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Review Article

Roles for PMP22 in Schwann cell cholesterol homeostasis in health and disease

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Underexpression, overexpression, and point mutations in peripheral myelin protein 22 (PMP22) cause most cases of Charcot-Marie-Tooth disease (CMTD). While its exact functions remain unclear, PMP22 is clearly essential for formation and maintenance of healthy myelin in the peripheral nervous system. This review explores emerging evidence for roles of PMP22 in cholesterol homeostasis. First, we highlight dysregulation of lipid metabolism in PMP22-based forms of CMTD and recently-discovered interactions between PMP22 and cholesterol biosynthesis machinery. We then examine data that demonstrates PMP22 and cholesterol co-traffic in cells and co-localize in lipid rafts, including how disease-causing PMP22 mutations result in aberrations in cholesterol localization. Finally, we examine roles for interactions between PMP22 and ABCA1 in cholesterol efflux. Together, this emerging body of evidence suggests that PMP22 plays a role in facilitating enhanced cholesterol synthesis and trafficking necessary for production and maintenance of healthy myelin.

Introduction

Schwann cells (SCs) and oligodendrocytes are dedicated to the production of myelin in the peripheral (PNS) and central nervous systems (CNS), respectively. Myelin provides the insulation to nerve axons that is required for rapid propagation of the action potential between neuron bodies and nerve endings. SCs differ from oligodendrocytes in that each SC myelinates only a single axon. The main adhesive protein for the spiraled layers of myelin membranes in the CNS is the proteolipid protein (a tetraspan membrane protein), whereas the single-span myelin protein zero (MPZ) plays this role in PNS myelin [1]. Defective PNS or CNS myelination is closely associated with a variety of diseases, including multiple sclerosis (CNS), Guillain-Barré syndrome (PNS), Pelizaeus-Merzbacher disease (CNS), Hansen's disease (leprosy, PNS), and Charcot-Marie Tooth disease (CMTD, PNS). It is this latter disorder that concerns this review.

CMTD is one of the most common genetic disorders, afflicting roughly 1:2500 humans [2,3]. CMTD is a peripheral neuropathy resulting from nerve degeneration. Symptoms usually appear between the ages of 5 and 15 years and include progressive muscle weakness and wasting, decreased sensation and pain in the extremities, and deformations of the hands and feet. Patients often experience mobility problems requiring the use of leg braces and/or a wheelchair. Types of CMTD fall into two broad categories: demyelinating (e.g. types 1 and 4) and axonal (e.g. type 2). Demyelinating CMTD arises primarily from genetic defects in SCs, which result in demyelinated or dysmyelinated axons of the peripheral nerves with axon degeneration occurring secondarily [4]. In cases of axonal CMTD the primary cause of disease is axonal degeneration [5]. The many subtypes of CMTD, as well as the closely related Dejerine-Sottas syndrome (DSS) and hereditary neuropathy with pressure palsies (HNPP) are caused by mutations in any one of over 100 known genes. However, roughly 75% of all CMTD cases are caused by mutations that impact a tetraspan membrane protein that is abundant in PNS myelin but scarcely expressed in the CNS: peripheral myelin protein 22 (Figure 1) [6]. Roughly 50% of all CMTD cases are caused by a duplication of the PMP22 gene, resulting in overexpression of

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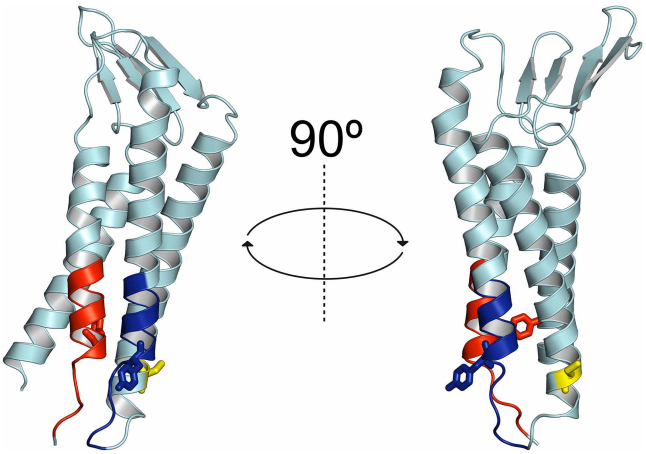

Figure 1. Cartoon representation for the AlphaFold2-predicted structure of PMP22.
Highlighted are locations of the CRAC motif in TM4 (residues 147–159, red), CARC motif in TM3 (residues 92–104, blue), and palmitoylation site (residue C85, yellow sticks). CRAC and CARC motifs are often observed in cholesterol-binding sites. Conserved tyrosine residues within these sites are known to be critical for cholesterol binding. Palmitoylation site C85 and CRAC/CARC residues Y97 and Y153 are represented by stick models.

the protein (type 1A CMTD; CMT1A), whereas deletion of a single allele of the gene leading to protein underexpression results in HNPP (20% of all cases) [6]. Rarer single nucleotide variations resulting in single amino acid mutations in PMP22 cause DSS or type 1E CMT (CMT1E) [6]. While the functions of PMP22 in SC and myelin biology are not yet fully understood, we here examine the mounting evidence that PMP22 plays critical roles in cholesterol homeostasis in SCs.

The area of the myelin membrane generated by a single SC can be *several thousand-fold* higher than the area of the plasma membrane of the pre-myelinated SC [7]. Myelin membranes are on the order of 70% by dry weight lipids, with the fraction of cholesterol relative to total lipids being on the order of 50 mol% [8,9]. Because cholesterol does not cross from blood serum across the blood-nerve barrier [10], most SC/myelin cholesterol is biosynthesized in SCs [11–13], with smaller amounts being acquired via phagocytosis [14–16] or uptake of cholesterol by lipoproteins/lipid protein receptors derived either from myelin fragments (from damaged nerves [17,18]) or from neighboring cells [10]. Cholesterol biosynthesis is rate-limiting to myelination [19]. SCs can therefore be thought of as cholesterol factories. Given that 18 molecules of ATP and 25 reducing equivalents are consumed in making each new cholesterol molecule [10], the energy demands of myelinating SCs are enormous, which may explain why the mitochondria of SCs seem to be configured for unusually high ATP output [20]. Indeed, given the large amounts of cholesterol that must be generated for supplying myelin, SCs likely have specially-adapted protein systems for facilitating cholesterol biosynthesis and surface transport [21,22]. This review examines recent evidence suggesting that PMP22 may play key roles in cholesterol homoeostasis in myelinating SCs under both healthy conditions and in conditions of myelin injury. We also examine the possibility that the failure of PMP22 to fulfill these key roles due to overexpression, underexpression, or mutation contributes to CMTD, where it is known that cholesterol biosynthesis is reduced [23].

CMT1A exhibits dysregulated lipid biosynthesis

Comparative microarrays were used to compare gene expression from sciatic nerves of WT rats with mildly and severely affected CMT1A model rats expressing a 3rd WT PMP22 allele [24]. It was found that dysregulation of 22 lipid metabolism genes correlated with disease severity. In both mildly and severely affected animals most examined lipid metabolism genes were down-regulated at both 1 week and 9 weeks of age. Interestingly, there was an age-dependent switch between mildly affected and severely affected rats with mildly affected rats exhibiting more lipid biosynthetic gene dysregulation at 1 week of age and severely affected rats exhibiting more lipid biosynthesis gene dysregulation at 9 weeks of age. Follow-up quantitative PCR experiments validated Adipoq, Lpl, Scd1, Pparg, Prkar2b, Ssg1, and Thrsp as being dysregulated.

Longitudinal RNA-seq experiments [25] found that lipid biosynthetic processes (phospholipid, cholesterol, and glycosphingolipid genes) were among the most prominently down-regulated transcripts in CMT1A rats during postnatal development (for a complete list of genes see Supplementary Figure S1 of Fledrich et al. 2018) [25]. mRNA expression of both lipid catabolizing and anabolizing transcripts were affected. This study further showed that during development, lipid metabolism genes (including those of sterol metabolism) failed to up-regulate in a CMT1A background compared with WT, suggesting a failure to engage lipid synthesis during myelination.

Lipidomics studies conducted on CMT1A rats and human serum samples [26] found that rat sciatic nerves exhibited impaired sphingolipid and glycerophospholipid metabolism in which ceramides, sphingomyelins, hexosylceramides, and sphingosine were all reduced in CMT1A samples [26]. An earlier study also found these same lipid species to be reduced in CMT1A rat sciatic nerve myelin and also cholesterol, PC, and PG lipid species [25,26]. The two studies tested regimens of lipid supplementation (by either adding lipids or various components of different lipid biosynthetic pathways) and observed improvements in myelination.

A transcriptomic analysis of C3 (CMT1A model) mice found that the most severely down-regulated genes were those involved in cholesterol biosynthesis [27]. This study additionally found that blocking the innate immunity complement system in C3 mice did not rescue cholesterol biosynthesis, nor did it improve motor function, ruling out a role for an immune cause in CMT1A pathology. More recently, C3 CMT1A mice and human patient-derived induced CMT1A pluripotent stem cell SC precursors (iPSC-SCPs) were used to examine lipid metabolism [28]. In lipidomic and transcriptomic experiments in C3 mice, decreased sphingolipids and cholesterol and their corresponding biosynthetic genes were observed. This study also demonstrated dysregulated transcriptional and lipidome networks in CMT1A iPSC-SCPs. Lipid metabolism gene expression was altered compared with the isogenic (WT) condition. These changes correlated with decreased lipid species in the CMT1A iPSC-SCPs lipidomic analysis. Sphingomyelin was significantly decreased in the CMT1A iPSC-SCPs.

In summary, data from multiple studies in rat, mouse, and human derived CMT models demonstrate dysregulated expression of numerous lipid biosynthesis genes including cholesterol. This results in altered lipidomes, as found in both animal and human derived samples. Combined, these data show that in CMTD SCs are unable to generate the necessary lipids of myelin production and that this begins at the level of gene expression.

PMP22 interacts with cholesterol biosynthesis enzymes

In their efforts to describe the glycosylation-dependent trafficking of PMP22 through the secretory phway to the cell surface, Marinko et al. [29] conducted quantitative proteomics to identify PMP22 interactors. Some 56 proteins were seen to co-immunoprecipitate (co-IP) with WT PMP22, some of which were previously-documented PMP22 interactors, with many others on pathways (e.g. membrane protein integration, ER chaperone network, and ERAD degradation) that make sense based on what we know about the cellular trafficking itinerary of PMP22. Included among these 56 proteins were PGRMC1, EMC4, DHCR7, DHCR24, TMEM97, and SURF4. All are related to cholesterol biosynthesis and cholesterol trafficking. Except for SURF4 and TMEM97, the other four PMP22 interactors are related to cholesterol biosynthesis in the ER, constituting biosynthetic steps taking place after squalene synthesis (Figure 2A) [30,31]. We point out, of course, that co-immunoprecipitation ('interaction') of any given protein with PMP22 does not prove *direct* interaction with that protein, only that they populate the same complex. However, in light of the limited number of proteins identified in the proteomic screen and given that many other interactors are proteins that are known or expected to interact with PMP22, it seems unlikely that co-IP of PMP22 with six different proteins all related to cholesterol homeostasis reflects experimental noise or another form of artifact.

PGRMC1 (the progesterone receptor membrane component 1) is an ER protein known to interact with proteins of the cholesterol biosynthesis pathway [32]. PGRMC1 has been shown to bind to and stabilize various members of the cytochrome P450 enzyme family in various steroidogenic pathways [32]. Its primary role in cholesterol homeostasis has been shown to be through regulation of sterol 14α-demethylase (CYP51) in *Schizosaccharomyces pombe*, HEK 293 cells, and in breast cancers cells where it promotes ergosterol/cholesterol biosynthesis [32–34]. CYP51 catalyzes the demethylation of lanosterol and dehydrolanosterol used by the Bloch and Kandutsch-Russell pathways respectively. PGRMC1 has also been shown to interact with SQS/FDFT1 (discussed below) and stearoyl-CoA desaturase (SCD1) [34]. SCD1 is an ER enzyme that catalyzes the rate limiting step of monounsaturated fatty acid formation [34].

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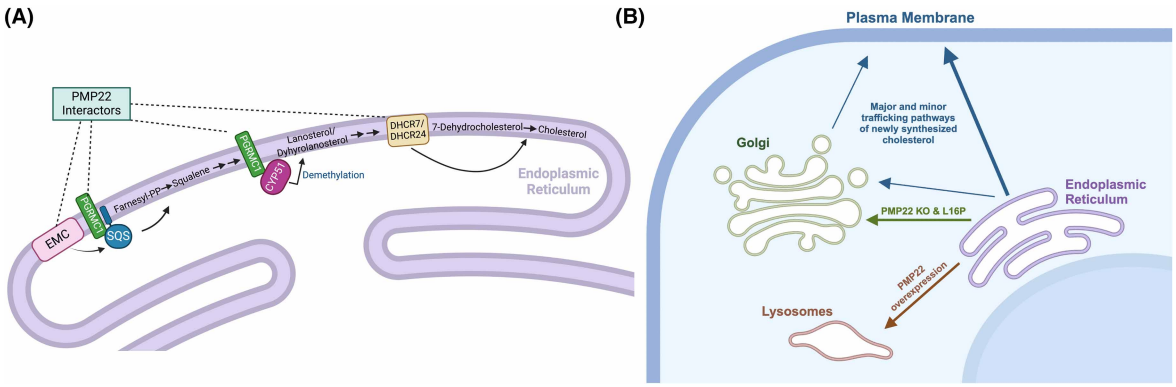

Figure 2. PMP22, cholesterol biosynthesis and cholesterol trafficking.

(**A**) Schematic of cholesterol biosynthesis pathway in the endoplasmic reticulum highlighting PMP22 interactors EMC4, PGRMC1, DHCR7 and DHCR24 as identified by proteomics. (**B**) Trafficking of newly synthesized cholesterol in Schwann cells. Typical pathways for cholesterol from ER to PM shown with blue arrows (thick arrow = major pathway, thin arrows = minor pathway). Major sites of cholesterol accumulation under different PMP22 genetic backgrounds shown.

EMC4 is a member of the ER membrane protein complex (EMC) which is broadly involved in membrane protein biogenesis and lipid metabolism [35,36]. Disrupting formation of the EMC complex disrupts cholesterol homeostasis in mammalian cells, sensitizing cells to both depleted and excess cholesterol [36]. EMC4 knockdown specifically inhibits the maturation of squalene synthase, (SQS, also known as FDFT1) [34]. SQS is an ER resident, tail-anchored enzyme that catalyzes the first committed step (squalene synthesis) of *de novo* sterol synthesis [37]. Interestingly, PGRMC1 was also shown to interact with SQS [34].

7-Dehydrocholesterol reductase (DHCR7) catalyzes the last step of the Kandutsch-Russell cholesterol biosynthesis pathway by converting 7-dehydrocholesterol to cholesterol. 24-dehydrocholesterol reductase (DHCR24) is the enzyme that catalyzes the conversion of desmosterol to cholesterol in the last step of the Bloch cholesterol biosynthesis pathway.

As noted, the steps of cholesterol synthesis that these four PMP22 interactors are involved with are from the latter (ER-localized) half of the cholesterol biosynthetic pathway that follows squalene synthesis [30,31]. The fact that a set of cholesterol biosynthetic enzymes co-IP with PMP22 suggests this pathway may be well-organized in time and space, perhaps as a super-complex or metabolon. It has previously been suggested that there is an organized metabolon for the latter stages of cholesterol biosynthesis [38]. Whether this is truly the case and what the role of PMP22 is in organizing or modulating this super-assembly is an interesting topic for future exploration.

The other two ER resident proteins identified in the Marinko et al. study that are linked to cholesterol homeostasis are SURF4 and TMEM97. SURF4 is an ER resident lipoprotein cargo receptor that facilitates the secretion of PCSK9 [39]. PCSK9 binds to and promotes the degradation of LDL receptors in endosomes or lysosomes, decreasing LDL uptake [40]. More studies will be needed to understand if association with PMP22 has any effect on SURF4 activity and its downstream effects on LDL uptake. TMEM97, also known as the sigma-2 receptor, is found in the ER, lysosomes, and the plasma membrane. It regulates lysosomal cholesterol storage through interactions with the intracellular cholesterol transporter NPC1 and forms a complex with PGRMC1 (another PMP22 interactor described above) [41,42]. TMEM97 and PGRMC1 form a complex with the LDL receptor to increase the rate of LDL internalization [41,42]. More studies will need to be conducted to elucidate the effect, if any, that PMP22 interaction with TMEM97 has on cholesterol homeostasis.

As described in the first section of this review, several studies have demonstrated that changes in PMP22 expression result in deleterious cholesterol metabolism. Here we have described six proteins directly involved with or related to cholesterol biosynthesis that co-IP with PMP22. And, while the interactions described in this section have not been validated by other methods, it seems very possible that PMP22 has a role in supporting cholesterol biosynthesis in the ER deserving of further exploration. Whether a loss of function of PMP22 in cholesterol biosynthesis contributes to CMTD or whether loss of cholesterol synthesis is secondary to other problems caused either by disease mutations in PMP22 (type E CMTD) or overexpression (type 1A CMTD) is an important issue for future study.

PMP22 regulates the subcellular localization of cholesterol

To understand the molecular events resulting in abnormal myelin formation in CMTD, the Notterpek lab has conducted multiple studies examining the relationship between PMP22 and cholesterol trafficking involving PMP22 knockout (KO), overexpression, and TrJ mouse (L16P disease mutant) conditions. Cholesterol was seen to be intracellularly retained (decreased levels at the plasma membrane) in SCs from PMP22 KO mice [43]. A follow-up 2019 study sought to further investigate where in the cell cholesterol accumulates in disease-causing PMP22 genetic backgrounds [44]. Once again, pronounced intracellular retention of cholesterol was observed in SCs from PMP22 KO mice, with a 44% increase in Golgi-retained cholesterol. shRNA knockdown of PMP22 in WT cells recapitulated the increased Golgi retention seen in the KO condition.

In a later study, the localization of cholesterol was tracked in SCs from mice with the PMP22 L16P mutation, which causes a severe form of CMT and is the basis for the TrJ mouse disease model [45]. A decrease in plasma membrane cholesterol was again noted and, as seen for the PMP22 KO, found a significant amount of the retained cholesterol in the Golgi [45]. The authors next examined the effects of PMP22 overexpression on cholesterol localization in mouse embryonic fibroblasts, once again finding that cholesterol was sequestered internally in cells overexpressing PMP22. However, in contrast with PMP22 L16P and KO conditions, overexpression of PMP22 resulted in internally retained cholesterol that was more abundant in lysosomes [45]. A different study using patient-derived induced CMT1A pluripotent stem cell SC precursors (iPSC-SCPs) also found decreased cholesterol at the PM and accumulation in the endosomes/lysosomes [28].

Typically, most newly synthesized cholesterol is transported directly from the ER to the PM via membrane contact sites, with only a fraction passing through the Golgi apparatus [46–51]. However, the data described above suggests that the latter may be more heavily relied on in myelinating SCs. It is possible that PMP22 directly or indirectly interacts with cholesterol and that they co-traffic together through the Golgi to the PM in SCs. PMP22 contains both CRAC and CARC motifs (see Figure 1), which are sometimes associated with cholesterol binding [52]. Evidence from mutations in the PMP22 CRAC motif suggests a direct interaction of PMP22 with cholesterol [45]. Mutations in the CRAC motif resulted in a decoupling of PMP22 and cholesterol trafficking with PMP22 primarily being retained in the ER and Golgi in SCs.

The above observation suggests that at least one other factor may be involved in shunting cholesterol to the Golgi, post-synthesis. MPZ is a possible candidate since it is known that its ER exit to the Golgi is cholesterol-dependent, a phenomenon diminished by mutations in its putative cholesterol binding sequence [53]. MPZ and PMP22 were recently shown to directly interact in a cholesterol-dependent manner via their transmembrane segments (the ectoplasmic end of the 2nd transmembrane helix of PMP22 interacts with the ectoplasmic end of the MPZ transmembrane helix) [54]. This interaction seems to be functionally important as evidenced by the fact that the A67T mutation, which causes a mild form of CMT, maps to this putative binding interface. However, trafficking of either protein to the PM does not appear to be dependent on the other [54,55]. It remains possible that MPZ 'hands off' its cholesterol to PMP22 in the Golgi, possibly by associating with cholesterol-enriched nanodomains (discussed below), where PMP22 then co-traffics with cholesterol to the plasma membrane.

In summary, PMP22 KO and L16P result in the retention of cholesterol in the Golgi while PMP22 overexpression results in cholesterol trafficking to endosomes/lysosomes (Figure 2B). The difference in cholesterol localization between the overexpressed, KO, and L16P conditions suggest different cellular responses to these genetic backgrounds and may partially explain their varying associated disease severities. Evidence also suggests PMP22 interacts with directly with cholesterol through its CRAC motif and they may co-traffic and that this trafficking may possibly also involve MPZ facilitating enhanced trafficking through the Golgi.

PMP22 associates with cholesterol-enriched domains

Further evidence for a direct relationship between PMP22 and cholesterol can be found by examining their co-association with liquid-ordered membrane domains. Ordered domains, also colloquially referred to as 'lipid rafts', are cholesterol and sphingolipid enriched regions that are thicker and more tightly packed areas of membrane within the bulk plasma membrane [56]. Lipid rafts have been extensively studied, especially in the context of signaling receptor clusters [57,58]. A number of biochemical studies have shown that PMP22 co-localizes with lipid raft cell fractions [43,59,60].

Cell-derived giant plasma membrane vesicles (GPMVs) have emerged as the best available platform for quantitative studies of ordered domains and their constituent proteins [61,62]. Elegant experiments in GPMVs

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have identified the structural determinants of the affinity of single pass proteins for ordered phase membrane domains [63]. However, only a handful of multipass membrane proteins, including PMP22, have been shown to partition into ordered domains in GPMVs [64,65]. Unsurprisingly, most of these proteins are myelin proteins, the myelin membrane is highly ordered, as it is enriched in cholesterol, sphingolipids, and contains an unusually high proportion of lipids vs protein [1]. The structural determinants that drive these proteins into ordered domains remain elusive. Palmitoylation is known to promote ordered phase association of single-pass membrane proteins; however, while PMP22 is palmitoylated at Cys85 located near the cytosol/membrane interface, this does not seem to influence its ordered domain affinity in GPMVs [65].

In GPMVs, 70–80% of WT PMP22 is seen to partition into the ordered phase [65]. It was also found that PMP22 expression stabilized ordered domains [65]. Moreover, when a panel of disease-causing PMP22 mutants were tested, five out of six showed a decrease in ordered phase partitioning including, for some mutants, a shift toward strong partitioning into disordered phases. The magnitude of the decrease in ordered partitioning also roughly correlates with the disease severity associated with the mutation, except for T118M which only rarely is associated with CMTD (as a risk factor) but was seen to strongly partition into disordered phases [66].

As mentioned above in their 2024 study, Prior et al. [28] found alterations in the plasma membranes of CMT1A iPSC-SCPs. It was observed that decreased levels of cholesterol in the PM, which corresponded with increased membrane disorder in GPMVs made from these cells using dyes that report on relative fluidity of membranes. A fluorescently labeled cholera toxin B-subunit (a raft cross-linker) was also employed to examine raft dynamics in isogenic (non-CMT) and CMT1A iPSC-SCPs via total internal reflection fluorescence imaging. Using particle tracking they observed that raft mobility in the PM was decreased in the CMT1A cells, suggesting the altered lipidome results in altered plasma membrane properties.

These data suggest that PMP22 partitioning into cholesterol-enriched ordered domains is critically important for healthy myelin formation. Combining these data with the cholesterol trafficking data above suggests the possibility that PMP22 stabilizes cholesterol- and sphingomyelin-enriched ordered nanodomains in the Golgi, facilitating the co-trafficking of lipids and protein to the plasma membrane. The necessity of lipid rafts to facilitate trafficking of cholesterol through the Golgi has been postulated before and may be crucial in SCs [50].

Interaction between PMP22 and ABCA1 mediates efficient cholesterol efflux

ABCA1 is an ABC transporter that is the primary cholesterol efflux transporter in SCs, responsible for HDL formation. Loss of function mutations in ABCA1 cause Tangier disease, which includes intracellular accumulation of cholesterol esters in SCs and polyneuropathy [67,68]. We here highlight a study from Zhou et al. [44] which demonstrated that PMP22 is required for efficient cholesterol export from the cell via ABCA1 at the plasma membrane.

An increase in total expression of ABCA1 was observed in nerves from PMP22 KO mice. However, it was found that ABCA1-dependent cholesterol efflux was decreased. This was detected as a sharp decrease in ApoE secretion (along with cholesterol) in PMP22 KO SC cultures. Decreased cholesterol efflux was explained by observation that trafficking of ABCA1 to the plasma membrane was significantly decreased. This was found when cyclosporin A-blocking endocytosis of plasma membrane-associated ABCA1 resulted in no effect on levels of secreted cholesterol, suggesting minimal levels of ABCA1 at the plasma membrane of PMP22 KO mouse SCs. Reduced levels of ABCA1 at the plasma membrane were confirmed by cell surface immunofluorescence microscopy in both nerves and cultured SCs.

These results in PMP22 KO mice suggest an important role for PMP22 in promoting ABCA1-mediated cholesterol export from SCs, although the mechanism remains uncertain. Interestingly, PMP22 protein levels in ABCA1 KO mouse nerves were increased 1.5-fold over WT while other myelin genes MAG, MPZ, and p75 remained relatively unchanged. However, most of this excess PMP22 was found to be intracellularly retained. In summary, observed increases in PMP22 protein levels by knocking out ABCA1 and *vice versa* strongly suggest an interplay between the two proteins in regulating cholesterol export. Direct interaction between the two may be possible, as immunofluorescence microscopy images of WT mouse SC cultures and longitudinal sciatic nerve sections showed extensive colocalization of PMP22 and ABCA1. Furthermore, both PMP22 and ABCA1 co-IP with one another in pulldowns from WT rat SC lysates.

As the trafficking and function of PMP22 and ABCA1 seem to depend on one another, it is tempting to speculate that they co-traffic, but this remains unclear. Also unclear is why PMP22 would promote cholesterol transport out of SCs. Perhaps this is a housekeeping role helping to clear excess cholesterol out of healthy SCs. An additional interesting possibility is related to the ability of SCs to actively de-myelinate axons after a nerve injury, prior to regeneration of healthy myelin. De-myelination may require the clearance of large amounts of cholesterol and other lipids from damaged myelinated SCs. Perhaps PMP22 and ABCA1 play a critical role in this process, but only additional data will tell.

Conclusions

The studies reviewed here suggest that PMP22 is involved in cholesterol biosynthesis, cholesterol trafficking to the SC surface (and thence to myelin), lipid raft formation, and cholesterol export. However, the detailed mechanisms and intermolecular interactions involved remain poorly understood. Moreover, the exact teleology of the seemingly SC-specific role of PMP22 in these systems remains to be deciphered. It is clear that too much or too little PMP22, as well as mutations in PMP22 result in defective cholesterol homeostasis, which likely contributes to the relevant phenotypes of CMTD (CMT1A, HNPP, DSS, and CMT1E). Future studies of the role of PMP22 in cholesterol homeostasis are likely to be fascinating from the standpoint of basic myelin biology and will also be highly significant by illuminating how these roles are aberrantly altered under CMTD conditions.

Perspectives

- PMP22 appears to play important roles in cholesterol homeostasis in SCs of the PNS, which is critical for healthy myelination of PNS nerve axons and the avoidance of CMTD.
- PMP22 has an affinity for partitioning into ordered cholesterol-rich membrane domains, co-IP with several proteins that that are directly or indirectly involved in lipid biosynthesis, may play a role in intracellular cholesterol trafficking, and appears to modulate the cholesterol (efflux) transporter ABCA1.
- While evidence is mounting that PMP22 plays central roles in SC cholesterol homeostasis, much future work will be required to confirm these roles and to determine the molecular mechanisms associated with each.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

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Abbreviations

CNS, central nervous systems; co-IP, co-immunoprecipitate; DSS, Dejerine-Sottas syndrome; GPMV, giant plasma membrane vesicle; HNPP, hereditary neuropathy with pressure palsies; iPSC-SCP, induced CMT1A pluripotent stem cell SC precursor; KO, knockout; MPZ, myelin protein zero; PNS, peripheral nervous system; SC, Schwann cell.

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