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Intra- and intercellular trafficking in sphingolipid metabolism in myelination

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Abstract

The myelin sheath, produced by oligodendrocytes in the central nervous system, provides essential electrical insulation to neurons, but also is critical for viability of neurons. Both the protein and lipid composition of this fascinating membrane is unique. Here the focus is on the sphingolipids that are highly abundant in myelin and, in particular, how they are produced. This review discusses how sphingolipid metabolism is regulated. In particular the subcellular localization of lipid metabolic enzymes is discussed and how inter-organelle transport can affect the metabolic routes that sphingolipid precursors take. Understanding the regulation of sphingolipid metabolism in formation of the myelin membrane will have a significant impact on strategies to treat demyelinating diseases.

I. Introduction-Myelination

The bulk of neurons in the central and peripheral nervous systems of vertebrates are enwrapped by a thick membraneous structure known as myelin. The development of myelin in the vertebrate nervous system marks a pivotal departure from that found in invertebrates and is thought to underlie the remarkable increase in complexity and size in vertebrate nervous networks. The major function attributed to myelin is as an electrical insulator. The high lipid content of myelin (discussed in detail below) generates a structure with low conductance. Placement of the myelin membrane along a neuron, with precisely localized gaps, allows changes in membrane polarization to be propagated far more rapidly and with less signal loss than along a naked neuron. While this function has been recognized for many decades, more recently the role of myelin in maintaining the health of neurons has become apparent. There is clearly a strategic relationship between neurons and their myelin sheaths involving signaling crosstalk and exchange of metabolites. Myelin is produced by highly specialized cells. In the central nervous system the myelin-producing cell type is the oligodendrocyte while in the peripheral nervous system myelin is produced by Schwann cells. The biology and differentiation of these cells and has been covered in several excellent

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reviews (Baumann and Pham-Dinh 2001; Emery 2010; Takebayashi and Ikenaka 2015; Woodhoo and Sommer 2008) and will, for the most part, not be covered in detail here. The focus of this review is on one of the essential lipid components of the myelin membrane, the sphingolipids. The unique physical characteristics of sphingolipids are key to the insulating properties of myelin membranes and also have been exploited to perform an important signaling function between the myelin membrane and its neuronal partner. Like all complex biological structures, the key to proper function is the assembly of the components in the correct order and proportion. Disruption of that coordination is thought to underlie many neuropatholgies. Therefore it is critical that we understand the pathways that govern assembly of the myelin membrane. The bulk of this review will focus on myelin in the central nervous system, although we will refer to myelin in the peripheral nervous system on occasion. Here we discuss one critical aspect of sphingolipids in the synthesis of myelin, how they move from their site of synthesis within the cell and how they move between cells. The trafficking of sphingolipids has been a difficult, but important area of study and considerable advances have been made in the cell biology of this process. Recently it has become apparent that not all of the lipids that are part of the myelin membrane are made in the cell types, oligodendrocytes and Schwann cells, which produce myelin, but instead appear to be produced by other cells and transported to the myelin-producing cells. Below we review what is known about both of these processes.

II. Composition of the myelin membrane

Myelin has a highly unique molecular composition when compared to other cellular membranes. As is often noted, myelin has an extremely high lipid to protein ratio. Most determinations put that ratio, on a weight to weight basis as 80:20 (lipid to protein) (Norton and Poduslo 1973). One striking aspect of the composition of the myelin membrane is that both the protein and lipid components are are highly specialized.

A. Protein Composition of Myelin.

While this review focusses on the lipid component of myelin, and the sphingolipids in particular, a full picture of the formation and function of the membrane would not be complete without mentioning the proteins of this membrane. We will not discuss these in detail here, but direct the reader to an excellent recent review by Han and Co-workers (Han et al. 2013), as well as a comprehensive review of myelin composition (Baumann and Pham-Dinh 2001). The most abundant myelin proteins are devoted to accomplishing the highly compact state of the myelin membrane in which membrane bilayers are closely opposed on both the cytoplasmic and extracellular sides of the bilayer. Extracellular compaction is accomplished in myelin of the CNS by myelin oligodendrocyte protein (MOG) and myelin associated glycoprotein (MAG), both members of the immunoglobulin superfamily. Myelin basic protein (MBP) is the predominant protein in the CNS responsible for drawing together the myelin leaflets on the cytoplasmic side of the membrane. The basic nature of this protein interacts with and shields the negative charged inner leaflet to accomplish this function. In addition to these two major proteins myelin associated oligodendrocyte basic protein (MOBP), a peripheral membrane protein with the FYVE membrane association domain

contributes to myelin stabilization. Proteolipid protein is a highly hydrophobic, membrane embedded protein of the CNS.

B. The lipid composition of the myelin membrane. Distinct properties of sphingolipids. Sphingolipid metabolism.

1. Lipid Composition of Myelin—One of the often cited features of myelin is the high lipid to protein ratio relative to the plasma membrane of most cells. Whereas the liver plasma membrane is approximately 50% lipid by weight, myelin membranes are closer to 70–80% lipid (O'Brien and Sampson 1965). What is equally striking however, is the composition of those lipids. A commonly cited analysis performed in 1965 reported that sphingolipids comprised 25% of the total wet-weight of myelin, while glycerolipids comprised 32% and cholesterol 19% (O'Brien and Sampson 1965). A more recent analysis reported that close to 75–80%(as mol%) of the non-sterol lipids of myelin are glycosphingolipids; the cerebrosides (glucosylceramide and galactosylceramide) and sulfatides (sulfated galactosylceramide). In this analysis the next most abundant lipid was reported to be phosphatidylethanolamine at approximately 15%, with phosphatidylserine, phosphatidylcholine, and sphingomyelin making up the remainder of the lipid (Camargo et al. 2017).

2. Sphingolipid physical effects on membrane structure.—Sphingolipids have a distinct physical character among lipids. The nitrogen in the sphingosine backbone that is the defining feature of this family allows for hydrogen bonding. Consequently sphingolipids have a high propensity for the formation of microdomains within membranes (reviewed in (Goni and Alonso 2006)). While the phospholipids in most biological membranes are in the so-called liquid crystalline, or fluid phase at physiological temperatures, sphingolipids generally are in the immobile gel phase at these temperatures. It should be noted, however, that each sphingolipid has distinct physical properties and therefore the exact mixture can strongly affect membrane properties. For example cerebrosides, as measured in giant unilamellar liposomes, form large, distinct domains in mixtures with phosphatidylcholine. (reviewed in (Longo and Blanchette 2010; Maggio et al. 2006)). These domains are modulated by cholesterol. As cholesterol levels rise, these domains become smaller, and the cerebrosides mix more readily with phosphatidylcholine. Cleary, therefore, changes in the ratio of cerebroside to cholesterol will have dramatic effects on the structure of the myelin membrane.

III. The basics of sphingolipid metabolism.

Here we will briefly review the pathway of sphingolipid metabolism. For a detailed description of the biosynthesis of sphingolipids, the reader is referred to a recent review (Davis, Kannan, and Wattenberg 2018).

A. The *de novo* biosynthetic pathway producing ceramides.

The initiating step in the biosynthesis of sphingolipids is the condensation of a fatty acyl-CoA, usually the 16 carbon fatty acid palmitate, with an amino acid, almost always serine, to produce a precursor of the sphingosine backbone, 3-ketodihydrosphingosine. This is further

metabolized to dihydrosphingosine, which lacks a 4/5 double bond characteristic of sphingosine itself. Dihydrosphingosine is then acylated on the characteristic nitrogen with fatty acids by one of the 6 members of the ceramide synthase family. These enzymes each have a selective preference for the fatty acids acylated to the dihydrosphingosine backbone, and therefore a spectrum of molecular species of dihydroceramides are produced. The 4/5 double bond is then introduced into the dihydroceramides to produce ceramide proper. **Ceramides assume a pivotal spot in sphingolipid metabolism as they form the backbone for the more complex sphingolipids including sphingomyelin and the glycosphingolipids.** Ceramides can be degraded by ceramidases to produce sphigosine for subsequent metabolism. The ceramidases have been implicated in a number of important physiological and pathophysiological processes (reviewed in (Coant et al. 2017). However if not degraded the subsequent metabolism of ceramides constitutes a critical decision point in terms of whether sphingolipid will be directed towards sphingomyelin, a structural component of the plasma membrane, or towards the glycosphingolipids, which have both structural and signaling roles in membranes. A central question with particular importance for production of the myelin membrane is what mechanism controls the diversion of ceramide to each of these two metabolic pathways and how that control is regulated to produce the required mix of downstream metabolites. This control mechanism is addressed in more detail below.

B. Beyond ceramide. The biosynthesis of sphingomyelin and glycosphingolipids.

Sphingomyelin is produced by the transfer of phosphocholine from phosphatidylcholine to ceramide by the sphingomyelin synthases. There are two isoforms of this enzyme, SMS1 and −2 (Reviewed in (Holthuis and Luberto 2010; Tafesse, Ternes, and Holthuis 2006)). SMS1 is considered the major route of sphingomyelin synthesis and resides in the trans Golgi. SMS2 resides in primarily in the plasma membrane, and is speculated to mediate the salvage of ceramide produced in the plasma membrane by sphingomyelinases.

Ceramide is also the backbone for the generation of glycosphingolipids. There are two glycosphingolipid biosynthetic pathways which differ by the initial carbohydrate that is conjugated to ceramide; either galactose or glucose. An overview of these pathways as well as diseases of compromised glycosphingolipid metabolism can be found in excellent reviews by Konrad Sandhoff (Kolter, Proia, and Sandhoff 2002; Kolter and Sandhoff 2006). The generation of galactosylceramide by the enzyme UDP–galactose ceramide galactosyl transferse (also known as ceramide galactosyl transferase or CGT) is a relatively specialized pathway predominantly found in the brain (Schulte and Stoffel 1993; Stahl et al. 1994). This is the first step in generating sulfatide, the sulfated form of galactosylceramide, which is found predominantly, and at high levels, in myelin. Sulfatide is generated by galactosylceramide sulfotransferase (Honke et al. 1997). The generation of sulfatide is the terminal step of the galactosylceramide/sulfatide arm of the glycosphingolipid metabolic pathway. In contrast the other arm of glycosphingolipid biosynthesis, which begins with the conjugation of glucose to ceramide by the enzyme ceramide glucosyltransferase, is the initiating step in the generation of a large and complex family of glycosphingolipids. Subsequent to the generation of glucosylceramide is the addition of galactose to form lactosylceramide, which serves as a building block for an array of glycosphingolipids

derived from elaboration of the carbohydrate structure (Reviewed in (Kolter, Proia, and Sandhoff 2002; Kolter and Sandhoff 2006)). Specific structures are produced by the selective addition of galactose, N-acetylglucosamine, N-acetylgalactosamine, and sialic acid (Reviewed in (Yamaji and Hanada 2015)), which are grouped according to the backbone carbohydrate chain. Of special note are the gangliosides, which possess terminal sialic acid. The negative charge of this sugar is exploited to generate strong binding interactions. The diverse carbohydrate structures serve as specific recognition motifs and are utilized by a variety of cell types for cell/cell recognition.

IV. Compartmentalization and trafficking in sphingolipid biosynthesis.

A dominant feature of biosynthetic sphingolipid metabolism is that the metabolites are highly hydrophobic and the enzymes that mediate sphingolipid metabolism are, without exception, membrane bound. This confines all of the metabolism of these interesting lipids to the membranes of specific organelles. Moreover some of these reactions occur on the cytosolic face of organelle membranes and some occur on the luminal face. Therefore the metabolism of sphingolipids can be controlled by the transport of substrates and products both from one organelle to another and also by transport across membranes. In this section we will outline the compartmentalization of biosynthetic sphingolipid metabolism to set the stage for a discussion of how that compartmentalization is utilized to control the specific synthesis of individual sphingolipid species. For a more details, the reader is referred to an excellent review that focusses on this topic (Yamaji and Hanada 2015).

A. The steps leading to ceramide production occur in the endoplasmic reticulum.

Serine palmitoyltransferase produces the precursor of the sphingosine backbone on the cytosolic face of the endoplasmic reticulum. All of the subsequent steps that produce ceramide also occur in the endplasmic reticulum with the reactions occurring on the cytosolic face (Hirschberg, Rodger, and Futerman 1993; Michel et al. 1997). Therefore the final metabolite in this portion of the sphingolipid metabolic pathway, ceramide, begins its life in the endoplasmic reticulum. As will be discussed in ensuing sections, the further metabolism of ceramide to more complex sphingolipids occurs in other compartments. As will become apparent, transport of ceramide to these compartments is a critical regulatory step that determines which metabolites are produced.

B. Sphingomyelin synthesis in the Trans-Golgi. Transport between the ER and Golgi by the ceramide transport protein CERT.

As noted above, whereas ceramide is produced in the endplasmic reticulum, the major sphingomyelin synthase, SMS1, is localized in the trans-Golgi. How, then, does ceramide reach the trans Golgi from the endoplasmic reticulum? The answer comes from marvelous work by Kentaro Hanada starting in the early 2000s and continuing to the present. Dr. Hanada discovered that for sphingomyelin synthesis, ceramide is delivered to the trans Golgi by a protein known as CERT. We refer the reader to excellent reviews by Dr. Hanada for details of CERT structure and activity (Hanada et al. 2009; Yamaji and Hanada 2015). CERT has three functionally important domains. The START domain, shared with other lipid binding and transport proteins, binds ceramide. Binding of CERT to the endoplasmic

reticulum is accomplished by a FFAT domain, which binds to the ER membrane protein VAP. The bridge to the trans-Golgi is accomplished through a plekstrin homology domain in CERT which binds to phosphatidylinositol-4-phosphate generated in the trans-Golgi. A current model of CERT action pictures the protein bridging the ER and Golgi at sites in which these two organelles are in close opposition. In this model the START domain swings between these two organelles, picking up ceramide in the ER and delivering it to the trans-Golgi to serve as a substrate for sphingomyelin synthase.

C. Glucose-based sphingolipid formation is initiated in the Cis/Medial Golgi.

The initial step in the biosynthesis of glucosylceramide-based sphingolipids is the addition of glucose to ceramide by UDP-glucose:ceramide glucosyltransferease (Ichikawa et al. 1996). Interestingly, the active site for glucosylceramide synthesis is on the cytosolic face of the cis/medial Golgi (Futerman and Pagano 1991; Marks et al. 1999). This has two important consequences. First, ceramide does not need to traverse a membrane bilayer to access the active site of the glucosyltransferase. Secondly, since the remainder of the enzymes in the glucosylceramide metabolic pathway have active sites oriented towards the Golgi lumen, glucosylceramide needs to be flipped across the Golgi membrane for subsequent metabolism.

D. Glucosylceramide transport determines how lactosylceramide is utilized.

Lactosyl ceramide is generated by the addition of galactose to glucosylceramide by the lactyosylceramide synthase B4GalT5 (Kumagai et al. 2010). The active site of this enzyme is localized in the lumen of the Golgi (Burger, van der Bijl, and van Meer 1996; Lannert et al. 1994). Therefore glucosylceramide must be both translocated across the Golgi membrane and also transported to the site of lactosylceramide synthesis. The identity of the glucosylceramide transmembrane transporter remains unknown. However the transport of glucosylceramide to other compartments of the Golgi for lactosylceramide synthesis has recently been shown to have a fascinating regulatory role (D'Angelo et al. 2013). Lactosylceramide is utilized for two major series of glycolipids, as well as more minor pathways. Addition of an additional galactose defines the Globo series whereas the addition of sialic acid defines the Ganglio series. Initial localization of lactosylceramide synthesis was to the Golgi (Burger, van der Bijl, and van Meer 1996), but it has become apparent that glucosylceramide synthesis occurs in a separate Golgi compartment from lactosylceramide synthesis. It was initially was shown by De Matteis and colleagues that a glucosylceramide binding and transport protein, known as FAPP2, was required for full lactosylceramide synthesis (D'Angelo et al. 2007). However subsequent study by this same group demonstrated a more complex picture(D'Angelo et al. 2013). While synthesis of the Globo series of lipids was reduced by FAPP2 knockout, synthesis of the Ganglio series was unaffected. These data are explained by the differential localization of the transferases that define these two glycolipid sub-families. The sialyltransferase that adds sialic acid to lactosylceramide (ST3Gal5), defining the gangliosides, is localized in the medial and trans Golgi (Halter et al. 2007). The transferase that adds galactose to lactosylceramde (A4GalT), to form the Globo series, resides in the trans Golgi network (TGN) a functionally and morphologically distinct compartment (D'Angelo 2013). The mystery is why FAPP2 affects one pathway, but not the other, considering that FAPP2 is required for glucosylceramide

transport for lactosylceramide production, and lactosylceramide is used for both the Globo and Ganglio series. The answer may lie in the distribution of the lactosylceramide synthase. These experiments indicate that this enzyme resides in multiple locations that determine whether the product is used for Globo or Ganglio synthesis. Taken together, these data suggest that transport of glucosylceramide from the cis/medial Golgi to the TGN requires transport by FAPP2, and the product is then utilized for Globo synthesis. However transport of glucosylceramide from its site of synthesis to the medial/trans Golgi is accomplished by vesicular trafficking and is then used for Ganglio synthesis (D'Angelo et al. 2013). Therefore the distribution of lactosylceramide between the Globo and Ganglio pathways relies on the relative activity of FAPP2 and vesicular trafficking. FAPP2 binds to two effectors that determine localization, phosphoinositol-4-phosphate (PI4P) and ADP ribosylation factor-1 (Arf1), a GTPase best characterized for the recruitment of coat proteins in vesicular trafficking (Godi et al. 2004). Therefore the relative levels of Globo and Ganglio-series production will be controlled by the levels of PI4P and Arf1 in the TGN. What has yet to be explored is if and how trafficking of glucosylceramide to the trans Golgi is regulated. It is conceivable that sorting of this lipid into transport vesicles is another layer of regulation of downstream metabolism of glycosphingolipids.

E. Galactose-based glycosphingolipid synthesis is initiated in the endoplasmic reticulum.

The generation of galactosylceramide is minor in most tissues, but critically important for myelin function. The enzyme that initiates this pathway, ceramide galactosyltransferase, is localized to the endoplasmic reticulum (Sprong et al. 1998). However unlike the ceramide glucosyltransferase, the active site of the galactosyltransferase is on the luminal site of the ER. Thus the product, galactosylceramide, is generated on the luminal leaflet and does not need to flip across a bilayer for subsequent metabolism. The major modification that occurs to galactosylceramide, and one that is critical for myelin function, is sulfation to generate the glycosphingolipid known as sulfatide. The galacosylceramide sulfotransferase, first cloned in 1997 (Honke et al. 1997), is localized to the Golgi apparatus (Yaghootfam et al. 2007). Therefore the transport of galactosylceramide to the Golgi is a controlling step in this essential lipid. Currently the mechanism that underlies this transport is unknown. Considering that galactosylceramide is generated on the luminal surface of the ER, it is likely that this transport occurs by vesicular trafficking. However this has yet to be directly tested.

V. In the central nervous system some lipids for myelin production are exclusively made in oligodendrocytes and some are contributed by astrocytes.

Oligodendrocytes produce myelin as extensions of the oligodendrocyte plasma membrane (Baron and Hoekstra 2010; Snaidero et al. 2014). These protrusions require a significant output of the membrane components that compose the myelin membrane. It was initially assumed that the lipids for myelin production were synthesized by the oligodendrocytes, but this view, while correct for some lipids, is now being challenged for others.

As noted above, galactosyl ceramide and its sulfated downstream metabolite sulfatide, are essential for functional myelin (Dupree et al. 1998; Honke et al. 2002; Marcus et al. 2006). These early studies utilized global knockouts of the enzymes. To test whether it is only the galactosylceramide produced by oligodendrocytes that is essential Matthias Eckhard's group tested whether re-expression of the galactosyl transferase only in oligodendrocytes could rescue the myelin defect in the global knockout animals (Zoller et al. 2005). The answer was that for myelin synthesis, expression of galactosyl transferase in the oligodendrocytes is sufficient for myelin function and therefore that galactosylceramide must be produced solely in the oligodendrocytes in myelin synthesis.

A very different picture emerges for other lipids from the work of Mark Verheijen and colleagues (Camargo et al. 2017). These workers analyzed a cell specific knockout of the transcription factor sterol regulatory element-binding protein (SREBP). SREBP was first identified as a transcription factor activated when cellular levels of cholesterol are reduced (Brown and Goldstein 1997). However it soon became apparent that SREBP activation regulates an array of lipid metabolic enzymes responsible for fatty acid as well as sterol synthesis (Reviewed in (Shimano 2001)). Verheijen and colleagues found that an oligodendrocyte-specific knockout of SREBP delayed myelination in the central nervous system, confirming an important, if expected, role for oligodendrocyte lipid metabolism in myelin formation. Surprisingly, however, after 3 months, myelination appeared normal. Where, then, were the lipids for myelin coming from at these later stages after birth if not the oligodendrocytes? Astrocytes, which perform a number of supporting roles in the brain, are known to have robust lipid metabolism (Hofmann et al. 2017). The Verheijen group decided to test whether astrocytes contribute lipids to myelin. The used a conditional astrocyte-specific knockout of SREBP to test this concept. Remarkably embryonic knockout of astrocyte SREBP led to a deficiency in myelin formation as did knockdown post-natally. This strongly indicates that astrocytes make a major contribution to the lipids in myelin. The notion that lipids for myelination are derived both from astrocytes as well as oligodendrocytes is emphasized by the observation that a combined knockout of SREBP in both cell types leads to an absolute absence of myelination, a much stronger phenotype that knockout in either cell type individually. Interestingly, lipids from the diet could be incorporated into myelin, indicating that oligodendrocytes have the ability to take up circulating lipids for myelin formation and therefore do not have to completely rely on endogenous synthesis. This is an unexpected result as the blood/brain barrier seems to block circulating lipoproteins from access to the brain (reviewed in (Dietschy and Turley 2001)). The identity of the lipids being transferred from the astrocytes to the oligodendrocytes has not been completely defined, but includes both fatty acids and sterols. The essential role of cholesterol in myelination has been very well reviewed and will not be discussed further here (Saher and Stumpf 2015).

How do the astrocyte lipids reach the oligodendrocytes? This has yet to be determined directly. One possible mechanism would utilize lipoprotein particles produced in the brain itself. Lipoprotein particles can be found in cerebrospinal fluid (reviewed in (Vitali, Wellington, and Calabresi 2014)). The most abundant of these is a particle that resembles serum high density lipoprotein, but contains apolipoprotein E (ApoE) rather than Apolipoprotein A (ApoA), the latter of which is the major apolipoprotein of serum HDL.

ApoE is mainly produced by astrocytes in the brain ((DeMattos et al. 2001), reviewed in (Vance and Hayashi 2010)). However there is a hitch in this explanation. ApoE knockout mice have been available for decades (Ishibashi et al. 1994). And because ApoE expression has been linked to Alzheimer's disease (Schmechel et al. 1993), the neurological consequences of ApoE knockout have been extensively studied (reviewed in (Rogers and Weeber 2008)). Despite this extensive study there are no reports that ApoE deletion affects myelination. There are many potential explanations for these data that would still implicate astrocyte-derived lipoproteins in lipid transport from astrocytes to oligodendrocytes. The loss of ApoE in the knockout animals could be balanced by the induction of a compensatory mechanism. These lipoproteins may utilize another apolipoprotein, such as ApoJ, which is also produced in astrocytes (Reviewed in (Vance and Hayashi 2010)). Another possibility is that lipids are transported from astrocytes to oligodendrocytes by astrocyte-derived microvesicles (also known as exosomes) (Reviewed in (Paolicelli, Bergamini, and Rajendran 2018)).

VI. Summary and Future Directions

A fascinating characteristic of the sphingolipid family of lipids is the complex and inter-related metabolism that ties them together. Especially pertinent to the formation of the myelin membrane is the distinct lipid composition, rich in sulfatides, and both galctosyl and glucosyl cerebrosides. The focus of this review is on how sphingolipid metabolism is regulated to produce this distinct composition and, in particular, the distinct intracellular localization of the sphingolipid metabolic enzymes. This distribution means that the transport of sphingolipid precursors between compartments can control which downstream metabolic pathway predominates when using a common precursor. This review also highlights the fascinating observation that not all of the lipids utilized for myelin production in the oligodendrocyte are produced by the oligodendrocytes themselves but are also derived from astrocytes. This implicates yet another point of regulation, the intercellular transport of lipids. This has been clearly shown for glycerolipids and sterols, but the transfer of sphingolipids seems limited, although this has not been exhaustively tested. There is intense clinical interest in the treatment of demyelinating diseases such as multiple sclerosis, so understanding the mechanisms of myelination, and how these might be manipulated to treat these diseases, is of significant translational importance. Sphingolipid metabolism has been implicated in these diseases (Kota and Hama 2014; Wang and Bieberich 2018). There is still much to be learned about how interorganelle transport regulates sphingolipid metabolism. Although much is known about some of the mechanisms involved, including CERT transport of ceramide for sphingomyelin production and FAPP2 transport of glucosylceramide for globoside production, the regulation of these mechanisms is poorly understood. Inter-compartmental transport of other sphingolipid substrates and products is generally thought to occur by vesicular trafficking. What is not well understood is to what extent the incorporation of these lipids into transport vesicles is regulated and how that selective incorporation occurs. In addition, much of the transport ascribed to vesicular transport is by inference rather than direct experimental determination. This leaves open the possibility that there are as yet undescribed transport mechanisms that remain to be uncovered. The exciting

prospect of elucidating these mechanisms and utilizing that knowledge to design therapeutic strategies to treat demyelinating diseases lies before us.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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