



Lipid Dyshomeostasis and Inherited Cerebellar Ataxia

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Abstract

Cerebellar ataxia is a form of ataxia that originates from dysfunction of the cerebellum, but may involve additional neurological tissues. Its clinical symptoms are mainly characterized by the absence of voluntary muscle coordination and loss of control of movement with varying manifestations due to differences in severity, in the site of cerebellar damage and in the involvement of extracerebellar tissues. Cerebellar ataxia may be sporadic, acquired, and hereditary. Hereditary ataxia accounts for the majority of cases. Hereditary ataxia has been tentatively divided into several subtypes by scientists in the field, and nearly all of them remain incurable. This is mainly because the detailed mechanisms of these cerebellar disorders are incompletely understood. To precisely diagnose and treat these diseases, studies on their molecular mechanisms have been conducted extensively in the past. Accumulating evidence has demonstrated that some common pathogenic mechanisms exist within each subtype of inherited ataxia. However, no reports have indicated whether there is a common mechanism among the different subtypes of inherited cerebellar ataxia. In this review, we summarize the available references and databases on neurological disorders characterized by cerebellar ataxia and show that a subset of genes involved in lipid homeostasis form a new group that may cause ataxic disorders through a common mechanism. This common signaling pathway can provide a valuable reference for future diagnosis and treatment of ataxic disorders.

Keywords Cerebellar ataxia · Lipid homeostasis · Common signaling pathway · Diagnosis · Treatment

Introduction

Ataxia is a neurological disorder characterized by clinical abnormalities of balance, gait, extremity, eye movement, and impaired speech due to degeneration of the cerebellum and its connections [1–4]. It may be divided into three types: sporadic, acquired, and inherited ataxias [4–6]. Inherited ataxias are further subdivided into autosomal dominant cerebellar ataxias (ADCAs/SCAs), autosomal recessive cerebellar ataxias (ARCAs), and X-linked cerebellar ataxias (XLCAs) [7–11]. The inherited ataxias are genetically diverse; thus far, 47 subtypes of ADCAs/SCAs [12–14], 59 subtypes of ARCAs [15], and more than 20 subtypes of XLCAs [11] have been identified. Moreover, approximately one-third of

patients with clinical suspicion of ADCAs/SCAs and 50% of ARCAs remain without a molecular diagnosis [16–18].

Regarding the pathological processes of different types of inherited ataxias, ADCAs mostly affect the cerebellum, brainstem, and spinal cord [2], while ARCAs and XLCAs involve both the central and peripheral nervous systems, and non-neurological systems in some cases [11, 18]. Based on shared molecular mechanisms, ADCAs/SCAs are mainly categorized into four groups (namely, the CAG repeat–polyglutamine ataxias, ataxias associated with ion channel dysfunction, ataxias associated with mutations in signal transduction molecules, and ataxias associated with noncoding repeats) [19, 20]. However, ARCAs and XLCAs are categorized into five and two groups, respectively [2, 11, 21]. Of note, due to the considerable variety and salient overlap of clinical features among different disorders, rational classification has been impeded [7, 8, 15, 22]. In particular, some ADCAs/SCAs are not significantly different from ARCAs, named autosomal recessive spinocerebellar ataxias (SCARs) [23].

For many years, cerebellar ataxia has been thought to be incurable, and the treatment options are mainly limited

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to managing the symptoms, rather than treating the direct cause of the diseases [12, 24, 25]. However, as a result of intensive studies involving the molecular mechanisms, several promising therapeutic strategies have been developed [26]. In particular, antisense oligonucleotides (ASOs) that target the polyQ-coding SCA genes are under development and have been used in preclinical animal models [27–30]. Clinical trials of ASOs in SCA patients have been planned [12]. In addition, targeting the deranged calcium signaling pathway has been proposed as another potential therapeutic strategy for the different types of ADCAs/SCAs, and pre-clinical experiments have obtained some promising results [31–34].

Although some important advances have been made, the pathogenesis of ataxia caused by many genes is still not fully understood [10, 19]. Accumulating evidence indicates that other common pathogenic mechanisms exist within each type of inherited ataxia [35–38]. For example, the emerging common pathways underlying ARCAs include three main clusters, namely mitochondrial dysfunction, impaired DNA repair, and complex lipid homeostasis [35]. Based on these new findings, we speculate that there may be a common mechanism for different types of disorders with cerebellar ataxia as hallmarks. However, to date, there have been no reports of this. Recently, we systematically and comprehensively reviewed the PubMed literature and screened the OMIM and GeneReviews databases. In the OMIM databank, when entering “cerebellar ataxia” as the search keyword, more than three thousand entries appear. We checked each entry individually and in combination with screening GeneReviews. We finally determined that more than 300 genes were closely associated with cerebellar ataxia, not including those whose defects are related to ataxia, but there is no clear evidence showing that their defects cause cerebellar disorders. We then sorted these genes and found that a group of genes involved in maintaining lipid homeostasis are linked to different types of cerebellar ataxia, including genes that are linked to ARCAs and have been reviewed by Synofzik et al. [35]. Since members of this gene set are not only linked to ARCAs, as mentioned above, but also to other types of cerebellar ataxia, we speculate that they may represent a common mechanism of disorders characterized by cerebellar ataxia. Thus, in this article, the literature on this gene set is reviewed to reveal their internal connections to cerebellar ataxia. Notably, some genes that have been reviewed by Synofzik et al. are also included, as new discoveries have been reported and/or more detail is necessary. We extracted the numbers of patients with and without clinical ataxic symptoms from tables, texts, and figures from references regarding the genes, and transferred these to a master MS Excel spread sheet (Table S1) for subsequent meta-analysis using “metafor” (R package) [39]. Our analyses indicate that all analyzed genes show high risk ratios for

ataxia (Fig. 1). It should be mentioned that this analysis is subject to many confounders which have not been taken into account. Interestingly, most proteins encoded by the genes reviewed in this manuscript are located in the endoplasmic reticulum (ER), which is an important organelle of lipid metabolism. In subsequent sections of this review, we have summarized the latest physiological and pathological functions of these proteins, as well as their intrinsic mechanisms leading to ataxia. Our goal is to determine the potential common mechanism underlying different ataxias and evaluate the possibility of a common signaling pathway as potential targets for future precision treatments.

Genes Involved in Lipogenesis or Lipolysis

ER-localized enzymes catalyze the synthesis of most cellular membrane lipids. These enzymes also drive carbohydrates and nutritionally derived lipids into storage lipids to maintain lipid homeostasis [40]. The vast majority of lipids synthesized in the ER include phospholipids, triacylglycerols (TAGs), cholesterol, and cholesteryl esters [41, 42]. Sphingolipid synthesis starts in the ER until the formation of ceramide, and is completed in the Golgi apparatus, where complex lipids are synthesized [43–45]. Besides being components of the cell membrane, these lipids also play vital roles in many biological processes [46, 47]. Therefore, both synthesis and decomposition of lipids must be finely regulated [48, 49].

Patatin-Like Phospholipase Domain-Containing Protein 6 (PNPLA6)

Phospholipids make up the bilayer membrane matrix, and their composition and complexity in various membranes of eukaryotic cells differ [50, 51]. The most abundant lipid in the ER membrane is phosphatidylcholine (PC) [51, 52]. In eukaryotic cells, PC is synthesized through the Kennedy pathway [53, 54] or another pathway that catalyzes the conversion of PE to PC [55–58]. In contrast, PNPLA6 is responsible for the degradation of PC into glycerophosphocholine [59–61]. In addition, PNPLA6 and its *Drosophila* ortholog can also hydrolyze lysophosphatidylcholine (LPC) [62–64]. PNPLA6 is localized in the ER membrane [60, 65]. It is highly expressed in cerebellar Purkinje cells and its deficiency causes reduced dendritic trees and loss of Purkinje cells [66–68]. Mutations in PNPLA6 are associated with a spectrum of neurodegenerative disorders, that present clinical features ranging from pure cerebellar ataxia to complex forms of ataxia associated with other symptoms [68–74].

Thus far, most pathogenic mutations in PNPLA6 were observed in its catalytic or regulatory domain [62, 71, 75]. These mutations have been shown to cause PC/LPC overload

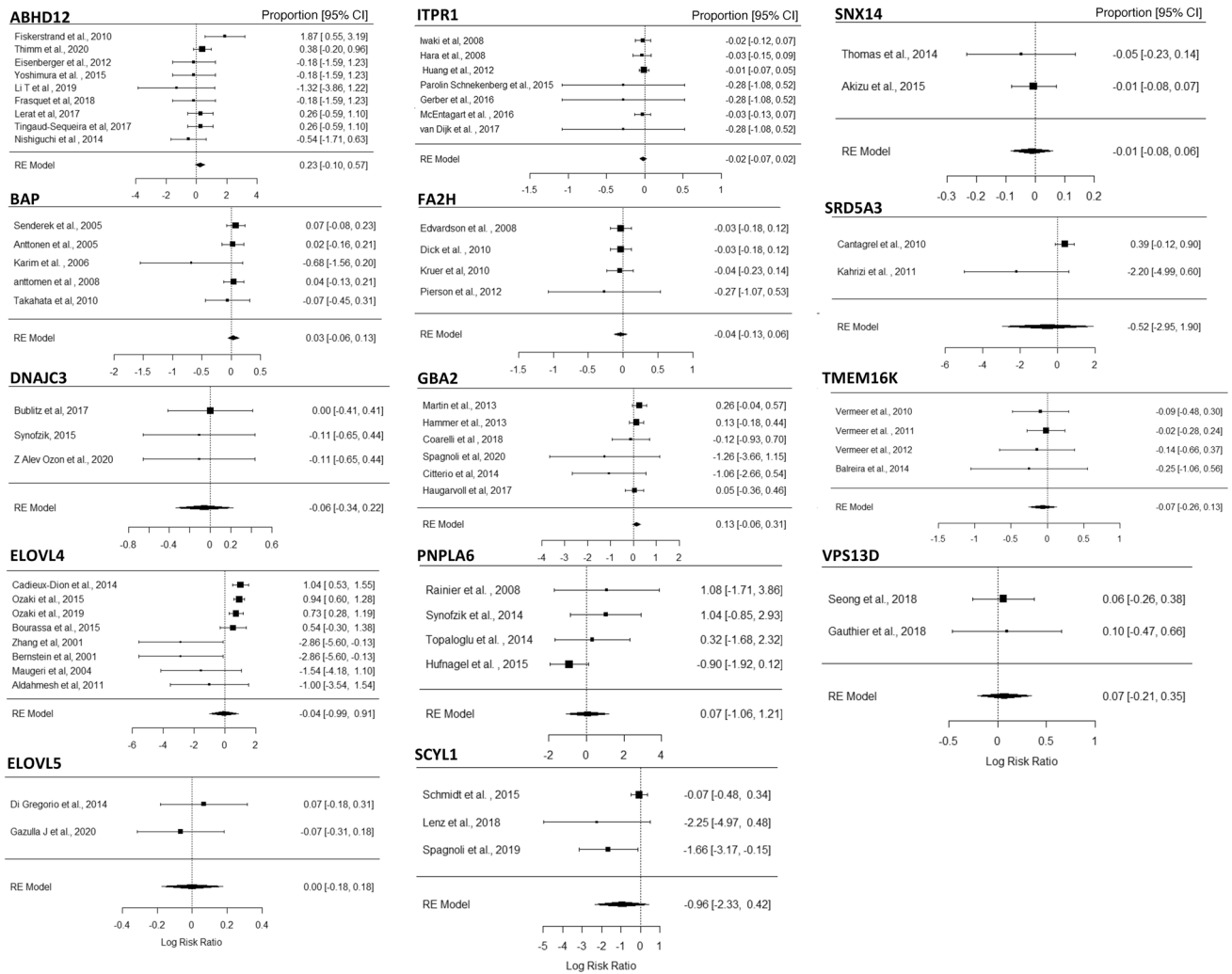


Fig. 1 Forest plot for frequency of ataxia related to genes involved in lipid homeostasis. We have that found 18 molecules related to lipid homeostasis are probably linked to cerebellar ataxia. We selected 14 of these for meta-analysis. However, regarding the remaining four genes, there are only animal cases available or the data is insufficient

and TAG shortage [65, 76], which can lead to Ca^{2+} dyshomeostasis [64], ER stress [77, 78], and abnormal lipid droplet (LD) formation [79–92]. Moreover, the catalytic domain of PLPLA6 was found to have a high intrinsic affinity for LDs and can cause LD clustering independent of its catalytic activity [65]. Interestingly, the catalytic domain of PNPLA7, another ER-localized member of the PNPLA family, is also associated with LDs [93, 94], and PNPLA6 may cooperate with PNPLA7 to regulate PC/LPC hydrolyzation and LD homeostasis [62, 63, 94–99]. In brief, PNPLA6 dysfunction leads to abnormal PC/LPC content in the ER membrane, which will cause lipid bilayer stress [100], thereby changing the protein structure and function in the membrane [101], and subsequently triggering ER stress and LD formation [79–92]. If any of these mechanisms fail or ER stress is

prolonged, the ER stress response will shift from an adaptive to a pro-apoptotic mechanism [81, 102], which will eventually cause cell death and depletion. This may explain why PNPLA6 deficiency can cause a spectrum of disorders. It is noteworthy that PC has a heterogeneous nature and plays pleiotropic roles, and its overload can produce many harmful effects [103]. Therefore, it cannot be excluded that other mechanisms may contribute to PLPLA6-associated ataxic disorders. Therefore, further studies are required.

α/β -Hydrolase Domain Containing 12 (ABHD12)

ABHD12 is a metabolic serine hydrolase in the ER membrane [104, 105], which has two main substrates, namely 2-arachidonoyl glycerol (2-AG) [106] and

lysophosphatidylserine (LPS) [107]. Importantly, its mutations are linked to neurodegenerative disorders, such as polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract (PHARC) [16, 108]. Although PHARC syndrome can be clinically variable [109–112], the cerebellum of PHARC subjects is the most atrophied brain region in any case [113].

Mechanistically, studies indicate that ABHD12 deficiency can cause neuroinflammation through very-long-chain LPS [105, 107] or arachidonic acid (AA)-derived lipids [114, 115]. Given that (1) the distribution of ABHD12 in the cerebellum is mainly found in microglia and Purkinje cells, (2) PHARC is characterized by age-dependent microglial activation and demyelination [108], and (3) microglia can cause Purkinje cell degeneration by engulfing and phagocytosing their dendrites [116], It would be very important to reveal how 2-AG and LPS act synergistically in the microglia demyelination process. The endocannabinoid (eCB) system is required for long-term depression (LTD) induction [117–119] and confers neuroprotection against demyelination [120]. However, chronic 2-AG overload can desensitize cannabinoid CB1 receptor signaling, resulting in functional antagonism of the cannabinoid system [121]. Further, LPS can induce inflammation and demyelination through several pathways [122–126]. Interestingly, during inflammation, LDs are required for both generation of AA-derived eicosanoids [127] and efficient phagocytosis by macrophages [128]. Thus, deletion of *ABHD12* may affect LD status in Purkinje and microglia cells, and LD dysregulation can play a key role in the entire pathological process of PHARC. In agreement with this, increased local concentration of DAG (the precursor of 2-AG) at specific ER sites promotes LD formation [129]. Interestingly, DAG also plays a critical role in autophagic flux [130, 131].

β-Glucosidase 2 (GBA2)

GBA2 is a glucocerebrosidase that mainly hydrolyzes glucosylceramide (GlcCer) to glucose and ceramide [132, 133]. It is ubiquitously expressed [132], but is especially abundant in cerebellar Purkinje cells [134–136]. Subcellularly, GBA2 is localized in the ER and Golgi membranes with its N and C termini facing the cytoplasm [134]. *GBA2* depletion can cause strong or mild locomotor defects in mice [137], while in humans, its mutations are associated with hereditary spastic paraplegia/cerebellar ataxia (SPG46) and Marinesco-Sjögren-like syndrome, both characterized by cerebellar ataxia [138–142].

Regarding the pathogenesis, it has been shown that *GBA2* depletion causes the accumulation of GlcCer outside the lysosomes [132, 143, 144] and leads to aberrant F-actin dynamics [137, 145]. However, the causality and detailed mechanism are unclear. Interestingly, GBA2 has

been found to be involved in several neurodegenerative diseases. Its expression was upregulated in Niemann-Pick type C (NP-C) [135, 146] and Gaucher disease [147, 148], and was downregulated in Parkinson's disease (PD) [149, 150]. The upregulation of GBA2 in NP-C caused defects in sphingolipid targeting from ER to Golgi and lysosomal pH adjustment [146, 151–153], whereas the downregulation of GBA2 in PD was associated with synucleinopathy, which was closely related to autophagic dysfunction [150, 154]. Taken together, GBA2 mutants may cause diseases via a similar mechanism, namely autophagic dysfunction because of GlcCer overload and abnormal lysosomal pH. F-actin dysfunction is probably only a secondary deficiency.

Elongation of Very Long Chain Fatty Acids-Like 4/5 (ELOVL4/5)

The biosynthesis of very long-chain FAs (VLCFAs) is catalyzed by a four-step reaction cycle; the first and also the rate-limiting step is carried out by the FA elongase family consisting of seven members [155–157], each with substrate specificity [156, 158, 159]. In mammals, while ELOVL5 catalyzes mainly polyunsaturated FAs with 18–20 carbons [156, 160, 161], the substrates of ELOVL4 are both saturated and polyunsaturated FAs with 20–26 carbons [156, 159, 162]. In the cerebellum, ELOVL5 expression is relatively late and is highly concentrated in Purkinje cells [161, 163]. In contrast, the expression of ELOVL4 begins in the embryonic stage, but only at a moderate level in Purkinje cells, and is mainly expressed in oligodendrocytes and other neurons [164].

Mutations in ELOVL4 and ELOVL5 have been linked to spinocerebellar ataxia 34 and 38 (SCA34/38), respectively [161, 165, 166]. SCA34 is a cerebellar ataxia combined with multisystem degeneration [165, 167, 168], while SCA38 is a relatively pure form [161, 169]. Thus far, all the known pathogenic mutations of ELOVL4 and ELOVL5 affect their catalytic sites [161, 170, 171]. However, in the serum of SCA34- and SCA38-affected individuals, only ELOVL5 products were reduced [161, 166]. This observation may reflect different degrees of damage by distinct mutants. ELOVL4 and ELOVL5 are diversely distributed; therefore, they may exert different functions in distinct cell populations. For example, the FA components of myelin lipids in oligodendrocytes are predominantly products of ELOVL4 [170, 172, 173], implicating ELOVL4 is mainly involved in myelination. Notably, dyshomeostasis of VLCFAs is directly related to cerebellar ataxia [174]. Furthermore, alterations in VLCFA-containing lipid species induces a drastic reduction of LDs [175], which also causes ataxia [176, 177]. Overall, in addition to the dominant negative effect of the ELOVL4 mutant on SCA34 [178, 179], abnormal VLCFAs may be the main contributor to SCA34 and SCA38 through various

mechanisms, in which LD dyshomeostasis may play a key role.

Run Domain- and Cysteine-Rich Domain-Containing Beclin-1-Interacting Protein (RUBCN)

Rubicon (RUBCN) is a ubiquitously expressed Beclin1-binding partner that is involved in PI(3)P production. It has been found on late endosomes/lysosomes (LELs) [180–182] and on LC3-associated phagosomes (LAPosome) [183]. It harbors several functional domains and forms different complexes [184, 185]. Particularly, its action in different complexes is functionally and genetically separable [186]. On LELs, Rubicon interacts with Beclin1-VPS34 and inhibits its lipid kinase activity, thus decreasing PI(3)P production for autophagy suppression [187]. On LAPosomes, Rubicon interacts with Beclin1-VPS34 and promotes local production of PI(3)P to recruit downstream conjugation systems for immunosuppression [188, 189].

An ancient mutation that causes the deletion of Rubicon FYVE-like domain is linked to autosomal recessive spinocerebellar ataxia (SCAR15) [190, 191]. Mechanistically, it was thought that mislocalization of Rubicon underlies the pathogenesis [192]. However, how the mislocalization causes SCAR15 is unclear. Rubicon depletion even improves autophagy flux and extends lifespan [154, 193]. It has been reported that proteins containing the FYVE domain can bind to PI(3)P [194, 195]. Therefore, we speculate that through PI(3)P binding, Rubicon FYVE-like domain may play a critical role in positioning Rubicon on both LAPosomes and LELs. Moreover, the Rubicon FYVE-like domain is located within the Rubicon homologous region, which interacts with Rab7 [184, 196], whereas Rab7 plays a key role in the conversion of endosomes to autophagolysosomes [197–199] and cholesterol incorporation into LDs [200]. Thus, depletion of the FYVE-like domain may not only cause LAPosome deficiency and inflammation, but also disrupt downstream fusion between LAPosomes and lysosomes and LD formation due to failure of Rab7 coordination. These factors may contribute to SCAR15 pathogenesis.

Fatty Acid 2-Hydroxylase (FA2H)

FA2H is a Ceramide 2-hydroxylase located in the ER membrane [201–204]. It catalyzes hydroxylation at the α C position of the N-acyl chain of sphingolipids [202, 205]. In the nervous system, α -hydroxylated sphingolipids are the most abundant lipids in the myelin sheath [203], and the FA components of sphingolipids are predominantly products of ELOVL4 [170, 172, 173, 206], indicating that both FA2H and ELOVL4 play vital roles in myelination.

FA2H mutations are linked to a complicated form of hereditary spastic paraplegia (SPG35) [207, 208], which is often associated with cerebellar ataxia [209–211]. Interestingly, homozygous mutations of ELOVL4 are also found in patients with spastic paraplegia [165]. It has been shown that in the cerebellum, FA2H products from oligodendrocytes are required for long-term myelin sheath maintenance [212], and their absence causes axonal degeneration [213, 214]. In addition, FA2H can form a complex with proteins that are involved in the biosynthesis and metabolism of cholesterol and AA-derived lipids [215–223]. Thus, we speculate that FA2H deficiency can also cause dyshomeostasis of these lipids. In support of this, loss of the *C. elegans* homologue of FA2H inhibits LD formation [224].

Steroid 5-Alpha-Reductase 3 (SRD5A3)

SRD5A3 is a polyprenol reductase that is necessary for dolichol biosynthesis [225]. Dolichol is the lipid used to build the lipid-linked oligosaccharide precursor, which plays a key role in glycosylation and glycosylphosphatidylinositol (GPI) anchor synthesis [226]. Mutations in SRD5A3 are associated with a new type of CDG characterized by cerebellar ataxia combined with other defects [225, 227, 228].

SRD5A3 is highly expressed in the fetal brain, especially in the cerebellum [227]. *SRD5A3* depletion from the cerebellum causes abnormal granule cell development and motor coordination defects in mice, but only mild N-glycosylation impairment [229]. However, the protein abundance or N-glycosylation level of a subset of glycoproteins with high N-glycans multiplicity per protein decreased [229]. Of note, several proteins described in this review, namely PNPLA6 [61], ELOVL4/5 [171], ABHD12 [105], TMEM30A [230], and NPC1 [231], are N-glycosylated proteins. Thus, impaired glycosylation of these proteins may contribute to *SRD5A3* mutation-induced CDG. Additionally, mutations in several genes involved in GPI anchor synthesis showed reduced myelination and defective Purkinje cell development with progressive ataxia [232–236]. Taken together, these observations demonstrate that N glycosylation disruption and GPI anchor synthesis deficiency can cause developmental impairment of cerebellar granule or Purkinje cells, thereby leading to cerebellar ataxia. Thus, clarification of these signaling pathways may help in the design of new therapeutic strategies for related disorders. For example, glycosylation inhibition can reduce cholesterol accumulation in *NPC1* knockout cells [237].

Genes Involved in Lipid Scrambling or Flip/Flop

Flippase/floppase and scramblase are involved in the heterogeneous distribution of lipids [238–240]. In this section, we review two of these genes that are involved in lipid flip-flopping and are closely related to cerebellar ataxia.

Transmembrane Protein 16 k (TMEM16K)

The TMEM16 family consists of ten integral membrane proteins that have diverse functions and are implicated in several human diseases [241–245]. TMEM16K is a Ca^{2+} -regulated phospholipid scramblase mainly located in the ER [246, 247]. It is highly expressed in the cerebellum and cerebral cortex [248]. Mutations in TMEM16K are linked to autosomal recessive cerebellar ataxia type 3 (ARCA3) [249–252].

Phospholipids are synthesized and deposited asymmetrically on the cytoplasmic surface of the ER [253, 254]. While the flippase/floppase establishes and maintains the asymmetric membrane structure, the scramblase disrupts the asymmetric status [240, 255–257]. It has been shown that TMEM16K and three G-protein-coupled receptors (GPCRs) mediate phospholipid scrambling in the ER membrane [246, 247, 258, 259], and these scramblases are able to scramble all common phospholipids [260, 261]. Interestingly, lipid disequilibrium in the ER membrane is closely related to ER stress [77, 78] and Ca^{2+} homeostasis [262, 263]. Consistent with this, all three GPCR scramblases can cause ER stress and apoptosis when they are dysfunctional [264–266], suggesting that TMEM16K mutants probably cause ARCA3 through the same mechanism. Indeed, TMEM16K defects result in deranged Ca^{2+} signaling [267] and Purkinje cell dysfunction [248, 251, 268]. It is notable that phospholipid disequilibrium of the ER membrane not only causes deranged Ca^{2+} signaling [267], but also LD dyshomeostasis [269, 270], both of which may contribute to ER stress and ultimately lead to cell death [271].

Transmembrane Protein 30A (TMEM30A)

TMEM30A is an accessory subunit of the heteromeric P4-ATPase complex [272–274]. The human genome encodes 14 members of P4-ATPases, which catalyze the translocation of aminophospholipids across cell membranes to establish phospholipid asymmetry [275, 276]. Some P4-ATPases translocate PS and PE, whereas others are selective for PC

[276–279]. Interestingly, the substrate preference of different P4-ATPase members is mainly determined by the accessory subunit, whereas the translocon is formed by transmembrane domains of P4-ATPases [276].

Among the three known accessory subunits, TMEM30A is the most widely expressed and forms a heteromeric complex with 11 of the 14 mammalian P4-ATPases [273, 274]. In particular, TMEM30A can form a complex with ATP8A2 and transports PS and PE across the membrane [230, 280, 281]. Deletion of TMEM30A from mouse cerebellar Purkinje cells was shown to cause early onset cerebellar ataxia [282], while ATP8A2 mutations are associated with CAMRQ syndrome characterized by cerebellar ataxia and quadrupedal locomotion [283–285]. Interestingly, although ATP8A2 is most abundant in the cerebellum, it is not expressed in Purkinje cells, but is expressed in deep cerebellar nuclei [282]. Thus, although both ATP8A2 and TMEM30A deficiencies cause cerebellar ataxia, the underlying cellular mechanisms differ. However, at the molecular level, both mutants cause phospholipid dyshomeostasis, especially loss of PS asymmetry on the plasma membrane, which can cause cell death [286, 287]. Additionally, since TMEM30A is involved in ER exit and proper targeting of several P4-ATPases [230, 282, 288], its dysfunction can cause accumulation of related P4-ATPases in the ER, thereby leading to ER stress. Indeed, in the absence of TMEM30A, the expression levels of CHOP and BiP are elevated in Purkinje cells prior to visible cell loss [282]. Taken together, both lipid dyshomeostasis and proteotoxicity may contribute to the pathology of the disease.

Genes Involved in Lipid Trafficking

In eukaryotic cells, the bounding membrane of each organelle possesses a characteristic lipid composition, which is required for its identity and function. Therefore, lipids that are synthesized at the ER or taken up from outside of the cell must be transported to various subcellular membranes or locations for their unique functions [289–291]. Thus far, there are two known routes for lipid transfer, namely vesicular and non-vesicular pathways [292–295]. Here, we highlight the genes that are involved in lipid trafficking and are related to cerebellar ataxia.

Sorting Nexin 14 (SNX14)

Sorting nexins are a large group of proteins, all of which contain a phosphoinositide-binding PX domain [296–298]. Based on its molecular structure, SNX14 is divided into the RGS-PX subfamily [299]. It is an ER transmembrane

protein highly expressed in the cerebellum [300, 301]. In the Hungarian Vizsla dog breed, a splice donor site mutation of *SNX14* is linked to progressive cerebellar ataxia [302]. In humans, its mutations cause pediatric-onset autosomal-recessive cerebellar ataxia and intellectual disability syndrome, namely SCAR20 [252, 303–305].

SNX14 is reportedly required for the correct flux and storage of neutral lipids among the ER, lysosomes, and LDs [301, 306], and autophagic dysfunction is thought to be involved in the pathogenesis of SCAR20 [307–309]. However, although the yeast homolog of *SNX14* was able to link ER to both vacuole and LDs [310, 311], *SNX14* only connects ER with LD [301, 306]. At the ER-LD junction, it controls lipid flux from the ER into LD [301, 306, 310–317]. However, it is unknown how autophagy is affected by *SNX14*.

Failure to package excess lipids into LDs is known to cause lipotoxicity [318, 319]. This mechanism most probably underlies SCAR20. Although the brain displays low levels of LDs under resting conditions [320], there are still many neuronal diseases that are related to LD dysfunction [321–325]. In particular, the neutralization of GRAF1, a GTPase-activating protein that is enriched in Purkinje cells at LD junctions and promotes LD clustering and growth, is associated with subacute cerebellar ataxia [192, 193]. Thus, LD dyshomeostasis may play a critical role in the pathogenesis of SCAR20. As for the autophagic dysfunction under *SNX14* deficiency, this may be caused by coupling disorders between LDs and lysosomes [326, 327].

Niemann-Pick Type C Protein 1 (NPC1)

NPC1 is a large polytopic transmembrane protein of LELs, which is critical for cholesterol trafficking from LELs to the ER, Golgi, and plasma membrane [328–331]. Mutations in the *NPC1* gene can cause cholesterol and glycosphingolipid overload in LELs [146, 332], which can eventually result in NP-C characterized by cerebellar Purkinje cell degeneration [333, 334] and cerebellar ataxia [335, 336]. Although in NP-C, microglia, oligodendrocytes, and GABAergic interneurons are all involved and contribute to Purkinje cell degeneration [337–343], it is believed that autonomous factors cause the susceptibility of Purkinje cells to *NPC1* deficiency [338]. However, thus far, the mechanism of this selective vulnerability is unclear.

In the brain, the blood–brain barrier restricts cholesterol in plasma from entering the CNS, therefore, cholesterol must be synthesized locally to meet the demand [344–346]. During development, oligodendrocytes synthesize large quantities of cholesterol for myelination; in adults, glial cells (mostly astrocytes) account for the steady-state production of cholesterol [347], with many proteins involved in the transportation from glia to neurons [331, 348–358].

Inside the cell, both vesicular and non-vesicular pathways operate in parallel to deliver cholesterol from LELs to ER [331, 359, 360]. Among them, *NPC1* forms two bridges at the membrane contact sites (MCSs) between LEL and ER to regulate cholesterol egress [360–362], implying that *NPC1* deficiency may lead to a defect in cholesterol delivery at MCSs, which can lead to its accumulation in LELs and simultaneous paucity in the ER.

The unavailability of cholesterol in the ER leads to its impaired esterification [358] and hydroxylation [363–366], which in turn will affect its incorporation into LDs [200] and its turnover [367]. In particular, the cytochrome P450 hydroxylases of both *NPC1* deleted mice and NP-C patients become defective in a cerebellum-specific manner [368–370]. Intriguingly, in *SCA2* and *SCA3*, *CYP46A1* also becomes defective, and delivery of *CYP46A1* to the cerebellum can prevent Purkinje cell loss and cerebellar atrophy [371]. Coincidentally, both *CYP46A1* delivery to *SCA3* mice and 14,15-EET (a cytochrome P450 metabolite) treatment of NP-C mice strongly improves autophagic flux [369, 371, 372]. Taken together, these findings suggest that *CYP46A1* defects and resultant metabolite dyshomeostasis contribute to NP-C disorder, possibly through autophagic dysfunction, and they can serve as promising therapeutic targets for cerebellar ataxia. Notably, it has been reported that Ca^{2+} , eCB, and other signaling pathways also contribute to NP-C pathogenesis [373–375]. These may be downstream or side effects of cytochrome P450 deficiency, which require further verification.

Vacuolar Protein Sorting 13 Homolog D (VPS13D)

VPS13D belongs to the *VPS13* protein family, which consists of four members (*VPS13A–D*) in eukaryotic cells, and a group of ubiquitously distributed and highly conserved proteins with phospholipid binding properties [376–380]. Mutations in each of the four members can cause movement disorders, among which *VPS13D* deficiency causes either autosomal recessive spinocerebellar ataxia-4 (*SCAR4*) [381–384], or hereditary spastic paraplegia (*HSP*) [384–386], both are characterized by cerebellar ataxia. Thus far, the underlying mechanism is poorly understood.

VPS13A and *VPS13C* reportedly participate in the transfer of phospholipids between the ER and other organelles in a non-vesicular manner [387]. Interestingly, although *VPS13A*, *VPS13C*, and *VPS13D* show high similarity [376], *VPS13D* does not have the predicted FFAT motif [388], which is responsible for the binding of *VPS13A* and *VPS13C* to VAP on the ER membrane [389], implying that *VPS13D* is not located at the MCSs between the ER and other organelles. Recently, *VPS13D* has been shown to be necessary for both mitochondrial dynamics and clearance. Surprisingly, *VPS13D* did not show clear

localization with mitochondrial markers, but co-localized with the lysosomal marker LAMP1 [390], while reduced phosphorylation at S2429 disrupted autophagy flux [391]. Crucially, VPS13D, with decreased phosphorylation at S2080/S2435 and increased phosphorylation at S15, targeted LDs [392]. Overall, it appears that the localization and subcellular rearrangement of VPS13D to lysosomes and LD membranes are involved in the phospholipid exchange between lysosomes and LDs, which may be tightly related to mitochondrial dynamics and clearance [393, 394]. Consistent with this, it was newly reported that loss of VPS13D in *Drosophila* larval motoneurons does not prevent mitophagy initiation, but causes the accumulation of mitophagy intermediates in cell bodies [395]. In addition, it has been shown that LD plays an essential role in autophagic flux, and autophagosomes appear to form in and around LDs [326, 327]. Thus, VPS13D deficiency may cause autophagic dysfunction by affecting lysosome and LD status. In agreement with this, a disease-causing mutation (N3521S) in the VAB domain of VPS13D blocks its membrane recruitment via adaptor binding [396].

SCY1-Like 1 (SCYL1)

SCYL1 is a widely expressed and catalytically inactive protein kinase [397]. In the CNS, it is confined to the perikarya of neurons, most prominently in the cerebellar Purkinje cells [397]. In mice, mutations in SCYL1 cause a recessive form of spinocerebellar neurodegeneration characterized by Purkinje cell loss and cerebellar atrophy [398]. In humans, its dysfunction causes SCAR21 characterized by cerebellar ataxia and atrophy in early childhood [399, 400]. Mechanistically, SCYL1 dysfunction has been shown to cause defects in both the nuclear pore [398, 401] and COPI complexes [402, 403]. Interestingly, mutations in the gene encoding the δ subunit of the COPI complex also caused Purkinje cell degeneration [404].

Interestingly, the COPI complex is involved in the maintenance of lipid homeostasis [405, 406]. Arf1/COPI proteins can directly localize to LDs and change the content of phospholipids in the LD membrane and thereby LD surface tension [407, 408]. Variations in LD surface tension affects not only the formation of ER-LD bridges, but also the recruitment of enzymes for lipid synthesis [407, 408]. Particularly, COPI together with a guanine nucleotide exchange factor recruits Rab18 to LD [409]. However, Rab18 has been shown to play a key role in LD growth and in maintaining ER-LD contact [410]. Taken together, these observations indicate that SCYL1 dysfunction may cause SCAR21 by inducing LD dyshomeostasis.

Calcium and Lipid Dyshomeostasis

The inositol 1,4,5-triphosphate receptors (ITPRs) are calcium release channels located in the ER membrane [411–413]. In mammals, there are three ITPR subtypes (ITPR1–3) [414, 415]. ITPR1 is the major subtype in the CNS and is predominantly concentrated in the cerebellar Purkinje cells [416–419]. Its mutations can cause Purkinje cell malfunction [420, 421], and are associated with several human disorders characterized by cerebellar ataxia [422–429]. Although, it is well documented that their pathogenesis is closely related to aberrant Ca^{2+} homeostasis [422, 424, 430, 431], the underlying pathogenic mechanism has not been well defined.

Intriguingly, ITPR1 is physically associated with STARD13 [432–435], which was found to be a lipid binding protein located in proximity to LDs overlapping with mitochondria [436]. STARD13 participates in both synthesis and transfer of phospholipids [436, 437], suggesting that Ca^{2+} signaling and lipid homeostasis are closely coupled with each other. In line with this, ITPR1 depletion caused lipid dyshomeostasis in both *Drosophila* and mice [438, 439]. Additionally, Ca^{2+} downregulation in the ER via calreticulin deletion increases lipid synthesis via the SCAP-SREBP signaling pathway [440], while Ca^{2+} upregulation in the ER via TMCO1 deletion reduces the number of LDs and the TAG content through ER stress-associated degradation of diacylglycerol acyltransferase 2 [441, 442]. Moreover, the ATAXIN2 mutant causing SCA2 binds with ITPR1 and results in deranged Ca^{2+} signaling [32, 443]. In addition, the brain lipidome of SCA2 patients showed prominent abnormalities in ceramide and sphingosine levels, and many enzymes, such as ELOVL4, serine palmitoyltransferase long-chain base subunit 2, and ceramide synthase 2, were affected.

Recently Rodríguez-Pascau et al. found that frataxin (a small mitochondrial protein encoded by nuclear genome) is present in ER-mitochondria associated membranes (MAMs) where it interacts with ITPR1 (IP3R) and GRP75, and that frataxin deficiency causes an impairment in both the ER-mitochondria communication and in the dysregulation of Ca^{2+} homeostasis [444]. Of particular importance, frataxin deficiency leads to Friedreich ataxia (FRDA), the most common hereditary ataxia in humans [2, 445]. Considering that frataxin directly interacts with ITPR1 and that accumulation of LDs and increased lipogenesis have been previously described in fibroblasts of FRDA patients, cardiomyocytes of mice and glial cells of *Drosophila* [446–448], it is conceivable that ITPR1-mediated signals may contribute to frataxin deficiency-triggered lipid dyshomeostasis together with other mechanisms [449, 450], which probably also occur in Purkinje and other cerebellar cells. In line with this notion, frataxin (like ITPR1)

Table 1 Proteins implicated in lipid homeostasis and cerebellar ataxia. Overview of the proteins, their targets, and the related disorders. Eighteen proteins were divided into five groups according to their functions. All proteins are involved in maintaining lipid homeostasis

Classification	Protein	Target molecules	Disease	Cell type	References
Lipid Lipogenesis or lipolysis	PNPLA6	PC; LPC	Cerebellar Ataxia	Purkinje cell	Wiethoff et al., 2017
	ABHD12	2-AG; LPS	PHARC	Purkinje cell and microglia	Fiskerstrand et al., 2010; Blankman et al., 2013
	GBA2	GlcCer; GalCer	SPG46; MSS	Purkinje cell	Martin et al., 2013; Hammer et al., 2013
	ELOVL4	VLC-SFA; VLC-PUFA	SCA34	Purkinje cell & other neurons	Cadieux-Dion et al., 2014; Ozaki et al., 2015
	ELOVL5	VLC-PUFA	SCA38	Purkinje cells & other neurons	Di Gregorio et al., 2014
	Rubicon	PI(3)P	SCAR15	Ubiquitous	Assoum et al., 2010; Seidahmed et al., 2020
	FA2H	α -hydroxylated FAs	SPG35	Oligodendrocyte	Edvardson et al., 2008; Rattay et al., 2019
	SRD5A3	dolichol	CDG	Granule cell & Purkinje cell	Cantagrel et al., 2010; Kasapkara et al., 2012
lipid scrambling or flip/flop	TMEM16K	Phospholipids	SCAR10 (ARCA3, ATX-ANO10)	Purkinje cell	Vermeer et al., 2010; Nanetti et al., 2019
	TMEM30A	PS; PE	Cerebellar ataxia	Purkinje cell	Yang et al., 2018
Lipid trafficking	SNX14	ACSL3;TAG; phospholipids	SCAR20 (ATX-SNX14)	Ubiquitous	Thomas et al., 2014; Shukla et al., 2017
	NPC1	Cholesterol; Sphingolipids	NP-C	Purkinje cell Oligodendrocyte	Vanier, 2010
	VPS13D	PS; PE	SCAR4; HSP	Microglia Ubiquitous	Seong et al., 2018; Koh et al., 2020
	SCYL1	Phospholipids	SCAR21	Purkinje cells & other neurons	Schmidt et al., 2015; Shohet et al., 2019
Calcium and lipid	ITPR1	PG, TAG	SCA15/16; SCA29	Purkinje cell	Gerber et al., 2016; Van de Leemput et al., 2007; Zambonin et al., 2017; van Dijk et al., 2017
UPR/ERAD and lipid	SEL1L	LDLR; HMGCR; LPL	Cerebellar ataxia	Ubiquitous	Kyöstilä et al., 2012; Sha et al., 2014;
	DNAJC3& BAP/Sil1	DAG; SCD1; FASN	Cerebellar ataxia; MSS	Ubiquitous	Kizhakkedath et al., 2018; Bobrovnikova-Marjon et al., 2012; Bobrovnikova-Marjon et al., 2008

PNPLA6 patatin-like phospholipase domain-containing protein 6; *ABHD12* α/β -hydrolase domain containing 12; *GBA2* β -glucosidase 2; *ELOVL4* elongation of very long chain fatty acids-like 4; *ELOVL5* elongation of very long chain fatty acids-like 5; *Rubicon* (*RUBCN*) run domain- and cysteine-rich domain-containing beclin-1-interacting protein; *FA2H* fatty acid 2-hydroxylase; *SRD5A3* steroid 5- α -reductase 3; *TMEM16K* transmembrane protein 16 K; *TMEM30A* transmembrane protein 30A; *SNX14* sorting nexin 14; *NPC1* Niemann-Pick type C protein 1; *VPS13D* vacuolar protein sorting 13 homolog D; *SCYL1* SCY1-like 1; *ITPR1* inositol 1,4,5-triphosphate receptor subtype 1; *SEL1L* suppressor of lin12-like; *DNAJC3* DNAJ/HSP40 homolog, subfamily c, member 3; *BAP* BIP-associated protein; *PC* phosphatidylcholine; *LPC* lysophosphatidylcholine; *2-AG* 2-arachidonoyl glycerol; *PS* phosphatidylserine; *LPS* lysophosphatidylserine; *PE* phosphatidylethanolamine; *PG* phosphatidylglycerol; *GlcCer* glucosylceramide; *GalCer* galactosylceramide; *VLC-SFA* very long chain saturated fatty acid; *VLC-PUFA* very long chain polyunsaturated fatty acid; *PI(3)P* phosphatidylinositol-3-phosphate; *TAG* triacylglycerol; *DAG* diacylglycerol; *ACSL3* long chain fatty acyl-CoA ligase 3; *LDLR* low-density lipoproteins receptor; *HMGCR* 3-hydroxy-3-methylglutaryl-coenzyme A reductase; *LPL* lipoprotein lipase; *SCD1* stearoyl-CoA desaturase 1; *FASN* fatty acid synthase; *PHARC* polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract; *SPG46* autosomal recessive spastic paraplegia-46; *MSS* Marinesco-Sjogren syndrome; *SCA34* spinocerebellar ataxia-34; *SCA38* spinocerebellar ataxia-38; *SCAR15* autosomal recessive spinocerebellar ataxia-15; *SPG35* autosomal recessive spastic paraplegia-35; *CDG* congenital disorder of glycosylation; *SCAR10* autosomal recessive spinocerebellar ataxia-10; *SCAR20* autosomal recessive spinocerebellar ataxia-20; *NP-C* Niemann-Pick disease type C; *SCAR4* autosomal recessive spinocerebellar ataxia-4; *HSP* hereditary spastic paraplegia; *SCAR21* autosomal recessive spinocerebellar ataxia-21; *SCA15/16* spinocerebellar ataxia-15/16; *SCA29* spinocerebellar ataxia-29

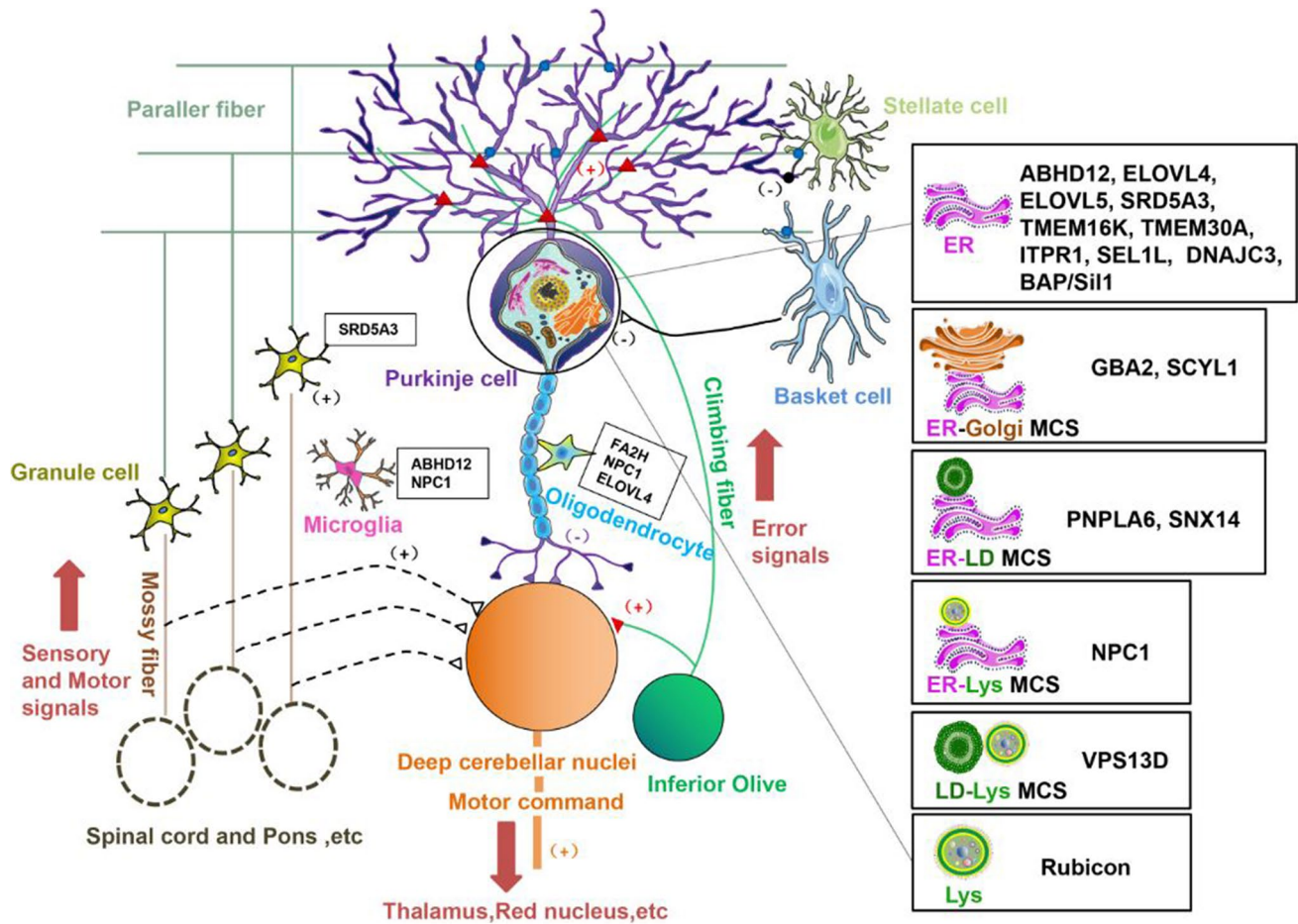


Fig. 2 Schematic illustration of the molecules involved in lipid homeostasis and cerebellar ataxia and their localization in Purkinje cells. In total, 18 molecules involved in cerebellar lipid homeostasis are illustrated. Except FA2H, all molecules are expressed in Purkinje cells. In addition, NPC1 in microglia and oligodendrocytes, ELOVL4 in oli-

godendrocytes, ABHD12 in microglia, and SRD5A3 in granule cells, are also abundant. In Purkinje cells, molecular localization is shown, indicating that most are located in the ER membrane or at MCSs between ER and other organelles

is highly expressed in cerebellar Purkinje neuron and large principal neurons of dentate nuclei (DN) [451]. Moreover, the neurological symptoms of Friedreich ataxia have been shown to be a consequence of lesions in the dentate nuclei (DN) and Purkinje cells of the cerebellum as well as degeneration of the large sensory neurons of the dorsal root ganglia and of the spinocerebellar tracts [445, 452]. Collectively, it seems that ITPR1 may affect the lipid landscape through several different pathways. Conversely, the ITPR1 function is also regulated by surrounding lipids [262, 453–461]. Overall, Ca^{2+} and lipid dysregulation may act in a synergistic manner to contribute to ataxic pathogenesis and result in neuronal cell death and cerebellar atrophy.

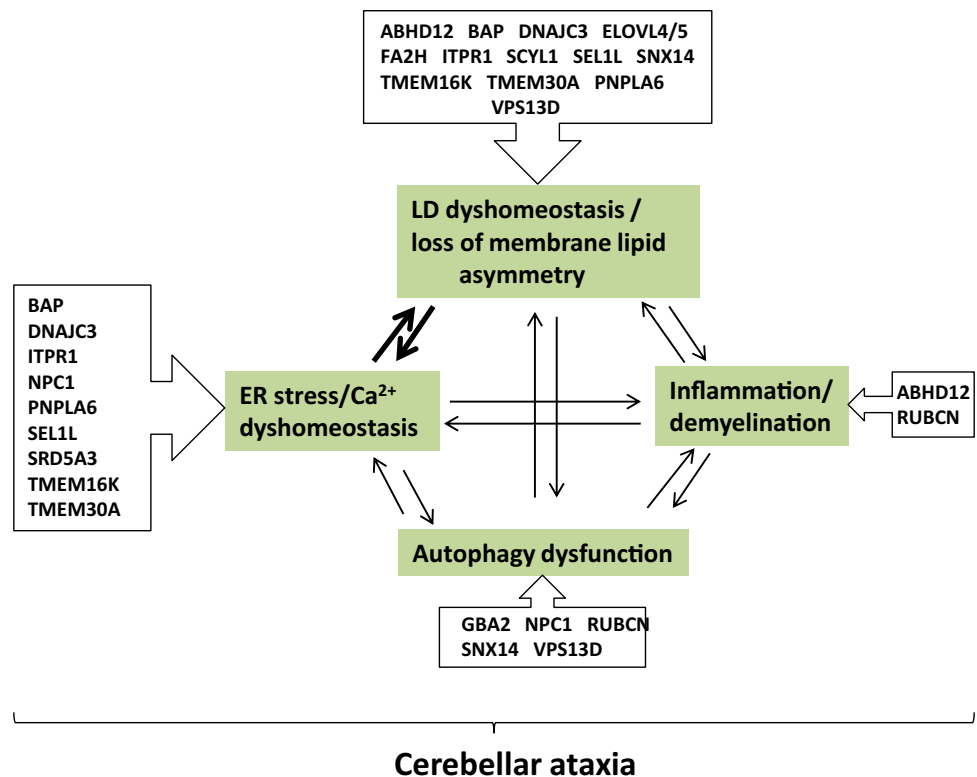
Unfolded Protein Response (UPR)/Endoplasmic Reticulum-Associated Protein Degradation (ERAD) and Lipid Dyshomeostasis.

Studies have shown that both UPR and ERAD are essential for maintaining lipid homeostasis [77, 462, 463]. While lipid

bilayer stress can activate all three branches of UPR transducers (IRE1 α , PERK, and ATF6) to buffer lipid imbalance [78, 464–467], ERAD is responsible for degrading many enzymes involved in lipid synthesis, degradation, and secretion [42]. In particular, ERAD is responsible for the degradation of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), adipose triglyceride lipase (ATGL) [468–472], and proteins from ER to LD [473]. All these are crucial for maintaining LD homeostasis. Additionally, ERAD is responsible for COX2 degradation, which plays a critical role in eCB hydrolysis and PGE2 production [474, 475], and for ITPR1 degradation [476–481], which is involved in lipid metabolism through Ca^{2+} mobilization [438, 439].

Furthermore, several components of the ERAD or UPR machinery have been linked to cerebellar ataxia. SEL1L deficiency leads to a canine progressive early-onset cerebellar ataxia [482, 483]. Loss-of-function mutations in DNAJC3 and BAP cause multisystemic neurodegeneration

Fig. 3 Possible pathological mechanisms of cerebellar ataxia caused by gene defects related to lipid imbalance. These gene defects mainly lead to four closely related pathological processes, namely LD dyshomeostasis, ER stress, Autophagy dysfunction and Inflammation. In particular, most of them cause LD dyshomeostasis and ER stress, suggesting ER-LD system is a key target for the treatment of cerebellar ataxia



and Marinesco-Sjögren syndrome, respectively [484–487]. SEL1L, which forms the ERAD complex with HRD1 and is involved in the degradation of LDLR and HMGCR [468–470, 488], forms another complex with lipoprotein lipase (LPL) and lipase maturation factor 1, which is essential for the secretion of LPL [482]. DNAJC3 and BAP form a complex with HSPA5 [489–491], which plays a key role in lipid metabolism [492–495] by interacting with the ER stress transducers and SREBP-SCAP complex [494–497]. In particular, DNAJC3 can directly bind and inhibit PERK [491, 498]. Interestingly, PERK harbors intrinsic lipid kinase activity, which favors the conversion of DAG to PA [499]. Furthermore, PERK inhibition can reduce stearyl-CoA desaturase 1 and fatty acid synthase expression [500]. Overall, these observations clearly indicate that URP and ERAD are both promising therapeutic targets for cerebellar ataxia.

Conclusion

We hypothesize that cerebellar Purkinje cells are especially susceptible to abnormal turnover of a subset of lipids. Most related genes are highly expressed in Purkinje cells, which may explain why Purkinje cells are more susceptible to lipid dyshomeostasis caused by their defects. Although some genes are ubiquitously expressed, it has been suggested that distinct cells may have different compensatory functions

for their defects [485]. This may be the case for Purkinje cells due to their complicated dendritic trees and long myelinated axons. These lipids mainly include PC/LPC, PS/LPS, PI(3)P, cholesterol, sphingolipids, VLCFAs, cannabinoids, and dolichol, and more than a dozen genes are involved in or closely related to their synthesis, degradation, storage, and distribution (Table 1). Crucially, the dysfunction of these genes or the lipid imbalances they induce are closely related to ER stress, autophagy, or inflammation/demyelination, which may eventually lead to cell death and cerebellar ataxia. Intriguingly, all but two of the proteins encoded by these genes are located in the ER membrane or other organelles, particularly at the MCSs between the ER and lysosome, LD, and Golgi (Fig. 2). The other two proteins are located in the ER lumen, but are also closely related to the regulation of ER membrane proteins in lipid metabolism. Lipid synthesis, deposition, distribution, and degradation are generally in the same streamline. In particular, many of these proteins are involved in or closely related to the maintenance of LD homeostasis, indicating that LD dyshomeostasis plays a key role in the pathogenesis of ataxic disorders. LDs are derived from the ER and encounter the ER and many other organelles. Accumulating evidence shows that LDs are not limited to the inert storage of excess lipids, but also dynamically participate in many cellular functions. Therefore, in addition to their roles in ER stress, autophagy, and inflammatory processes, LDs may play important roles in Purkinje cells (Fig. 3), which requires further investigation. Overall,

our review implies that the ER-LD system is the core facility for maintaining lipid homeostasis in cerebellar Purkinje cells, and its defects, caused by dysregulation of many lipid species, can lead to cerebellar ataxia. We believe that these findings will provide a valuable reference for future diagnosis and treatment of ataxic disorders.

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Code Availability Not applicable.

Declarations

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Conflict of Interest The authors declare no competing interests.

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