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Regulation and functions of membrane lipids: Insights from *Caenorhabditis elegans*

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ABSTRACT

The *Caenorhabditis elegans* plasma membrane is composed of glycerophospholipids and sphingolipids with a small cholesterol. The *C. elegans* obtain the majority of the membrane lipids by modifying fatty acids present in the bacterial diet. The metabolic pathways of membrane lipid biosynthesis are well conserved across the animal kingdom. In *C. elegans* CDP-DAG and Kennedy pathway produce glycerophospholipids. Meanwhile, the sphingolipids are synthesized through a different pathway. They have evolved remarkably diverse mechanisms to maintain membrane lipid homeostasis. For instance, the lipid bilayer stress operates to accomplish homeostasis during any perturbance in the lipid composition. Meanwhile, the PAQR-2/IGLR-2 complex works with FLD-1 to balance unsaturated to saturated fatty acids to maintain membrane fluidity. The loss of membrane lipid homeostasis is observed in many human genetic and metabolic disorders. Since *C. elegans* conserved such genes and pathways, it can be used as a model organism.

1. Introduction

Biological membranes are made up of a lipid bilayer with proteins embedded in it. The lipids in the bilayer are free to rotate, move laterally, or exchange between bilayers [41]. Apart from being a structural framework, the cellular membrane is equipped with receptors, signaling molecules and enzymes involved in membrane fusion, fission, endocytosis, and communication between cells and the surrounding environment [137]. The membranes also form curvature, pore and membrane domains and interact with the cytoskeleton and surrounding matrix [3,32,41,85]. The highly complex lipid composition, versatility, interactions, and distribution are essential to the structural and functional characteristics of the membrane and to define cell type. In several cases, understanding membrane lipid homeostasis is the key to comprehending complex cellular mechanisms related to pathogenesis [3,33,34,48]. Thus, the composition and organization of biological membranes have become a focus research area of biology and medicine.

Caenorhabditis elegans is a powerful animal model for dissecting genetics, development, nervous system function, and aging. Their membranes are composed of glycerophospholipids and sphingolipids with small amounts of cholesterol [135]. However, cholesterol does not contribute to the bulk properties of the plasma membranes in *C. elegans* [79]. Among glycerophospholipids, 54.5% are ethanolamine-containing, 32.3% are choline-containing, along with 8.1% sphingomyelin and 5.1% others [103]. Besides, the lipid composition of the plasma membrane varies among different tissues and between the plasma membrane and organelles membranes. For example, mitochondrial membrane comprises 44% phosphatidylcholine, 34% phosphatidylethanolamine, and 14% cardiolipin, while ER membrane is composed of 60% phosphatidylcholine (PC), 23% phosphatidylethanolamine, 10% phosphatidylinositol. Furthermore, mitochondrial and ER membrane composed small amounts of sterols, phosphatidylinositol, phosphatidylserine, and sphingomyelins [51,52]. The maintenance of the lipid composition is vital for cellular and organismal health. For instance, any change in PE composition results in impaired mitochondrial energy metabolism ([52]; Calzada et al., 2016).

This review introduces *C. elegans* as a simple animal model for lipid research at the organismal level. In the upcoming sections, we considered and explored the biogenesis of membrane lipids, the significance of membrane lipid homeostasis and mechanisms that maintain homeostasis, and the *C. elegans* model for various human disorders with defective lipid homeostasis.

; PC, Phosphatidylcholine; PE, Phospahtidylethanolamine; PS, Phosphatidylethanolamine; SFA, Saturated Fatty Acid; UFA, Unsaturated Fatty Acid; LBS, Lipid Bilayer Stress.

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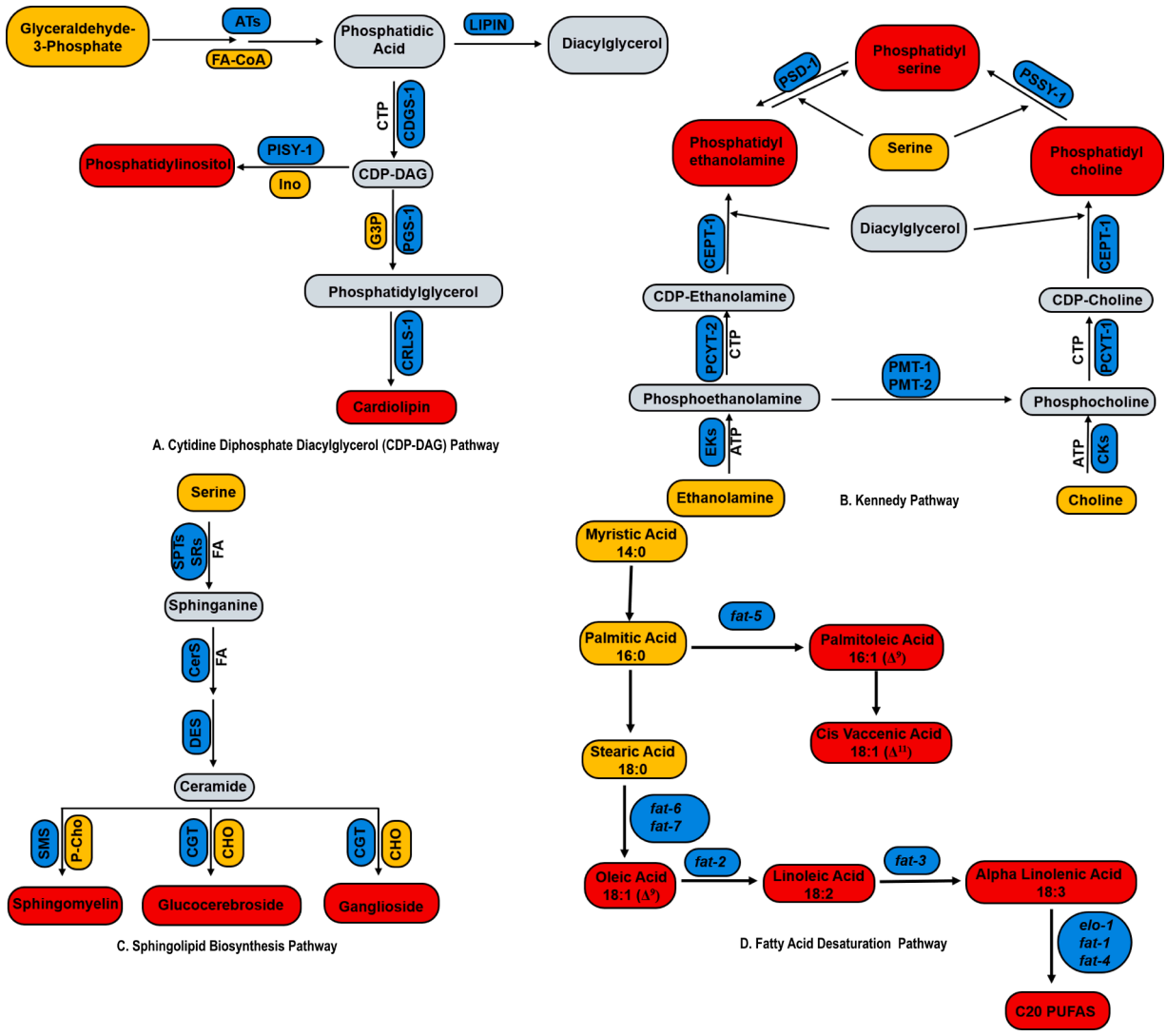

Fig. 1. Diagramatic representation of membrane lipid biogenesis and fatty acid desaturation in *Caenorhabditis elegans.* (A) The CDP-DAG pathway which produces cardiolipin (CL), phosphatidylinositol (PI) and diacylglycerol (DAG). (B) Kennedy pathway which produces phosphatidylethanolamine (PE), phosphatidylserine (PS) and phosphatidylcholine (PC). (C) Biosynthesis of sphingolipid. (D) Fatty acid desaturation Abbreviations used are CDGS-1: cytidine diphosphate diacylgycerol synthase-1, PISY: phosphatidylinositol synthase 1, CDP-DAG: cytidine diphosphate diacylglycerol, PGS-1: phosphatidylglycerol synthase 1, CRLS-1: cardiolipin synthase 1, EKs: ethanolamine kinase, CKs: choline kinase, PMT-1 & 2: phosphoethanolamine methyltransferase 1 & 2, PCYT-1 & 2: phosphocholine cytidylyltransferase and phosphoethanolamine cytidylyltransferase, CEPT-1: choline/ethanolamine phosphotransferases 1, PSSY-1 & 2: phosphatidylserine synthase 1 and 2, PSD-1: phosphatidylserine decarboxylase 1, SPTs: serine palmitoyl transferases, SR: sphinganine synthase, CerS: ceramide synthase, DES: dihydroceramide desaturases, SMS: sphingomyelin synthase, CGT: glucosyltransferases, *fat-1* to 7: fatty acid desaturases.

2. Biogenesis of membrane lipids in *C. elegans*

In *C. elegans*, the biosynthesis of phospholipids occurs through several pathways. The *C. elegans* obtain fatty acids (mainly 16:0) from *E. coli* and later modify it [87]. The biosynthesis usually begins with activating the acyl group to acyl-CoA by acyl CoA synthase [135]. In cytidine diphosphate diacylglycerol (CDP-DAG) and the Kennedy pathway, the two acyl groups are added to glycerol-3-phosphate (G3P). The reaction is catalyzed by acyl-transferase enzymes sn-Glycerol-3-phosphate 1-O-acyltransferase (GPAT) and lysophosphatidic acid acyltransferase (LPAAT) homologs producing phosphatidic acid (PA). CDP-DAG synthase of the CDP-DAG pathway converts PA and cytidine triphosphate (CTP) to CDP-DAG. This pathway synthesizes phosphatidylinositol (PI) and phosphatidylglycerol (PG) by adding the inositol and glycerol-3 phosphate to CDP-DAG The cardiolipin, vital component of the mitochondrail membrane, is synthesized by mitochondrial cardiolipin synthase (CRLS-1) from two PG molecules [101, 135] (Fig. 1A).

In the Kennedy pathway, choline and ethanolamine kinases phosphorylate choline and ethanolamine, respectively. After that, CTP-phosphocholine cytidylyltransferase and CTP-phosphoethanolamine cytidylyltransferase activate phosphocholine and phosphoethanolamine. The activated CDP-choline and CDP-ethanolamine react with DAG to form phosphatidylethanolamine (PE) and phosphatidylcholine (PC). The reaction is catalyzed by the enzyme choline/ethanolamine-phosphotransferase 1 (CEPT-1). Alternatively, *C. elegans* produces PC from PE by phosphoethanolamine methyltransferase enzymes PMT-1 and PMT-2, similar to plants [7]. Phosphatidylserine synthase 1 (pssy-1) forms phosphatidylserine (PS) by exchanging serine with choline or ethanolamine of PC or PE (Fig. 1B).

Sphingolipid biosynthesis begins with forming a sphingoid base by condensing the branched-chain fatty acid C15:isowith serine to form a d17:isosphinganine. Serine palmitoyltransferase and sphinganine reductase catalyze this synthesis [16,139]. Three genes *sptl-1, sptl-2*, and *sptl-3* encode homologs of serine palmitoyltransferase in *C. elegans*. When long-chain saturated or hydroxylated fatty acyl-CoA is added to

17 iso-sphinganine, d17iso-dihydroceramide is formed, which is then desaturated to produce ceramide. The ceramide synthase, which is encoded by three genes, *hyl-1, hyl-2*, and *lagr-1*, catalyzes the first step of the reaction, and the latter step is catalyzed by dihydroceramide desaturases which are encoded by *ttm-5* and *f33d4.4* genes [16,22,139]. Ceramides are modified to form more complex sphingolipids by the addition of phosphate or carbohydrate groups to form sphingomyelins, cerebrosides, or gangliosides. The *sms-1, sms-2, sms-3* genes encode homologs of sphingomyelin synthases, and this enzyme adds a phosphatidylcholine group to C1 of ceramide to produce sphingomyelin [54]. Similarly, three glucosyltransferases CGT-1, CGT-2, and CGT-3 add carbohydrate groups to ceramide to produce glucocerebrosides [76].

C. elegans are auxotroph for sterols and obtain sterols through food [15]. Though sterols are not used as structural components of the cell membrane, they are essential for C. elegans since they produce sterol-derived hormones (e.g., dafachronic acids), which regulate development and mating behavior [40,56]. Moreover, signals from lipid rafts containing sphingolipids and cholesterol are required for membrane fusion with PM and pseudopod extension, necessary for sperm activation (J et al., 2012).

3. Membrane lipid homeostasis

Apart from regulating traffic, the phospholipid bilayer provides a platform for proteins that participate in catalysis or function as channels or signaling molecules [28]. For instance, the fluid-like phase of membranes is essential to allow dynamic interactions between lipids and other membrane components, including proteins and many membrane-related processes such as deformation, budding, trafficking, and reformation. Therefore, maintaining membrane lipid homeostasis is crucial for cells. In case of the loss of lipid homeostasis, cells become incapable of alleviating stress or toxic influx leading to programmed cell death. In the coming section, we discuss the crucial mechanisms controlling membrane lipid homeostasis in *C. elegans*.

3.1. Significant role of the constituent membrane lipids

3.1.1. The PC:PE ratio is important to prevent desiccation

The anhydrobiotic state allows organisms to thrive during a period of intense desiccation. In such circumstances, organisms lose most of their water content and cease metabolism [2]. Nevertheless, they quickly resume life activities upon rehydration. Such survival phenomenon is observed in several taxa, including *C. elegans*, which showcase two alternative life cycles. When the resources are plenty, newly hatched individuals pass through four larval stages (L1, L2, L3, L4) and form adults after three days. On the other hand, when the resources are limited, newly hatched L1 larvae can take an alternative developmental route to enter the pre-dauer stage, followed by the non-feeding diapause stage called dauer [38]. They are resistant to various stresses and can live several months without food. They feed and resume development by returning favorable conditions [38].

Dauer larvae of *C. elegans* is an example of an anhydrobiotic state [2]. The larvae of *C. elegans* undergo preconditioning before entering the dauer state, which includes increased biosynthesis of trehalose and reduction in PC content. The anhydrobiotes experience significant challenges during fast rehydration with the onset of the rainy season. The sudden change could cause excessive swelling in various cellular compartments of the organism. The organisms have evolved lyotropic (hydration-induced) phase transition mechanisms of membrane lipids which are critical to preserving membrane integrity during the exit from the dry state. PC develops strong water connections and tilted acyl chain packing at extremely low hydration, whereas PE does not. As a result of the coupling of the sub-headgroup H-bond network, the lyotropic transition entails lowering the PC content, resulting in a three-fold increase in acyl chain free volume [2,93]. Thus, the PC:PE ratio regulation in vivo is a crucial factor resisting the cell membranes desiccation.

3.1.2. The PE level and mitochondrial health

In *C. elegans*, PE makes up to 54.5% of membrane phospholipids [103]. The PE is a multifunctional membrane lipid associated with several cellular pathways, including membrane fusion and mitochondrial stability [109], an important event of mitochondrial functioning. Thus, reduction in PE disrupts mitochondrial morphology and function [106]. One instance of PE reduction is associated with caffeine intake. Sustained cAMP signaling in the presence of caffeine activates important lipid metabolizing enzymes, increasing lipid breakdown [30,61]. In *C. elegans*, caffein intake significantly reduces PE. The resulting elevation of mitochondrial ROS, upregulation of HSP-6 (heat shock protein-6), GST-4 (glutathione S-transferase), and AMPK (AMP-activated protein kinase) induces the mitochondrial stress response. Also, caffeine promotes the localization of phospho-AMPK and DAF-16 in the nucleus, which suppresses lipogenesis mediated by the increased mitochondrial stress response. Conversely, the supplementation of PE reduces the expression of HSP-6, GST-4, and AMPK. It suppresses the mitochondrial stress response by improving lipid metabolism and fat storage in caffeine-fed animals [81]. However, the mechanism of how supplemented PE evades digestion by lipases and alleviates the adverse effects of caffeine needs to be explained further.

3.1.3. UFA level enhances sensory signaling, manages DNA damage, and extends lifespan

The transient receptor potential (TRP) ion channels play a prominent role in sensory signaling. The TRP family consists of subfamily channels such as TRPC, TRPV, TRPM, TRPP, TRPML, and TRPA. They are involved in nociception, thermosensation, olfaction, pheromone sensation, osmosensation, and mechanosensation [17]. Several reports suggested the role of lipids and their derivatives modulating the activity of such signal transducers [17]. In humans, intake of PUFA rich food (omega-3 fatty acids, for example) improved cognition, cardiovascular and neuronal function, metabolism, and extended lifespan. The PUFAs are expected to facilitate such effects via modulating TRP channels [115]. However, how PUFAs affect TRP channel activity is still unknown. Five TRPV genes, such as osm-9 and ocr-1, ocr-2, ocr-3, and ocr-4 targeted by PUFAs in C. elegans [42]. The TRPV gene osm-9 functions in the olfactory, chemosensory, osmosensory, and mechanosensory neurons. Meanwhile, the four ocr TRPV genes cooperate with osm-9 in such neurons [121].

The AWA and AWC neurons of *C. elegans* detect odors through ciliated dendrites at the nose tip, facilitating long-range chemotactic response. The sensory transduction through AWA neurons relies on TRPV proteins OSM-9 and OCR-2 [121]. Similarly, the ASH polymodal neurons use TRPV channel OSM-9 and OCR-2 for nociception. Besides, the olfaction through AWA neurons requires PUFAs such as arachidonic acid (AA), eicosapentanoic acid (EPA), or omega-3-arachidonic acid (O3AA). Furthermore, *C. elegans* touch receptor neurons (TRN) express fatty acid desaturases FAT-1 and FAT-4 from larvae to adults, suggesting the production of AA and EPA continuously during their life cycle. The AA and EPA are also required for ASH-mediated mechanosensation [127]. Meanwhile, touch sensitivity and mechanoelectrical transduction via TRN were improved by phospholipids containing arachidonic acid (AA) [57,127]. Therefore, lack of PUFA synthesis disrupted chemotaxis and touch sensation, compromised ASH-mediated avoidance of heavy metals and volatile repellants [57,127]. However, the dietary supplementation of PUFAs alleviated such behavioral defects [57]. Meanwhile, the omega-3 PUFAs and their eicosanoid derivatives 17,18-EEQ (Epoxyeicosatetraenoic acid) activate the TRPV4 function in endothelial cells by increasing the intracellular $Ca^{2+}$to modulate vascular reactivity [12,36]. Here the PUFAs drive conformational rearrangements to modulate TRPV4 function [120]. Thus, changing the local TRPV4 phospholipid microenvironment by fatty acid composition favors membrane protein interaction and modulates channel gating.

The hyperactivated ion channels cause excitotoxic cell death. In *C. elegans*, it is suppressed by a functional LET-23 and its ligand LIN-3

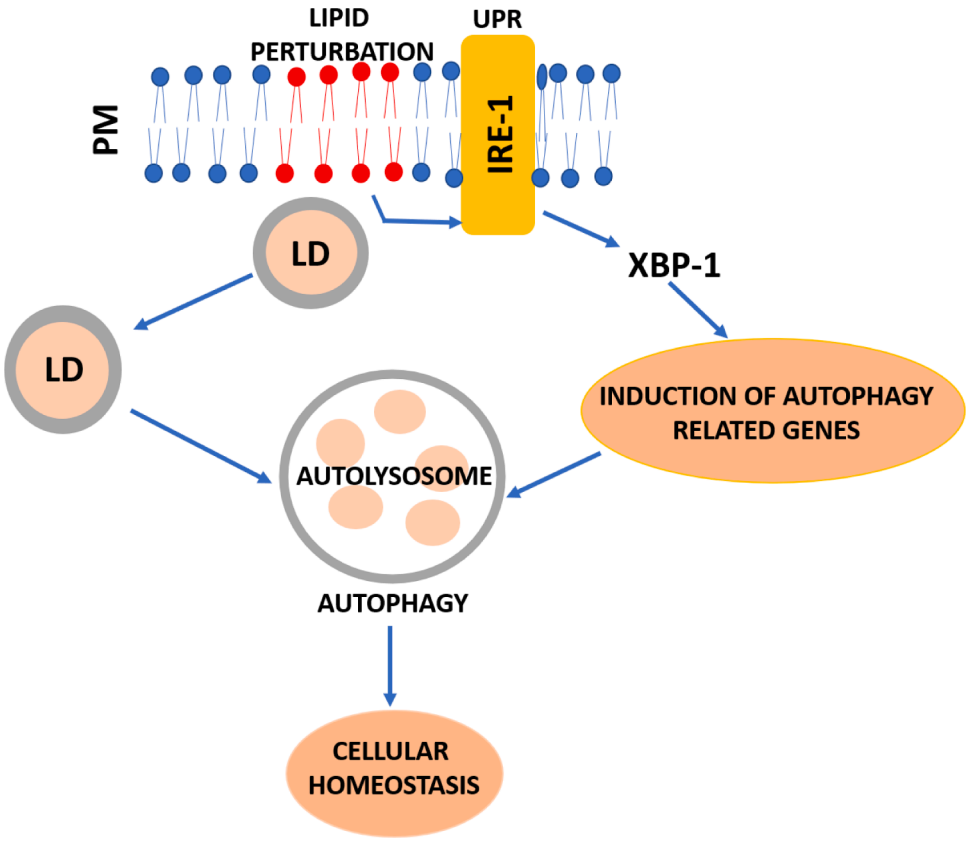

Fig. 2. Change in PLs composition resulting in ER stress-activated unfolded protein response (UPR) through upregulation of IRE-1-dependent autophagy. Perturbing PLs levels also affect the abundance and size of lipid droplets as a compensatory response to LBS. The model provided here shows the cross-talk between UPR^{LBS} and autophagy during lipid bilayer stress (LBS) to maintain homeostasis.

EGF [53]. LET-23, the sole EGFR of *C. elegans* is well-known for pro-survival functions [19]. The LET-23 signaling most likely protects cell-autonomously through specific downstream pathways like let-60 Ras. Meanwhile, high PC content protects cells by interfering directly with TRPV channel gating, construction, or activity or acting on downstream events that execute cell death [19]. It is suggested that the signal molecules derived from PC are remarkably involved in such cell protection downstream or parallel to LET-23 signaling pathways [19]. Besides, nematodes have evolved several survival programs to mitigate persistent DNA damage [31,83]. For instance, the UV exposure-induced DNA damage increases specific UFA containing complex lipids. Intriguingly, the UFA containing PC, which remarkably increases UPR^{ER} (Unfolded Protein Response of Endoplasmic Reticulum). The UFA containing PC is required to activate IRE-1/ XBP-1 genes/proteins during DNA damage [25]. As a result, the loss of function of *pcyt-1* (phosphocholine cytidylyltransferase-1) or *pmt-2* (phosphoethanolamine N-methyltrasferase-2) genes abrogated UV-induced UPR^{ER} gene activation [7,25]. Conversely, unsaturated PC supplementation protected cells from excitotoxic cell death in *pnc-1* mutant worms while significantly increased ER stress resistance in *pcyt-1* or *pmt-2* mutant worms [19]. It is now unclear how supplemented PC contributes to ER stress tolerance or protects mutant worms from excitotoxic cell death. However, it explains that the aged worms have a lower DNA damage response due to poor PC production [5,25,80].

3.2. Mechanism of membrane lipid homeostasis

3.2.1. Genetic regulation

Autophagy during starvation recycles molecules that help cellular survival during adverse conditions. It delivers lipid droplets for lysosomal degradation on demand [107]. The starvation during early larval development induces entry into the dauer stage, which coincides with reducing insulin/IGF-1-like signaling, increased lipid storage, and metabolic changes that support long-term survival under extreme conditions [38,66]. Meanwhile, compromised autophagy in dauer larvae reduces lipid storage in the intestine and hypodermis, two significant lipid storage and regulation sites [66].

In developing *C. elegans, bec*-1, VPS30, ATG6, BECN1, and other autophagy genes regulate lipid storage [66]. The bec-1 is required to store neutral lipids during development, and its loss of function causes extremely lean adult animals. Similarly, loss of vps-34, lgg-1, and unc-51 significantly reduced fat content in adult animals. It is not because of the reduced pharyngeal pumping, nutrient absorption, or defecation but due to impaired autophagy. Moreover, in daf-2 receptor glp-1 double mutants, the impaired autophagy reduced lipid storage capacity during development [66,77,122]. As a result, lipid recycling efficiency between lipogenesis or lipid absorption and autophagy accomplishes lipid homeostasis and extends lifetime [66].

3.2.2. Lipid bilayer stress (LBS)

The "ER unfolded protein response" (UPR^{ER}), has evolved to safeguard against ER stress due to the accumulation of misfolded proteins in the ER [13,65]. Three parallel sensor pathways: the inositol-requiring-enzyme 1 (IRE-1) branch, the protein kinase RNA-like ER kinase (PERK) branch, and the activating transcription factor 6 (ATF-6) branch regulate the expression of hundreds of genes involved in UPR^{ER} [97]. Approximately 30% of proteins fail to fold correctly and are degraded by the proteasome shortly after translation [104]. These defective ribosomal proteins (DRiPs), if not removed, can result in proteotoxic stress (UPR^{PT}) [50]. Also, the ER membrane disequilibrium activates UPR^{ER} in yeast, mammalian cells, and mice [86,91]. Intriguingly, the IRE-1 and PERK activated the UPR^{ER} upon membrane lipid

perturbations even without a functional unfolded protein sensing domain [60,128].

The MDT-15 is a mediator subunit that regulates the expression of *fat-5, fat-6*, and *fat-7*, encoding Δ9-desaturases in *C. elegans* [9,117,118, 134,136]. Although PC and PE are critical membrane phospholipids, the loss of MDT-15 resulted in an overall rise in saturated FAs, with a significant influence on PC desaturation [117,136]. The extend of saturation and acyl chain length strongly influence the structure and function of cellular organelles [45,65,123]. For instance, the ER requires a more fluidic membrane to accommodate the extensive protein and lipid biosynthesis workforce. However, ER membrane experiences an accumulation of saturated PC and membrane rigidification due to the loss of function of MDT-15 [118,136]. It also resulted in the rise in UPR^{ER} markers *hsp-4* and spliced *xbp-1* (XBP-1 s) [52].

The active form of the transcription factor, XBP-1 s, in the nervous system or intestine can activate UPR^{ER} in *C. elegans*, leading to increased resistance to ER stress and extended lifespan [119]. The XBP-1 s activate lysosomal lipase and intestinal *fat-6* encoded Δ9 desaturase [55]. The resulting monounsaturated oleic acid (OA) increases lifespan [43,47]. Consistent with this, the expression of XBP-1 s in *fat-6* mutant animals only slightly improved the lifespan [55]. It indicates the ability of the UPR^{ER} to cell non-autonomously modulate lipid metabolism and extend lifespan.

The activation mechanism of UPR due to LBS is independent of proteotoxicity-induced ER stress. However, both UPR^{LBS} and UPR^{PT} activation require the amphipathic helix of IRE-1. A recent study suggested that the rotational orientation of amphipathic helix activates IRE-1 during proteostatic (UPR^{PT}) and lipostatic (UPR^{LBS}) ER stress [46]. At the same time, an arginine residue at the amphipathic and transmembrane helix interface (R537) acts as an LBS sensor. The substitution of arginine (R537) with glutamine renders IRE-1 incapable of sensing LBS while sensing proteotoxic stress [49]. It is now clear that both UPR^{LBS} and UPR^{PT} require IRE1; however, regulated by distinct activation mechanisms.

In *C. elegans*, both UPR^{LBS} and UPR^{PT} upregulated the expression of a different set of genes to restore ER homeostasis in IRE-1 dependent manner [62]. The two upregulated genes during UPR^{LBS}, ATG11, and ATG32 enhance autophagy and ER-phagy, suggesting their role in buffering UPR^{LBS} [37]. For instance, perturbation of PC content due to mutation of *pmt-2* (phosphoethanolamine N- methyl transferase-2) activate IRE-1, which in turn activates XBP-1. The XBP-1 activates autophagy genes that work to achieve cellular homeostasis through LBS (Fig. 2) [62]. On the other hand, when PC content changes affect membrane function, SBP-1/SREBP-1 were activated to ensure adequate SAMe (S-adenosyl methionine) levels for PC production. The SBP-1/SREBP-1 simultaneously activates other pathways like TAG production. It indicates that low PC contributes to SREBP-1-dependent lipogenesis under compromised methyl group metabolism [129]. To conclude, the activation mechanism of IRE-1, which senses fluctuation at the ER membrane, is distinct from the activation mechanism of proteotoxic stress. The activated IRE-1 upregulates the expression of a set of genes required for UPR^{LBS} to restore the ER homeostasis.

3.2.3. Balancing between saturated and unsaturated fatty acids

The cell membrane is built mainly from saturated or unsaturated fats found in the diet. The fully extended saturated fatty acids (SFA) closely pack to form crystalline arrays stabilized by hydrophobic interactions. Conversely, the cis-double bond of unsaturated fatty acids (UFA) produces a kink in the hydrocarbon chain and packs loosely. The amount of polyunsaturated fatty acids (PUFAs) and resulting fluidity is critical for membrane deformation [92], domain stability [70], and membrane fission events [74]. Conversely, excess SFA rigidifies the membrane. Nearly 80% of phospholipids in adult *C. elegans* membranes are replaced daily, mainly by employing dietary fatty acids as building blocks. It indicates the extensive traffic between the intestine and the membranes of other organs and tissues. Thus, the dietary proportion of UFA to SFA can influence membrane fluidity and present a challenge to the organisms [23].

There are few proteins in humans and *C. elegans* that alert cells when the membrane is too rigid, and the cells respond by converting SFA in the membrane into UFA. The *C. elegans* proteins PAQR-1 and PAQR-2 (progestin and adipo Q receptor-like protein 1 &2) are homologous to the mammalian proteins AdipoR1 and AdipoR2 [114]. Both PAQR-1 and PAQR-2 are expressed in metabolically significant tissues. The PAQR-2 enhances FA desaturation by exposing more FA to Δ9 desaturase. Consequently, PAQR-2 increases the relative abundance of unsaturated fatty acids in the plasma membranes and maintains membrane fluidity during cold adaptation or excess intake of saturated fatty acids ([27,44, 90,112,113]). Therefore, the mutation of PAQR-2 resulted in the accumulation of saturated fatty acids in their phospholipids with a concomitant increase in membrane rigidity [113]. The PAQR-2 mutant worms are intolerant to cold and excess saturated fatty acids. They have a malformed tail tip, poor autophagy, and smaller brood size, as well as poor motility and a short lifetime ([14,27,68,113,114]). The low phosphatidylcholine synthesis or FA metabolism suppress the effects *paqr-2* null phenotype via sbp-1 activation and overexpression of downstream desaturases [129]. On the other hand, the *paqr-1* mutation does not cause direct phenotypic defects but intensifies *paqr-2* null phenotype [113,114].

Recently, the protein IGLR-2 was identified as an obligate partner of PAQR-2. The cells possessing both PAQR-2 and IGLR-2 are adapted to cold temperatures or saturated fatty acids-rich diets ([90,113] & [26, 112]; Bodhicharla et al., 2018; Pilon 2021). The PAQR-2 interacts with IGLR-2 via their transmembrane domains depending on membrane rigidity. It causes displacement of the PAQR-2 cytoplasmic domain and opens access to the catalytic site [11,26,112]. There are three functionally redundant Δ9 desaturases in *C. elegans*, namely *fat-5, fat-6*, and *fat-7* [8]. Among these, *fat-6* and *fat-7* primarily carry out the desaturation of stearate (18:0) [23]. The PAQR-2/IGLR-2 complex in the hypodermis or other tissues acts as a fluidity sensor. Consequent to the extensive flux of saturated fatty acids, the PAQR-2/IGLR-2 complex promotes systemic fatty acid desaturation by FAT-6. The FAT-6 catalyzes desaturation until the fluidity is retained throughout the worm ([9]; Bodhicharla et al., 2018; [26]). Alternatively, the PAQR-2/IGLR-2 complex produces a signaling molecule that diffuse to the intestine and promotes fatty acid desaturation. The resulting unsaturated fatty acids in the intestine is supplied to every cell in *C. elegans*, probably through the pseudocoelom.

C. elegans also possess protein FLD-1 (membrane fluidity homeostasis-1), a multi-domain protein limiting unsaturated fatty acids in the membrane. FLD-1 belongs to the TLC family of proteins characterized by a TLC domain. The human possesses two orthologs of FLD-1, TLCD1, and TLCD2. The TLCD1 is localized to the plasma membrane (Papanayotou et al., 2013). Like TLCD1, FLD-1 is expressed in the plasma membrane throughout the developmental phase and in adults. The FLD-1 in *C. elegans* and TLCD1/2 in mammalian cells limit the integration of LCPUFA (long-chain polyunsaturated fatty acid) into phospholipids [99]. Therefore, silencing of FLD-1 or TLCD1/TLCD2 fluidizes the membrane by incorporating LCPUFA into phospholipids in worms and mammals, thereby mitigating lipotoxicity [99]. Consistently, FLD-1 helps maintain membrane fluidity in *paqr-2/iglr-2* mutant worms grown at low temperatures or in the presence of glucose, which is readily converted to saturated fatty acids by the dietary *E. coli* [27,112]. On the other hand, the worm was intolerant of glucose and cold, with a defective withered tail tip by the introduction of wild-type *fld-1* [99]. It indicates that the loss of function allele *fld-1* primarily suppresses *paqr-2/iglr-2* mutant phenotype [99]. It is critical because the *paqr-2* and *iglr-2* mutants exhibit clear membrane fluidity abnormalities ([27,99, 113] & [112,114]). The preceding discussion explicitly confirmed that the PAQR-2/IGLR-2 complex and FLD-1 work in concert to maintain membrane fluidity in *C. elegans*. Recently, a genome wide screening in *C. elegans* identified another protein, ACS-13 (human ACSL1 homolog),

similar to FLD-1. The inhibition of ACS-13 increases the number of LCPUFA-containing phospholipids, reducing SFA-induced membrane rigidification and lipotoxicity [98].

3.2.4. Phospholipid asymmetry of the lipid bilayer

Asymmetrically distributed phospholipids form the lipid bilayer of biological membranes, which is vital for cell integrity and physiology. Two types of ATP-dependent transporters move lipids across the bilayer to maintain the asymmetry [78,100]. The first type belongs to the P-type ATPases of Class IV. They are aminophospholipids translocases (APLTs), which transport PS and PE from outer to the inner leaflet of the plasma membrane [[94],[108]]. *C. elegans* possesses six homologs of the human aminophospholipid translocases (*tat-1* through *tat-6* [trans bilayer amphipath transporters]). However, only germ cells lacking *tat-1* exposes PS on their surface. The PSR-1 (PS-recognizing phagocyte receptor) and CED-1 (cell death protein-1) recognize exposed PS, leading to apoptosis and corpse clearance. The loss of function mutation of the other tat genes *tat-2* to *tat-6* did not expose PS on the cell surface. It implies that *tat-1* is the putative aminophospholipid translocator in *C. elegans* [14]. Conversely, the floppases transport lipids, for instance, PC, from the cytosolic to the exoplasmic leaflet of the bilayer. Though work contradictorily, the flippases and floppases contribute to the phospholipid asymmetry and extend lifespan.

3.3. Factors affecting membrane lipid homeostasis

3.3.1. Aging

The membrane theory of aging suggested the accumulation of toxic compounds in the cellular membrane with age. It results in the decline of membrane function, and cells become inefficient for the cell to cell or cell to ECM communication [24]. For example, PC is one of the major membrane phospholipids known for its antioxidant activity and modulating brain function in neurodegenerative diseases. The low PC also affects nutrient uptake and toxin excretion. Such membranes accumulate excessive cholesterol and toxic lipofuscin, causing solidification of the membrane [75]. A decline in PC content in the membrane was observed with age. Nonetheless, in *C. elegans* Alzheimer model, phosphatidylcholine supplementation delayed paralysis caused by Aβ accumulation [59].

Another membrane lipid, phosphatidylserine, is abundant in the brain and improves neuronal function [1,67]. Like PC, the level of phosphatidylserine (PS) decreases with age, contributing to the cognitive impairment and pathogenesis of Alzheimer's disease (AD) [20,110]. Like PC, the dietary supplementation of PS reduced Aβ toxicity and delayed paralysis in *C. elegans* Alzheimer's model CL4176 strain [58,72]. Also, the supplemented PS augmented resistance to oxidative stress, extended mean lifespan, delayed age-associated decline in motility in *C. elegans* model [58]. The PS reduces insulin/IGF-1 signaling, which depends on DAF-16 expression. Moreover, the supplemented PS also triggered ROS with a concomitant rise in the expression of stress response genes *hsp-16.2* and *sod-3* [58]. However, the mechanism that makes the animal tolerant to different toxicity and increases lifespan with the supplemented PC and PS needs more clarification. The different studies considered here pointed that decline in the phospholipids, PC, and PS contributes to the age-related complexities.

3.3.2. The loss of fluidity

The biological membranes are fluid-structure by nature. The fluid-like phase of membranes is essential to allow dynamic interactions between lipids and other membrane components, including proteins. It also allows processes like membrane deformation, budding, and trafficking. It is strongly influenced by saturation and the length of fatty acyl tails of membrane phospholipids [45,65,123]. The close packing of saturated fatty acids increases the rigidity of the membrane, while the unsaturated fatty acids reduce the rigidity by the loose packing. Therefore, a stringent regulatory mechanism is required to maintain the balanced unsaturated fatty acid-saturated fatty acid content. The detailed investigation in *C. elegans* has identified the concerted action of PAQR-2/IGLR-2 complex and FLD-1 maintain their balance and membrane fluidity [Refer to Section 3.2.3 above for detailed mechanism].

Besides the balanced UFA-SFA content, the amount of ether lipid is pivotal to maintain the physical properties of the membrane. The ether-linked phospholipids are formed by the ether linkage between long-chain fatty alcohols and phosphoglycerol [35,125]. The peculiar structure of ether-linked phospholipids is essential to maintain membrane fluidity, produce lipid signaling molecules, and facilitate the functions of integral membrane proteins [6,130]. The ether lipids provide strong intermolecular hydrogen bonding between lipid headgroups due to the lack of carbonyl oxygen at position sn-1, contributing to membrane rigidity [73]. Three peroxisomal enzymes such as ACL-7 (DHA acyltransferase (GNPAT), ADS-1 (alkyl-DHAP synthase (AGPS) and FARD-1 (fatty acyl-CoA reductase 1) catalyze initial steps of ether lipid biosynthesis in *C. elegans* [105]. The *C. elegans* with mutation in the genes *fard-1, acl-7* and *ads-1*, were deficient in ether lipids. Such worms experience a concomitant increase in saturated stearic acids (18:0). It means that *C. elegans* overcome ether lipid deficiency by increasing the amount of saturated fatty acids [105].

3.3.3. The loss of phospholipid asymmetry

Section 3.2.4 explained the activity of PL transporters and asymmetric distribution of PL in the membranes. However, a collapse in PL asymmetry has observed several cellular processes. For instance, the externalization of PS, observed in cells undergoing apoptosis. In humans, the externalization of phosphatidylserine is induced by the apoptotic inducing factor (AIF) [111]. Similarly, in *C. elegans*, mutation of WAH-1, an AIF homolog, significantly reduced PS externalization, compromised apoptotic DNA degradation, and delayed normal progression to apoptosis [132]. WAH-1, on the other hand, collaborates with phospholipid scramblase 1 (SCRM-1), another plasma membrane protein [132]. There are eight PL scramblases homologs in *C. elegans* [39]. However, only the deletion of scrm-1 significantly decreased PS exposure and cell corpse engulfment [132]. Scramblases are proteins that mediate bidirectional lipid translocation upon increasing intracellular Ca^{2+}. Consistent with this, SCRM-1 showed head group independent trans-bilayer phospholipid translocation in artificial membranes [64]. It indicates that the SCRM-1 can mediate phospholipid translocation, which is enhanced by the interaction with WAH-1, resulting in loss of phospholipid asymmetry.

Sequence analysis exposed a CRAC motif (Cholesterol Recognition Amino acid Consensus) at the C-terminal of SCRM-1. A similar motif in human phospholipid scramblase 1 (hPLSCR1) exhibited strong intermolecular interaction with cholesterol [95]. Such interaction of SCRM-1 with cholesterol in a liquid-ordered (L_o) artificial membrane has significantly reduced scramblase activity in the artificial membrane [63]. It indicates plasma membrane cholesterol can regulate lipid asymmetry through PL scramblase. However, concluding it without in vivo experiments is currently inequitable.

4. *C. elegans* models for human disorders relevant to lipid homeostasis

4.1. C. elegans as a model to study ether lipid abnormality

The deficiency of ether lipids causes respiratory disease in infants and neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and Neimann-Pick type C disease [6]. The biosynthesis of ether lipids initiates in peroxisomes with two key enzymes glyceronephosphate O-acyltransferase (GNPAT), alkylglycerone phosphate synthetase (AGPS) [105]. Congenital deficiency of the GNPAT and AGPS cause rhizomelic chondrodysplasia punctata (RCDP) in humans [6,131]. A similar phenotype was observed in families with mutation of the third enzyme FAR-1, which delivers fatty alcohol for ether lipid biosynthesis

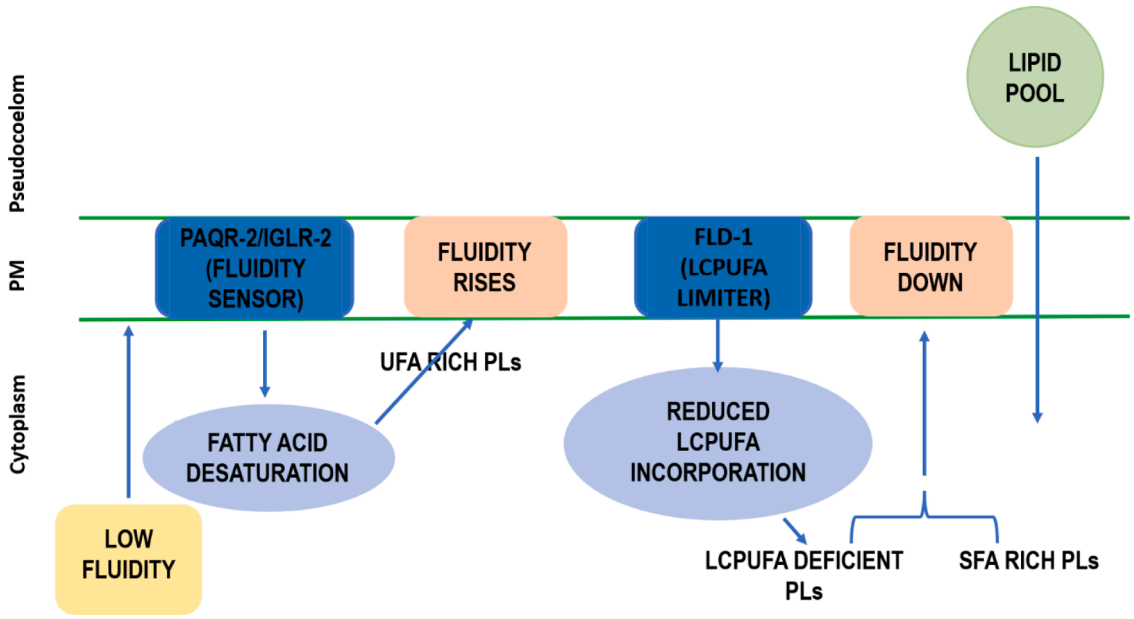

Fig. 3. The modified model explains how FLD-1, homolog of human TLCD1/TLCD2, and PAQR-2, homolog of AdipoRS/IGLR-2 complex act antagonistically to maintain membrane fluidity. FLD-1 limits the incorporation of UFA into the membrane, thereby keeping the membrane rigid and thus known as LCPUFA limiter. FLD-1 also provides an alternate pathway for reducing membrane rigidity by inhibiting FLD-1 production or its removal. Under cold stress or during excess intake of SFA, the PAQR-2/IGLR-2 complex detects the lowering of membrane fluidity and promotes a rise in fluidity by promoting fatty acid desaturation; thus, the PAQR-1/IGLR-2 complex is known as a fluidity sensor.

[10]. Overexpression of AGPS, on the other hand, resulted in the accumulation of ether lipids, which aided tumor growth [4]. Nonetheless, knocking down AGPS affected cancer cell survival, migration, and invasion [4].

Despite their widespread use and crucial roles across organisms, the precise mechanisms through which ether lipids contribute to optimal membrane functioning are unknown. The lipidomic study revealed many lipid species containing alkyl and alkenyl ether bonds in *C. elegans* [105]. Such ether-linked lipids represent approximately 10% of the phospholipids in the adult nematode, making them significant contributors to the overall phospholipid landscape [29]. Like in human cancer cells, the presence of ether lipids make *C. elegans* germ cells tolerant to ferroptosis induced by dietary dihomogamma-linolenic acid (DGLA) [88]. Moreover, *C. elegans* strains with deficient ACL-7 (ATP-Citrate synthase)/GNPAT, ADS-1(Alkyl dihdroxyacetonephosphate/AGPS and FARD-1/FAR1 enzymes have lipid profiles and phenotype similar to humans. Though mutant worms are sensitive to oxidative stress, less fit, and accumulate high levels of saturated fatty acids, but are viable and fertile, unlike humans. Human babies born with similar mutations do not survive past childhood [10]. Thus, the ACL-7/ GNPAT, ADS-1 and FARD-1/FAR1 mutant *C. elegans* present an attractive model to study ether lipid deficiency.

4.2. Diabetes model to study membrane fluidity

In *C. elegans, E. coli* converts excess glucose into saturated fatty acids, increasing their relative abundance in the cellular membranes [27]. As a result, saturated fatty acids accumulate in the membrane and cause loss of membrane fluidity [69,133]. In *C. elegans*, it contributes to glucotoxicity, poor microcirculation, and decreased insulin signaling, a phenotype similar to diabetes [89,102]. The action of the PAQR-2/IGLR-2 complex gave insight into maintaining fluidity in diabetic patients in such circumstances. The low membrane fluidity facilitates the formation of PAQR-2/IGLR-2 complex that presumably sends signals to its downstream effectors, NHR-49, MDT-15, or SBP-1, to promote fatty acid desaturation [112]. The protein FLD-1, mammalian TLCD1/2 homolog, on the other hand, limits the number of LCPUFA-containing phospholipids in *C. elegans* by inhibiting PUFA incorporation into phospholipids [99]. Interestingly, the *fld-1* single mutant worm has no obvious phenotype, suggesting the potential to inhibit TLCD1/2 to treat lipotoxicity and excess membrane rigidity in diabetes patients [89]. Together, these findings from the *C. elegans* model open up new avenues for diabetes therapeutics.

4.3. Niemann pick-type C1 disease

In humans, protein NPC1 is involved in redistributing cholesterol after endocytosis. The loss of function of NPC1 causes Niemann-Pick type C1 (NP-C1), an autosomal recessive neurodegenerative disorder [126]. It is characterized by the accumulation of unesterified cholesterol in the trans-Golgi network (TGN) and by the formation of abnormal lysosome-like structures. The *C. elegans* possesses two NPC1 homologs, *ncr-1* and *ncr-2*, primarily expressed in the intestine, pharyngeal muscles, spermatheca, excretory cells, rectal epithelial cells, neurons in head and tail cells. The *ncr-1* and *ncr-2* function upstream of *daf-9* and *daf-12* in a hormonal branch of the dauer formation pathway. Correlating this finding, *ncr-1* and *ncr-2* double mutants present a constitutive dauer formation (Daf-c) phenotype [116]. However, the Daf-c phenotype of the double mutants is significantly suppressed by the elevated level of cholesterol in the media.

The *ncr1 and ncr-2* mutation caused neuronal abnormalities, resembling human ectopic dendritogenesis caused by the ganglioside GM2 [84,138,140]. Moreover, the NCR function is required to maintain the morphological integrity of some selective neurons like ASER neurons, phasmid neurons, ASJ neurons during the transient dauer stage [71]. These characteristics make the *ncr* mutant *C. elegans* a suitable model for studying neurodegeneration and pathogenesis in Niemann Pick type C disease.

4.4. X-linked adrenoleukodystrophy (X-ALD)

X-linked adrenoleukodystrophy (X-ALD) is the most common peroxisomal disease. It is a complex inherited syndrome caused by the loss of function mutation of ABCD1 protein, which transports long-chain

fatty acids (VLCFAs) to peroxisomes, resulting in the accumulation of VLCFAs in tissues and plasma [82,124]. Five orthologs of mammalian ABCD transporters have been studied in *C. elegans*. These include *pmp-4* orthologous to ABCD1 and ABCD2, *pmp-1* and *pmp-2* orthologous to ABCD3 and *pmp-3* and *pmp-5* orthologous to ABCD4. The *pmp-4* is expressed in intestines and hypodermis and possesses a PEX19 binding site, suggesting peroxisomal localization [21]. Besides, the *pmp-4* mutant worms accumulated VLCFAs in complex lipids, a hallmark of X-ALD.

Axonal degeneration of corticospinal tracts leads to locomotor disability in X-ALD patients [96]. A similar phenotype was observed in *pmp-4* mutant *C. elegans*. The loss of *pmp-4* induces mitochondrial ROS which is detrimental to axonal integrity. Moreover, mutants worm accumulated lipid granules compared to wild-type worms [141,142]. However, introducing *pmp-4* in the hypodermis maintained axonal integrity and locomotion in a cell nonautonomous manner [18]. Thus, the *pmp-4* mutant worms can serve as an adequate animal model for studying debilitating neurometabolic conditions, revealing the critical molecular processes to underpin disease progression.

5. Conclusion

Working with membrane lipids presents a significant challenge for scientists. The metabolic pathways of lipid biosynthesis are well conserved across the animal kingdom. Therefore, the membrane lipid research in *C. elegans* has been beneficial for unraveling the roles of specific lipids in maintaining homeostasis under normal or during stress and aging. Uniquely, the worm possesses the potential to serve as a lipid metabolic disorder model. Future research on lipid metabolism in *C. elegans* will also benefit from the updated tools and techniques. However, such research needs to be extended to other metabolites like proteins. With the help of a genetic approach, *C. elegans* research will provide more insights into mechanisms of cellular homeostasis and roles for macronutrients in development, aging, and stress response.(Fig. 1, Fig. 3).

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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