. Although physically disconnected, the communication between organelles is critical for maintaining cellular homeostasis and cell survival. However, the specific mechanisms behind the maintenance and regulation of this crosstalk are still unknown and under investigation.

Generally, organelles have been found to communicate with the use of signals and metabolites through diffusion or active transport through the cytoplasm, vesicular trafficking, and more recently, through regions of close contact, termed membrane contact sites[1]. The communication between organelles has been looked at in various settings and among different organelles. A common area of previous investigation includes the crosstalk between the endoplasmic reticulum (ER) and mitochondria in the kidney. Organelle stress in the ER via the unfolded protein response (UPR) pathway and altered energy metabolism in mitochondria contribute to further damage to either organelle, causing various kidney disorders[2]. This theme of bidirectional communication in which damage to one organelle results in further damage to another organelle is critical and universal in numerous settings.

Inborn errors of metabolism (IEMs), also commonly referred to as inherited metabolic disorders (IMDs), comprise a group of genetic disorders characterized by defects in metabolic proteins[3]. These metabolic pathway disruptions frequently cause a toxic accumulation of substances that affects other organelles in the cell, constituting the basis of organellar crosstalk. In many cases, this buildup of toxic substances affects neurodevelopment and can lead to neurodegeneration[4].

Neurodegeneration is greatly debilitating and often progresses rapidly and severely. Disruption in crosstalk between various organelles has been shown to play a critical role in neurodegenerative conditions, frequently causing further damage to organelles and leading to numerous downstream effects such as increased oxidative stress, inflammation, and other harmful events. While each organelle plays its own specialized roles in cells, the crosstalk between mitochondria, peroxisomes, the ER and lysosomes is often a key player in rare neurodegenerative diseases but is insufficiently understood. As these diseases can be highly debilitating, it is imperative that more research is performed to better understand the connections between these organelles. In this review, we focus on interactions between mitochondria, peroxisomes, ER, and lysosomes, looking specifically at the role of organellar crosstalk in Gaucher disease and adrenoleukodystrophy.

GAUCHER DISEASE

Gaucher disease (GD) is a rare lysosomal disease caused by mutations in the *GBA1* gene, which encodes for glucocerebrosidase, commonly abbreviated as GCase[5]. These mutations result in a deficient and dysfunctional GCase, an enzyme that normally hydrolyzes glucosylceramide (GlcCer) into glucose and ceramide in the lysosome[6]. The dysfunction leads to the accumulation of GlcCer, primarily in the lysosomes of macrophages, but also in other tissues. The buildup of this lipid substrate interferes with critical cellular processes and induces secondary inflammatory and immunological responses[5].

There are three major phenotypes of GD, including type 1 GD (GD1), which is most common in individuals of European ancestry and may be characterized by hepatosplenomegaly, anemia, and thrombocytopenia[5]. Although labeled as "non-neuronopathic", patients with GD1 may potentially still

develop peripheral neuropathy and symptomatic Lewy body-associated parkinsonism in later years. Type 2 (GD2) and type 3 GD (GD3) are both characterized as neuronopathic GD (nGD), with GD2 being an acute and severe neurological disease that presents at a very early age, neonate to 6 months, with death occurring at 2 to 3 years of age. GD3 is chronically neuronopathic and more clinically heterogeneous[5].

While GD is primarily a lysosomal disorder, it also involves complex interactions with mitochondria and the ER, which play a significant role in its pathophysiology, though the mechanisms remain unknown[6]. Current treatments, enzyme replacement therapy (ERT) and substrate reduction therapy (SRT), face many limitations and have several unresolved issues. While these therapies are effective for managing systemic and visceral symptoms in all types of GD, they are ineffective in treating the neurological manifestations of GD2 and GD3 due to their inability to cross the blood-brain barrier[5]. Ultimately, GD can be severely debilitating and disruptive to everyday life, requiring investigations into the complex mechanisms and role of organelle crosstalk in this disease.

ORGANELLAR FUNCTIONS IN GD PATHOLOGY

Role of lysosomes

Lysosomes are a particularly important contributor to the pathophysiology of GD and their role has been investigated extensively. Typically, lysosomes contain various hydrolytic enzymes that degrade substrates within the cells, and their primary functions include degradation of intracellular and extracellular material through endocytosis and autophagy, cell signaling, and secretion of various proteins[7]. Therefore, lysosomes play a critical role in breaking down and recycling old or dysfunctional components in cells. However, the accumulation of GlcCer in the lysosomes due to the impairment of the GCase enzyme leads to global lysosomal impairment, inflammation, and cell death, ultimately resulting in microglial activation, astrocytosis, and neuronal death in layers III and V of the cortex and hippocampal regions as observed in GD2 models[8]. Through bidirectional crosstalk, lysosomal impairment can disrupt the function of mitochondria and the ER.

Role of mitochondria

Mitochondria are among of the cell's most important organelles, as their production of Adenosine Triphosphate (ATP) is essential for metabolic processes in neurons and is a major source of energy for synaptic function[7]. However, an alteration of mitophagy, a process that would normally act to remove damaged or aged mitochondria via lysosomes, is observed in GD. Impairment of mitophagy allows the accumulation of faulty mitochondria, contributing to cellular quality control failure and accelerating disease progression[9].

Mitochondrial dysfunction has been demonstrated in both *in vitro* and *in vivo* models of GD. Notably, fibroblasts from patients with the L444P/L444P GCase mutation exhibit diminished mitochondrial membrane potential, elevated reactive oxygen species (ROS), inactivated mitophagy activity, and disrupted autophagic flux[10]. Similarly, defective GCase function has been associated with mitochondrial dysfunction and proteinopathies in a GD mouse model[11]. In a study involving GD2 mouse models, lysosomal defects linked to impaired autophagy were shown to drive the accumulation of dysfunctional organelles, including mitochondria[9].

The mitochondrial impairments are further corroborated by studies in related disorders and by findings that current therapies for GD enhance mitochondrial function. For instance, a study in human dopaminergic cells identified a connection between pharmacological inhibition of GCase activity and mitochondrial dysfunction, characterized by reduced ADP phosphorylation leading to impaired ATP

synthesis, decreased membrane potential, oxidative stress, and elevated alpha-synuclein[12]. Additionally, alterations in mitochondrial morphology, membrane potential, ATP production, and increased ROS are all observed in patients with nGD[6]. Along with this, dysregulation of calcium homeostasis and increased aggregation of alpha-synuclein, a protein involved in regulating synaptic trafficking and neurotransmitter release, have been reported[13]. Moreover, in peripheral blood mononuclear cells derived from patients with GD, lysosomal dysfunction was shown to impair autophagy and mitochondrial function, which are partially improved by ERT[14]. Furthermore, it has been shown that SRT and a pharmacologic chaperone enhance GCase activity, improve autophagy-lysosome dynamics, and restore mitochondrial function by improving mitochondrial membrane potential in cells from patients with GD2-3[15]. Moreover, both mitochondrial dysfunction and deficient GCase activity were partially alleviated through treatments such as Coenzyme Q_{10} (CoQ_{10}), which targets mitochondrial function, and the chaperone NAdBT-AIJ, which facilitates protein folding. Notably, these findings highlight the potential of targeting these organelles as a promising therapeutic strategy for neurological forms of GD[10].

Role of endoplasmic reticulum

The ER is affected by damage to both lysosomes and mitochondria, which, through bidirectional crosstalk, can further impair these organelles. Normally, the ER is responsible for synthesizing proteins and lipids, regulating calcium levels, and activating signaling pathways within the cell[16]. The ER is a main intracellular calcium store, with calcium acting as a key regulator in many critical cell processes including cell death, mitochondrial function, and autophagy[17]. Additionally, the ER plays a critical role in ensuring proper folding and modification of translated proteins. If proteins are mutated, they may be unable to undergo the correct conformation, as seen with GCase, and ultimately build up in the ER. Typically, the Endoplasmic Reticulum-Associated Degradation (ERAD) pathway help identify and clear misfolded proteins from the ER for the degradation by cytosolic proteasomes[18]. In addition, the UPR pathway is activated to reduce the accumulation of misfolded proteins, but if this response becomes chronic, it can trigger oxidative stress and apoptosis, exacerbating cell damage[19].

Organellar crosstalk in GD

While the lysosome is the initial organelle impaired by the *GBA1* mutation and resulting deficient enzyme activity, these defects will impede the function of other organelles, such as the ER and mitochondria, through organellar crosstalk. This will further increase the dysfunction of the involved organelles through their bidirectional communication and exchange of material, ultimately leading to faster progression of GD.

For instance, the GlcCer accumulation in lysosomes leads to excessive calcium release from the ER, altering calcium homeostasis, a key regulator of many critical pathways including autophagy. Conversely, evidence suggests a connection between changes in ER calcium levels and lysosomal autophagy defects, including the demonstrated inhibitory role of IP3R-mediated calcium release on autophagy[17]. Further, the decrease in GCase activity is also associated with ER stress triggered by the unfolding of mutant GCase and impaired mitophagy[13]. This stress on the ER further activates the ER-associated degradation and UPR pathway. As mentioned previously, prolonged activation of UPR can result in increased production of ROS[20].

Along with this, ER stress due to the UPR may impair calcium transport from the ER to the mitochondria, resulting in increased levels of calcium release from the ER. The excess calcium is likely taken up by the mitochondria, harmfully altering membrane potential and further increasing ROS production[21]. The increased ROS levels in the mitochondria may further accumulate α-synuclein in the mitochondria. One study indicates that a contributing factor for this accumulation may be due to the reduced activity of DJ-1, a gene whose expressed protein would typically act to mitigate oxidative stress[22]. This α-synuclein aggregation would continue to impair the mitochondria further, as well as its contacts with other

organelles[23].

Previous studies have shown that lysosomal and mitochondrial functions are closely interconnected and essential for cellular homeostasis. Mitochondria-lysosome membrane contact sites mediate their bidirectional crosstalk, facilitating dynamic interactions and metabolite exchange[24,25]. Dysregulated mitochondria-lysosome contacts can impair the function of these organelles, playing a key role in multiple lysosomal storage diseases. For instance, prolonged mitochondria-lysosome tethering has also been observed in cells derived from patients with *GBA1* mutations, and may occur with other organelles, impairing the proper tethering time necessary for crosstalk[26]. Understanding the organization and dynamics of mitochondria-lysosome contact sites, their role in inter-organellar communication, and their interactions with other organelles will be important for revealing their complete impact on cellular health, disease, and therapeutic strategies[24].

Ultimately, the complex interactions that occur between lysosomes, mitochondria, and ER play a clear role in advancing the pathological effects of GD, leading to an escalation of dysfunction and damage within cells. Figure 1 summarizes how damage to one organelle can easily spread to other organelles in the cell, causing further impairment over time in GD.

Crosstalk in other lysosomal diseases

Organellar crosstalk is not a phenomenon unique to GD; it is also observed in other lysosomal diseases. Mitochondrial function anomalies are commonly observed among various lysosomal diseases. For instance, lysosomal dysfunction in Fabry disease, a rare X-linked lysosomal disorder characterized by a buildup of globotriaosylceramide (Gb3) due to a deficiency of the lysosomal enzyme, alpha-galactosidase (GLA), has shown a decline in mitochondrial function and mitochondrial energy metabolism in renal cells[27]. However, no information was available regarding the effects of lysosomal dysfunction on the ER in Fabry disease, prompting the need for more research into these areas.

Mitochondrial function has also been noted to be directly impacted in Pompe Disease, a rare autosomal recessive disease caused by a deficiency of lysosomal alpha-glucosidase. For instance, analysis of Pompe disease-specific induced pluripotent stem cell-derived cardiomyocytes showed impaired fusion and mitophagy, as well as decreased expression of mitochondrial complexes, highlighting disrupted respiratory function and ATP production with an overall decreased number of mitochondria[28]. Similar to Fabry disease, there is sparse information about any ER defects related to lysosomal impairments observed in Pompe disease.

Crosstalk between organelles similar to GD has been noted among the mucopolysaccharidoses (MPSs), a group of rare inherited lysosomal diseases characterized by the accumulation of glycosaminoglycans (GAGs) from a deficiency of lysosomal enzymes[29]. Though the lysosomes are the main organelles affected by the buildup of GAGs, impairments have also been noted for mitochondria, ER, and even Golgi apparatus. For instance, alterations in autophagy, increased ROS levels from mitochondrial dysfunction, elevated ER stress, apoptosis, and triggering of immune responses leading to inflammation in MPSs secondary to the initial lysosomal impairment have all been reported in recent years[30].

ADRENOLEUKODYSTROPHY

Adrenoleukodystrophy (ALD) is a rare X-linked disorder characterized by the accumulation of very long-chain fatty acids (VLCFA) in plasma, cerebral white matter, spinal cord, adrenal cortex, and testis[31]. Mutation in the *ABCD1* gene, which encodes a peroxisomal ATP-binding cassette (ABC) transporter,

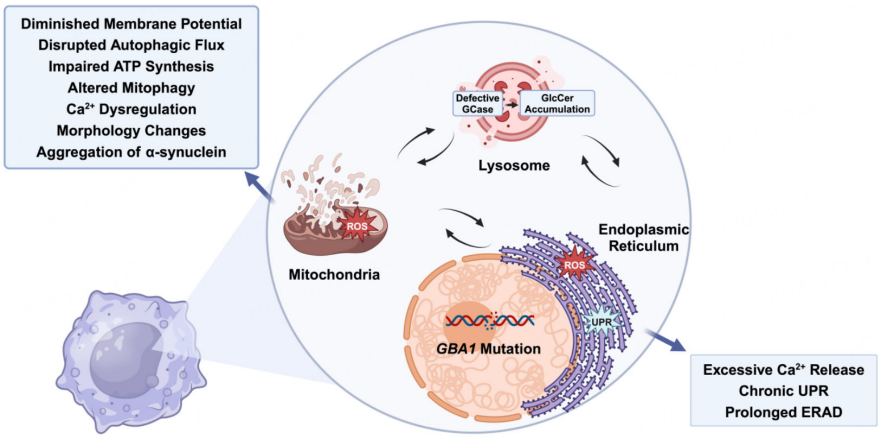

Figure 1. Schematic Representation of the Organellar Contribution to Gaucher disease (GD) Pathophysiology (Created in https://BioRender.com. Mutations in the *GBA1* gene, which encodes for glucocerebrosidase (GCase) enzymes, can lead to lysosomal impairment. This can cause accumulation of glycosphingolipids such as glucosylceramides (GlcCer), which can trigger oxidative stress, impair cellular energetics by reducing adenosine triphosphates (ATP) synthesis, and cause mitochondrial dysfunction and inflammation. Moreover, misfolded GCase proteins can accumulate in the endoplasmic reticulum (ER), triggering the Unfolded Protein Response (UPR), increasing reactive oxygen species (ROS), disrupting calcium signaling, and causing prolonged ER-associated degradation (ERAD).

results in impaired transport of VLCFA into the peroxisome and subsequent buildup within the cytoplasm[32]. The accumulation of VLCFA leads to a variable and heavily debilitating clinical spectrum, spanning from primary adrenal insufficiency without neurologic manifestations to adrenomyeloneuropathy (AMN) and rapidly progressive cerebral ALD[33]. In AMN, VLCFAs accumulate in the spinal cord and peripheral nerves, inducing a slowly progressive dying-back axonopathy in adults, which is recognized as the core clinical syndrome of ALD[34]. On the other hand, the accumulation of VLCFA in the brain triggers inflammatory cerebral demyelination, which is predominantly observed in childhood, resulting in rapid neurodegeneration and often death within a few years[35]. Importantly, although all patients with ALD harbor mutations in the *ABCD1* gene, there is no established genotype-phenotype correlation, making it difficult to predict disease prognosis prior to the onset of clinical symptoms[36]. The severe outcomes of ALD and the absence of effective treatments for all patients evoke the critical need to further investigate the molecular mechanisms underlying its pathogenesis (as depicted in Figure 2). Organelles involved in ALD pathology, particularly mitochondria and peroxisomes, along with their interactions, thus become central targets for investigation.

ORGANELLAR FUNCTIONS IN ALD PATHOLOGY

Role of peroxisomes in ALD

Peroxisomes play a major role in ALD, which is recognized as the most common peroxisomal disorder. These organelles are versatile, dynamic, and metabolically active, functioning to modulate essential metabolic and biochemical pathways, including fatty acid oxidation, ether lipid synthesis, glyoxylate detoxification, and ROS metabolism[37]. Depending on environmental conditions and cell types, the abundance, size, morphology, composition, and function of peroxisomes vary significantly and are regulated by complex processes[38]. The ability of peroxisomes to rapidly produce and eliminate the superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2) makes them key organelles in regulating redox homeostasis[39]. Impaired peroxisomes are thought to trigger cellular oxidative stress, which is implicated in the pathogenesis of various diseases, including neurodegeneration, aging, cancer, and diabetes[40]. Furthermore, the absence of functional peroxisomes was found to impair the maturation of the cerebellum and migration of cortical neurons, as well as to contribute to multifocal axonal damage and

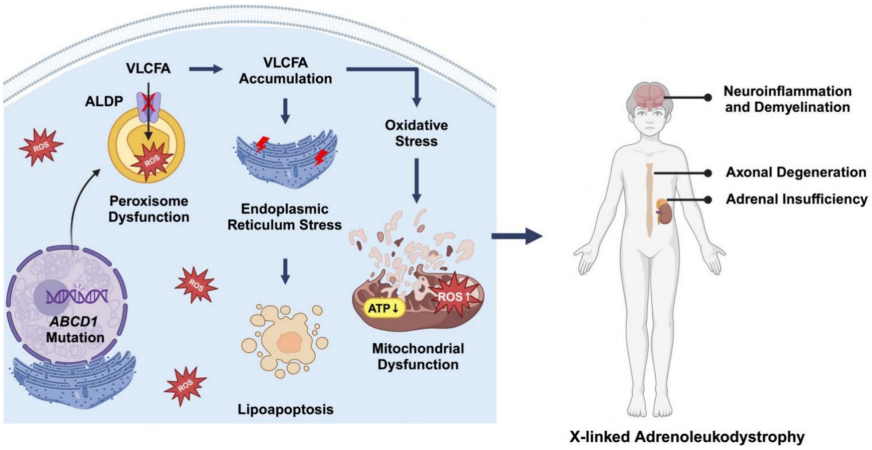

Figure 2. Schematic Representation of the Molecular Mechanisms, Biochemical Defects, and Organellar Dysfunctions Driving the Pathogenesis of ALD (Created in https://BioRender.com). In ALD, *ABCD1* gene mutation results in impaired ALD protein (ALDP), which plays a critical role in very long-chain fatty acid (VLCFA) metabolism; therefore, a defect in ALDP leads to VLCFA accumulation. Excessive VLCFAs trigger endoplasmic reticulum (ER) stress, ultimately leading to lipoapoptosis. Additionally, VLCFAs induce the production of reactive oxygen species (ROS) and oxidative stress, which in turn cause mitochondrial dysfunction. This creates a vicious cycle that exacerbates disease progression. Taken together, these processes contribute to the clinical manifestations in patients with ALD, including neuroinflammation, demyelination, adrenal insufficiency, and axonal degeneration. ALD: Adrenoleukodystrophy.

dysmyelination[41,42]. From a biochemical perspective, ALD is marked by the accumulation of VLCFA due to defective peroxisomal β-oxidation of free fatty acids and very long-chain acyl-CoA esters[43]. Excessive VLCFA has been found to disrupt redox equilibrium, leading to increased ROS levels and oxidative stress[44]. VLCFA-induced oxidative damage can lead to a cascade of detrimental effects and is thus considered a key disease-driving factor in the development of ALD. For instance, oxidative stress has been found to cause malfunction of the ubiquitin-proteasome system, as well as upregulate the immunoproteasome machinery in an ALD mouse model[45]. Moreover, impaired autophagic flux, as a result of elevated mammalian target of rapamycin (mTOR) signaling, has been found to contribute to ALD pathogenesis, while autophagy is also downregulated by accumulated VLCFA[46]. Collectively, the accumulating evidence suggests that oxidative stress is a major driver of ALD, positioning it as a potential therapeutic target.

Role of mitochondria in ALD

Mitochondrial dysfunction is also highly intertwined with ALD pathophysiology. As the predominant source of cellular energy production, mitochondria play a pivotal role in sustaining cellular homeostasis and driving essential metabolic processes, as described in detail above. In ALD, elevated VLCFA levels lead to increased production of mitochondria-derived ROS, impaired ATP synthesis, diminished calcium uptake capacity, mitochondrial DNA oxidation, and impaired mitochondrial oxidative phosphorylation[47,48]. In addition, significant defects in mitochondrial biogenesis, along with reduced mitochondrial DNA content, have been observed in ALD mice, which are presumably caused by the accumulation of VLCFA[49]. This is because mitochondria are not only the main source of ROS but also the primary target of oxidative stress. Oxidative stress induced by VLCFA accumulation can subsequently lead to mitochondrial damage, including a reduction in ATP production, loss of mitochondrial inner membrane potential, necrosis, and increased oxidative modifications of cyclophilin D protein, which further aggravate the disease condition[50]. Taken together, the processes described above contribute to mitochondrial dysfunction and bioenergetic failure, ultimately leading to axonal degeneration and cell death. Such a phenomenon, coupled with defective proteostasis, is not confined to ALD but is also a prominent hallmark in multiple neurodegenerative diseases and age-related conditions[44].

Organellar crosstalk in ALD

Organellar interactions, particularly between mitochondria and peroxisomes, play a synergistic role in exacerbating the pathophysiological mechanisms underlying ALD. Under physiological conditions, the oxidation of fatty acids relies on the coordinated functions of peroxisomes and other organelles. VLCFAs are predominantly synthesized in the ER through an elongation process and are subsequently incorporated into different lipid species or transported to peroxisomes for β-oxidation to maintain VLCFA homeostasis. Peroxisomes catalyze the initial shortening of VLCFA into acetyl-CoA, medium-chain acyl-CoAs, and propionyl-CoA. These end products of peroxisomal β-oxidation must then be transported to mitochondria for complete oxidation into CO_2 and H_2O[51]. In ALD pathogenesis, VLCFAs accumulate due to the deficiency of peroxisomal transmembrane proteins, which thereafter triggers a series of primary and secondary pathological effects such as oxidative stress and mitochondrial dysfunction, ultimately leading to significant cellular and tissue dysfunction. Saturated VLCFAs have also been demonstrated to induce ER stress, as indicated by the upregulation of mRNA levels for the spliced variant of X-box binding protein 1 (XBP1), endoplasmic reticulum degradation-enhancing α-mannosidase-like protein 1 (EDEM1), growth arrest and DNA damage-inducible protein, and C/EBP homologous protein (CHOP). These changes ultimately lead to lipoapoptosis, which is among the downstream effects observed in ALD[52].

In addition, we have previously discussed that both mitochondria and peroxisomes are significant sources of ROS production, thereby acting as key regulators of cellular redox homeostasis. These two organelles are closely interconnected, both structurally and functionally, to enable normal cellular communication and regulation[53]. Here, we illustrate the interactions between organelles for maintaining fatty acid and redox balance, as depicted in Figure 3. Excess VLCFA in ALD directly triggers oxidative damage, which subsequently induces an inflammatory response and increases the gene and protein expression of proinflammatory mediators such as cytokines (TNF-α and IL-1β), ultimately leading to generalized peroxisomal dysfunction[54,55]. Furthermore, excessive cellular ROS leads to energetic failure, which in turn causes extensive calcium efflux into the cytoplasm and activates calpains that impair the microtubule structure and ultimately axonal destruction[56]. The interplay between mitochondrial and peroxisomal dysfunction results in ROS/ATP/Ca^{2+} dyshomeostasis, generating a vicious circle that contributes to progressive inflammatory demyelination and axonal degeneration[44,57].

Organellar crosstalk in other peroxisomal disorders

Beyond ALD, interconnections between organelles have also been documented in various other peroxisomal disorders, underscoring their collaborative role in cellular dysfunction and disease pathogenesis. Zellweger syndrome is an example of a peroxisome biogenesis disorder caused by dysfunction in PEX genes, which encode peroxins essential for peroxisome biogenesis and function[58]. Clinical investigations of female infants with Zellweger syndrome revealed significant mitochondrial abnormalities in muscles, indicating the concomitant involvement of mitochondria and peroxisomes in this disease[59]. Another example is the finding of impaired respiratory chain function in patients with HSD17B4 deficiency, a peroxisomal enzyme involved in VLCFA β-oxidation, which causes D-bifunctional protein deficiency and Perrault syndrome[60]. Furthermore, mutated genes that encode the mitochondrial ATP-dependent protease (*CLPP*) and mitochondrial histidyl tRNA synthetase (*HARS2*) have also been identified as leading causes of Perrault syndrome, highlighting the biochemical overlap between mitochondrial and peroxisomal dysfunction in this disease[61,62]. In addition, the absence of functional peroxisomes in hepatocytes has been found to cause smooth ER proliferation, impaired respiration, mitochondrial inner membrane perturbation, and mtDNA depletion[63,64].

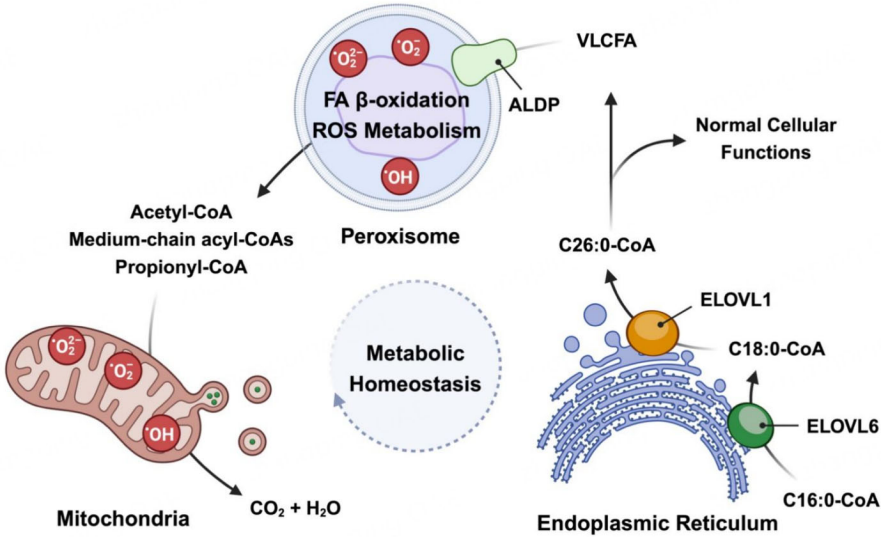

Figure 3. Interactions between organelles for maintaining metabolic homeostasis under physiological conditions (Created in https://BioRender.com). Under healthy conditions, organelles work synergistically to maintain fatty acid and redox homeostasis within cells. Fatty acids are primarily synthesized in the endoplasmic reticulum (ER) by the elongation of very long-chain fatty acids proteins (ELOVL), with ELOVL1 and ELOVL6 being primarily responsible for elongating C16:0-coenzyme A (CoA) to C26:0-CoA. These long-chain and very long-chain fatty acids (VLCFAs; ≥ C22:0) are then utilized to support normal cellular functions or transported to peroxisomes and mitochondria for complete oxidation. Simultaneously, peroxisomes and mitochondria serve as major sites for reactive oxygen species (ROS) production but also possess antioxidant defense systems to mitigate oxidative stress. Accordingly, these organelle functions and interactions are essential for maintaining cellular metabolic homeostasis.

Given the above information, it is evident that in ALD and other peroxisomal diseases, organelles are not simply affected individually; instead, they experience coordinated damage through complex mechanisms, ultimately forming a detrimental feedback loop. Further investigation is warranted to elucidate the detailed interactions among these organelles and the underlying pathomechanisms, which could provide broader insights into the selection of therapeutic targets and the design of effective therapies.

Using lysosomal and peroxisomal diseases as examples, our goal is to highlight the inter-organellar communication that may also occur in other inherited disorders. Some of the known major signaling pathways and specific mechanisms underlying these interactions are summarized in Table 1. In the subsequent section, we provide an overview of potential therapies aimed at targeting these interactions.

POTENTIAL THERAPEUTICS TARGETING ORGANELLAR CROSSTALK

Currently, effective treatments for both GD and ALD are very limited. Considering the severity and rapid progression of these diseases, it is imperative that more research should be conducted to search for potential treatments. Given that organellar crosstalk plays a critical role in the pathophysiology of these conditions, targeting impaired organelles and their interconnected pathways may represent a promising approach for developing therapeutic candidates, both as stand-alone and adjunctive treatments.

A novel dual-organelle targeting probe, the rhodamine-coumarin pH probe (RCPP) was recently developed as a fluorescent sensor to simultaneously facilitate the measurement of the pH alterations between mitochondria and lysosomes[76]. This probe enables a better understanding of the crosstalk between mitochondria and lysosomes and can be further used to regulate organelles in the cell, providing a potential area for further investigation and understanding of treatment mechanisms. Additionally, researchers at Mount Sinai and the National Center for Advancing Translational Sciences (NCATS) found that increasing

Table 1. Mechanisms of organellar interactions and key signaling pathways

Organelle interaction	Mechanism	Signaling pathways	References
Mitochondria-lysosome	Dynamic contact sites regulated by Rab7 GTP hydrolysis influence mitochondrial fission and lysosomal function	Rab7 GTP hydrolysis: tethers lysosomes to mitochondria Drp1-mediated fission: promotes mitochondrial division ROS signaling: lysosomal dysfunction can trigger oxidative stress	[26,65,66]
Mitochondria-ER	Formation of mitochondrial-associated membranes (MAMs) for lipid transfer, calcium signaling, and mitochondrial dynamics	Calcium transfer: IP3 receptor-mediated calcium release UPR: affects mitochondrial function during ER stress Lipid metabolism: lipids transferred for β-oxidation	[67-69]
Lysosome-ER	Exchange of materials and signaling molecules at membrane contact sites impacts autophagy and lipid homeostasis	mTORC1 regulation: autophagy control via nutrient sensing Cholesterol transport: essential for membrane homeostasis Calcium signaling: regulates metabolic pathways	[70,71]
Mitochondria-peroxisome	Collaboration in fatty acid metabolism and ROS detoxification	β-oxidation: peroxisomes shorten VLCFAs, which mitochondria further oxidize ROS balance: shared role in maintaining redox homeostasis	[37,72,73]
ER-peroxisome	Membrane contact sites (MCS): proteins such as ACBD4/5 enable direct lipid transfer by physical anchoring Lipid metabolism: collaboration in the synthesis of plasmalogen and the regulation of phosphoinositide signaling Biogenesis: ER supplies the building blocks needed to generate peroxisomes	Phosphorylation dynamics: modulates peroxisomal protein activity and lipid metabolism Retrograde signaling: peroxisomes transmit signals to modulate gene expression in reaction to stress	[74,75]

ROS: Reactive oxygen species; ER: endoplasmic reticulum; GTP: guanosine triphosphate.

the activity of TRAP1 (tumor necrosis factor receptor-associated protein 1), a molecular chaperone of the heat shock protein 90 (HSP90) family, which maintains mitochondrial function and metabolism, helped restore the function of both the mitochondria and lysosomes through crosstalk in Niemann-Pick disease type C1 (NPC1), Fabry disease, and other lysosomal disorders[77]. Another possible therapeutic target for lysosomal diseases involves stimulating the critical autophagic pathways that are so greatly affected and contribute to the pathophysiology of these disorders. For instance, overexpression of the transcription factor EB (TFEB) gene, a regulator of many crucial cellular processes including autophagy and lysosomal biogenesis, has been shown to modulate autophagy and lysosomal exocytosis with improved cellular clearance and delayed disease progression in Pompe disease[78,79].

As mentioned earlier, protein misfolding plays a very detrimental role in the pathophysiology of GD, as well as many other neurodegenerative diseases. Cellular chaperones, or stress-induced proteins, are found to be greatly beneficial in preventing the misfolding of various disease-causing proteins and subsequently the severity of neurodegenerative diseases. Therefore, pharmacologically made chaperones may act as potential therapeutics to target organellar crosstalk and mediate misfolded protein response, which could be especially helpful in GD, as well as other protein-misfolding diseases[80]. Furthermore, a study has investigated targeting the critical calcium dysregulation that occurs between the ER, lysosomes, and mitochondria in Parkinson's disease[81]. Given that alterations in calcium homeostasis are observed in both GD and ALD, this represents a promising area for further investigation.

Several studies have been conducted to develop potential therapies for ALD by directly targeting mitochondrial dysfunction. Sirtuin 1 (SIRT1) is a pivotal NAD+-dependent deacetylase involved in

mitochondrial biogenesis. Reduced levels of SIRT1 have been observed in the spinal cord of ALD mice and the brain white matter of patients, suggesting that it is a potential therapeutic target. Treatment with a SIRT1 activator significantly enhances mitochondrial biogenesis and respiration, mitigates oxidative stress, and prevents axonal degeneration in an ALD mouse model[82]. Another important regulator of mitochondrial dynamics, histone deacetylase, has been found to be associated with the development of peripheral neuropathy and neuropathic pain[83]. Treatment with a Histone Deacetylase (HDAC) inhibitor suberoylanilide hydroxamic acid (SAHA) has been shown to normalize mitochondrial dysfunction and promote mitochondrial biogenesis in *ABCD1*-silenced rat oligodendrocytes and human astrocytes[84].

Nervonic acid (NA), a naturally occurring monounsaturated fatty acid, has recently been investigated as a promising therapy for multiple neurological diseases. We have found that in ALD, NA can biochemically reverse VLCFA accumulation, specifically, reduce hexacosanoic acid (C26:0, the primary VLCFA involved in ALD) levels in complex lipids, and concurrently increase ATP production in patient-derived fibroblasts[85]. In addition, NA treatment in an Alzheimer's disease mouse model was found to significantly decrease malondialdehydes, TNF-α (tumor necrosis factor), and interleukin (IL-6 and IL-1β) levels, as well as enhance the expression of PI3K, Protein Kinase B (AKT), and mTOR genes, suggesting its potential effects against inflammation and oxidative stress[86]. Similar findings have been observed in a study using a Parkinson's disease mouse model, which demonstrated that NA exhibits anti-inflammatory effects by downregulating the TNF-α and nuclear factor kappa B signaling pathways[87]. The combined evidence indicates that NA has the potential to enhance ATP levels and reduce neuroinflammation, making it a promising candidate for the management of ALD. However, the specific mechanisms by which it improves mitochondrial function remain to be elucidated.

While mitochondria serve as the primary cellular powerhouse, playing a central role in various biosynthetic and metabolic pathways, sufficient levels of essential nutrients are necessary to support and sustain the normal function of these bioenergetic and metabolic processes. Accumulating evidence indicates that deficiencies in nutrients such as B vitamins/NADH, vitamin D, and CoQ_{10} have been identified in various neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis[88]. Accordingly, dietary supplementation with these nutrients may represent a promising therapeutic approach for various neurological diseases, including GD and ALD. For instance, the efficacy of high-dose biotin (60 mg/kg/day), one of the B complex vitamins, has been evaluated in an ALD mouse model, demonstrating improved mitochondrial biogenesis and ATP levels, as well as restored locomotor function and lipid balance[89]. In addition, a combination of antioxidants to mitigate oxidative stress in adults with AMN provided positive signals of efficacy[90]. Another phase 1 study reported that vitamin D is well tolerated in patients with ALD when achieving the target plasma 25-hydroxyvitamin D level (40-80 ng/mL), which is considered optimal for inflammatory disorders such as multiple sclerosis, and increases glutathione levels in the brain[91]. However, further efficacy clinical trials would be necessary to better assess vitamin D as a potential therapeutic strategy. CoQ_{10}, a key component of the inner mitochondrial membrane involved in electron transport, has also gained considerable attention in various diseases, primarily due to its antioxidant and anti-inflammatory effects[92]. A clinical study on CoQ_{10} revealed that a daily dose of 2,400 mg was generally well-tolerated in patients with Huntington's disease[93]. Current clinical evidence on CoQ_{10} still shows inconsistencies, mainly due to the limited number of clinical trials and participants[92]. However, its potential to preserve mitochondrial function and reduce oxidative damage still makes it a promising candidate for future investigations. Other dietary interventions that are being tested in lysosomal disorders to target mitochondrial impairments include N-acetyl cysteine and N-acetyl leucine[94,95]. A summary of the above discussed potential strategies is given in Table 2.

Table 2. Potential therapeutics targeting organellar crosstalk

Therapeutic approach	Mechanism/Target	Disease/Condition	Key ideas
Rhodamine-coumarin pH probe (RCPP)	Fluorescent sensor to regulate pH changes between mitochondria and lysosomes	General organellar crosstalk	Mitochondria-lysosome interactions
TRAP1 activation	Maintains mitochondrial function and metabolism via organellar crosstalk	Niemann-Pick disease, Fabry disease, lysosomal disorders	Restores lysosome and mitochondrial function, highlighting its role in various lysosomal diseases
TFEB gene overexpression	Regulates autophagy and lysosomal biogenesis	Pompe disease	Modulates autophagy, improves lysosomal exocytosis, enhances cellular clearance, and delays disease progression
Pharmacological chaperones	Prevent protein misfolding	GD, protein-misfolding disorders	Addresses misfolded proteins to mitigate disease progression in GD and other neurodegenerative diseases
Calcium dysregulation targeting	Corrects ER, lysosome, and mitochondria calcium homeostasis	Parkinson's disease, GD, ALD	Promising for correcting critical dysregulations observed in these diseases
Sirtuin 1 (SIRT1) activators	Enhances mitochondrial biogenesis and respiration	ALD	Mitigates oxidative stress, prevents axonal degeneration, and improves mitochondrial function
HDAC inhibitors	Normalizes mitochondrial dysfunction and promotes mitochondrial biogenesis	ALD, Peripheral Neuropathy	Suberoylanilide hydroxamic acid (SAHA) improves mitochondrial health in ALD mouse models
Nervonic acid (NA)	Reduces VLCFA accumulation, inflammation, and oxidative stress	ALD, Neurodegenerative Disorders	Enhances ATP levels, reduces inflammatory markers, and holds potential as a therapy for ALD and other neurological conditions
Nutrient supplementation	B vitamins, Vitamin D, CoQ10, N-acetyl cysteine, N-acetyl leucine supplementation.	ALD, GD, Niemann-Pick disease, Alzheimer's disease, Parkinson's disease	Improves mitochondrial function and reduces oxidative damage; biotin and CoQ10 have shown promise in preclinical and clinical studies

ALD: Adrenoleukodystrophy; GD: Gaucher disease; ER: endoplasmic reticulum; ATP: adenosine triphosphate.

Overall, research focusing on the crosstalk between organelles as a therapeutic strategy for rare neurological diseases is still limited. Given the critical role of organellar dysfunction in these conditions, this area holds significant promise for future research and deserves greater attention.

CONCLUSIONS

Crosstalk among the diverse organelles within cells plays a critical role in various disorders, including rare neurodegenerative diseases, as highlighted in this paper. In GD, lysosomes, mitochondria, and ER are all highly intertwined. As a result, when one organelle is damaged, i.e., the lysosomes, the function and role of the other organelles are also compromised. This exacerbates cellular damage and oxidative stress, contributing to the rapid progression and symptomatic development of the disease. Similarly, in ALD, peroxisomes, mitochondria, and the ER are intricately interconnected, working together to maintain redox and metabolic homeostasis. Impaired peroxisomal β-oxidation of VLCFAs initiates the disease pathophysiology, generating excessive ROS that subsequently damage other organelles, creating a vicious cycle. This cascade of downstream detrimental effects leads to inflammation in the brain and spinal cord, and neurodegeneration contributing to the rapid and severe progression of ALD. These two diseases share a common theme of impaired organelle crosstalk, which plays a critical role in their pathogenesis but they differ in the specific organelles and pathways involved.

In this review, we underscore the importance of organellar interactions in lysosomal and peroxisomal diseases, with a focus on GD and ALD. We also discuss potential therapeutics that warrant further investigation. Understanding of organellar crosstalk remains incomplete and requires more extensive

research. This area offers opportunities to develop effective treatments targeting organellar dysfunctions, providing hope for treating diseases associated with these processes.

DECLARATIONS

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Authors' contributions

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Kartha RV is an Editor on the Editorial Board of the journal *Rare Disease and Orphan Drugs Journal*. Kartha RV was not involved in any steps of editorial processing, notably including reviewer selection, manuscript handling, and decision making. The other authors declared that there are no conflicts of interest.

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Not applicable.

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