

# Myelin lipid metabolism and its role in myelination and myelin maintenance

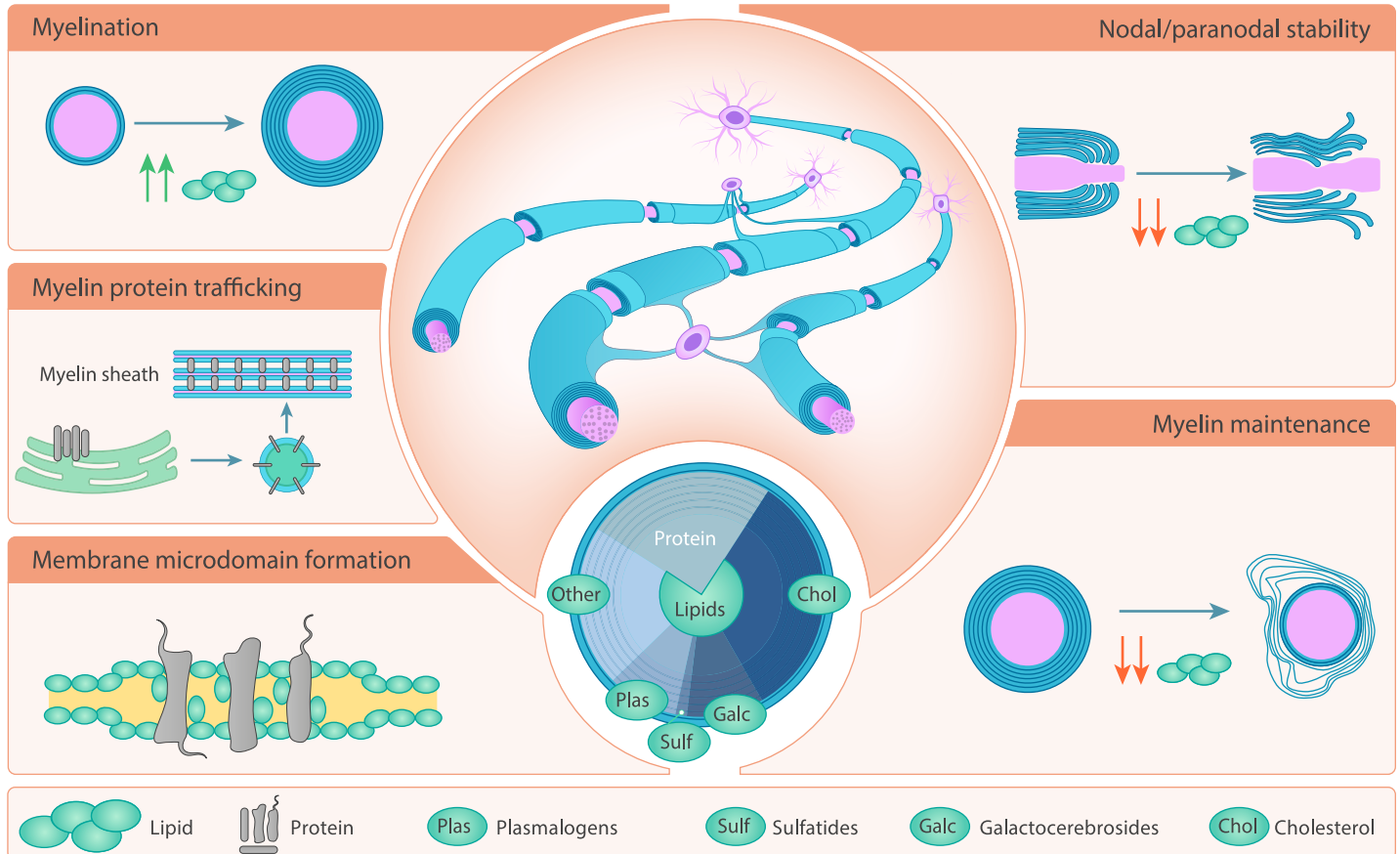
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## GRAPHICAL ABSTRACT



## PUBLIC SUMMARY

- Myelin is an electrical insulator required for rapid nerve conduction.
- Myelin is lipid-rich and has a unique lipid composition.
- Disruption of lipid metabolism adversely affects myelin homeostasis.
- Targeting lipid dysmetabolism could help address disease-associated myelin loss.



# Myelin lipid metabolism and its role in myelination and myelin maintenance

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Myelin is a specialized cell membrane indispensable for rapid nerve conduction. The high abundance of membrane lipids is one of myelin's salient features that contribute to its unique role as an insulator that electrically isolates nerve fibers across their myelinated surface. The most abundant lipids in myelin include cholesterol, glycosphingolipids, and plasmalogens, each playing critical roles in myelin development as well as function. This review serves to summarize the role of lipid metabolism in myelination and myelin maintenance, as well as the molecular determinants of myelin lipid homeostasis, with an emphasis on findings from genetic models. In addition, the implications of myelin lipid dysmetabolism in human diseases are highlighted in the context of hereditary leukodystrophies and neuropathies as well as acquired disorders such as Alzheimer's disease.

## INTRODUCTION

Myelin is a lipid-rich, multilamellar membrane that insulates axons and enables an ion channel configuration necessary for saltatory action potentials that markedly enhance nerve conduction velocity (Figures 1A and 1B).<sup>1,2</sup> In the central nervous system (CNS), myelin primarily forms postnatally and is produced by multiprocessed, neuroepithelium-derived oligodendrocytes (OLs). OL numbers peak in early life and are highly stable during the human lifespan, yet new OLs continually arise and initiate adaptive myelination throughout adulthood.<sup>3–5</sup> In the peripheral nervous system (PNS), large-caliber (>1  $\mu$ m) axons are myelinated by neural crest-derived Schwann cells (SCs), whereas small-caliber axons are wrapped by non-myelinated SCs, which form the bundles of Remak.<sup>6</sup> Similar to OLs, SC-mediated myelination occurs postnatally; moreover, once established, SC numbers are stable with minimal cell turnover.<sup>7,8</sup>

Among the biochemical properties unique to myelin compared with other cell membranes is the relatively high ratio of lipids to proteins, as more than 70% of myelin consists of lipids.<sup>9–11</sup> In contrast to myelin proteins, many of which are myelin specific, myelin lipid species are non-specific; however, the myelin lipid composition is distinctive, with a characteristic overrepresentation of cholesterol, galactocerebroside (GalC), sulfatides, and plasmalogens (Figure 1C).<sup>12,13</sup> Great strides have been made in deciphering the role of myelin-specific proteins and their contribution to health and disease. Yet various questions involving myelin lipids remain unaddressed, particularly regarding the contribution of lipid metabolism to myelin maintenance, as well as the underlying molecular determinants of myelin lipid homeostasis. This review aims to help bridge this gap of knowledge by addressing past and recent discoveries associated with the function of myelin lipid metabolism in both the CNS and the PNS, summarizing their known molecular determinants, and addressing the relevance to human disease.

## MYELIN LIPIDS: COMPOSITION AND RESPECTIVE ROLES

Myelin lipids are paramount to myelin sheath generation and maintenance. Beyond the structural need inherent in synthesizing immense volumes of myelin membrane, myelin lipids provide the intermolecular forces necessary for myelin anchorage against the axonal membrane and afford a platform for myelin proteins in the form of specialized lipid rafts or microdomains.<sup>14–16</sup> The three lipid classes most abundant in myelin are cholesterol, GalC, and plasmalogens. Here we review their respective roles in myelination as elucidated through genetically engineered mouse models.

## CHOLESTEROL

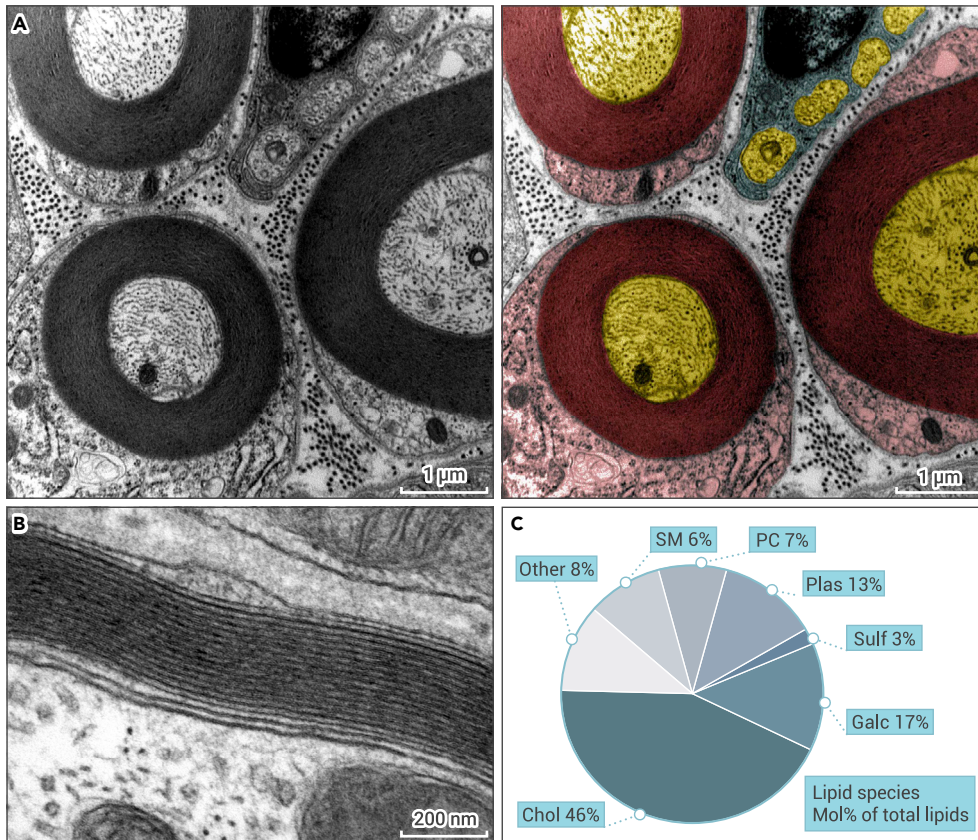
Cholesterol is highly enriched in myelin compared with other cell membranes and is the most abundant lipid in both the CNS and the PNS.<sup>9–11,17</sup> Cholesterol resides within the phospholipid bilayer, where it stabilizes membrane proteins and helps establish the fluidity and permeability of plasma membranes.<sup>14,18</sup> Importantly, cholesterol synthesis and trafficking in myelinating glia have critical functions in myelin development and homeostasis.

### Cholesterol synthesis and import by myelinating glia are necessary for myelination

The significance of cholesterol's role in myelination was first appreciated in seminal studies wherein the rate-limiting enzyme for cholesterol biosynthesis, farnesyl-diphosphate farnesyltransferase 1 (FDFT1) (Figure 2A), was conditionally depleted in myelinating glia using Cre-lox recombination.<sup>19</sup> Despite expressing normal levels of myelin proteins, mice harboring *Cnp-Cre*, *Fdft1*<sup>L/L</sup> alleles were hypomyelinated, with a substantial deficit in brain cholesterol levels.<sup>19</sup> Moreover, the diminished myelination that occurred was attributed to an associated reduction in non-sterol lipid classes, which preserved the cholesterol-to-non-cholesterol lipid ratio in myelin.<sup>19</sup> Interestingly, myelination and motor function in *Fdft1*-knockout mice improved with age, likely through the uptake of exogenous cholesterol from neighboring cells. This robust capability to maintain myelin cholesterol stoichiometry by attenuating non-sterol lipid synthesis and scavenging for extracellular cholesterol highlights the importance of sterols in myelin.<sup>20</sup> As the *Cnp* promoter is active in both OLs and SCs, *Fdft1*-null mutants also displayed significant PNS hypomyelination. In the PNS, cholesterol is required for shuttling the myelin structural protein, P0, from the endoplasmic reticulum (ER) to the myelin membrane.<sup>21,22</sup> Impaired cholesterol synthesis in SCs accompanied a compensatory upregulation of genes responsible for exogenous cholesterol uptake, including *ApoE* and *ApoD*.<sup>22</sup> These findings established a significant role for cholesterol in developmental myelination of both the CNS and the PNS and demonstrated that, although *de novo* cholesterol synthesis is critical, it can be compensated for, at least partially, by environmental sterol uptake.<sup>16,20</sup>

Studies targeting lipid transporters further illuminated the impact of lipid influx on myelination and myelin repair. In adult mice with inducible whole-body depletion of low-density lipoprotein receptor-related protein 1 (LRP1), a cholesterol importer, remyelination was significantly impaired after toxin-induced demyelination (Figure 2B).<sup>23</sup> Inducible and conditional knockout of *Lrp1* in OL precursor cells (OPCs) replicated the remyelination deficits; moreover, depletion of *Lrp1* across the OL lineage led to hypomyelination, indicating that cholesterol uptake specifically by OLs is important to myelin development and repair.<sup>23</sup> Mechanistically, *Lrp1* depletion in OPCs reduced cellular cholesterol and hindered their differentiation to myelinating OLs. Of interest, myelination was partially rescued by dietary cholesterol supplementation.<sup>23</sup>

In addition to lipid transporters, structural myelin proteins have been shown to play a critical role in maintaining myelin cholesterol levels.<sup>16,24</sup> Loss of proteolipid protein (PLP) alone or concomitant with knockout of a homolog glycoprotein, M6B, reduced myelin cholesterol, with the double knockout also causing hypomyelination.<sup>25,26</sup> More recently, one of the major peripheral myelin proteins, peripheral myelin protein 22 (PMP22), was shown to be critical for proper cholesterol homeostasis in myelin via its interaction with and regulation of the cholesterol efflux transporter ATP-binding cassette family protein 1 (ABCA1) in SCs.<sup>27</sup>



**Figure 1. Representative images of myelinated fibers and myelin sheath from mouse nerve** (A) Left: transmission electron micrograph of myelinated and non-myelinated nerve fibers from cross-sectioned mouse sciatic nerve. Right: pseudo-colored overlay of the electron micrograph on the left. Red regions denote the myelin sheath, and yellow regions represent axon fibers. (B) High-magnification micrograph of mouse sciatic nerve to illustrate the multiple layers of myelin membrane that together compose the myelin sheath. (C) Pie chart delineating myelin lipid composition as molar percentage of total lipids as reported for bovine myelin from the CNS.<sup>11,12</sup> Chol, cholesterol; GalC, galactocerebrosides; Sulf, sulfatides; Plas, plasmalogens; PC, phosphatidylcholine phospholipids; SM, sphingomyelin.

### Astrocyte-derived cholesterol complements myelin development and integrity

In search of the major cell types responsible for brain cholesterol levels, Camargo et al. depleted SCAP in astrocytes using *Gfap-Cre*, *Scap<sup>L/L</sup>* alleles.<sup>34</sup> The knockout mice died prematurely with significant motor deficits and substantially reduced brain cholesterol levels. Of interest, however, they exhibited a compensatory uptake of dietary lipids.<sup>34</sup> High-fat diet (HFD) enriched with monounsaturated fatty acids (MUFAs), cholesterol, and saturated fatty acids improved motor function and survival in contrast to either standard diet or HFD enriched for polyunsaturated

fatty acids (PUFAs). Furthermore, deletion of *Scap* at P20 in astrocytes using *Glast-Cre<sup>ERT</sup>*, *Scap<sup>L/L</sup>* mice also induced hypomyelination, further supporting the hypothesis that astrocyte-derived lipids are critical for myelination and myelin maintenance.<sup>35</sup> OL-specific depletion of *Scap* using *Cnp-Cre*, *Scap<sup>L/L</sup>* mutants also caused hypomyelination, although, in contrast to *Gfap-Cre*, *Scap<sup>L/L</sup>* mice, the myelin deficits in OL-specific knockouts improved with age, becoming comparable to controls by late adulthood.<sup>19,34</sup> Finally, relative to knockouts restricted to single lineages, mutants with *Scap* depleted in both astrocytes and OLs (*Cnp-Cre*, *Gfap-Cre*, *Scap<sup>L/L</sup>*) displayed greater hypomyelination and worse survival and were refractory to HFD supplementation.<sup>35</sup>

In summary, myelin is highly dependent on both astrocyte- and OL-derived cholesterol in the CNS; however, whether other astrocyte-derived lipids contribute to myelination and myelin maintenance remains elusive.

### GALACTOCEREBROSIDES AND SULFATIDES

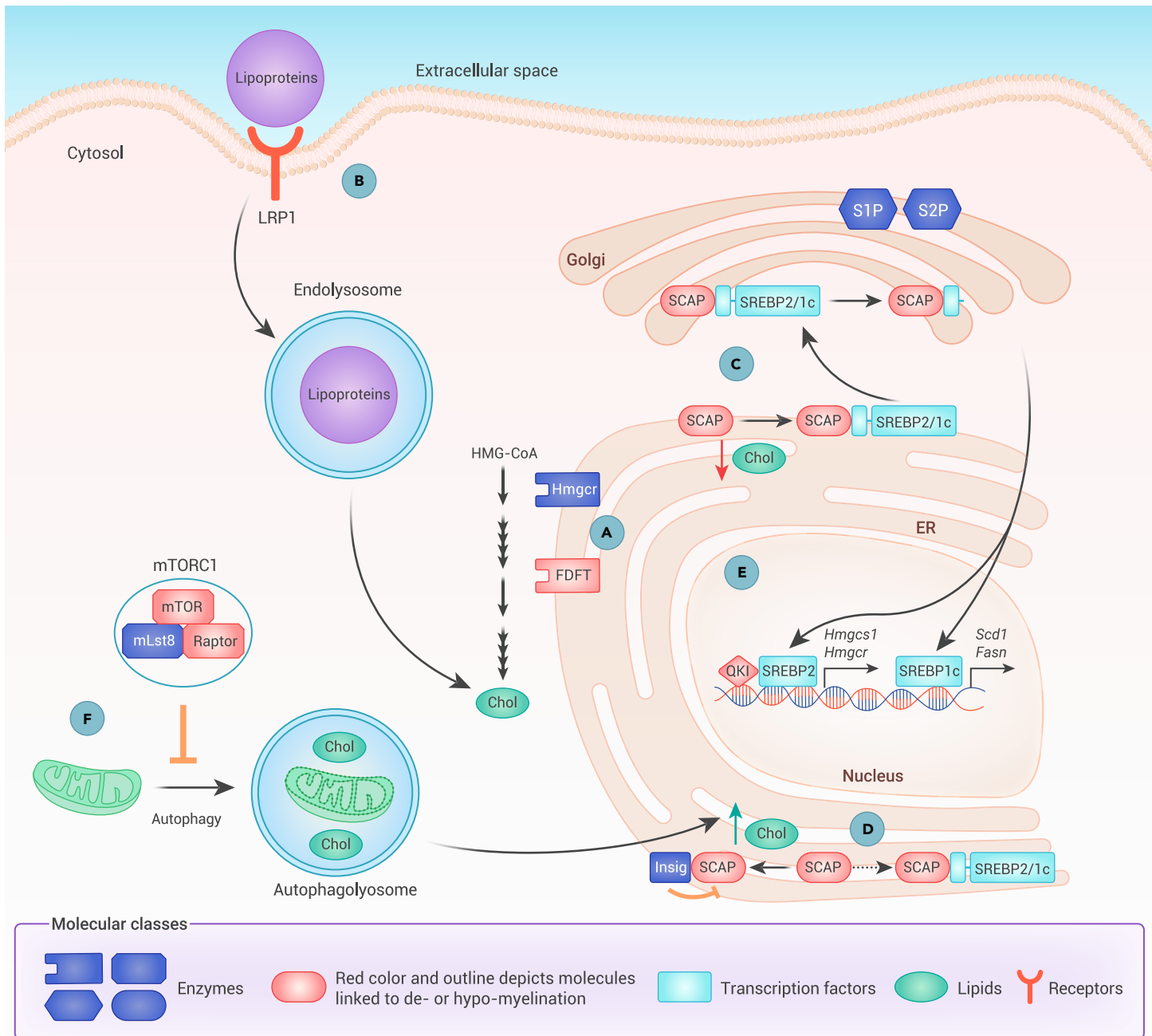
Glycosphingolipids (GSLs) are a major glycolipid subtype that includes GalC and their sulfated form, sulfatides. GSLs are derivatives of ceramide lipids, which consist of a fatty acid attached to a sphingosine backbone and are synthesized in the ER. Galactose is added to a ceramide lipid base to produce GalC, whereas the addition of sulfate to GalC in the Golgi apparatus generates sulfatides (Figures 3A and 3B).<sup>36,37</sup> GalC and sulfatides are abundantly present in myelin<sup>38</sup> and enhance myelin compaction stability through *trans* interactions between apposing lipid bilayers.<sup>39–42</sup> Although not essential for *de novo* myelination, GalC and sulfatides are indispensable for normal myelin structure and long-term myelin stability.<sup>43–46</sup>

### GalC and sulfatides promote myelin maintenance and nodal organization

Despite the relative abundance of GalC and sulfatides in myelin, myelination follows unimpaired, albeit defectively, in mice lacking the GalC-synthesizing enzyme cerebroside galactosyl-transferase (CGT), loss of which blocks GalC and sulfatide production.<sup>44,46</sup> However, by 2 months of age, myelin vacuolization and demyelination occurred in mutants.<sup>43,44</sup> Nerve conductivity in *Cgt*-null mice diminished due to paranodal defects, accompanied by tremors and ataxia.<sup>44</sup> Interestingly, targeted loss of sulfatides through knockout of ceramide sulfotransferase (CST), which impaired sulfatide synthesis while leaving GalC levels intact, evinced a milder phenotype relative to mutants lacking both GalC and sulfatides, possibly indicating a greater role for GalC in myelin sheath compactness and stability.<sup>47,48</sup>

Complementary approaches reinforcing cholesterol's role in myelination have included pharmaceutical and genetic targeting of upstream regulators of cholesterol synthesis. For instance, challenging adult mice with simvastatin, a cholesterol-lowering drug that inhibits sterol synthesis, induced demyelination, reduced mature OL numbers, and decreased OPC differentiation.<sup>28</sup> After cuprizone-mediated demyelination in adult mice, simvastatin treatment also impaired remyelination by lowering mature OL density, possibly by disrupting OPC differentiation or migration.<sup>28</sup> Targeting the master transcriptional regulators of cholesterol metabolism, namely the sterol-response-element-binding proteins (SREBPs), has also been very informative, although a limitation to this approach is the significant cross talk with fatty acid metabolism regulated by SREBPs.<sup>29</sup> SREBP transcription factors were first linked to the PNS when Verheijen et al. demonstrated that myelination onset correlated with upregulation of *Srebp1* and *Srebp2*.<sup>30</sup> Shortly thereafter, Leblanc et al. confirmed that both *Srebp1* and *Srebp2*—as well as their critical regulator, SREBP cleavage-activating protein (SCAP)—were induced during PNS myelination (Figure 2C).<sup>31</sup> Furthermore, PNS myelination was found to be dependent in part on the cooperation between SC differentiation factor EGR2 and SREBPs, which together activated downstream fatty acid and cholesterol biosynthesis gene expression.<sup>31</sup> These findings prompted the use of *Scap* knockouts to interrogate the role of SREBP-mediated sterol metabolism in myelination. Although germline knockout of *Scap* is embryonically lethal, haploinsufficient *Scap*-mutant mice were viable and had up to 30% reduction in brain cholesterol, which was accompanied by behavioral and cognitive defects.<sup>32</sup> Conditional depletion of *Scap* in SCs using *Mpz-Cre*-driven recombination further emphasized the importance of SREBP-mediated sterol and fatty acid metabolism during myelination.<sup>33</sup> In *Mpz-Cre*, *Scap<sup>L/L</sup>* mice, the sciatic nerve was hypomyelinated, and although the myelinated axon percentage recovered with age, reduced myelin thickness persisted.<sup>33</sup> As expected, myelin lipid composition in mutant mice was altered, with an estimated 50% reduction in lipids, accompanied by downregulation of SREBP targets such as *Hmgcr* and *Fasn*.<sup>33</sup> Finally, studies using explanted dorsal root ganglia (DRG) showed that SCAP-mutant DRG neurons had reduced myelination in lipid-free media, which was partially rescued by lipid supplementation.<sup>33</sup> In line with previous work, these findings indicated that extracellular lipid uptake may have supported myelination in *Scap*-mutant nerves.<sup>22</sup>





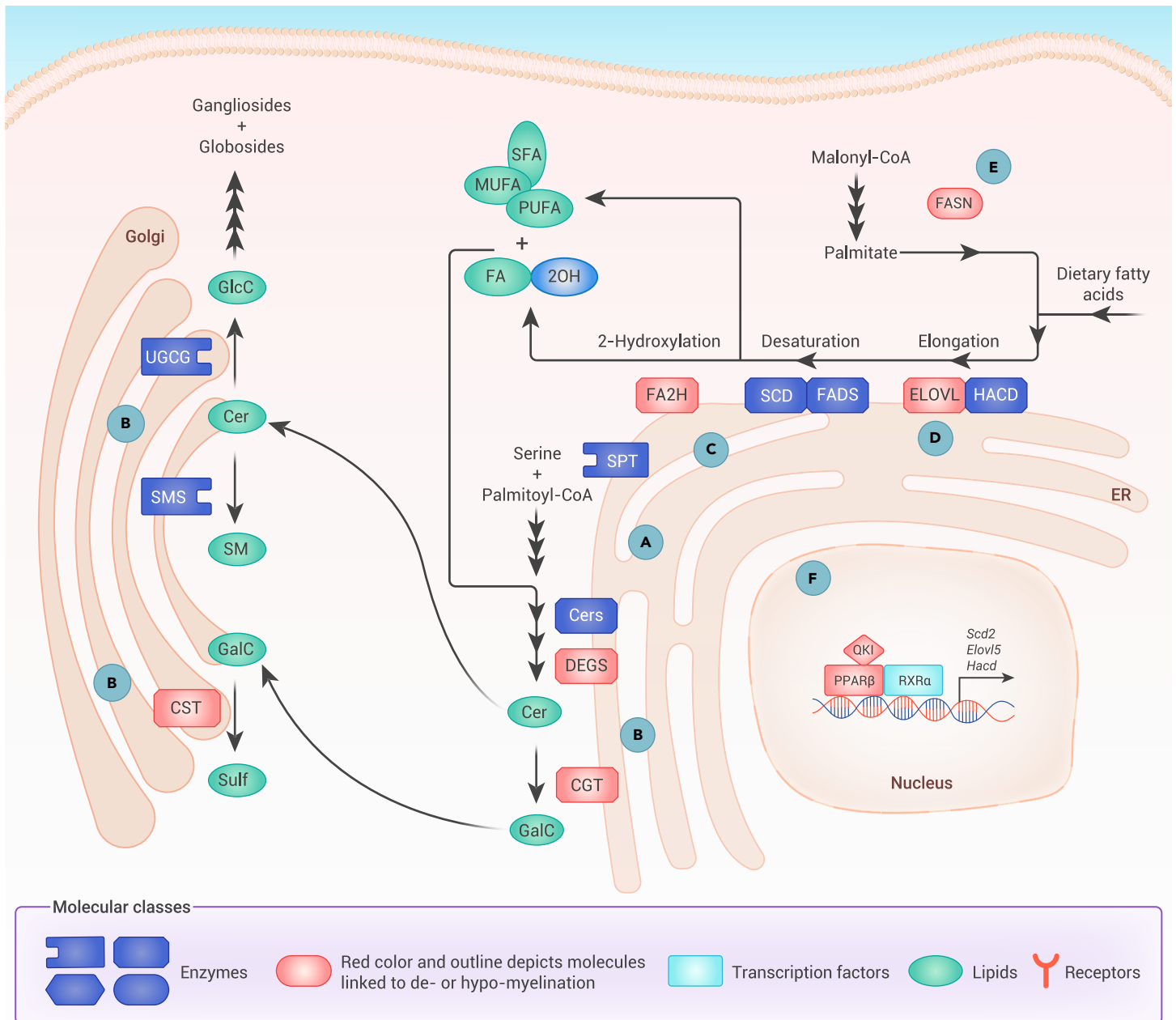
**Figure 2. Cholesterol, sterol-response-element-binding protein (SREBP), and mammalian target of rapamycin (mTOR) pathways necessary in myelination** (A) Farnesyl-diphosphate farnesyltransferase 1 (FDFT1) synthesizes squalene, a key intermediate in cholesterol synthesis. (B) Low-density lipoprotein receptor-related protein 1 (LRP1) enables endocytosis of lipoprotein particles, which deliver exogenous cholesterol. (C) Sterol cleavage-activating protein (SCAP), in response to decreased ER cholesterol, shuttles the SREBPs to the Golgi apparatus for cleavage-mediated activation by site-1 and site-2 proteases (S1P and S2P). (D) Elevated ER cholesterol induces SCAP to associate with and be inhibited by insulin-induced gene protein (Insig), reducing SCAP-mediated SREBP2 activation. (E) Quaking (QKI) is a critical co-activator for SREBP2 in OLs that is necessary for transcription of cholesterol-synthesizing genes. (F) mTOR, regulatory-associated protein of mTOR (Raptor), and mTOR-associated protein, LST8 homolog (mLst8) are subunits of the mTORC1 complex that increase SREBP activity through multiple mechanisms. One reported mechanism includes inhibiting the flux of autophagolysosome-derived cholesterol to the ER and preventing cholesterol-mediated inhibition on SREBP activation. OL, oligodendrocyte.

Nevertheless, sulfatide reduction in *Cst*-null mice precipitated mild demyelination that progressed with age, and by 8 months of age, *Cst*-null mutants demonstrated significant paranodal defects accompanied by hindlimb weakness and tremor. In addition, myelin in *Cst*-null mice demonstrated vacuolar degeneration and aberrant paranodal loops that were aggravated with age. These findings, in line with previous myelin ultrastructural analyses, suggest that sulfatides are necessary for maintaining paranodal junctions.<sup>45,47–49</sup> GalC and sulfatides also contribute to myelin protein expression.<sup>50</sup> In adult *Cst*-null mice, myelin-associated glycoprotein (MAG) and PLP were downregulated, along with neurofascin-155 (NF155), a critical paranodal junction protein.<sup>51,52</sup> Thus, myelin stability and compactness, nodal and paranodal organization, and myelin protein regulation depend on GalC and sulfatide metabolism.<sup>45,47,48,53,54</sup> Finally, whereas ani-

mal studies investigating myelin sphingolipids typically used whole-body knockout, the few available conditional models indicated that myelinating glia are the main producers of myelin sphingolipids, as OL-specific overexpression of *Cgt* was sufficient to rescue late-onset demyelination in *Cgt*-null mice.<sup>55</sup>

## 2-Hydroxylated sphingolipids contribute to myelin stability

2-Hydroxylated fatty acids (2-HF) are common components of both GalC and sulfatides.<sup>56</sup> Fatty acid 2-hydroxylase (FA2H) catalyzes fatty acid hydroxylation for 2-hydroxylated glucosylceramides (HFA-GlcC) and 2-hydroxylated sphingomyelin (HFA-SM) (Figure 3C).<sup>57–59</sup> Of interest, HFA-SM levels were significantly diminished in *Cgt*-null mutants,<sup>43,44</sup> whereas in *Cst*-null mice, HFA-SM levels were unaffected, coinciding with the less severe phenotype relative to *Cgt*-null



**Figure 3. Fatty acid, galactocerebroside, and sulfatide synthesis pathways implicated in myelination and myelin maintenance** (A) Condensation of serine and palmitoyl-CoA by serine palmitoyltransferase (SPT) initiates Cer synthesis, which is then completed through the activity of ceramide synthase (Cers) and dihydroceramide desaturase (DEGS). (B) Ceramide galactosyl-transferase (CGT)-mediated addition of galactose to Cer generates GlcC. Following translocation to the Golgi, addition of sulfate to GlcC by UDP-glucose ceramide glucosyltransferase (UGCG), which can be further glycosylated into complex glycosphingolipids including globosides and gangliosides. (C) Fatty acid 2-hydroxylase (FA2H) catalyzes FA hydroxylation. Hydroxylated FA (2OH-FA) are used as substrates by sphingolipid-synthesizing enzymes to generate hydroxylated sphingolipids. (D) The rich heterogeneity of sphingolipids stems from the multiple species of FA used as substrates for dihydroceramide acylation, including saturated (SFA), monounsaturated (MUFA), and polyunsaturated (PUFA) FA. Elongation of endogenous or diet-derived FA requires fatty acid elongases (ELOVL) and hydroxyacyl dehydratases (HACD). FA desaturation depends on FA desaturases, including FADS and SCD. (E) Fatty acid synthase (FASN) generates palmitate, a principal source for endogenous SFA and MUFA. (F) The nuclear receptors peroxisome proliferator-activated receptor  $\beta$  (PPAR $\beta$ ) and retinoic X receptor  $\alpha$  (RXR $\alpha$ ), following co-activation by quaking (QKI), drive transcription of the FA biosynthesis pathway. FA, fatty acid; Cer, ceramide; GlcC, galactocerebroside; Sulf, sulfatides; GlcC, glucocerebroside.

mutants.<sup>47</sup> To explore the role of 2-hydroxylated sphingolipid species in myelin, *Fa2h* was targeted. *Fa2h*-null mice experienced no impairments during developmental myelination despite notable depletion of 2-hydroxylated sphingolipids in both CNS and PNS myelin.<sup>60</sup> By 18 months of age, however, *Fa2h* knockouts demonstrated severe myelin degeneration and demyelination in both CNS and PNS, accompanied by hindlimb paralysis.<sup>60</sup> Myelinating glia-specific knockout of *Fa2h* using *Cnp-Cre* led to similar late-onset demyelination at age 12 months, specific to the CNS.<sup>61</sup> This model also recapitulated the cerebellar degeneration phenotype observed in the germline *Fa2h* deletion, demonstrating that 2-HF sphingolipids are essential for long-term myelin stability and subsequent motor function.<sup>61</sup> Moreover, these results identified OLs as the main producers of the

2-HF sphingolipids in CNS myelin<sup>61</sup> and emphasized the overall stronger phenotype relative to the PNS, which developed findings only at a later time (18 months).<sup>60</sup>

Initial studies depleting GSL species also noted a subsequent increase in other lipids, such as HFA-GlcC, alluding to potential compensatory mechanisms by other sphingolipid counterparts.<sup>43,44,47</sup> This hypothesis was disputed, however, with the *Cnp-Cre*, *Ugcg*<sup>L/L</sup> knockout model, which depleted glucosylceramides in the OL lineage by deleting UDP-glucose ceramide glucosyltransferase (UGCG) (Figure 3B). Loss of glucosylceramides in CNS myelin led to no observable phenotypes, even in aged mice (age 1.5 years). Of interest, double knockout of *Ugcg* and *Cgt* using *Cnp-Cre*, *Ugcg*<sup>L/L</sup>, *Cgt*<sup>L/L</sup> mutants did not precipitate more

severe demyelination despite the absence of HFA-GlcC in myelin.<sup>62</sup> In addition, germline *Fa2h*<sup>-/-</sup>, *Cgt*<sup>-/-</sup> double-knockout mice in which sulfatides, GalC, HFA-GlcC, and HFA-SM, were reduced by 80%, still formed compact myelin.<sup>63</sup> These mice did not display any dysmyelination by 4 weeks of age, demonstrating that non-hydroxylated sphingolipids are resilient in forming intact myelin despite missing their 2-hydroxylated counterparts.<sup>63</sup>

For future studies, cell-autonomous roles of GSL synthesis enzymes in the context of myelination and myelin maintenance require further elucidation. Moreover, the difference in the strength of observed hypomyelination phenotypes between the CNS and the PNS upon loss of specific GSLs, despite similar overall myelin lipid composition, necessitates detailed comparative analyses of myelin GSL homeostasis between the CNS and the PNS.

## PLASMALOGENS

Most phospholipids are formed through the esterification of fatty acids to a glycerol backbone, forming a diacylglycerol lipid moiety with an attached polar head group. However, an estimated 10%–20% of phospholipids possess only one ester-linked acyl chain together with an ether-linked alkyl chain forming ether phospholipids.<sup>64–67</sup> Ether phospholipids with a vinyl bond are classified as plasmalogen phospholipids or, more commonly, as plasmalogens and constitute the vast majority of ether phospholipids.<sup>65</sup>

### Plasmalogens are enriched in the myelin phospholipid pool

Plasmalogens are partially synthesized in peroxisomes and are particularly abundant in myelin. In myelin-rich white matter, plasmalogens make up more than 30% of total phospholipids, a higher proportion relative to that in gray matter, which tends to be less than 20%.<sup>9,66,68</sup> Plasmalogens exist primarily as phosphatidylethanolamine (PE) phospholipids,<sup>65,68,69</sup> which have an ethanolamine head group and constitute the third most abundant myelin lipid class.<sup>9,10,70</sup> In myelin, more than 80% of PE lipids are constituted by plasmalogens, making them a significant contributor to myelin lipid composition.<sup>9,70</sup> Moreover, brain plasmalogen levels increase postnatally in parallel with myelination, likely reflecting a rise in myelin-associated plasmalogens.<sup>69,71</sup> Given their ether-linked alkyl chain, plasmalogens possess a hydrophobic tail with a narrower cross-sectional area, which increases lipid order in a cell membrane.<sup>72,73</sup> Other roles attributed to plasmalogens include serving as a reservoir for arachidonic acid, modulating intracellular radical oxygen species propagation, regulating cell death, and contributing to lipid raft formation.<sup>74–78</sup>

### Plasmalogens contribute to myelination and myelin integrity

Plasmalogen deficiency through knockout of peroxisome-related genes, such as *Pex7* and *Gnpat*, is detrimental to myelination and myelin stability.<sup>79,80</sup> Up to 70% of *Pex7*-null neonates do not survive past weaning, and although remaining survivors can live more than 18 months without serious morbidity, they experience reduced body weight, impaired ossification, congenital cataracts, testicular atrophy, and infertility.<sup>81</sup> *Gnpat*-null mice similarly have reduced survival after birth, with 40% not surviving more than 6 weeks and experiencing reduced body weight and size, infertility, cataracts, and optic nerve hypoplasia.<sup>82</sup> Both adult *Pex7*-null and *Gnpat*-null mice experience hypomyelination with delayed myelination in PNS, followed by demyelination after a year of life.<sup>79</sup> In *Gnpat*-null mice, a similar pattern of hypomyelination, delayed myelination, and demyelination was also reported in the CNS, which adversely affected action potential conductivity.<sup>80,83</sup> In both knockout models, plasmalogens were significantly reduced in the nervous tissue. These genetic models substantiate that plasmalogens are imperative for normal myelination during development and myelin maintenance later in life. Of interest, upregulation of PE with diacylglycerol moieties can compensate for plasmalogen deficiency and likely support some degree of myelination<sup>84</sup>; however, it is insufficient for long-term myelin stability. In summary, plasmalogens contribute to multiple processes, including the genesis and integrity of myelin, likely in part due to their ability to increase lipid membrane packing and order.

### De novo fatty acid synthesis in myelinating glia is required for normal myelination

Fatty acids are the essential building blocks for the various major myelin lipid species detailed above, and loss of fatty acid metabolism-related gene products has further elucidated the importance of lipid metabolism in myelin homeostasis

(Figure 3D). First, whole-body knockout of ELOVL fatty acid elongase 5 (ELOVL5), an enzyme essential for PUFA elongation, induced significant reduction of PUFAs longer than 18 carbons, accompanied by increased myelin layer periodicity, paranodal junction gaps in the PNS, and motor deficits.<sup>85</sup> Elsewhere, knockout of fatty acid synthase (*Fasn*) in SCs using *Dhh*-Cre induced severe and persistent hypomyelination in the PNS, with motor neuropathy (Figure 3E).<sup>86</sup> Lipidomic profiles of the peripheral nerves revealed depletion of myelin complex lipids such as ceramides and cerebroside.<sup>86</sup> Of interest, dietary supplementation did not ameliorate the mutant phenotype, suggesting that *de novo* fatty acid synthesis by SCs is indispensable. Conversely, this study demonstrated that peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ )-dependent activity contributed to fatty acid synthesis in SCs, as treatment with PPAR $\gamma$  agonists partially rescued PNS hypomyelination.<sup>86</sup> These findings were later recapitulated in the CNS, as *Fasn* conditional knockouts using an OL-specific *Olig2*-Cre system also developed hypomyelination.<sup>87</sup> In contrast to the PNS, however, HFD supplementation partially ameliorated CNS hypomyelination in *Olig2*-Cre, *Fasn*<sup>L/L</sup> knockouts.<sup>87</sup> The mechanisms for these contrasting outcomes between the CNS and the PNS remain undefined but are possibly related to differences in exogenous lipid use between SCs and OLs or through contributions of dietary lipids mediated by other cell types not shared between the CNS and the PNS, such as astrocytes.<sup>35,87</sup>

## MOLECULAR DETERMINANTS OF MYELIN LIPID METABOLISM

Myelin lipid metabolism is tightly regulated by various molecular determinants, the most prominent of which include SREBPs, mammalian target of rapamycin (mTOR) complexes, PPARs, and quaking (QKI). Below, we summarize currently described mechanisms by which these regulators contribute to myelin and myelin lipid homeostasis.

### PPAR $\beta$ is a regulator of myelin lipid metabolism

The PPARs comprise a family of three closely related ligand-activated transcription factors, namely PPAR $\alpha$ , PPAR $\beta$ , and PPAR $\gamma$ .<sup>88,89</sup> Lipids, including eicosanoids and phospholipids, serve as endogenous ligands for PPARs. Heterodimerization with retinoic X receptor (RXR), binding to PPAR-response elements, and ligand-dependent activation are requisite for PPAR-mediated gene transcription.<sup>88–90</sup> PPARs regulate multiple pathways that contribute to various biological processes, including mitochondrial homeostasis, adipogenesis, and inflammation.<sup>90–93</sup> Within the PPAR family, PPAR $\beta$  has been particularly associated with myelination and myelin homeostasis. PPAR $\beta$  is abundantly expressed in the brain, with differential expression in neurons and OLs.<sup>94–98</sup> PPAR $\beta$  activation *in vitro* can increase OL sheet deposition, myelin protein expression, and OL differentiation.<sup>99–101</sup> In addition, PPAR $\beta$  expression is upregulated in OLs during tissue repair following spinal cord injury.<sup>102</sup> Interrogating the effects of whole-body *Ppar $\beta$*  deficiency using a hypomorphic *Ppar $\beta$*  allele revealed partial hypomyelination in the corpus callosum, indicating a role for PPAR $\beta$  in myelination.<sup>103</sup> More recently, inactivation of *Ppar $\beta$*  in adult OLs was shown to disrupt myelin maintenance in the CNS through dysregulation of fatty acid biosynthesis, findings which were replicated when *Ppar $\beta$*  was conditionally depleted in OLs.<sup>104</sup> *Ppar $\beta$*  and its heterodimerization partner, *Rxra*, interact and functionally cooperate with the KH-domain RNA-binding protein QKI, which is necessary for the transcriptional activation of fatty acid biosynthesis genes (Figure 3F). Loss of QKI in adult OLs using *Plp*-Cre<sup>ERT2</sup>, *Qk*<sup>L/L</sup> mice severely affected the ability of the *Ppar $\beta$* -*Rxra* complex to transcribe fatty acid biosynthesis pathways, leading to morbid demyelination.<sup>104</sup> Both the PPAR $\beta$  agonist KD3010 and the RXR agonist bexarotene ameliorated the lipid loss and consequent demyelination in *Qki*-null mutants.<sup>104</sup>

Although less described than PPAR $\beta$ , other PPAR members may also affect myelination. For instance, an abnormal lipid profile in SCs secondary to loss of SREBP1c leads to dysregulated PPAR $\alpha$  activation, elevated fatty acid oxidation, and aberrant hypermyelination, highlighting the need for a balance between lipogenic and oxidative processes in myelin-forming glia, in which distinctive PPARs may have opposing roles.<sup>105</sup>

### SREBPs are versatile regulators of myelin lipids

SREBPs are basic helix-leucine-zipper proteins that initially reside in the ER and depend on SCAP-mediated cleavage for activation.<sup>29</sup> The SCAP-SREBP complex is hindered by insulin-induced gene (Insig), which inhibits SREBP activation by preventing its translocation to the Golgi, where SREBP cleavage occurs (Figure 2D).<sup>106</sup> Once in the nucleus, SREBPs activate transcription of cholesterol

and fatty acid biosynthesis genes that are critical for myelination. While SREBP1 has been shown to regulate both fatty acid and cholesterol metabolism, SREBP2 is regarded as the primary regulator for cholesterol metabolism.<sup>106</sup> During cellular lipid homeostasis, both family members can act as lipid sensors, providing feedback for intracellular cholesterol levels in order to fine-tune expression of lipid biosynthesis genes in response to lipid supply and demand.<sup>107</sup>

As described above, both Srebp and Scap expression correlated with myelin formation during development.<sup>30</sup> Moreover, loss of Scap in SCs disrupted myelination, downregulated SREBP targets, and impaired lipid synthesis.<sup>33,108</sup> *In vitro* inhibition of SREBPs impaired OL differentiation and reduced expression of myelin lipid metabolism targets, similar to earlier findings in SCs *in vivo*.<sup>33</sup> Finally, myelin cholesterol and lipid homeostasis was dependent on Scap-mediated activation of Srebp in both OLs and astrocytes.<sup>34,35</sup> Additional findings have further highlighted the significance of the SCAP-SREBP axis to myelin lipid homeostasis. For instance, loss of Srebp1c is accompanied by peripheral neuropathy, secondary to an imbalance in SC fatty acid utilization.<sup>105</sup> Likewise, loss of Srebp2 activity significantly hinders CNS myelination. As similarly seen with Ppar $\beta$ , Qki was recently identified as a co-activator for Srebp2 in OLs.<sup>109</sup> Loss of Qki-dependent co-activation in OLs significantly disrupted Srebp2-mediated transcription of cholesterol biosynthesis pathways, which blunted myelination and caused severe congenital hypomyelination accompanied by motor deficits and high morbidity (Figure 2E).<sup>110</sup>

In summary, SREBP1 and SREBP2 are critical to myelin lipid synthesis owing to their transcriptional downstream targets. To date, our knowledge of SREBP proteins' involvement in myelination has been limited to developmental mouse models; however, understanding how SREBPs work in the adult nervous system could provide significant implications in the clinical setting.

### mTOR is an upstream regulator of lipid metabolism

mTOR is a serine/threonine protein kinase that controls cellular metabolism and growth. mTOR constitutes the catalytic kinase domain for two distinct complexes,<sup>111</sup> mTORC1 and mTORC2. Together, mTOR, regulatory-associated protein of mTOR (Raptor), and mTOR-associated protein, LST8 homolog (mLST8 or G $\beta$ L) form the mTORC1 complex, which regulates autophagy and lipid, nucleotide, and protein synthesis. mTORC2 is composed of mTOR, rapamycin-insensitive companion of mTOR (Rictor), and regulatory subunits mSin1 and Protor1/2.<sup>111,112</sup> mTORC2 influences cellular proliferation and survival. Of note, mTORC1 has been shown to activate the lipid master regulators SREBP1a, SREBP1c, and SREBP2, leading to increased transcription of fatty acid and cholesterol biosynthesis genes.<sup>111,112</sup> The proposed mechanisms of mTORC1-mediated activation of SREBPs include modulating the availability of cholesterol in the ER by regulating autophagic and lysosomal pathways (Figure 2F).<sup>113</sup> Owing to its intricate relationship with cell growth and lipid metabolism, as well as its position upstream of other myelin regulators such as SREBPs and PPAR, mTOR function has been investigated extensively in glia and myelin.<sup>114</sup> For instance, *Cnp*-Cre-driven depletion of mTOR in myelinating glia, which disrupts both mTORC1 and mTORC2, causes hypomyelination in the PNS and CNS that persists into adulthood.<sup>115,116</sup> Of interest, *Dhh*-Cre-driven ablation of Raptor or Rictor in SCs demonstrated that mTORC1, but not mTORC2, is necessary for proper PNS myelination.<sup>117</sup> Although mTOR activity correlates with myelination onset in SCs, mTOR was not found to be essential for SC survival.<sup>115</sup> However, loss of mTORC1 function led to a severe reduction in fatty acids and cholesterol in peripheral myelin through downregulation of SREBP family proteins.<sup>115</sup>

Unlike the PNS, CNS myelination is regulated by both mTORC1 and mTORC2.<sup>118,119</sup> Loss of Raptor alone or in combination with Rictor induced hypomyelination in the CNS in both congenital and adult-onset experimental settings using *Cnp*-Cre and *Plp*-Cre<sup>ERT2</sup>, respectively.<sup>118,119</sup> Of interest, the spinal cord demonstrated greater myelin defects relative to the corpus callosum after mTORC1 signaling was blocked.<sup>112,118–121</sup> Although Raptor was found to be more critical for CNS myelination relative to Rictor,<sup>117–120,122</sup> double knockout of both Raptor and Rictor induced greater demyelination in adult animals relative to single knockouts,<sup>118</sup> as well as loss of mature OLs in the spinal cord, a striking difference from PNS findings.<sup>120,122</sup> These observations suggest that both mTORC complexes critically contribute to myelin maintenance in the spinal cord.

Interestingly, mTOR activity requires tight control during myelination, as both suppression and hyperactivation disturb myelin homeostasis. For instance, loss of tuberous sclerosis complex subunits 1 and 2 (TSC1/2), which inhibit

mTORC1, precipitated severe hypomyelination in the CNS and PNS.<sup>123,124</sup> These findings are consistent with clinical observations in tuberous sclerosis patients and mouse models, which experience white matter abnormalities.<sup>125–128</sup> However, more studies are needed to uncover the intricate mechanisms behind the regulation of CNS and PNS myelination by mTOR complexes.

### QKI is both a transcriptional and a posttranscriptional regulator of myelin pathways

QKI belongs to the KH-domain family of proteins characterized by their ability to bind single-stranded RNA and DNA.<sup>129,130</sup> Qki was first identified in quaking viable (qk<sup>v</sup>) mutant mice in which Qki is downregulated secondary to loss of regulatory elements in a 1 Mb deletion upstream of the *Qk* gene.<sup>131,132</sup> Qk<sup>v</sup> mice demonstrate hindlimb paralysis and tremors due to severe hypomyelination, primarily in the CNS.<sup>131</sup> Qk knockout is embryonically lethal; however, OL-specific depletion of Qki using *Olig2*-Cre phenocopied the motor deficits and histopathology exhibited in qk<sup>v</sup> mutants, highlighting that loss of OL-specific Qki accounted for the myelin deficits.<sup>133</sup>

Mechanistically, earlier findings described a regulatory role for Qki in alternative splicing of transcripts for myelin-related proteins, including myelin basic protein (MBP), MAG, PLP, and NF155.<sup>133–135</sup> In addition, our laboratory uncovered a novel transcriptional function for Qki in the regulation of myelin lipid synthesis.<sup>104,110</sup> Depletion of Qki in OLs in adult mice induced severe demyelination in the CNS. Although myelin protein expression remained stable, lipidomic profiling revealed a substantial loss of myelin lipids, with a differential reduction in MUFAs and very-long-chain fatty acids (VLCFAs).<sup>104</sup> In OLs, Qki served as a critical co-activator for the Ppar $\beta$ -Rrx $\alpha$  heterodimer, as target gene promoter occupancy and transcriptional activation by Ppar $\beta$ -Rrx $\alpha$  were Qki dependent (Figure 3F).<sup>104</sup> Importantly, HFD supplementation or PPAR $\beta$  agonist treatment provided a substantial rescue effect, supporting the hypothesis that Qki regulates myelin maintenance through PPAR $\beta$ -mediated lipid biosynthesis.<sup>104</sup> Beyond myelin stability, the role of Qki in lipid metabolism is also critical for *de novo* myelination.<sup>110</sup> Induced knockout of *Qk* in either neural/glia precursor cells or OPCs during postnatal myelination onset led to severe hindlimb paralysis, significant CNS hypomyelination, and poor survival after weaning. Of interest, loss of Qki during developmental myelination significantly reduced cholesterol in myelin as well as downregulating sterol synthesis genes.<sup>110</sup> Similar to its interaction with Ppar $\beta$ , which drives expression of fatty acid metabolism-related gene targets, Qki functionally cooperated with cholesterol master regulator Srebp2 during developmental myelination to enable expression of cholesterol synthesis pathway enzymes (Figure 2E).<sup>110</sup> Thus, Qki is a transcriptional co-regulator for fatty acid and cholesterol metabolic pathways essential for myelin maintenance and myelination.

Beyond its physiological roles, QKI is associated with a variety of neurological diseases, including 6-q terminal deletion syndrome, schizophrenia, multiple sclerosis, and glioma.<sup>136–138</sup> Given QKI's importance to myelin synthesis and maintenance as well as its correlation with human diseases, further investigation into upstream regulators of QKI, as well as cross talk with other molecular pathways, is warranted.

### CONTRIBUTION OF LIPID METABOLISM TO MYELIN MAINTENANCE

As alluded to above, lipids play diverse roles in myelin homeostasis and are regulated by various key molecular determinants. However, one aspect less appreciated but no less vital is the role of lipid metabolism in supporting myelin maintenance specifically, which merits special focus given the growing attention to myelin maintenance and plasticity in adults.

### Myelin maintenance is an active process

Although myelin has been traditionally regarded as highly stable and metabolically inert, its maintenance is now more appreciated as a dynamic and active process, wherein myelin membrane turnover represents a significant component. Myelin sheath renewal rate independent of cell turnover was best appreciated through carbon-dating studies in postmortem tissues and cell lineage tracing.<sup>5,139</sup> <sup>14</sup>C levels in OL nuclei isolated from human brains revealed that the majority of OLs are formed within the first 5 years of life, with an annual turnover of 0.32% in adult life.<sup>5</sup> Similarly, OLs are very stable in mice, with an estimated half-life of up to 10 years, depending on the CNS region, with up to 90% of OLs surviving 20 months in the corpus callosum.<sup>139</sup> In the PNS, SC stability in the



sciatic nerve is even more robust than that of OLs, since *in vivo* proliferation assays revealed minimal turnover in myelinating SCs and an estimated turnover rate of more than 70 months for non-myelinating SCs.<sup>8</sup> In contrast to the slow turnover of myelinating glia, myelin membrane undergoes a more frequent renewal, with <sup>14</sup>C measurements in humans indicating a continual turnover of myelin on a yearly basis.<sup>5</sup> Interrogation of myelin-specific proteins and lipids has revealed that continual synthesis is required for myelin maintenance, albeit at significantly varied degrees.

### Myelin proteins exhibit robust stability with durable lifespans

Within the myelin sheath, myelin-specific proteins enjoy a high degree of stability with a relatively low exchange rate. For instance, Plp protein expression can remain stable months after inducible knockout in adult mice.<sup>140</sup> Likewise, the half-life for Mbp was approximately 11 weeks following induced knockout in adult mice, with Mbp protein expression remaining at 26% more than 6 months after injection.<sup>141</sup> Moreover, in rats ante- and postnatally exposed to <sup>15</sup>N, 18.5% of <sup>15</sup>N-labeled Plp protein persisted 6 months after eliminating <sup>15</sup>N exposure.<sup>142</sup> Similarly, 20.2% of <sup>15</sup>N-labeled Mbp protein remained intact during the same time course.<sup>142</sup> In a complementary <sup>15</sup>N pulse study, Plp and Mbp exhibited turnover rates of 0.003 day<sup>-1</sup>, which corresponded to half-lives that exceeded well beyond 6 months.<sup>143</sup> Furthermore, the use of SILAC mouse labeling with [<sup>13</sup>C] lysine further substantiated that Plp and Mbp are long-lived, both surpassing the 99th percentile of measured protein lifetimes in the brain.<sup>144</sup> Blocking protein translation in adult OLs minimally affects myelin stability in the short term,<sup>145</sup> although longer-term impairment can likely induce late-onset demyelination.<sup>140</sup> Moreover, continual myelin protein synthesis, such as for Mbp, is necessary for adult myelin renewal and maintenance.<sup>141</sup> Therefore, although the estimated half-life for myelin proteins can vary between experimental approaches, myelin-specific proteins are robustly stable with durable lifetimes.

### Continual and frequent myelin lipid self-renewal is necessary for myelin maintenance

In contrast to proteins, myelin lipids experience faster exchange rates, and myelin maintenance is more vulnerable to lipid dysmetabolism. For instance, isotope tracing demonstrated continual turnover of myelin lipids, although at different rates across lipid species.<sup>146</sup> By measuring deuterium incorporation rates in myelin lipids in mice, half-replacement times for myelin-specific cholesterol, phosphatidylcholine, PE, and GalC were estimated to be 359, 20, 25, and 94 days, respectively.<sup>146</sup> Thus, although cholesterol has a fairly stable half-life, phospholipids experience more rapid turnover, with a half-life approaching 3 weeks.<sup>146</sup> In addition to lipid tracing, investigation of Qki demonstrated a critical link between lipid turnover and myelin maintenance for the first time through genetic approaches. As discussed above, QKI functions as a transcriptional co-activator that regulates lipid synthesis in OLs through activation of PPAR $\beta$ .<sup>104</sup> Metabolic disruption in OLs secondary to Qki loss decreased fatty acid elongation and desaturation, impairing lipid synthesis necessary for myelin turnover.<sup>104</sup> The altered myelin lipid metabolism arrested membrane turnover, impaired myelin maintenance without affecting OL survival, and induced significant and morbid demyelination, illuminating a greater need for lipid renewal relative to proteins in myelin homeostasis, at least in the short term.<sup>104</sup> Of note, OL-specific Qki depletion resulted in rapid demyelination within 1 week, highlighting the fast turnover rate of the myelin lipids that are regulated by Qki.<sup>104</sup> Thus, in myelinating OLs, PPAR $\beta$  with QKI coactivation is critical for driving myelin lipid renewal and myelin maintenance.

Beyond the CNS, it remains unclear whether lipid metabolism has similar importance in peripheral myelin stability, although some recent studies have helped address this question. For example, excessive production of sphingolipids, including ceramide and sphingosine, through elevated serine palmitoyltransferase activity in adult SCs caused significant neuropathy accompanied by loss of myelinated fibers and formation of excessive or redundant myelin membrane.<sup>147</sup> Thus, excess of simple sphingolipids appears deleterious to peripheral myelin homeostasis, indicating a possible dependency on a balanced lipid turnover. Supporting this notion, albeit indirectly, mitochondrial dysfunction through knockout of mitochondrial transcription factor A (*Tfam*) in SCs led to peripheral demyelination coupled with attenuated expression of lipid synthesis genes, including *Srebp1*, *Fasn*, and *Hmgcr*, as well as depressed cerebroside and sulfatide levels in nerves.<sup>148</sup> Conversely, impaired oxidative phosphorylation secondary to

Cox10 deficiency in SC induced significant neuropathy and PNS dysmyelination similar to *Tfam* knockout; however, here insufficient energy production was the ascribed mechanism.<sup>149</sup> Separately, loss of Lkb1 in SCs induced peripheral neuropathy and axonal degeneration without causing demyelination, despite decreases in important myelin lipid species such as cholesterol, cerebroside, and phospholipids within nerves.<sup>150</sup> Thus, further investigation is warranted to resolve these contrasting observations and to further define how lipid metabolism and myelin maintenance relate in SCs.

### LIPID DYSMETABOLISM CONTRIBUTES TO MYELIN DISORDERS

To summarize the relevance of myelin lipid physiology to human diseases, a brief discussion regarding the interrelationship between myelin-related disorders and lipid metabolism is next provided.

### Leukodystrophies highlight an intersection between lipid dysmetabolism and myelin pathology

Hypomyelinating and demyelinating disorders known as leukodystrophies provide a genetic link between lipid metabolism and myelin maintenance, as their underlying mutations commonly occur in genes directly involved in lipid metabolic pathways (Table 1). For instance, mutations affecting fatty acid oxidation in peroxisomes can lead to leukodystrophy. Loss of function of ATP-binding cassette subfamily D member 1 (ABCD1) causes X-linked adrenoleukodystrophy (ALD), one of the most common leukodystrophies. ABCD1 is a peroxisome lipid transporter for VLCFAs, which require ABCD1 for import and subsequent degradation in peroxisomes (Figure 4A).<sup>151,152</sup> VLCFA accumulation in the CNS following ABCD1 loss is considered detrimental for white matter integrity and possibly causative for ALD. Beyond transport of VLCFA, mutations in the peroxisome fatty acid oxidizing enzymes ACOX1, HSD17B4, and SCP2 also contribute to leukodystrophies that, similar to those in ALD, are ostensibly secondary to the deleterious accumulation of lipid substrates in myelin and brain tissue.<sup>153–155</sup> Animal models of peroxisome-related leukodystrophies, which include dACOX1-mutant fruit flies<sup>156</sup> and Hsd17b4- and Pex5-mutant mice,<sup>157,158</sup> further reinforce the association of perturbed peroxisome lipid oxidation and glial and myelin homeostasis (Figure 4A).

Myelin integrity is also sensitive to changes in phospholipid and plasmalogen synthesis. Rhizomelic chondrodysplasia punctata (RCDP) is a disorder characterized by abnormal facies, impaired growth of the proximal long bones (rhizomelia), and myelination abnormalities.<sup>159,160</sup> RCDP is secondary to mutations in PEX7, GNPAT, and AGPS, proteins critical for the plasmalogen biosynthesis pathway in peroxisomes,<sup>161,162</sup> as well as to mutations in PEX5, which indirectly perturb PEX7 function (Figures 4B and 4C).<sup>163</sup> Severely decreased levels of plasmalogens are characteristic of RCDP and may contribute to myelin anomalies, given that most myelin PE phospholipids are derived from plasmalogens. Another RCDP-like disorder with significant neurological impairments follows from plasmalogen deficiency due to loss of FAR1, a critical ether phospholipid biosynthetic enzyme (Figure 4D).<sup>164</sup> Of interest, separate gain-of-function mutations in FAR1 that aberrantly increase plasmalogens also correlate with disrupted neurodevelopment,<sup>165</sup> suggesting that neurological and, likely, myelin homeostasis rest on delicately balanced plasmalogen levels. Conversely, individuals with mutations undermining the generation of PE phospholipids present with severe hereditary spastic paraplegias and white matter pathology, as seen with loss-of-function mutations in *SELENO1*<sup>166,167</sup> and *PCYT2*,<sup>168</sup> which are necessary for *de novo* synthesis of PE phospholipids (Figure 4E).<sup>169,170</sup> Of note, these mutations lead to substantial changes in plasmalogens that may be major contributors to disease.

Additional lipid and fatty acid metabolic pathways can affect myelin homeostasis and development. For instance, mutations of FA2H, which catalyzes the synthesis of 2-HFs, cause a leukodystrophy accompanied by iron accumulation and neurodegeneration.<sup>57,171,172</sup> Sjogren-Larsson syndrome (SLS) is caused by mutations in fatty aldehyde dehydrogenase, which converts fatty aldehydes into fatty acids and is encoded by ALDH3A2, disruption of which causes an imbalance of fatty aldehydes and ether lipids in the brain (Figure 4F).<sup>173,174</sup> SLS presents as a childhood-onset leukodystrophy accompanied by ichthyosis and macular dystrophy. Impaired sphingolipid metabolism is also associated with myelin abnormalities. Dihydroceramide desaturase (DEGS1) contributes to the synthesis of ceramide, the simplest form of sphingolipid. DEGS1 mutations cause hypomyelinating leukodystrophy-18, which is characterized by accumulations in the



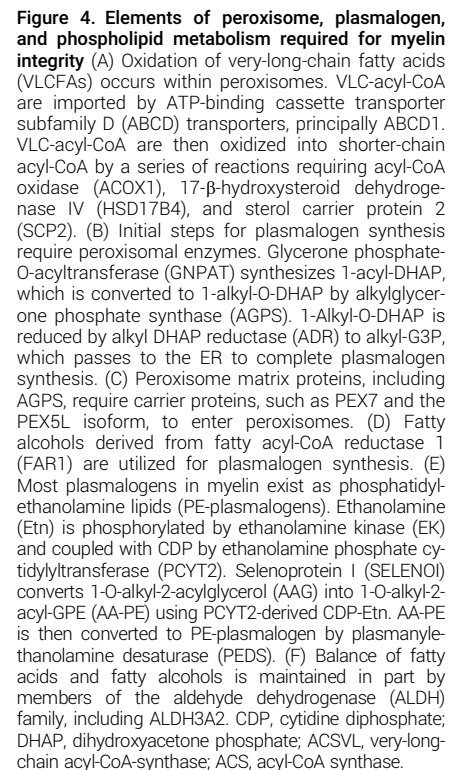
**Table 1.** Hereditary myelin disorders secondary to mutations in lipid metabolic pathway-related genes

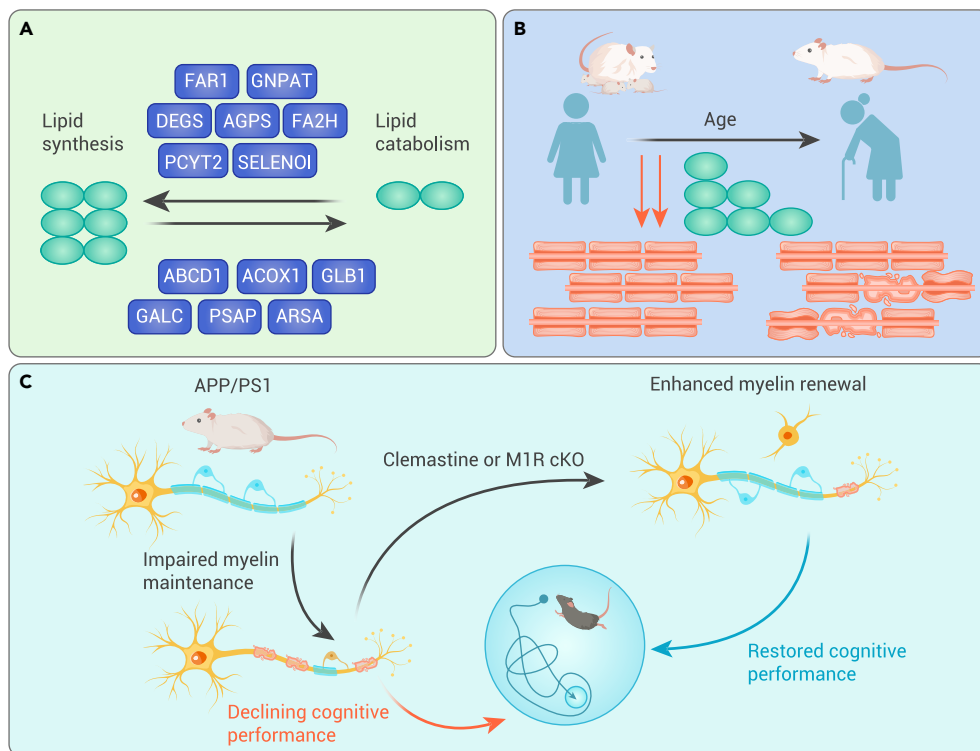
Name	OMIM	Gene	Gene product/function	Description	Ref.
Peroxisomal acyl-CoA oxidase deficiency	264470	<i>ACOX1</i>	Peroxisomal acyl-coenzyme A oxidase 1; catalyzes 1st reaction in peroxisomal fatty acid $\beta$ -oxidation	Leukodystrophy, hypotonia, seizures, developmental regression, mean survival of 5 years	Ferdinandusse et al. <sup>153</sup> Watkins et al. <sup>216</sup>
D-bifunctional protein deficiency	261515	<i>HSD17B4</i>	D-bifunctional protein; catalyzes 2nd and 3rd reactions in peroxisomal fatty acid $\beta$ -oxidation	Leukodystrophy, seizures, hypotonia, delayed development, neuronal migration defects, mean survival of <2 years	Ferdinandusse et al. <sup>154,217</sup>
X-linked adrenoleukodystrophy	300100	<i>ABCD1</i>	ATP-binding cassette subfamily D member 1; importation of very long chain fatty acids into peroxisomes	Leukodystrophy, dementia, adrenal insufficiency, paralysis, audiovisual impairment	Moser et al. <sup>151,152</sup> Schamburg et al. <sup>218</sup>
Fatty acid hydroxylase-associated neurodegeneration	612319	<i>FA2H</i>	Fatty acid 2-hydroxylase; hydroxylation of position 2 of the N-acyl chain of ceramide moieties	Leukodystrophy, spastic paraplegia, cognitive impairment	Edvardson et al. <sup>171</sup> Kruer et al. <sup>172</sup> Dick et al. <sup>219</sup>
Sjogren-Larsson syndrome	270200	<i>ALDH3A2</i>	Aldehyde dehydrogenase family-3 member A2; oxidation of lipid-derived aldehydes	Leukoencephalopathy, intellectual disability, macular dystrophy, spastic paresis	Lossos et al. <sup>220</sup> Sjogren et al. <sup>221</sup> Willemsen et al. <sup>222</sup>
Metachromatic leukodystrophy	250100, 249900	<i>ARSA</i>	Arylsulfatase A; catalyzes hydrolyzation of sulfatides	Late infantile: seizures, hypotonia, developmental regression	Mahmood et al. <sup>177</sup> MacFaul et al. <sup>223</sup> Zafeiriou et al. <sup>224</sup>
		<i>PSAP</i>	Prosaposin; precursor of saposins A-D, catalyzes hydrolysis of glycosphingolipids	Juvenile/adult: behavioral disturbances, dementia, ataxia, pyramidal signs, neuropathy	
Globoid cell leukodystrophy	245200	<i>GALC</i>	Galactosylceramidase; catalyzes hydrolysis of galactoceramide	Infantile: developmental delay, hypotonia, quadriparesis, seizures, survival of <2 years Juvenile/adult: behavioral disturbances, motor-sensory neuropathy, cognitive decline	Komatsuzaki et al. <sup>178</sup> Wenger et al. <sup>179</sup>
Hypomyelinating leukodystrophy-18	618404	<i>DEGS1</i>	Dihydroceramide desaturase 1; catalyzes final step of ceramide <i>de novo</i> synthesis	Failure to thrive, poor psychomotor development, severe intellectual disability	Karsai et al. <sup>175</sup> Pant et al. <sup>176</sup> Dolgin et al. <sup>225</sup>
Smith-Lemli-Opitz	270400	<i>DHCR7</i>	7-dehydrocholesterol reductase; catalyzes reduction and conversion of 7-dehydrocholesterol into cholesterol	Congenital malformations, photosensitivity, intellectual disability, abnormal brain MRI (corpus callosum, white matter lesions)	Anstey et al. <sup>226</sup> Irons et al. <sup>227</sup> Lee et al. <sup>228,229</sup>
Rhizomelic chondrodysplasia punctata (types 1, 2, 3 and 5)	215100, 222765, 600121, 616716	<i>PEX7</i>	Peroxin 7; import of PTS2 peroxisome matrix proteins	Abnormal facies, rhizomelia, congenital cataracts, intellectual disability, developmental delay, joint deformities, myelination abnormalities	Bams-Mengerink et al. <sup>159</sup> Sztriha et al. <sup>160</sup> Barøy et al. <sup>163</sup>
		<i>GNPAT</i>	Dihydroxyacetone phosphate acyltransferase; catalyzes synthesis of plasmalogens		
		<i>AGPS</i>	Alkyl dihydroxyacetone phosphate synthase; catalyzes synthesis of plasmalogens		
		<i>PEX5-L</i>	Peroxin 5, long isoform; co-transporter for PTS2 peroxisome matrix proteins		
Peroxisomal fatty acyl-CoA reductase 1 disorder	616154	<i>FAR1</i>	Fatty acyl-CoA reductase 1; catalyzes reduction of long chain fatty acyl-CoA to fatty alcohols	Intellectual disability, epilepsy, growth retardation, spastic paresis, cataracts	Buchert et al. <sup>164</sup> Ferdinandusse et al. <sup>165</sup>

(Continued on next page)

Name	OMIM	Gene	Gene product/function	Description	Ref.
Spastic paraplegia 81	<a href="#">618768</a>	<i>SELENO1</i>	Ethanolamine phosphotransferase 1; catalyzes transfer of ethanolamine phosphate group to AAG or DAG	Hypomyelination, spastic paraplegia, epilepsy, sensorineural hearing loss, blindness	Ahmed et al., <sup>166</sup> Horibata et al. <sup>167</sup>
Spastic paraplegia 82	<a href="#">618770</a>	<i>PCYT2</i>	Ethanolamine-phosphate cytidylyltransferase; required for CDP-ethanolamine synthesis	Brain atrophy, spastic paresis, epilepsy, intellectual disability	Vaz et al. <sup>168</sup>
Leukodystrophy, progressive, early childhood-onset	<a href="#">617762</a>	<i>ACER3</i>	Alkaline ceramidase 3; hydrolysis of ceramides into sphingosine.	Developmental regression, spastic paresis, dystonia, abnormal facies	Edvardson et al. <sup>230</sup>

Charcot-Marie-Tooth disease (CMT) represents a genetically diverse spectrum of hereditary neuropathies with a population prevalence estimated to be 1 in 2,500.<sup>180,181</sup> CMT can occur as a primary axonopathy or, more frequently,





**Figure 5. Myelin disruption in leukodystrophies and Alzheimer's disease** (A) Leukodystrophy-associated lipid dysregulation occurs from mutations in genes that contribute to lipid synthesis or catabolism (see Table 1). (B) With aging, there is a decline with brain lipids enriched in myelin and a decrease in myelin renewal. (C) APP/PS1 mice experience demyelination, which exacerbates AD-like memory deficits. Clemastine treatment or conditional knockout (cKO) of M1R in OPCs restored myelin renewal and ameliorated cognitive decline.<sup>207</sup>

### Myelin instability and lipid dysregulation are featured in Alzheimer's disease

Brain lipids, including those enriched in myelin, decrease with age. Moreover, with aging there is a concomitant decline in myelin stability (Figure 5B).<sup>194–196</sup> Beyond age-related changes, loss of myelin integrity is further compounded in Alzheimer's disease (AD), one of the most common causes of dementia. Two observations related to myelin are noteworthy in AD. First, AD is accompanied by significant perturbations in brain lipid metabolism, particularly for lipids abundant in myelin. Second, myelin instability contributes to AD progression.

In early-stage AD, sulfatides were decreased in postmortem brain tissues, including in specimens from mildly affected individuals.<sup>197</sup> Sulfatide depletion was also detected in the cortex of two transgenic AD mouse models after 10 months of age.<sup>198</sup>

In severely affected AD brain samples, plasmalogens were reduced, and VLCFAs accumulated<sup>199</sup>; moreover, in the cortices of transgenic AD mice, plasmalogens were likewise reduced.<sup>200</sup> In the 5×FAD AD mouse model, MALDI-MS revealed decreases in myelin lipids, including sulfatides and plasmalogens, which spatially correlated with amyloid-β plaque deposition and myelin loss.<sup>201</sup>

### Myelin stability deficits accompany brain lipidome dysregulation in AD

MRI studies of healthy controls and AD patients demonstrated accelerated decline in white matter integrity in AD patients versus age-matched controls.<sup>202</sup> In addition, imaging studies revealed white matter perturbations in presymptomatic familial AD cases<sup>203</sup> and intracortical demyelination in preclinical AD.<sup>204</sup> Focal demyelination associated with amyloid-β plaque deposition occurred in both AD patients and animal models.<sup>205</sup> Moreover, transcriptomic changes in the OL lineage from patients and 5×FAD mice have been reported.<sup>206,207</sup> Myelination in adult mice significantly declines with age, which can contribute to age-related deficits in memory.<sup>195</sup> In aged APP/PS1-mutant mice, however, myelin membrane turnover was augmented, with increased myelin degradation partially compensated for by new myelin from newly differentiated OPCs.<sup>208</sup> Nonetheless, by age 8 months, AD mice exhibited significant cortical and hippocampal demyelination that exacerbated memory-related deficits (Figure 5C).<sup>208</sup> Augmenting myelin renewal by repressing muscarinic signaling, either by providing clemastine (a muscarinic receptor antagonist) or by conditional knockout of the muscarinic receptor M1R in OPCs, restored myelin renewal and ameliorated cognitive deficits in AD mice (Figure 5C). The correlation between lipid dysregulated and demyelination observed in AD remains largely unexplored and merits deeper investigation because such studies could both improve our understanding of lipid-dependent myelin homeostasis and uncover new therapeutic approaches to AD-related myelin instability.

### PERSPECTIVE

Myelin requires enrichment of diverse lipids, including cholesterol, GalC, and plasmalogens. Disruption of lipid metabolism is detrimental to myelin formation and stability, an observation reinforced by mouse and human genetic studies. Various mutations associated with demyelination suggest that myelin health requires intact lipid pathways with a steady equilibrium between lipid synthesis and degradation. Recent findings indicate that myelin loss contributes to AD evolution

as a demyelinating neuropathy, with the latter representing more than 80% of CMT cases in Sweden and Iceland.<sup>182</sup> Demyelinating forms of CMT include CMT1, CMT4, and CMTX1 and are most often caused by mutations in proteins expressed in SCs and related to myelination, such as PMP22, GJB1, MPZ, and EGR2.<sup>183,184</sup>

Of note, some studies have associated these common variants of CMT with disturbances in lipid metabolism in SCs that could impair myelin maintenance. First, a rat model of CMT1A, the most frequent subtype of CMT1, revealed altered lipid metabolism in sciatic nerves of animals with severe neuropathy relative to moderately affected animals.<sup>185</sup> A phospholipid-enriched diet was able to rescue the motor neuropathy in CMT1A rats when given either postnatally or during adulthood.<sup>186</sup> Although major myelin proteins remained unaltered, multiple lipid species were significantly reduced in peripheral myelin from mutant rats; however, the high-phospholipid diet partially improved the myelin lipid profile, which was associated with attenuated loss of myelinated fibers and rescue of the disrupted myelin ultrastructure.<sup>186</sup>

Separately, lipidomics of CMT1A rat nerve, matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) of nerve endoneurium, and targeted lipidomics of isolated myelin all demonstrated significant dysregulation of sphingolipid and phospholipid levels.<sup>187</sup> Moreover, lipid profiling of sera from patients with CMT1A reflected similar and pronounced changes in phospholipid and sphingolipid metabolism.<sup>187</sup> In a separate mouse model of CMT1, supplementation with HFD in adult animals improved myelinated fiber density and myelin thickness and mitigated inflammatory infiltrates.<sup>188</sup> Of interest, CMT1A is most frequently caused by duplication of PMP22, which was recently demonstrated to contribute to lipid raft formation and cholesterol homeostasis in SCs<sup>27,189</sup>; moreover, overexpression of PMP22 in SCs induced cholesterol sequestration in lysosomes.<sup>190</sup> Similar observations were reported for PLP, the most abundant myelin protein in the CNS, which is likewise associated with lipid raft formation and lipid trafficking.<sup>191,192</sup> Overexpression of Plp, which occurs in the hypomyelinating leukodystrophy called Pelizaeus-Merzbacher disease (PMD), dysregulates trafficking of cholesterol and sphingolipids to the plasma membrane, leading to intracellular lipid accumulation.<sup>191</sup> Retention of cholesterol in the ER depresses *de novo* cholesterol synthesis and arrests myelination.<sup>193</sup> Thus, the lipid dysmetabolism and demyelination related to PMP22 duplication in CMT1A may in part be attributed to interrupted lipid trafficking and lipid raft formation, as similarly ascribed to aberrant PLP expression in PMD.



and age-related memory deficits. As AD and aging are also associated with myelin lipid dysmetabolism, the relationship between myelin lipids and demyelination in these contexts warrants further investigation.

Multiple studies have addressed the interrelationship between myelin and myelin lipids; however, various questions remain unaddressed. For instance, the functions of diverse lipid classes in myelin maintenance remain poorly understood. In addition, the source of these lipids is not always clear. Myelin-producing glia have naturally been the focus of this question, but this could leave underappreciated the contributions of supporting cells and circulating lipids. Moreover, how lipids are exchanged between myelin and cytosolic compartments within glia is unknown. Also unclear is the heterogeneity of myelin lipid dynamics between the PNS and the CNS and among the different subsets of myelinating glia present in both compartments.

Exciting prospects derived from the expanding knowledge of myelin lipid metabolism include the development of novel therapeutic approaches. For instance, dietary supplementation with neutral lipids was beneficial in a mouse model of CMT,<sup>188</sup> while cholesterol-enriched diets were beneficial in separate models of acute demyelination and PMD-associated leukodystrophy.<sup>193,209</sup> High-fat, ketogenic diets also ameliorated PMD in a preclinical model.<sup>210</sup> Targeted modifications of lipid metabolism in the context of lipid dysregulation have also shown positive signs. In a fly model of ACOX1 loss of function, improving oxidation of VLCFAs with the PPAR $\alpha$  agonist bezafibrate ameliorated the mutant phenotype.<sup>156</sup> Conversely, in models of ALD, induction of the fatty acid desaturase SCD1 significantly corrected the disease-associated lipid profiles.<sup>211</sup> Finally, the discovery of the QKI-PPAR $\beta$ -RXR $\alpha$  axis and its role in maintaining myelin lipid homeostasis revealed that PPAR and RXR agonists could be favorable in cases of progressive multiple sclerosis that exhibit reduced QKI-PPAR $\beta$ -RXR $\alpha$  activity.<sup>104</sup>

Investigating myelin lipid metabolism could also help predict adverse effects on myelin health. For instance, given cholesterol's importance in providing new myelin, further studies may be warranted to investigate the effects of widely used statins on cognition and learning, which can be myelin dependent. This is especially relevant for individuals of advanced age or with dementia in whom myelin renewal is already impaired.<sup>195,212,213</sup> Although mTOR inhibition has received positive attention for its anti-aging effects,<sup>214,215</sup> caution should be exercised in inhibiting this axis, especially in patients with compromised myelin maintenance, given how mTOR supports myelin development.

In conclusion, mechanistic research in the field of myelin lipid homeostasis has promising potential for harnessing new approaches to reinforcing myelin health and redressing disease-related myelin loss.

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## AUTHOR CONTRIBUTIONS

J.A.B.-V. and F.B.A.Y. contributed equally to the literature search, conceptual design, drafting and editing of the manuscript, and figure design. J.H. contributed to manuscript editing, conceptual design, and scientific discussion.

## DECLARATION OF INTERESTS

The authors declare no competing interests.

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