Physiol Rev 99: 1381–1431, 2019
Published May 8, 2019; doi:10.1152/physrev.00031.2018

MYELIN IN THE CENTRAL NERVOUS SYSTEM: STRUCTURE, FUNCTION, AND PATHOLOGY

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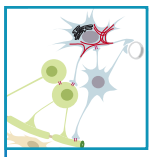

Stadelmann C, Timmler S, Barrantes-Freer A, Simons M. Myelin in the Central Nervous System: Structure, Function, and Pathology. *Physiol Rev* 99: 1381–1431, 2019. Published May 8, 2019; doi:10.1152/physrev.00031.2018.—Oligodendrocytes generate multiple layers of myelin membrane around axons of the central nervous system to enable fast and efficient nerve conduction. Until recently, saltatory nerve conduction was considered the only purpose of myelin, but it is now clear that myelin has more functions. In fact, myelinating oligodendrocytes are embedded in a vast network of interconnected glial and neuronal cells, and increasing evidence supports an active role of oligodendrocytes within this assembly, for example, by providing metabolic support to neurons, by regulating ion and water homeostasis, and by adapting to activity-dependent neuronal signals. The molecular complexity governing these interactions requires an in-depth molecular understanding of how oligodendrocytes and axons interact and how they generate, maintain, and remodel their myelin sheaths. This review deals with the biology of myelin, the expanded relationship of myelin with its underlying axons and the neighboring cells, and its disturbances in various diseases such as multiple sclerosis, acute disseminated encephalomyelitis, and neuromyelitis optica spectrum disorders. Furthermore, we will highlight how specific interactions between astrocytes, oligodendrocytes, and microglia contribute to demyelination in hereditary white matter pathologies.

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I. INTRODUCTION

In 1854, Rudolf Virchow coined the term *myelin* from the Greek word for marrow (myelos) to describe the structure particularly abundant in the core of the brain (70). He speculated that myelin was secreted by neurons and acted as an insulating mass. A century later, the histological stainings by Pio Del Rio Hortega and Wilder Penfield suggested that myelin is not of neuronal origin, but is formed by oligodendrocytes. Using silver carbonate stainings, they were able to visualize oligodendrocytes with their thin processes connected to myelin sheaths. These stainings showed that oligodendrocytes are enriched in the white matter but are also found in the grey matter, and are mostly localized intrafascicularly, sometimes also perineuronally or perivascularly. Oligodendrocytes generate up to 80 different myelin sheaths on various axons to promote rapid saltatory conduction by concentrating voltage-dependent sodium channels at the nodes of Ranvier (693). The prevailing view since the discovery of this mechanism in 1949 has been that the only function of myelin is to enable maximum conduction velocity and to reduce axonal energy consumption (269). However, there are now a number of recent observations challenging this notion. Increasing evidence supports a role for activity-dependent, plastic changes in myelin-forming oligodendrocytes that influence neuronal circuit function (181, 190, 417). Furthermore, evidence is accumulating that oligodendroglia provide metabolic support to neurons via their myelin sheaths (197, 344). These new developments are not only expanding our knowledge of myelin in normal physiology, but also of its role in the pathology of various neurological and psychiatric diseases. This notion of a broader interaction between oligodendrocytes and neurons requires an in-depth molecular understanding of how oligodendrocytes and axons interact and how they generate, maintain, and remodel their myelin sheaths. In this review, we discuss the structure, composition, formation, and function of myelin in normal development, and its disturbances in various diseases. We focus in particular on myelin architecture and its underlying biology and pathology, but will not cover how oligodendrocyte progenitor cells (OPCs) are specified or how they migrate, proliferate,

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and differentiate into myelinating cells. For a discussion on oligodendrocyte biology, we refer to previous reviews on the various aspects of this topic (157, 158, 167, 168, 211, 351, 407, 519, 535, 609, 662).

II. MYELIN STRUCTURE

Most of what we know about myelin ultrastructure is based on electron microscopy studies that illustrate its multilayered stack with its characteristic periodic structure of alternating electron-dense and light layers, the so-called major dense line and the intraperiod line. The major dense line represents the closely condensed cytoplasmic surfaces, whereas the interperiod line consists of the tightly apposed outer membranes (7, 546). The compaction between the membranes in each of these layers results in a periodicity of ~12 nm. At the edges of each myelin segment, individual myelin lamellae attach to the axon as cytoplasm-containing terminal loops. In a typical myelin sheath, the paranodal domain is ~4 μm long, which allows the apposition of up to 40 loops (248). The 10- to 15-μm-long domain adjacent to the paranode is called the juxtaparanode. In between the paranodes of two neighboring myelin sheaths is the 0.8- to 1.1-μm-wide nodal region. The axon is usually constricted in the nodal region, and this diameter reduction is more marked in larger fibers (247). The constriction starts at the paranodes where the axon diameter is reduced to ~30–50% of its internodal value. In particular, nodes of large fibers are completely covered by astrocytic processes (61, 98, 247, 249, 500) which are embedded in a granular material mostly composed of extracellular matrix. Ultrastructural analysis of large nodes shows that perinodal astrocytic processes form microvilli-like processes that contact to the outer paranodal loops of the oligodendrocytes.

In chemically fixed samples, the paranodal axoglial junctions, which are similar to invertebrate septate junctions, are characterized by intercellular "transverse bands" that anchor the paranodal loops tightly to the axon (47, 256). The "radial component," a further feature of myelin observed by electron microscopy, appears on cross section as radially oriented, linear thickenings of the intraperiod line extending across the myelin sheath (468). These nearly parallel strands of autotypic tight junctions (formed between membrane lamellae of the same cell) are arranged both through the stack of membranes and in the planes of the membranes parallel to the fiber axis, mostly in the region between the inner and outer tongue (220).

These tight seals of myelin with their apposing lamellae are crucial for the insulating properties of myelin, preventing current leakage and allowing for efficient and fast nerve conduction. The downside of such a tight arrangement is the difficulty of maintaining molecular exchange within the myelin sheath and its associated axon. Thus pathways enabling molecular transport are necessary. These noncompacted regions comprise the outer and inner, periaxonal tongues of myelin membranes and the paranodal loops (62, 206, 576). Since electron microscopic studies performed on chemically fixed and dehydrated tissue often lead to shrinkage and collapse of intracellular spaces, cytoplasmic regions have been difficult to detect in the thin myelin sheaths of the central nervous system (CNS). However, with the use of high-pressure freezing electron microscopy to enhance tissue architecture or by dye injections, cytoplasmic channels can be seen. Three-dimensional reconstructions of cytoplasmic spaces reveal an extensive network of interconnected cytoplasmic pockets (~1.9 pockets per 10-μm sheath length) (652). Together with the paranodal loops, these cytoplasmic channels provide the means to distribute molecules or organelles such as peroxisomes and lysosomes through the internode (521). During development, when these channels are particularly abundant, they have a crucial function in enabling myelin growth by connecting the oligodendroglial cell body, the major site of membrane biosynthesis, with the innermost layer of myelin, which is in direct contact with the axon (581). In the adult nervous system, they may also provide a functional connection between the oligodendrocyte and the periaxonal space, allowing the distribution of glial metabolites to the axonal compartment.

For very small molecules (<1 kDa) such as cyclic nucleotide, vitamins, and ions, there are other possible routes across the myelin sheath. Freeze-fracture replicas of myelinated axons have shown abundant intramembrane particles in the external leaflet of the juxtaparanodal membrane of the axon and the innermost myelin layer as well as between the myelin lamellae at the paranodes (406, 600, 601). Subsequent work has shown that these structures represent gap junctions composed of connexins (4, 290, 425, 440, 448, 549). These gap junctions form a radial pathway that shortens transport through the myelin sheath by up to 1,000-fold compared with the circumferential route following the noncompacted areas within myelin. The gap junctions not only couple the periaxonal space with myelin, but also connect to a vast network of interconnected glial cells, the so-called panglial syncytium (507). Astrocytes, the most abundant cell of the panglial syncytium, are coupled to oligodendrocytes at the cell body and at the paranodes where gap junctions directly link the outer layer of the myelin sheath with an astrocytic process. Astrocytes are also extensively connected to each other, thereby pervading the entire brain parenchyma including the perivascular space at the blood-brain barrier (79, 96). Furthermore, gap junctions are formed between astrocytes and ependymal cells providing a drainage pathway into the ventricles (508). This system joins the periaxonal space to a highly interconnected system of glial cells to provide widespread osmotic and ionic homeostatic regulation of the axon-myelin unit. There is also a second route for small molecules into the periaxonal space. Although paranodal axoglial junctions form an effi-

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cient diffusion barrier for most molecules, they leave small triangular junctional clefts near the axonal surface where paranodal membranes curve away from each other and into which small molecules can diffuse into the internodal periaxonal space (405).

III. MYELIN COMPOSITION

A. Proteins

1. Major dense line

A striking feature of membrane compaction is the generation of a uniform, 3-nm-wide, electron-dense compartment between two lipid bilayers, into which only few other proteins intermix. This unique structure is stabilized by a variety of adhesion mechanisms, of which myelin basic protein (MBP) is essential for the compaction of the two adjacent cytoplasmic membrane surfaces into the major dense line of myelin (511, 524, 525). MBP is an intrinsically unstructured polypeptide chain; however, upon association with membranes, MBP adopts both α-helical and β-sheet structures (237). The interaction of MBP with the membrane is mainly based on electrostatic forces between the basic residues of MBP and the negatively charged headgroups of the inner leaflet lipids, phosphatidylserine and phosphatidylinositol 4,5-bisphosphate (423, 433). By binding to the cytosolic membrane surfaces, opposite charges are neutralized, allowing other forces such as hydrogen bonding and hydrophobic factors to be unmasked. Membrane binding switches the properties of MBP, thereby promoting self-interaction into a tightly packed protein phase that occupies the major dense line and binds the cytoplasmic surfaces of the bilayers tightly together (6, 498). Such a phase transition from a soluble to a polymerized pool of molecules is frequently observed for many structurally disordered proteins, in particular those engaged in RNA binding (34).

2. Intraperiod line

In contrast to the compaction of the cytosolic surfaces, the mechanisms that mediate the close interaction of myelin lamellae at their external surfaces are less well understood. Interactions of plasma membranes over long distances are rarely observed in nature as they are, in general, prevented by repulsive forces generated by thermal undulation and glycocalyx components on the cell surface (541). The proteolipid protein (PLP) together with its splice isoform DM20 is the most abundant transmembrane protein in CNS myelin and an ideal candidate for the tight apposition of membrane sheaths via its hydrophilic extracellular domains (67, 310, 431). Although abnormally compacted myelin is often seen in aldehyde-fixed tissue from mice lacking PLP and DM20, this is not the case when using high-pressure freezing electron microscopy, indicating that myelin is physically unstable during processing for conventional electron microscopic analysis (32). Even if these studies suggest a possible function of PLP in myelin adhesion and stability, the major phenotype observed in mice lacking PLP and DM20 is axonal degeneration and swelling (333). Related molecules such as the PLP homolog, glycoprotein M6B, or the structurally related tetraspanins or claudins may compensate the adhesive function of PLP (122, 146, 665). Another possibility is that loss of repulsive forces from the external surface of myelin is sufficient to uncover the weak generic interactions necessary for membrane compaction (32). The reason why oligodendrocytes use weaker forces for the apposition of their extracellular membrane surfaces, as compared with the cytoplasmic leaflets, might lie in the way myelin is formed. During myelin wrapping, the external membrane surfaces of myelin need to glide along each other, and this is only possible if the membranes are of low adhesiveness.

3. Radial component

The radial component is a network of interlamellar tight junctions composed of claudin-11 that connect the outer leaflets of the myelin lamellae (220, 420). Mice lacking claudin-11 suffer from mild tremors, gait abnormalities, motor defects, and electrophysiological abnormalities, including a 50% decrease in conduction velocity in small-diameter axons (220). These abnormalities do not arise from disruption of myelin or axonal architecture, but from the changes in the barrier function of myelin (152, 154). Tight junctions potentiate the insulative properties of myelin, in particular of small caliber axons, reducing current flow through myelin and allowing for efficient saltatory nerve conduction.

4. Cytoplasmic regions

When MBP is bound to two adjacent cytoplasmic membrane surfaces, it drives membrane zippering at the cytoplasmic surfaces of the myelin bilayer. The zippering results not only in the extrusion of cytosol, but also in the formation of a narrow and dense protein phase that limits the entry of most proteins into the myelin sheaths (7). To maintain functional cytoplasm-rich compartments within myelin, there must be mechanisms to oppose MBP-mediated membrane compaction. 2′,3′-Cyclic nucleotide 3′-phosphodiesterase (CNP1) is such a factor, as CNP1-deficient mice have a lower number of cytoplasmic channels within their myelin sheaths (582) **(FIGURE 1)**. CNP1 directly associates with the actin cytoskeleton, forming a firm structure that is able to antagonize the adhesive forces exerted by polymerizing MBP molecules (141, 582). It is possible that CNP1 together with the actin cytoskeleton forms struts that keep the cytoplasmic leaflets at a sufficient distance to prevent membrane compaction. Cytoplasmic channels may be required to support efficient diffusion of metabolites and

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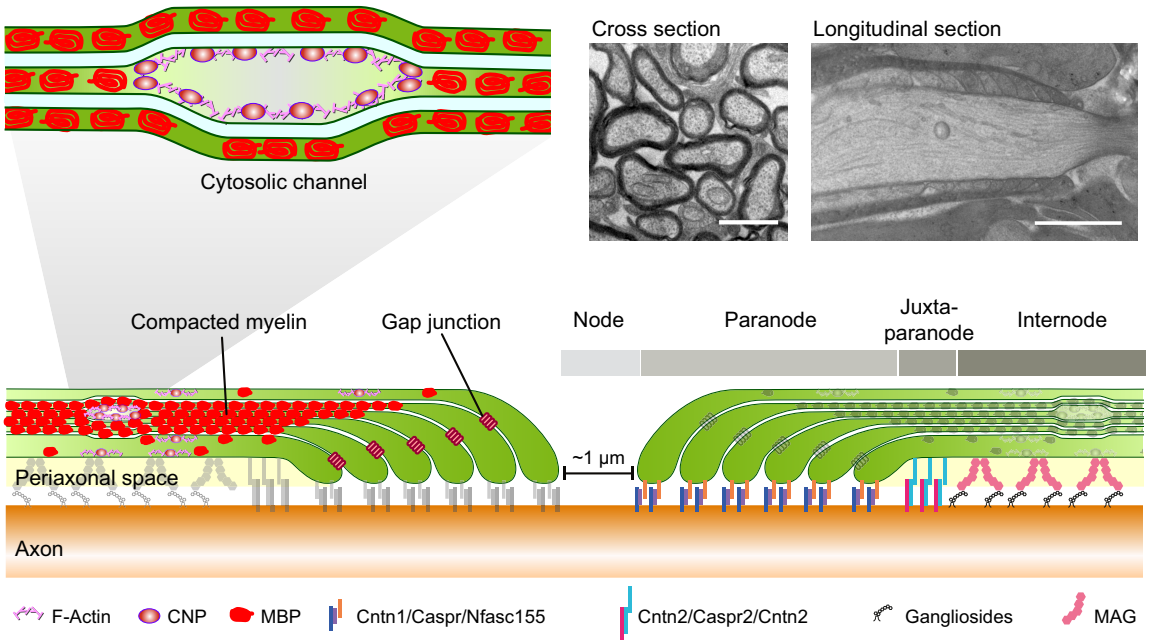

FIGURE 1. Schematic illustration of central nervous system myelin structure. Graphical illustration of myelin structure including the different domains of myelinated axons. Myelin basic protein (MBP) is essential in generating compacted myelin membrane stacks by zippering the cytoplasmic surfaces closely together. 2′,3′-Cyclic nucleotide 3′-phosphodiesterase (CNP) interacts with the actin cytoskeleton and counteracts the polymerizing forces of MBP, thereby generating cytoplasmic channels within the myelin sheath. Gap junctions connect the paranodal loops of myelin at the lateral edges of myelin. MAG, myelin-associated glycoprotein. [Adapted from Saab and Nave (536).]

allow motor-driven transport of vesicular cargo within myelin. Cytoplasmic channels may also be necessary for the transport of trophic molecules to the periaxonal space to maintain functional axon-glial units. This model concurs with the finding that CNP1-deficient mice exhibit progressive axonal pathology with axonal swellings and spheroid formation (333). CNP1-deficient mice have also disrupted paranodes and swollen inner tongues, often containing amorphous granular material, microtubules, and, occasionally, mitochondria and autophagic vacuoles, possibly as a consequence of a traffic jam (165, 506). By reducing MBP levels, cytoplasmic channels are restored in CNP1-deficient mice and axonal pathology is reduced in large-caliber axons (582).

5. Gap junctions

Gap junctions are composed of connexins, a family of integral membrane proteins composed of four transmembrane domains joined by two extracellular loops (4). Six connexins oligomerize into a hemichannel, and two hemichannels on apposing cell membranes form the gap junctions, permeable to diffusion of ions and small molecules (typically <1 kDa). Paranodal homotypic gap junctions are composed of a single connexin protein ("homotypic gap junction"), whereas oligodendrocyte/astrocyte gap junctions are composed of different connexin proteins forming "heterotypic gap junctions." Oligodendrocytes express connexin (Cx) 32, Cx47, and Cx29, whereas astrocytes mainly contain Cx30 and Cx43. Cx32 is localized to oligodendrocyte cell bodies, to the abaxonal membrane, and at the paranodes, where it forms Cx32/Cx32 channels (15, 290, 309, 388, 443). Oligodendrocyte/astrocyte gap junctions are mainly composed of Cx47/Cx43 and Cx32/Cx30 channels, of which Cx47/Cx43 channels are largely localized adjacent to oligodendrocyte somata, whereas the Cx32/Cx30 channels are mainly found on the outer layer of myelin sheaths. Cx29 hemichannels are localized at the internode, along the adaxonal membrane of small myelinated fibers (8, 14). These gap junctions enable metabolic transport, spatial buffering, and electrical coupling between the cells. Disturbances of gap junction coupling lead to various forms of leukodystrophies and may also be involved in the pathogenesis of neuromyelitis optica (364).

6. Axon-glial junction

The paranodal axon-glial junction attaches the myelin sheaths at each end of the myelin segment to the axon. A single junction is an extremely large structure with an area occupying up to 150 μm^2 (533). The main function of the junction is to provide electrical insulation by restricting current flow beneath the myelin sheath. To do so, the junction fixes the paranodal membrane close to the axon, leading to the formation of a barrier separating the nodes from the internodal axon. However, the barrier that is formed is not absolutely tight. There are small junctional gaps between the paranodal loops which can be used for the diffusion of

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ions, nutrients, and other metabolites in between the axon and the myelin sheaths (405). These gaps are so narrow, and the junctions so long, that short-circuiting of nodal action potential currents is efficiently restricted, while slow diffusion of metabolites to the internodal axon is permitted. The junction consists of a tripartite complex of cell adhesion molecules, composed of contactin-associated protein (Caspr) and contactin-1 at the axonal and neurofascin (NF155) at the glial side (57, 72, 113, 214, 504). The lateral organization of these complexes into larger protein arrays leads to the appearance of electron-dense transverse bands when visualized by electron microscopy. These complexes are further interconnected through the attachment to a submembranous layer of cytoskeletal scaffolding proteins (456). These are ankyrinG at the glial side and the scaffolding proteins 4.1B, αII spectrin, and βII spectrin at the axonal side of the paranode (18, 111, 257, 445, 696). The subcortical axonal cytoskeleton is composed of repeating ringlike arrangement of short actin filaments (135, 683). These actin filaments are capped at their barbed ends by α-adducin and connected longitudinally by spectrin tetramers. This arrangement results in the formation of quasi-one-dimensional lattice structures with a periodicity of ~180–190 nm. Super-resolution microscopy of myelinated sciatic nerve fibers has shown that many of the nodal and paranodal components such as ankyrinG, Caspr, NF168, and voltage-gated sodium channel associate with these ringlike actin structures (134, 136). Such a structural arrangement of the cell adhesion to several layers of cytoskeleton components is a common theme in domain organization at the axon-glial interface and is also seen at the juxtaparanode.

One important function of the paranodal axon-glial junction is to segregate the voltage-gated sodium channel at the nodes from the Kv1 K^+ channels consisting of Kv1.1, Kv1.2, Kv1.4, and KVβ2 subunits at the juxtaparanodes (503). The localization of Kv1 channels depends also on the interaction with axonal Caspr2 and glial TAG-1 (also known as contactin-2). Caspr2 and TAG-1 most likely form a diffusion trap that in turn forms "sticky spots" which result in the clustering and the immobilization of Kv1 channels at the juxtaparanodes (481, 629). The association of Kv1 with ADAM22 and with PSD95 and PSD93 via its PDZ-binding motive may serve as an additional mechanism involved in the clustering and/or stabilizing of the channels at the juxtaparanode (261, 444).

7. Axon-glial internodal domain

The internodal region of the myelinated axon is also organized into a specialized domain. In addition to the paranodal staining, an internodal strand of Caspr extends into the internodal domain, contacting the inner lamellae of the myelin sheath. Unlike axons in the PNS, there is no internodal strand of Kv1.1, Kv1.2, Kvβ2, and Caspr2 in the CNS (23). While Caspr is confined to a thin band of the internodal region, myelin-associated glycoprotein (MAG) localizes around the entire circumference of the adaxonal myelin membrane (497). MAG interacts with specific neuronal gangliosides, such as GT1b and GD1a (127, 299, 558, 685). High-pressure freezing electron microscopy has revealed an axon-myelin spacing of ~10 nm (581). This periaxonal diameter matches exactly with the crystal structures of the MAG-full ectodomain (495). Whereas monomeric MAG could span intermembrane distances of ~16 nm, the *cis*-dimerization of MAG brings the cytosolic regions into close proximity and restricts the periaxonal diameter to 10 nm. The dimerization of MAG may also trigger downstream signaling cascades. MAG-induced signaling involves various kinases such as fyn tyrosine kinase in oligodendrocytes and Cdk5 and ERK1/2 in axons (138, 241, 636). Whereas fyn activation occurs by the association to its cytoplasmic domain, it is not known how the extracellular domain of MAG communicates the signal to the axoplasma. MAG-induced Cdk5 and ERK1/2 activation, in turn, induces the phosphorylation of neurofilaments and microtubule-associated proteins, thereby contributing to the maturation of the axonal cytoskeleton and to the thickening of the axon diameter. Consequently, MAG-deficient mice exhibit reduced neurofilament phosphorylation and axonal caliber, possibly leading to progressive axonal loss in aged animals (689). Surprisingly, myelin ultrastructure is relatively normal, with only subtle abnormalities such as redundant hypermyelinations (418, 636). Whether MAG contributes to the selection of axons for the initiation of myelination is not known, but it is possible that it acts together with immunoglobulin cell adhesion molecules (Cadm) (i.e., Cadm3/Necl1/SynCAM1 and Cadm4/Necl4/SynCAM4) that have also been found to localize to the myelin-axon internodal interface (382, 591).

Yet another stabilizing structure of the axon-myelin unit are filamentous scaffolds in the innermost layer of myelin that extend longitudinally along the internode. These filaments are composed of distinct septin monomers (Sept2/Sept4/Setpt7/Sept8) and are associated with the adaptor protein anillin (461). Lack of septins causes myelin focally to detach from the axon and to form outfoldings.

B. Lipids

Intermolecular cohesions between lipid molecules play a major role in the generation of myelin (7, 123, 441, 557). Myelin contains high levels of saturated, long-chain fatty acids and is enriched in glycosphingolipids (~20% molar percentage of total lipids) and cholesterol (~40% of molar percentage of total lipids) (557). Galactosylceramides and sulfatides with long-chain fatty acid moieties, in particular 24:0 and 24:1 fatty acids, are the most typical myelin lipids. Long-chain fatty acids are also observed in other lipid classes. The high proportion of saturated, long-chain fatty

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acids influences membrane structure such as membrane thickness and the packing density of lipids within myelin. The role of long-chain fatty acids in ceramides has been analyzed by targeting ceramide synthase 2 gene (CerS2), one of six members of the ceramide synthase gene family. CerS2 null mice have reduced levels of galactosylceramides and sulfatides with very-long-chain fatty acyl chains (C22:0-C24:0). However, they form relatively normal myelin with mild structural defects, such as focal detachments of myelin lamellae (271, 473).

Mice that lack the UDP-galactose:ceramide galactosyltransferase (CGT) do not synthesize galactosylceramide and sulfatide and develop severe neurological deficits a few weeks after birth (69, 125, 161). Myelin is formed, but its thickness is reduced, redundant myelin outfoldings are observed, and the paranodes are disorganized with the loops facing away from the axon.

A similar paranodal phenotype is found in mice lacking cerebroside sulfotransferase (CST), an enzyme required to generate sulfatides (260). CGT- and CST-null mice express axonal paranodal Caspr and Contactin-1, but lack glial paranodal NF155 (551). Since total cellular NF155 levels are unaltered in these mice, it is likely that sulfatides are required to cross-link and/or to stabilize NF155 at the paranodes.

Another class of myelin-enriched lipids are ethanolamine plasmalogens. Plasmalogens contain a vinyl ether linkage at the *sn*-1 position and an ester linkage at the *sn*-2 position. The *sn*-2 acyl chain is oriented perpendicularly, favoring a closer alignment of both acyl chains in plasmalogens. In addition, the lack of carbonyl oxygen at the *sn*-1 position increases the hydrophilicity and results in stronger intermolecular hydrogen bonding between the headgroups (557). Thus plasmalogens may increase the packing density and as a consequence the stability of myelin. However, mice deficient in PEX7, a receptor for a class of peroxisomal matrix enzymes, or deficient in the peroxisomal dihydroxyacetonephosphate acyltransferase gene (DAPAT), the key enzyme involved in plasmalogen biogenesis, produce relatively normal myelin, although with an unaltered lipid composition, again pointing to compensatory mechanisms (82, 528).

Due to its unique structural properties, cholesterol is one of the few lipid classes that cannot be replaced by other lipids. However, after oligodendrocyte-specific deletion of squalene synthase, catalyzing the first committing step of cholesterol biosynthesis, myelination is still possible, but is severely delayed (543). Surprisingly, these mutant oligodendrocytes are able to take up cholesterol from extracellular sources and to initiate myelination. In squalene synthase-deficient oligodendrocytes, the rate of myelination is slower, but some myelin sheaths are formed with almost normal morphology. Even under physiological conditions oligodendrocytes receive a substantial fraction of cholesterol from astrocytes, and this pathway is likely to be upregulated when oligodendrocytes are unable to synthesize it by themselves (102).

Taking these studies together, it is clear that myelin structure is particularly insensitive to perturbations of individual lipids (but also proteins), and has a strong capacity to maintain its specific organization. The reason may be that lipids behave and act as collectives. Thus, after deleting the synthesis of one lipid class, the synthesis of structurally related lipids increases and takes over function. How oligodendrocytes sense the lack of one component and adjust the synthesis of another structurally related molecule is one of the unsolved mysteries.

C. Myelin Function

1. Action potential propagation

A hallmark of myelinated fibers is saltatory nerve conduction, which enables faster and more efficient propagation of signals as compared with unmyelinated axons of the same diameter (522). To allow for saltatory conduction, the myelin sheath must be tightly sealed to the axon to prevent current leakage below the myelin sheath. Not surprisingly, mice lacking the essential components of the paranodal axon-glial junction such as Caspr, contactin-1, and NF155, develop severe neurological phenotypes that lead to death within a few weeks after birth (57, 72, 566). Notably, the neurological phenotype is much more severe as compared with MBP-deficient *shiverer* mice. *Shiverer* mice form less myelin, and the myelin that is formed consists of loosely compacted myelin lamellae with only up to four wraps of unstable myelin (525, 581). Some of the basic structural elements of myelin such as the radial component and the axo-glial junctions are still present in *shiverer* myelin (532), but most of the axonal surface lacks myelin entirely. Thus the noninsulated nerve fibers in *shiverer* mice may still be able to propagate action potential, albeit in an immature continuous manner, whereas mice lacking paranodal junctions suffer from conduction blocks caused by current leakage. A major function of the paranodal junction is to separate voltage-gated sodium and potassium channels. This spatial segregation of conductance is of vital importance for the isolation of the potassium-sensitive nodes from exposure to high potassium levels. Potassium levels beyond 4–5 mM cause repetitive depolarization, and further increases can lead to conduction blocks due to an inactivation of the sodium channels (507). To avoid this, the outward potassium current is confined to the juxtaparanodal and internodal membrane. Since the number of axonal potassium leak channels and Na^+-K^+-ATPase may not be sufficiently high to handle the increased potassium load in the periaxonal space, one important function of myelin is potassium

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siphoning (45). This may occur by potassium leak channels such as $K_{ir}4.1$ and/or gap junctions in the innermost layer of the myelin sheath (335). Oligodendrocyte-specific deletion of $K_{ir}4.1$ leads to slower clearance of extracellular K^+ and delayed recovery of axons from repetitive stimulation, as well as spontaneous seizures (335, 554). Because oligodendrocytes express Cx29, which lacks coupling partners, at the paranodal loop, it is also possible that Cx29 functionally couples with the axonal expressed Kv1 channels that localize to the same area (507). Within the cytoplasmic areas of the paranodal loops and/or the inner myelin tongue, potassium must be rapidly transferred out of the myelin sheath (389). This can be achieved by Cx32/Cx32 channels linking the cytoplasmic spaces of the paranodal loops to each other, providing a shortcut to the outermost myelin lamellae onto which astrocytes connect using another set of gap junctions (348). Depending on the distance of the coupled astrocytes to the drainage system, these intercellular fluxes of water and potassium may either be directly transferred to the astrocyte endfeet or travel through another layer of astrocytes using astrocyte-to-astrocyte gap junctions. Efflux of potassium and water occurs from the astrocytes endfeet at the glia limitans into the circulation or at the meninges into the cerebrospinal fluid. Potassium efflux is likely mediated by $K_{ir}4.1$ and water by aquaporin-4 (AQP4) channels at the endfeet (96). Electrical voltage and osmotic gradients are thought to be the driving forces for water and potassium siphoning (507). Following an action potential, the periaxonal space depolarizes to as high as +75 mV, whereas the negative membrane potential of astrocyte endfeet of −85 mV provides a potential difference of +160 mV which may drive the potassium from the periaxonal space, through the myelin sheath and into astrocytes (139, 140). In addition, the high potassium concentration of 20–100 mM at the periaxonal space as compared with 2 mM in the capillary lumen may provide an osmotic driving force.

2. Metabolic coupling

The formation of tight barriers and compacted layers of insulating membrane are needed to prevent ion leakage, but this arrangement comes at a price. The axonal surface becomes disconnected from the extracellular, nutrient-rich environment, and as a consequence, the axon must work together with the myelin sheath to obtain vital metabolites. This dependency of axons on oligodendrocytes to meet metabolic demand has led to the idea of their metabolic coupling. The built-in system of cytoplasmic channels that run through the myelin sheath and connect the oligodendrocyte soma to the innermost layer of the myelin sheath is a necessary structural requirement for myelin to function as a metabolic supporter of neurons. The concept that glial cells contribute to neuronal metabolism was initially proposed for astrocytes and led to the astrocyte-neuron lactate shuttle hypothesis (295, 464). However, astrocytes contact neurons mainly at the cell body, synapses, and nodes, but not along the length of the axon. Axons are covered by myelin, and space at the nodes is limited; therefore, it does not appear feasible that nodes harbor all essential surface molecules that are required for uptake of nutrients and metabolites from the extracellular environment. Instead, it is more likely that metabolic uptake occurs in part via myelinating oligodendrocytes (475, 537) **(FIGURE 2)**. The capacity of oligodendrocytes to generate high levels of lactate was demonstrated in conditional Cox10 (protoheme IX farnesyltransferase) mutant mice, in which oxidative phosphorylation was specifically prevented in oligodendrocytes (197). Cox10-conditional mutants form normal myelin, but magnetic resonance spectroscopy reveals increased brain lactate concentrations, pointing to the capacity of oligodendrocytes to maintain ATP levels by glycolysis alone. Oligodendrocytes may not only use lactate for their own metabolism, but also to support neurons. Indeed, oligodendrocytes were found to express monocarboxylate transporters (MCT1) at the adaxonal membrane of the myelin sheath (344). The main function of MCT1 is to cotransport lactate, pyruvate, and ketone bodies together with H^+ ions across membranes along a concentration gradient. Oligodendrocyte-specific knockdown of MCT1 in organotypic slices leads to axonal injury, which is corrected by addition of lactate into the culture medium. In addition, *Mct1* heterozygous aged knockout mice or mice with oligodendrocyte-specific *Mct1* deletion develop axonal degeneration without any visible alterations of myelin. Together, this has led to the concept that oligodendroglial lactate (or pyruvate) is used by axons when energy levels are low. Oligodendrocytes appear to sense the metabolic demands of axons by *N*-methyl-D-aspartate (NMDA) receptors that are associated with the internodal/paranodal membrane (538). These receptors respond to axonal glutamate release, resulting in the incorporation of additional glucose transporters into oligodendrocytes and myelin to fuel glycolysis. Thus the oligodendrocyte-lactate shuttle might be driven by neuronal activity, which controls production of lactate to adapt to high axonal energy needs.

An alternative pathway for the transport of nutrients is through a gap junction. The pan glial syncytium, connecting the vasculature with glial cells via gap junctions to the axon, is perfectly poised to participate in supporting the metabolic demands of neurons. Since most polar molecules with a mass of less than ~1 kDa can pass through gap junctions, many metabolites including sugars, amino acids, and nucleotides can flow between the interiors of the cells. These metabolites can diffuse down their concentration gradient to other astrocytes within the large syncytium, and possibly also to oligodendrocytes and from there to neurons. The contribution of gap junctions to the metabolic support of neurons has been difficult to test, as these gap junctions also contribute to other processes such as myelination and potassium siphoning.

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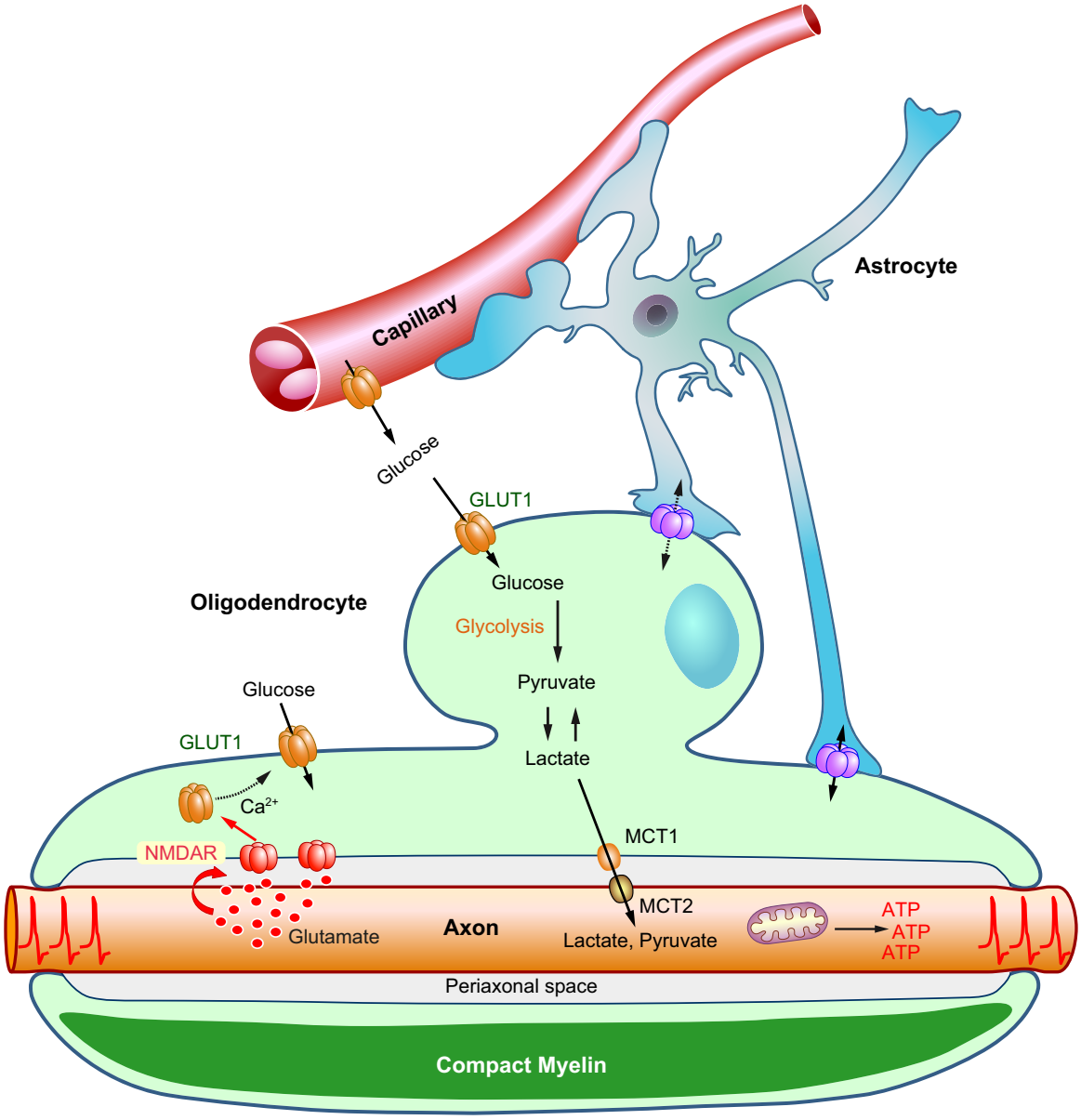

FIGURE 2. Schematic illustration of the metabolic coupling of oligodendrocytes, astrocytes, and neurons. Oligodendrocytes (green) take up glucose, which is metabolized to lactate and pyruvate, and delivered to the axons using monocarboxylate transporters (MCTs) to fuel the axon with energy. Neuronal activity results in the release of glutamate into the periaxonal space, where it activates *N*-methyl-D-aspartate (NMDA) receptors at the inner myelin membrane. This in turn triggers the translocation of glucose transporters (GLUT1) into the surface of the myelin sheath and/or oligodendrocyte cell body to increase glucose uptake and the availability of lactate/pyruvate. Astrocytes (blue) are connected to oligodendrocytes by gap junctions to enable metabolite transfer between the cells. [Adapted from Saab and Nave (536).]

Yet, another pathway in oligodendrocyte and neuron communication is through the exchange of exosomes/microvesicles. Oligodendrocytes produce relatively larg amounts of microvesicles (33, 322, 628), and these vesicles have been shown to be secreted in response to activity-dependent release of glutamate (195). Neurons ar able to internalize the released microvesicles by endocytosis. Improving neuronal viability under conditions of cell stress appears to be one function of microvesicles (195). Further research will be necessary to define the molecules that mediate these neuroprotective effects.

D. Myelin Formation

1. Axon selection

Myelination progresses according to a relatively fixed chronological and topographic sequence. It starts in areas dedicated to basic homeostasis, proceeds to regions controlling more complex tasks, and ends in areas required for the highest intellectual functions (83, 304). Within a neuronal pathway, myelination often progresses in a proximal to distal direction, and within a brain region from a central

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region to the poles. Fiber systems that mediate sensory input are usually myelinated before the systems carrying motor output are. As a simplified general rule, myelination usually ascends along a hierarchical order of increasing complexity of nervous system functions, and axons in regions that are myelinated early are also myelinated more rapidly and more completely. For example, all axons in the optic nerve are myelinated, and this happens early and fast, whereas myelination of axons in the frontal cortex is late, slow, and incomplete. Within the cortex, there are not only myelinated and nonmyelinated axons next to each other, but also partially myelinated axons. Such a patchwork pattern of myelinated segments with long unmyelinated stretches of up to ~50 μm was initially observed in axons that arise from cortical neurons (624). A large proportion of these incompletely myelinated axons appear to be parvalbumin-positive basket cells (402) with myelinated segments preferentially localizing to the axon arbor near the cell body (402, 597). These complex patterns raise the question of how oligodendrocytes select which axons and which part of the axons are to be myelinated. So far, the search for factors in axons that determine whether they will be myelinated or not has been unsuccessful. In fact, oligodendrocytes are able to ensheath and/or wrap myelin around artificial glass or polymer substrates (48, 342). Such experiments have led to the concept that physical cues such as axon caliber size play a major role in regulating myelination (49). Axons of large caliber with a diameter of 1 μm or more are notably not only the first to be selected for myelination, but are usually also fully myelinated. In contrast, axons with a diameter of 0.2 μm or less are generally left completely unmyelinated. One possible explanation for size-dependent myelination is the inability of myelin to bend beyond a certain curvature, making wrapping of small-caliber axons difficult. Indeed, when oligodendrocytes are cultured together with inert fibers of different diameters, there is a size-dependent ensheathment of fibers with a diameter of 0.4 μm or more (342). However, in the brain there is an intermediate range of axon diameter, between 0.2 and 0.8 μm, where axons can be myelinated or not (515, 660). In addition, there are many tubular structures such as dendrites and glial processes that are never myelinated. Clearly, diameter cannot be the only factor determining which axons oligodendrocytes select for myelination. Oligodendrocytes constantly sample their environment using highly dynamic processes equipped with yet unidentified sensing molecules, which upon interaction with membranes either mediate retraction or, once the appropriate axon is found, stabilize contact (133, 266, 307). Sheath retraction is mediated by elevation of intracellular Ca^{2+} levels, which in turn activates Ca^{2+}-dependent proteases such as calpain to mediate cytoskeleton breakdown (35, 323).

Most cells are covered by a shell of inhibitory cell surface molecules, forming the negatively charged glycocalyx that mediates electrostatic repulsion between the negatively charged cell surfaces, thereby preventing unspecific contact. In addition, repulsive guidance molecules inhibit the interaction or the outgrowth of oligodendroglial processes (574). A number of such inhibitory molecules such as polysialylated neural cell adhesion molecule (PSA-NCAM) on immature neurons (112), junctional adhesion molecule 2 (JAM2) on the somatodendritic compartment (513), limbic system-associated membrane protein (Lsamp) on neurons of the limbic system (565), and class 3 semaphorins (477, 607) have been identified. How specificity is provided to this interaction remains an enigma. The current model, based on the combination of physical cues and loss of negative inhibitory factors, is likely to be only part of the answer. Repulsive molecules may operate together with instructive molecules to ensure that contacts are made where they should. However, the search for such instructive signals has been disappointing. Most factors such as electrical activity, glutamate release, neuregulin signaling, or interactions with extracellular matrix receptors of the integrin family modulate myelination to some extent, but do not determine whether myelination will occur or not (54, 81, 101, 142, 151, 339, 363, 403, 656, 668).

2. Myelin growth

One of the initial ideas of how myelin is generated was by neuronal secretion of lipid-protein droplets, which would "crystallize out" into myelin with its characteristic fine structure. In a seminal study, Betty Ben Geren showed that myelin is not axon-derived, but a continuous membranous extension of Schwann cells (52). She showed that the thickness of the forming myelin sheath is dependent on the number of concentric lamellae, and the younger the fiber, the smaller the number of layers. Bunge et al. (95) observed the motion of the Schwann cell nucleus during myelination and concluded that as the cell does not change its position, the inner tongue of the myelin membrane must be responsible for its movement underneath the growing sheath. Together, these studies established the "jelly roll or carpet crawler" model of spiral wrapping in the peripheral nervous system (PNS).

The connection of a Schwann cell to the myelin sheath is relatively easy to visualize by electron microscopy in the PNS, but the association of oligodendrocytes to myelin is difficult to observe in the CNS, where fine processes separate the cells from their myelin sheaths. With the progress of sample preparation and fixation conditions, it was eventually possible to visualize the outer tongue of myelin connected to an oligodendroglia process (381, 469). Using serial sectioning for electron microscopy, the Bunge laboratory discovered that a single oligodendrocyte generates multiple myelin internodes wrapped around different axons (94). To understand how each of these processes wraps around an axon to form myelin has been challenging, and has led to the proposal of various models. Some of them diverge considerably from the "jelly roll or carpet crawler"

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model of the PNS. One model proposes that myelin forms by coalescence of intracytoplasmic membranes (147), or by the fusion of glial processes from one or different oligodendrocytes (366). A recent study using three-dimensional electron microscopy came to a very similar conclusion (608). According to this model, myelin membrane is synthesized in the perikaryon and transported as tubules which eventually fuse inside of oligodendroglial processes where they form "myelin" (608). Another study proposed that myelin wrapping is accomplished by the addition of new layers on top of the inner ones in a "croissant-like" manner (583). Alternatively, myelin may twist as a coil across the axon in a corkscrew motion ("yo-yo" model) (462). This is supported by time-lapse light microscopy analysis of oligodendroglial processes revealing their movement in a corkscrew-like manner around the axon, followed by focal expansion of these processes (272). According to these models, one single glial process encircles spirally the future internode, followed by the lateral growth of all layers over each other. The reason for the multitude of models lies in the complicated pattern a developing myelin sheath displays in the CNS. In the PNS, the glial membrane extends along a large portion of the axon before it makes one turn and moves underneath the growing sheet (93). Thus the number of layers is relatively uniform at all stages of its formation. In the CNS, in contrast, the number of myelin layers can vary along the length of the myelinated segment, resulting in the formation of a coil with an average periodicity of 5.7–7 μm (97, 462, 583). With three-dimensional electron microscopy techniques together with high-pressure freezing for fixation of the tissue, it is possible to determine the structure of the developing myelin sheath in sufficiently large volume and close to its native state (581). When determining myelin structure from development to maturation, a model arises that brings together several features of the above-mentioned studies. This model suggests that myelin grows towards the node, wrapping the leading edge at the inner tongue around the axon and underneath the previously deposited membrane **(FIGURE 3)**. Each myelin layer always remains in close contact with the axonal surface, thus forming the coiling helical pattern previously described (97, 462, 583). These lateral edges move towards the future node where they align and position as paranodal loops. How the layers become fixed to the axon is not known. One possibility is that they are attached to the axon by axo-glial adhesion molecules such as NF155, Caspr, and contactin-1 (462, 700). However, these molecules do not seem to be required for myelin growth, as myelin is still generated when the axo-glial junctions are not formed (126, 604, 700).

3. Contribution of myelin in node formation

Concomitant with the further lateral extension of the myelin sheath, sodium channels start to cluster adjacent to the edges of lateral loops (505, 604). Further longitudinal growth of myelin leads to movement of such "heminodes" towards each other, until ultimately two neighboring heminodes fuse, thereby forming a node of Ranvier. Along most axons of the CNS, sodium channels are positioned by direct contact to the developing myelin sheath. In most cases, the clustering of sodium channels follows the formation of paranodes (505). However, paranodes are not absolutely required for the formation of nodes. Disruption of paranodal junctions causes only mild perturbations to sodium channel clustering (57, 478, 619). In addition, soluble factors have been described that promote sodium channel clustering in the absence of myelin deposition (192, 292, 293). It appears that there are three distinct mechanisms at work in the formation of nodes: *1*) a glia-derived extracellular matrix complex containing proteoglycans and adhesion molecules such as versican, brevican, and Bral1 that cluster NF186; *2*) axonal cytoskeletal scaffolds consisting of ankyrinG-βIV spectrin that stabilize nodal sodium channels; and *3*) the already mentioned paranodal axoglial junctions that function as barriers to restrict the position of nodal proteins. To arrive at this model, compound knockout mice had to be generated in which at least two of these overlapping mechanisms were targeted simultaneously. Mice with two mechanisms disrupted at once had profound disruptions in node formation as compared with mice lacking just a single clustering mechanism (604).

4. Forces and signals driving myelin wrapping

To wrap myelin around the axons, a mechanism is required to overcome the adhesive forces that are generated when the inner tongue crawls underneath the forming myelin sheath. Actin dynamics appear to play a crucial role in this process (434, 703), but these are still not completely understood. Strikingly, actin depolymerizing drugs (which in most cells lead to process retraction) promote the extension of a developing myelin sheet in culture (434, 703) and even in vivo (703). One possibility is that actin-depolymerizing agents enhance actin dynamics by supporting the iterative cycles of polymerization/depolymerization at the leading edge that drives its protrusion. Actin is dynamically remodeled by both polymerizing/nucleating factors (such as members of the Wiskott-Aldrich syndrome protein family) which regulate the Arp2/3 (actin-related proteins) complex, and depolymerizing factors (ADF/cofilin family members) which break down actin behind the front and free actin monomers for reassembly. Conditional ablation of members of the Wiskott-Aldrich syndrome or ADF/cofilin1 proteins results in profound defects in myelination (180, 284, 303, 434, 439). Arp2/3 has been deleted at different stages of myelin development (702), and its deletion at early stages of the oligodendrocyte lineage impairs myelination as expected. Surprisingly, the conditional ablation at a later stage does not affect myelin growth. One possible explanation is that actin-mediated forward propulsion at the leading edge is only required for ensheathment, but not for later stages of myelin wrapping, which may instead be driven by other forces such as hydrostatic pressure built up by MBP.

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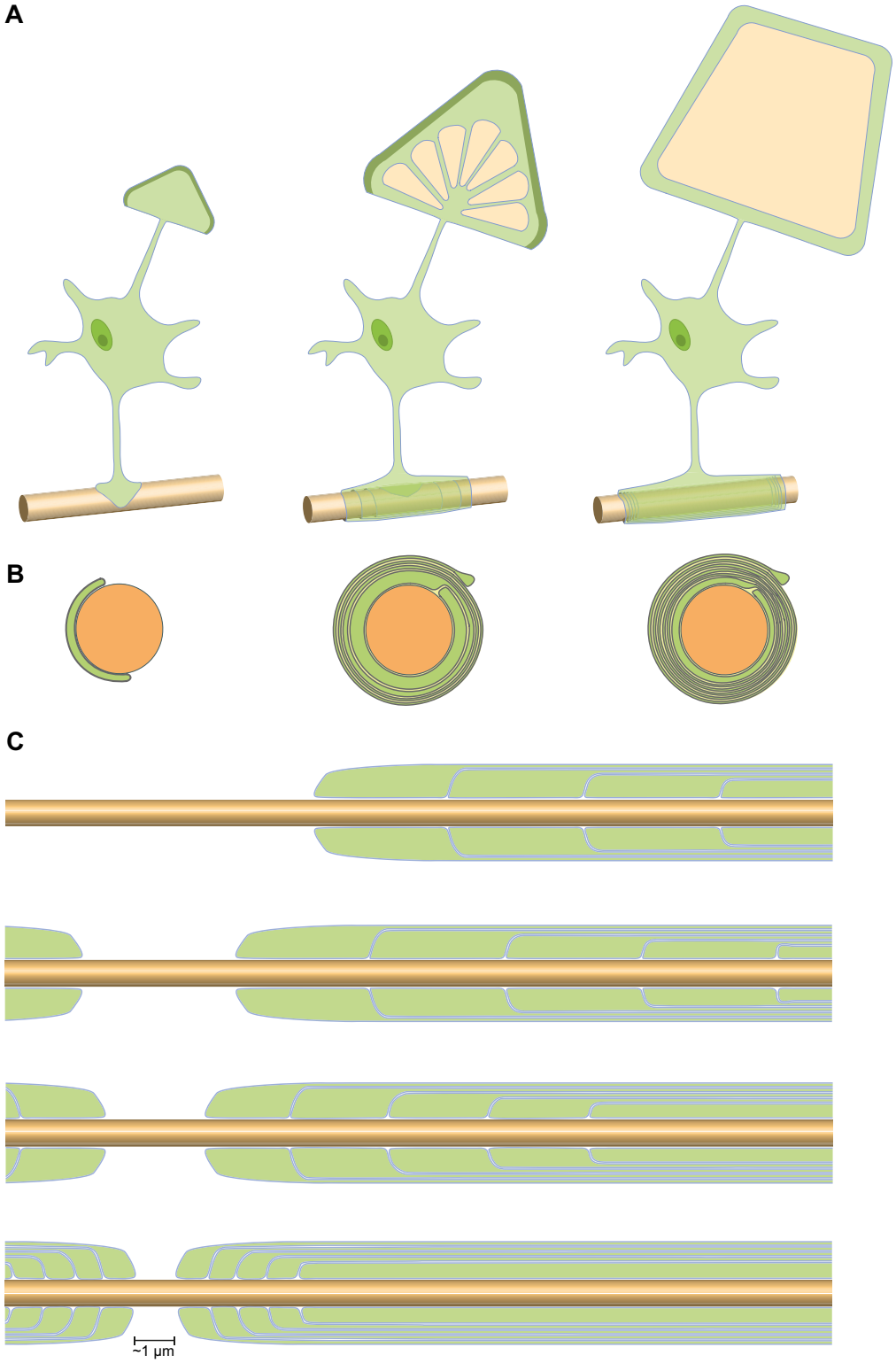

FIGURE 3. Model of myelination in the central nervous system. *A*: an oligodendrocyte is shown at different stages of myelination. *Top panel* illustrates a virtually unrolled myelin sheath with the compacted areas shown in orange and the uncompacted areas in green. *B*: the corresponding cross sections are depicted below the axon. *C*: the longitudinal view of a myelinated axon is displayed at different stages of the myelination process. [Adapted from Chang et al. (110) and Snaidero et al. (581).]

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Lengthening of the myelin sheath is controlled by the rate of Ca^{2+} transients (35, 323). Such Ca^{2+} transients may regulate the activity of proteins involved in cytoskeletal dynamics or in signaling such as the PI3K-AKT-mTOR pathway, which is Ca^{2+}-activated and which promotes myelin growth when activated in oligodendrocytes (699).

Myelin biogenesis is associated with the synthesis of huge amounts of membrane. Oligodendrocytes that form myelin around small-diameter axons generate as many as 80 internodes ranging from 20 to 200 μm in length with up to 60 different myelin layers, whereas oligodendrocytes that myelinate larger caliber axons have fewer processes, but longer internodes and thicker myelin sheaths (121, 248, 380, 422, 516). The surface area of myelin formed by one oligodendrocyte, estimated at 20×10^5 μm^2, appears to be relatively constant between cells (474). Myelin synthesis occurs along the biosynthetic pathway, where myelin lipids preassemble together with PLP, followed by its vesicular transport to the myelin sheath using motor proteins (40, 41, 573, 577, 669). Using the glycoprotein G expressed by vesicular stomatitis virus to follow membrane trafficking in myelin showed that newly synthesized proteins are delivered to the inner tongue close to the axon (581). The transport of the vesicles occurs through cytoplasmic channels that connect the oligodendroglial cell body with the innermost layer of myelin. For the lateral growth, membrane needs to be transported to the lateral cytoplasm-enriched loops of each myelin layer. Some of the cytoplasmic channels extend laterally within the myelin sheath and appear to end within myelin outfoldings (581). These myelin outfoldings are abundant in the growing myelin sheath, suggesting that they are a physiological structure and part of normal myelin development, possibly formed by not fully matching radial and longitudinal growth rates.

To generate myelin, radial and longitudinal growth need to be coordinated. A variety of signaling systems have been identified using mouse mutants that show distinct overgrowth phenotypes. Mice in which phosphatidylinositol 3,4,5-trisphosphate [PtdIns(3–5)P_3] levels are specifically elevated by genetic disruption of *Pten* in oligodendrocytes have thicker myelin and display myelin outfoldings (210). Increase in myelin thickness occurs also when constitutively active AKT kinase, a downstream target of PtdIns(3–5)P_3, is expressed in oligodendrocytes (188). The scaffold protein, Disks large 1 (Dlg1), has been identified as a brake on myelination in the PNS (130); however, in the CNS, Dlg1 enhances AKT activation and promotes myelination (438). Other phosphatidylinositol signal pathways are also known to regulate myelination. In mice, mutations of Fig4, Pikfyve, or Vac14, encoding key components of the PtdIns(3,5)P_2 biosynthetic complex, lead to impaired oligodendrocyte maturation and severe hypomyelination (409). In addition, FAM126A, also known as hyccin, that regulates the synthesis of PtdIns(4)P, is associated with hypomyelination and congenital cataract in humans (44). Apart from phosphoinositol signaling and the PI3K-AKT-mTOR pathway, ERK/MAPK signaling has emerged as a key pathway in myelin growth (198, 199, 275, 429, 634).

There are also examples of mouse mutants that produce focal outfoldings in the absence of myelin thickening. For example, the deletion of Cdc42 or Rac1 in oligodendrocytes results in the formation of myelin outfoldings, but with reduced overall myelin thickness (622). Furthermore, mutants have been identified that affect radial and longitudinal growth in a converse manner. Conditional mouse mutants of scribble, a conserved regulator of cell polarity, show increased myelin thickness, but decreased longitudinal myelin extension, indicated that these two modes of growth are differentially regulated (283).

5. Myelin compaction

Myelin membrane compaction occurs when the extracellular and cytoplasmic leaflets of the adjacent myelin lamellae connect so tightly that most of the water is removed and electron-dense lines can be seen by electron microscopy. Whereas the extracellular leaflets appear to associate already as the first wrap is made, the generation of the major dense line occurs in most cases later and often only after a few wraps have been formed. Compaction at the cytoplasmic surfaces starts in the outermost layers of myelin and progresses inward, moving towards the inner tongue (581). The spatial segregation of myelin growth and compaction is a way to protect the vital cytoplasm at the inner tongue. In addition, it could serve as a mechanism to generate hydrostatic pressure, which could be used as a force to drive membrane wrapping. It is not clear how the initiation of compaction is regulated. One possibility is that compaction starts at the site of local MBP mRNA translation. Several studies have shown that MBP mRNA is transported all the way down to the innermost layers close to the axon (9, 128, 340, 367, 630, 656, 668), but whether this is also the site where translation occurs is unknown. Compaction needs to be restricted to one single place within the myelin sheath to drive the zippering processes and to prevent the formation of cytoplasmic pockets with myelin. This is most easily achieved by making the initial association of the two apposing cytoplasmic leaflets rate limiting. In addition, spacer may be placed into the growing myelin sheath that keeps the inner leaflets of two myelin layers apart. CNP1 may function as such a spacer, as in its absence, myelin loses some of its cytoplasmic channels (581). Overexpression of CNP1, in contrast, increases the amount of cytoplasm within myelin (221, 690). With such a mechanism at work, the site of MBP synthesis could occur at the innermost tongue, possibly regulated in part by axonal signals (656), followed by diffusion of MBP towards the outer layers, where the lamellae are closer together, and compaction is initiated. Initially, the highly positively charged MBP is attracted to the negatively charged cytoplasmic leaflet by electrostatic interac-

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tions, thereby starting the compaction cascade. When opposite charge is neutralized, hydrogen bonding and the hydrophobic forces are uncovered and cause MBP to fold and subsequently insert into the inner membrane leaflet. This most likely starts in one leaflet, leaving one end of MBP elongated where it maintains its positive net charge. When MBP is able to reach the apposing surface, another insertion and possible folding event occurs (498). After MBP is bound to the two adjacent cytoplasmic surfaces of the myelin bilayer, a nucleation site has been initiated which then directs additional molecules of MBP towards this localization where they polymerize into a dense protein network, thereby providing the forces for unidirectional membrane zippering (6, 7).

IV. INTRINSIC AND ADAPTIVE MYELINATION

A useful concept to explain how CNS myelination occurs is to divide it into an intrinsic and adaptive phase (49, 110, 181, 421). The intrinsic phase of myelination is genetically predefined, occurs around birth and in early childhood, and leads a chronological and topographically fixed sequence of myelination. Adaptive myelination, in contrast, is modified by experience, occurs according to the need of a neuronal network, and leads to inter-individual variability in myelination. The extent of adaptive myelination depends on the brain region. For example, there may be very little adaptive myelination in most "one way" information paths whose task is simply to conduct as fast as possible. For example, axons in the spinal cord or the optic nerve are myelinated in such a way that myelin internode length and thickness as well as the size of the nodes are optimized for maximum conduction velocity. In contrast, axons in the cortex are often myelinated in two phases. The first wave occurs early in development and lays the groundwork, often resulting in a patchy arrangement of myelin segments along the axons. This is followed by a second phase that likely depends on sensory input, followed by signaling from neurons to oligodendrocytes. Longitudinal in vivo two-photon imaging of oligodendrocytes shows that myelination occurs for a long time in the mouse cerebral cortex with only half of the myelinated segments formed until 4 mo of age (267). Continuous myelin formation occurs on both partially myelinated and unmyelinated axons, and the total myelin coverage along individual axons progresses into old age (250, 267). Since the function of myelin within such neuronal networks is not only to increase conduction velocity to maximal level, but also to finely tune neuronal network function by synchronizing the firing pattern, more intricate mechanisms are required (145, 185). Neuron and glia communication is likely to be important to shape myelination according to the need of the neuron and its network.

First evidence for the existence of adaptive myelination came from human magnetic resonance imaging studies pointing to experience-dependent changes in the white matter. Such changes were found upon learning new motor tasks, for example, practicing piano, playing baduk, or juggling, and were confirmed using various other learning paradigms such as acquiring specific visuomotor skills or learning a new language (53, 343, 452, 556, 598). One drawback, however, is that experiments in humans can only be performed with magnetic resonance imaging, which so far lacks sequences specific for myelin. Until methods are established that enable specific detection of changes in myelin structure in living humans, the concept of adaptive myelination in humans remains speculative. In experimental animals such as rodents or zebrafish, intravital two-photon imaging, histological or electron microscopical analyses can be applied to determine changes in myelin structure or patterns upon learning new tasks. Such experiments have revealed that voluntary exercise on running wheels (571) or motor learning on complex wheels with irregularly spaced rungs triggers the generation of more oligodendrocytes and new myelin sheaths (384, 571, 682). Likewise, fined motor training in adult rats (one paw reaching/grasping) results in an increase in myelin generation (547). Conversely, sensory-motor deprivation results in decreased myelination, and trimming of a whisker results in fewer myelinated axons in the barrel cortex (43, 251). Social isolation, another form of sensory-motor deprivation, leads to hypomyelination in the prefrontal cortex (350, 374). Collectively, these studies provide indisputable evidence that myelin biogenesis is influenced by experience. However, the underlying mechanisms that drive adaptive myelination have not yet been clarified.

The role of neuronal activity in modifying myelination, initially described in cell culture, has up to now received the most attention (151). There are now a larger number of studies in various model systems that confirm that electrical activity promotes myelination. For example, stimulating somatosensory neurons in the cortex by optogenetics or pharmacogenetics increases OPC proliferation and myelin formation (207, 414). Since OPC are in close contact with axons, where they form postsynaptic sites that receive neuronal synaptic input via glutamate and GABA receptors (55, 143, 321, 327, 698), they are ideally positioned to respond to neuronal firing. There is also evidence that electrical activity determines which axons oligodendrocytes choose for myelination. Time-lapse imaging in zebrafish has shown that oligodendrocytes use their processes to probe the surfaces of different axons at the same time (133, 252, 320, 390).

The growth factor Neuregulin 1 type III has been implicated in adaptive myelination. Neuregulin 1 and its cognate ErbB receptors are key signaling molecules in Schwann cells (374, 401, 616). However, in the CNS, the role of Neuregulin-ErbB signaling is more subtle, where it appears to regulate

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the switch between the adaptive and intrinsic mode of myelination (363).

In addition to neurons, astrocytes play an important role supporting myelination (306). There are a number of factors secreted by astrocytes that facilitate the different steps of myelination including OPC proliferation, differentiation, and myelination. Among soluble factors secreted by astrocytes are platelet-derived growth factor (PDGF), basic fibroblast growth factor (FGF2), leukemia inhibitory factor-like protein (LIF), insulin-like growth factor 1 (IGF-1), ciliary neurotrophic factor (CNTF), metalloproteinase-1 (TIMP-1), and endothelin-1 (ET-1) (66, 202, 236, 274, 419, 437, 520, 596, 687, 694).

Adaptive myelination not only results in formation of new myelin sheaths, but may also change the shape of existing myelin. By employing an optogenetics mouse model in which the excitatory opsin channel rhodopsin was specifically expressed in projection neurons, it was possible to demonstrate myelin remodeling by neuronal activity (207). Stimulation resulted in an increase in myelin thickness along their cortical and subcortical projections. What are the physiological consequences of thicker myelin sheaths? Theoretical calculations have shown that axons have an optimal g-ratio of 0.6 (120). Axons in the CNS often have g-ratios higher than 0.6 (relatively thinner myelin sheaths). The intrinsic activity of oligodendrocytes could be responsible for generating thin myelin, but upon increased neuronal activity, the final thickness of myelin could be adjusted. Interestingly, structural changes can be observed when myelin growth is restimulated in adult mice. During early development, the growing myelin sheath is characterized by abundant cytoplasmic channels that largely disappear in adults. However, by increasing PtdIns(3–5)P_3 in oligodendrocytes, cytoplasmic channels are able to expand. This is likely an important structural requirement to reinitiate growth in adult mice (581).

An important question is whether oligodendrocytes are capable of adapting myelin sheath formation throughout their lifetime. There is now accumulating evidence that generation of new oligodendrocytes, some of which generate myelination, extends well into adulthood (691). OPCs continue to divide at a slow rate in adult mice. The rates of cell division depend on the location (being slower in gray matter than in white matter) and on the age of the mice (being slower in old than in young mice) (250, 267, 691). Some of these OPCs differentiate into oligodendrocytes, a fraction of which survives and forms myelin, even in the almost fully myelinated adult optic nerve. The rate of OPC division correlated with the local density of unmyelinated axons, suggesting that one function of adult-born OPCs is to myelinate axons de novo in the adult. A subpopulation of oligodendrocytes, distinguished by the selective expression of the breast carcinoma amplified sequence 1 (Bcas1) protein, was identified as a marker for oligodendrocytes in an intermediate stage of differentiation, between early progenitors and mature cells (175). These cells represent a population of newly generated and early oligodendrocytes that are transiently present during the active phase of myelination. Continuous generation of Bcas1$^+$ cells was observed both in the white and grey matter of mice until at least 1 yr of age in mice. In humans Bcas1$^+$ cells were mainly found in the first year of postnatal white matter development, but were also present, albeit at low levels, in the frontal human cortex into adulthood. These data are consistent with the birth-dating of oligodendrocytes by ^{14}C integration, which showed that the number of oligodendrocytes in the white matter is established during the first years, whereas grey matter myelination continues at low levels in adults (688).

The question arises as to whether this ongoing adult myelination is classified as intrinsic or adaptive. How much of adult myelination is inborn and determined by genetic factors intrinsic to the oligodendrocyte, and how much is modified by experience and environmental factors? Some studies indicate that there is a critical time period when oligodendrocytes are receptive to extrinsic influences. In mice, social isolation during early postnatal development from 3rd to 5th weeks after birth affected myelin sheath number, length, and thickness, while 2 wk of social isolation after 5 wk did not (374). Another study, in which social isolation was prolonged to 8 wk, revealed differences in myelin formation in older animals (350). Moreover, motor learning and optogenetic or pharmacogenetic stimulation of neurons enhance the formation of oligodendrocytes generating new myelin sheaths in adult mice.

Such continuous generation of oligodendrocytes associated with active myelination in adult regions raises the intriguing prospect of continued myelin plasticity well into adulthood. A key question is whether myelin is truly plastic, and whether it can shrink or retract after it has been formed (162). Time-lapse imaging is necessary to visualize myelin remodeling. This has been performed in mice, and the recordings provide some initial evidence for few retracting myelin sheaths in the cortex using intravital label-free and fluorescence optical imaging (250). Retractions are more frequently observed in zebrafish during early development in the developing spinal cord (133), where they are regulated by high Ca^{2+} (35, 323). In addition, remodeling of mature myelin sheaths was visualized in the zebrafish by targeted ablation of individual sheaths from single axons (27). However, whether these myelin sheaths are made of several wraps of compacted myelin or only represent early stages of ensheathed axons is not known. Mechanistically, it is difficult to imagine how a multilayered compacted membrane can retract. There is very little space for enzymes or proteases that could modify MBP in such a way that the multilayer stacks are loosened. Intracellular increase of

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Ca^{2+} results in rapid release of MBP from the cytosolic leaflets of the myelin membrane triggering myelin breakdown (663), but how this could be modified in a controllable fashion remains to be determined. Recent findings provide evidence that detachment of the outermost paranodal loops of myelin from the axon can regulate myelin thickness (162).

V. MYELIN AGING

A variety of white matter changes have been observed by magnetic resonance imaging in normal aging brains. White matter volume starts to decrease gradually from 50 yr of age onwards (589). In addition, white matter lesions are frequently seen as hyperintensities on T_2-weighted magnetic resonance imaging. As the deep white matter areas lie at the ends of the arterial circulation, they are particularly susceptible to decreases in blood flow and oxygenation. In addition, some white matter areas are located in watershed zones between the anterior and middle cerebral arteries and the middle and posterior cerebral arteries. These anatomical features may explain how age-related vascular alterations contribute to the increased vulnerability of aged white matter to hypoperfusion (353, 430). Electron microscopy studies performed in non-human primates have established that the major changes observed during normal aging are not a loss of neurons, but rather changes in myelinated nerve fiber morphology (467). With age, a substantial number of myelin sheaths exhibit degenerative changes. The most common age-related defects are splitting at the major dense line leading to accumulation of dense cytoplasm with vesicular inclusions. Another type of age-related change in myelin sheaths are "balloons" (177). With light microscopy, these balloons appear as holes, but electron microscopy shows that they arise from the interperiod line of myelin, causing the myelin sheaths to bulge out. Myelin outfoldings containing several layers of compacted myelin lamellae are another feature often observed in aged brains. In addition, the number of lamellae appears to increase in some of the sheaths of the old brain. Multilamellar myelin fragments have also been detected in brains of old mice (250, 542). Some of these fragments represent myelin outfoldings, while others are engulfed by microglia, raising the possibility that microglia actively strip off damaged myelin. There is an almost twofold increase in the number of microglia with an expanded lysosomal compartment in the aged brain of mice. Aged microglia accumulate autofluorescent material reminiscent of lipofuscin (542). Lipofuscin contains nondegradable oxidized lipids, some of which represent remnants of indigestible myelin. Thus the increased burden of myelin clearance in the older brain may not only lead to an increase in microglia with lysosomal inclusions, but could also contribute to age-associated microglial dysfunction.

VI. MYELIN PATHOLOGY

As expected from its major role in mammalian nervous system physiology, myelination defects in humans usually have significant neurological manifestations. Diseases of myelin represent a large, heterogeneous group with regard to clinical characteristics, pathophysiology, and etiology. Hereditary and acquired pathologies can be distinguished, of which inflammatory, infectious, toxic, and metabolic are the most prevalent.

Novel insights into molecular mechanisms governing the interactions between cellular populations of the nervous system have influenced the current pathophysiological thinking about myelin disorders. Recent advances showing the interdependence between astrocytes, oligodendrocytes, microglia, and axons indicate that myelin dysfunction should be understood in the broader context of nervous system pathophysiology.

In this section we do not intend to provide an exhaustive overview of myelin disorders, but instead discuss selected pathophysiological aspects of prototypic diseases. We focus on the distinct and characteristic features of myelin pathology and the specific contribution of different cellular populations in acquired and inherited diseases. First, we consider the mechanisms of lesion formation and myelin damage in inflammatory demyelinating diseases, using as an example multiple sclerosis, the most frequent acquired demyelinating disease of the CNS, the etiology of which is not completely understood. We also discuss acute disseminated encephalomyelitis and neuromyelitis optica spectrum disorders (NMOSD), diseases with well-established autoimmune etiology. Furthermore, we highlight how specific interactions between astrocytes, oligodendrocytes, and microglia might contribute to demyelination in hereditary white matter pathologies (leukodystrophies). Finally, we discuss the disruptive influence of a viral agent, the JC virus, in CNS homeostasis in progressive multifocal leukoencephalopathy (PML), a fatal disease with ever increasing prevalence in the context of immune suppression.

Research on myelin pathology must focus on a better understanding of the mechanisms leading to myelin degeneration and myelin removal, and on the cellular interactions involved in damage to the axon-oligodendrocyte-myelin unit. Understanding the interactions between cell types in the CNS is not only relevant for disease pathogenesis, but is equally important for lesion repair.

A. Multiple Sclerosis

Multiple sclerosis (MS) is a chronic inflammatory disease of unknown etiology that occurs in all age groups but mostly manifests in young adulthood (for recent review, see Ref. 514). It is the most frequent human disease affecting CNS

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myelin. Patients may initially present with visual disturbances due to optic neuritis, or with sensory and motor symptoms (620). In brain magnetic resonance imaging (MRI), circumscribed hyperintense lesions disseminated in space and time, frequently adjacent to the ventricles or located juxtacortically, are characteristic of the disease. Gadolinium contrast enhancement indicates a disruption of the blood-brain barrier that is frequently associated with active immune cell recruitment (183). Symptoms initially resolve fairly well (relapsing-remitting MS), but in ~70% of the patients, disability tends to increase independent of relapses after 10–15 yr of disease duration (secondary progressive MS). Primary progressive MS patients typically experience an insidious worsening of clinical disability, mostly lower limb function, from the beginning of the disease on and independent of relapses (355, 356).

MS is 2.3 times more frequent in females and has a higher incidence in northern latitudes and populations of Northern European ancestry (24, 36). Disease susceptibility is strongly related to the HLA locus, and homozygosity at the HLA-DRB1*15 gene locus confers an odds ratio of 7 to develop the disease. In addition, multiple common variants contribute to disease susceptibility, and multiple genome-wide association studies during the last years have identified over 200 risk loci (36). A higher disease risk is associated with polymorphisms in genes regulating both adaptive and innate immunity, cytotoxic and regulatory T cell and microglia function in particular, such as IL2RA, IL7RA and TNFRSF1A (460, 550). However, monocygotic twins have a concordance rate of only 20–30%, indicating a substantial contribution of environmental factors to MS susceptibility. Infection with Epstein-Barr virus, and especially a history of infectious mononucleosis, low vitamin D levels, childhood obesity, and smoking have been related to an increased likelihood of developing the disease (51). For unknown reasons, the disease incidence is increasing in western countries, particularly in women (312).

1. Myelin pathology in MS

MS lesion evolution frequently extends over months and years and follows a typical sequence of cellular events **(FIGURE 4)**. We focus here on the pathology of myelin and oligodendrocyte damage and only briefly touch on the role of inflammatory cell infiltration and inflammatory mediators. For this introduction into myelin pathology in MS, we start out with the features of the prototypic, fully demyelinated late-stage lesion and then move on to earlier lesion stages. Cortical and neuroaxonal pathology are discussed in more detail in separate sections, as they demonstrate additional principles of the disease that are in part unrelated to focal myelin pathology. The immediate repair response seen in the glial cell compartment is similarly discussed in more detail in a later section.

At autopsy, brain tissue from patients with long disease duration is most prominently characterized by grayish, well demarcated lesions around the lateral ventricles and in the deep hemispheric white matter, the cerebellar peduncles, brain stem, or spinal cord that are visible to the naked eye. Histological sections stained for myelin, e.g., with Luxol fast blue (LFB), identify demyelinated lesions with very few if any residual myelin sheaths and a sharp border to the periplaque white matter. No evidence for myelin phagocytosis is detected in and at the edge of these chronic inactive demyelinated MS lesions. They are hallmarked by reduced cellularity due to a substantial reduction in mature oligodendrocytes, microglia, and frequently oligodendrocyte precursor cells (71, 235, 326, 677, 701). Signs of adaptive or innate immune activation are sparse or absent (193, 548, 701). Axonal reduction is variable, but may reach substantial levels of up to 80% (396, 472, 553, 610). Glial-fibrillary acidic protein (GFAP)-positive astrocyte processes extend along the demyelinated axons, whereas astroglial cell bodies are small and inconspicuous at this lesion stage. Areas of less intense myelin staining frequently accompany the edge of chronic demyelinated lesions and depict remyelinated lesion areas, as evidenced by electron microscopy (465,

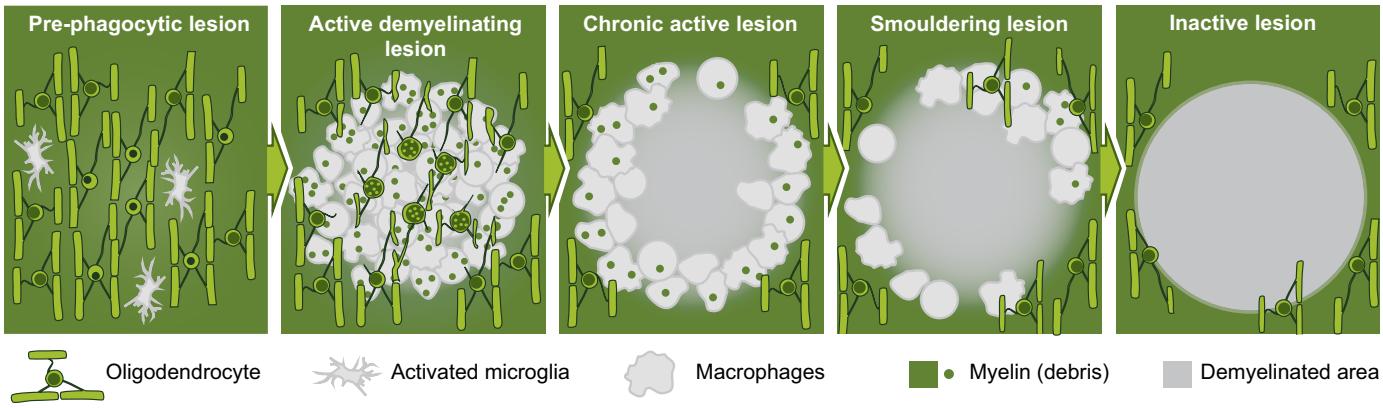

FIGURE 4. Multiple sclerosis focal lesion pathology. A continuum of phagocyte activation and demyelination characterizes multiple sclerosis lesion evolution that occurs over months to years.

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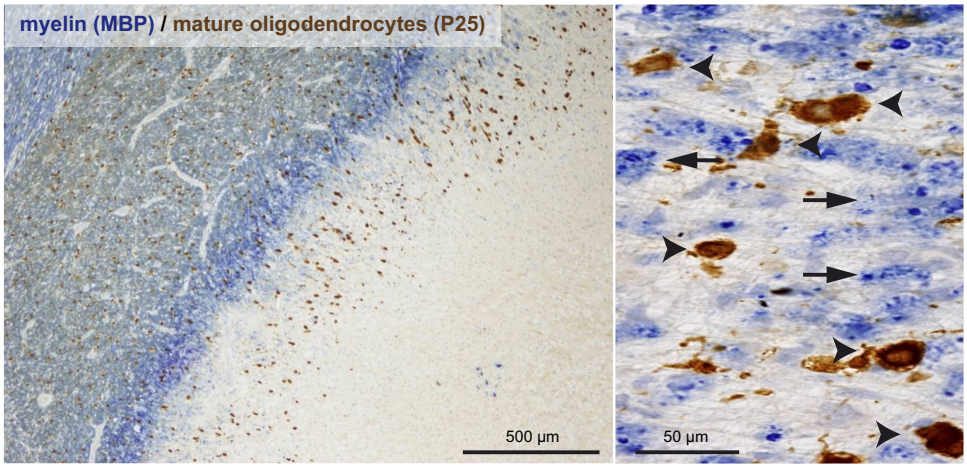

FIGURE 5. Centrifugally expanding chronic active multiple sclerosis (MS) lesion. TPPP/p25+ mature oligodendrocytes (arrowheads) amidst myelin-phagocytosing macrophages (arrows) at the actively demyelinating edge of a chronic active MS lesion in a 30-yr-old female with progressive MS. Note the loss of TPPP/p25+ cells in the central part of the lesion. Double immunohistochemistry for TPPP/p25 (brown) and myelin basic protein (MBP; blue); nuclear counterstain: hematoxylin.

488, 605). Chronic inactive demyelinated lesions represent an end stage of lesion formation without ongoing myelin destruction and inflammation, comparable to a scar with only partial recovery.

In contrast, chronic active and smoldering or slowly expanding MS lesions are characterized by a rim of activated, in part foamy phagocytes surrounding an otherwise chronic demyelinated lesion (489) (**FIGURES 4 AND 5**). At the lesion rim, a variable degree of myelin degradation reflected by LFB or myelin protein-positive degradation products in phagocytes is observed (325). Acute axonal transport disturbances visualized by immunohistochemistry for amyloid precursor protein (APP) further support the concept of ongoing disease activity at these lesion edges (179, 193). Scattered parenchymal T cells frequently accompany smoldering lesion activity (193), and deposition of fibrinogen supports low-grade blood-brain barrier damage (341). The opsonin C3d generated by complement activation is observed in close association with degraded myelin, axons, activated microglia, and microglia nodules (400, 489). MRI studies visualizing iron-laden macrophages/activated microglia at the lesion edge confirm lesion expansion over time (5, 137). Chronic active lesions do not regularly contain areas of remyelination, but nevertheless may show an activation and expansion of premyelinating and early myelinating oligodendrocytes (175). Smoldering lesions are rare in the acute or relapsing-remitting phase of the disease, but represent a stable lesion phenotype encompassing 15–20% of lesions in primary and secondary progressive MS patients in a cohort of 120 patients (194). Chronic active and smoldering lesions represent foci of non-remitting, ongoing disease activity that may involve an imbalance of counterregulatory anti-inflammatory mechanisms in the perilesional and normal-appearing white matter (695). It is yet unclear what determines whether an MS lesion remyelinates successfully, turns into an inactive chronic demyelinated lesion, or continues with variable degrees of ongoing demyelinating activity.

Active demyelinating lesions show a dense infiltration of foamy macrophages throughout the lesion area (**FIGURE 4**). Here, macrophages take up ultrastructurally normal myelin sheaths (487). Macrophages may contain myelin degradation products throughout the lesion, but frequently display radial lesion expansion with more recent myelin phagocytosis at the lesion edge (42). This frequently coincides with the detection of MRP14, a proinflammatory S100-related protein that is specifically expressed by myeloid cells recently recruited from the blood (87, 704). The active lesion rim correlates well with ring enhancement on MRI (84, 182, 360). The concept of radial lesion expansion is further supported by recent MRI data demonstrating initial contrast enhancement in the lesion center that later localizes to the lesion periphery (5). A mild to moderate, perivascularly accentuated lymphocyte infiltrate accompanies the dense macrophage infiltration (242). In the majority of cases, only few B and plasma cells are found (42, 193, 368). Active demyelinating MS lesions are characterized by a near-normal density of oligodendrocytes and a slight reduction of OPC (88, 132, 326, 451). Mature oligodendrocytes expressing Nogo-A, p25/TPPP, or MOG are regularly found amidst myelin phagocytosing macrophages (**FIGURE 5**). This is in stark contrast to early neuromyelitis optica (NMO) lesions in which oligodendrocyte and OPC densities are markedly reduced (86, 358, 492, 679). In the periplaque white matter immediately adjacent to the expanding lesion rim, few oligodendrocytes with condensed nuclei and sparse myelin fragments are frequently observed (131, 242, 451, 492) (**FIGURE 6**). Here, beyond the area of the most intense myelin phagocytosis, early MS lesions may show reduced immunoreactivity for MAG and CNP compared with the major myelin proteins PLP and MBP (277, 357, 359, 378).

Although the initiating insult leading to oligodendrocyte death and myelin damage has not yet been identified, it is generally agreed that a prephagocytic or initial lesion stage precedes full-blown myelin phagocytosis (**FIGURE 4**). Initial lesions in patients dying acutely from MS were reported to

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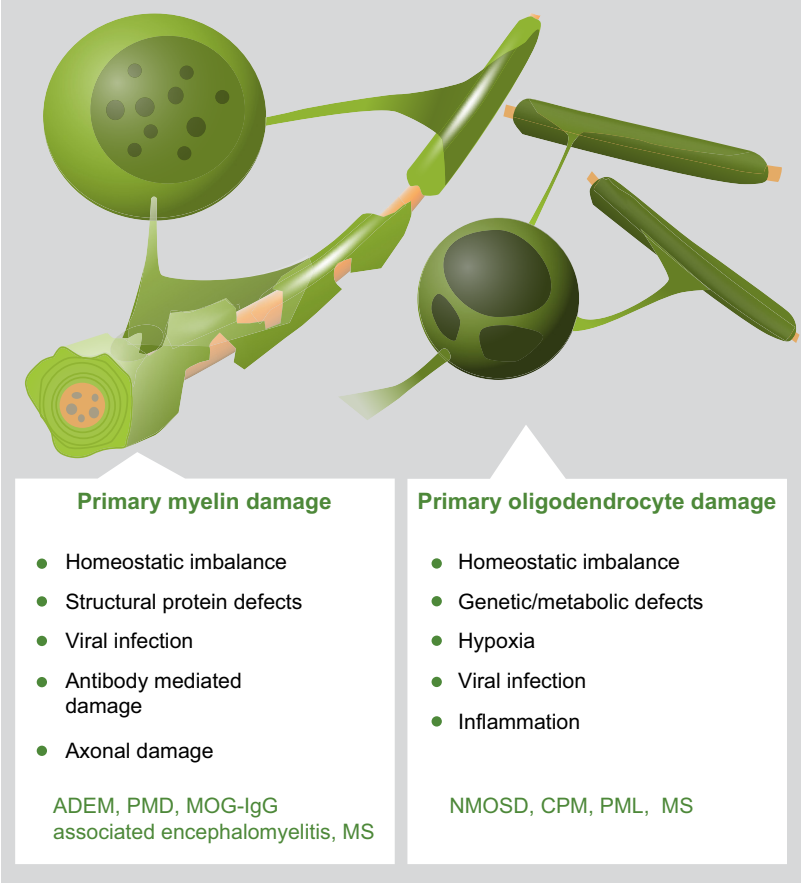

FIGURE 6. Mechanisms of demyelination. Demyelination arises most frequently as a consequence of two nonmutually exclusive pathophysiological mechanisms: primary myelin (*left*) or oligodendrocyte damage (*right*). Antibody-mediated diseases, primary axonal pathologies, and structural protein defects are preferentially associated with myelin damage while viral infection as well as genetic and metabolic deficiencies negatively influence oligodendrocyte survival. ADEM, acute disseminated encephalomyelitis; CPM, central pontine myelinolysis; NMOSD, neuromyelitis optica spectrum disorder; PMD, Pelizaeus-Merzbacher disease; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy; MOG, myelin oligodendrocyte glycoprotein.

contain abundant oligodendrocytes with condensed nuclei but did not regularly show the typical features of apoptosis (39, 242, 492, 594). Immunoreactivity for activated caspase-3 was often lacking, indicating alternative cell death pathways (357, 655). Myelin in these initial, prephagocytic areas may appear pale in LFB histochemistry, in part smudgy and edematous (39, 242, 378). Microglia activation but not overt myelin phagocytosis is seen at this stage of lesion evolution (144, 203, 548). It is currently a matter of discussion whether different pathological aspects of early MS lesions indicate interindividual disease heterogeneity or reflect stages of lesion formation (38, 76, 602). The concept of an initial lesion characterized by subtle oligodendrocyte and myelin pathology preceding active demyelination may correspond to the so-called prelesions described in MRI and MR spectroscopy that within weeks to months will evolve into gadolinium-enhancing typical MS lesions (176, 184, 378, 527, 615).

2. Cortical demyelination

Predilection sites of demyelinated lesions in MS include the optic nerves, brain stem, spinal cord, subcortical and periventricular white matter, as well as the superficial cortical layers (63, 471). Bandlike subpial cortical demyelination is specific for MS and not found in patients suffering from other inflammatory or neoplastic conditions, underlining the specificity to MS of the mechanisms involved (186). In contrast, subpial demyelinated lesions are only rarely observed in the spinal cord, where white matter abuts the subarachnoid space. However, grey matter lesions in the cord are more frequent than white matter lesions (472). Thus the grey matter microenvironment specifically favors the local generation of demyelinated lesions. The cellular and molecular factors predisposing to preferential lesion development in MS have not yet been defined. They may include the proximity to the cerebrospinal fluid, facilitated antigen presentation in the meninges, increased vascular permeability, and high antigen density, among others (212, 234, 329, 330, 369, 555). Meningeal lymphocyte infiltrations were reported to correlate with the extent of cortical demyelination (262). Also, the severity of axonal loss in the spinal cord and neuronal loss in upper cortical layers associate with the extent of meningeal adaptive inflammation, highlighting the role of adaptive inflammation for the disease process (20, 119, 370).

3. Remyelination

In contrast to the rather limited capacity for neuroaxonal regeneration, myelin repair is well established in the human CNS. Our recently expanded understanding of the axon-myelin unit highlights the importance of functional myelin and oligodendrocytes for axonal metabolic support (197,

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344, 538). At the beginning of the last century, Otto Marburg (1906) already interpreted well delineated, thinly myelinated white matter areas in patients with MS to be signs of myelin repair and termed them "shadow plaques" (376a). This was later confirmed by electron microscopic studies (465, 605). Remyelinated axons with thin myelin sheaths and short internodes were not only observed in established lesions, but also in the earliest stages of demyelination amidst phagocytosing macrophages (486). On the light microscopic level, contiguous areas of successful remyelination, either throughout a lesion or at the edge of a mostly chronic lesion, appear as sharply delineated areas of pale LFB histochemistry, reflecting thinner myelin sheaths (37, 336, 484). Of note, prephagocytic initial lesions also may present with myelin pallor; however, in contrast to these, successfully remyelinated lesion areas show no oligodendrocyte death, myelin damage, or edema (39, 459).

Post mortem studies of large hemispheric brain sections of patients with MS showed a correlation between disease duration and age with remyelinated plaque area. However, inter-individual heterogeneity in the extent of remyelination was high, and no association with the clinical disease course could be established (459). Similarly, in a detailed analysis of MS lesion types at autopsy that were correlated with disease duration and disease phenotype, shadow plaques represented a quite stable proportion (15–20%) among relapsing-remitting, secondary as well as primary progressive patients (194). However, other studies found that remyelination is most efficient in early demyelinating lesions, and declines thereafter (213, 451).

In early demyelinating lesions, oligodendrocytes are present at high density, and the generation of new internodes has been shown in light and electron microscopic studies (88, 326, 358, 451, 485), indicating efficient early stimulation of lesion repair. However, no evidence of efficiently remyelinated lesions was found in patients dying rapidly after disease onset (194, 459), which points to the transience of newly formed myelin sheaths at this stage of disease. In line with the vulnerability of newly formed myelin, demyelinated lesions are frequently superimposed on already remyelinated plaque areas (75, 485). In a large autopsy study in progressive MS patients, active demyelination correlated with a reduction in remyelination efficacy (75), again suggesting that the demyelinating disease process efficiently counteracts lesion repair. More extensive remyelination in later disease stages and after longer disease duration, as demonstrated by Patrikios et al. (459), may thus indicate a close interplay of remyelination with the underlying disease activity and inflammation in general, both of which are known to subside with increasing disease duration (193). In agreement with the notion that the ability to remyelinate may not be restricted to early stages of lesion formation, premyelinating and actively myelinating oligodendrocytes can be visualized around chronic MS lesions (109, 175) **(FIGURE 7)**.

However, even if myelin repair is well documented during the disease, the major lesion type found at autopsy is the chronic demyelinated plaque (194). OPCs are detected, albeit in small numbers, also in chronic lesions (326, 676, 677). So far, it is not well understood why remyelination

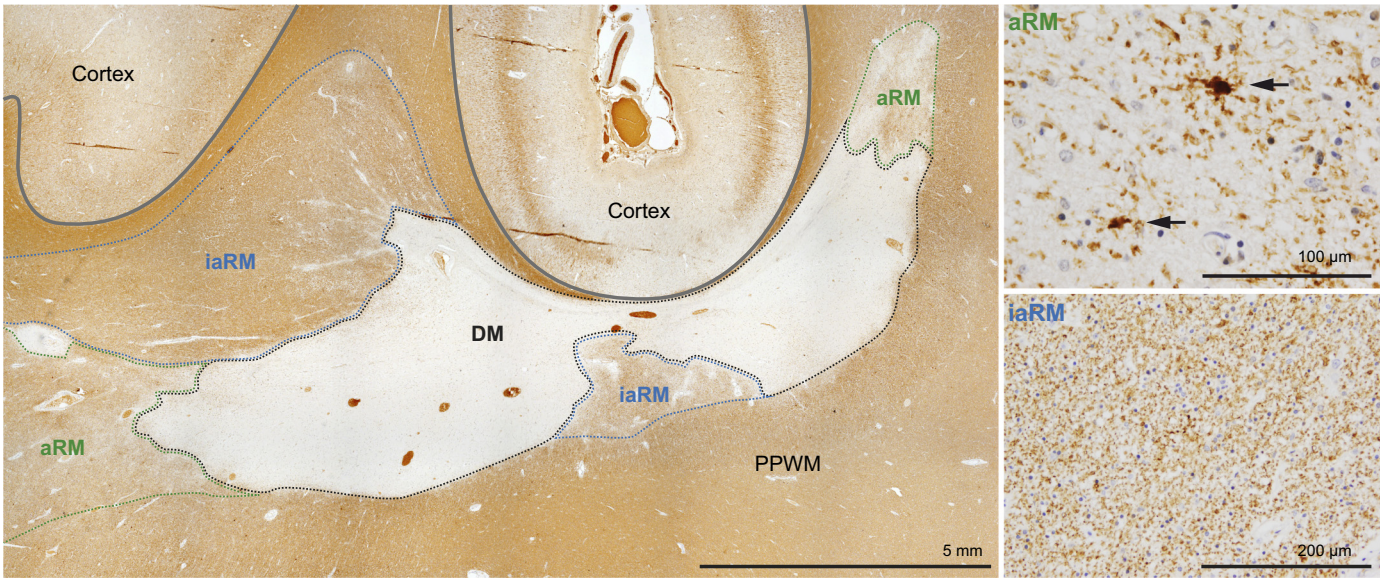

FIGURE 7. Active remyelination around a chronic multiple sclerosis (MS) lesion. Extensive subcortical chronic demyelinated MS lesion (DM, black dotted line) in a 47-yr-old patient with progressive disease surrounded by areas of established, inactive (iaRM, blue dotted line) and active (aRM, green dotted line) remyelination representing "shadow plaques." Active remyelination is characterized by the presence of BCAS1+ myelinating oligodendrocytes (arrows). Immunohistochemistry for BCAS1 is in brown. The cortical ribbon is outlined in gray. PPWM, periplaque white matter.

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fails in these lesions, an issue that was reviewed in detail recently (191). Repeated bouts of demyelination may lead to a substantial reduction in OPCs (485, 530). Furthermore, OPC differentiation may be inhibited by an unfavorable lesion microenvironment, culminating in increased activity of Notch and canonical WNT signaling (174, 658). An imbalanced expression of the chemorepellent semaphorin 3A and the chemoattractant semaphorin 3F may also contribute to insufficient recruitment of OPCs to demyelinated lesions (71).

Interestingly, remyelination efficacy at least in part depends on lesion location. In contrast to periventricular lesions, deep white matter lesions and cortical lesions show more thorough and more extensive remyelination (11, 213, 392). Increased survival of OPCs or a more favorable lesion microenvironment, i.e., less inflammation, less gliosis, and less astrocytic expression of hyaluronic acid, CD44, and versican, have been proposed (31, 108). However, despite this strong regenerative response, remyelination eventually also fails in the cortex (530). The extra- and intracellular deposition of fibrinogen in the cortex of patients with progressive MS may contribute through an activation of bone morphogenetic protein (BMP) signaling in OPCs (470, 686).

Apart from disease-related factors, repeated insults to the myelin-oligodendrocyte-axonal unit, altered signaling in OPCs (89, 166), as well as an age-related decrease in repair capacity may contribute to the observed lack of efficient remyelination in MS (191).

A targeted therapeutic approach aimed specifically at modulating the repair-inhibiting lesion microenvironment in MS is currently being tested in clinical trials. Leucine-rich repeat and Ig-containing Nogo receptor interacting protein-1 (LINGO-1) is expressed on oligodendrocytes and neurons, and forms part of the Nogo-66/p75NTR complex. LINGO-1 is a negative regulator of oligodendrocyte differentiation and remyelination which may involve modulation of cytoplasmic gelsolin activation (398, 564). LINGO-1 antagonism was found to enhance remyelination in several experimental models of the disease (397, 399), and the results of phase 2 clinical trials in patients with a first unilateral optic neuritis (99) and MS (387) prompt cautious optimism.

High-throughput chemical screening approaches have been used to identify small molecules that stimulate OPC proliferation and differentiation (153, 216, 263, 334, 385, 386, 426). Recently, a study revealed that a wide range of these pro-myelinating small molecules do not function through their canonical targets, but instead by inhibiting enzymes within the cholesterol biosynthesis pathway, leading to the accumulation of the 8,9-unsaturated sterol, which by unknown mechanisms promotes OPC differentiation (264). Among the most effective compounds for promoting oligodendrocyte differentiation that has emerged from such cell-based screens is clemastine. Clemastine has already been tested in a first small, randomized controlled trial, which revealed some efficacy in improving the latency in visual-evoked potential in patients with chronic demyelinating injury (222). To track the regenerative potential of drugs, an important task will be to identify imaging outcomes for clinical trials of remyelination in MS. Recent advances in MRI and positron emission tomography (PET) imaging show promising results and may allow the detection of remyelination in situ in patients with MS (5, 64).

Another approach to improve remyelination is to target the innate immune system, as the activity of microglia/macrophages is an important regulator of oligodendrocyte proliferation and differentiation. Upon injury, microglia/macrophages can be polarized to distinct functional phenotypes, of which the anti-inflammatory polarized microglia/macrophages secrete the pro-regenerative activin-A, which enhances differentiation of oligodendrocytes (408). After microglia/macrophages have performed their immunological functions and pro-regenerative tasks within the lesion, it is important that inflammation resolves. However, myelin debris clearance is impaired in aged phagocytes (567), leading to retention of microglia/macrophages within lesions (105). These aged microglia/macrophages accumulate excessive amounts of cholesterol-rich myelin debris, which overwhelms the efflux capacity of phagocytes and induces a maladaptive immune response that impedes tissue regeneration (105).

The clinical relevance of oligodendrocyte protection and efficient remyelination in MS is based on the concept that a functional oligodendrocyte-myelin-axonal unit provides metabolic support and physical protection to the axon. Axonal density is higher in remyelinated as opposed to chronic demyelinated plaques, suggesting that timely remyelination may protect from further axonal loss (319, 559). Alternatively, repeated demyelination of the same tissue area might also explain more severe tissue damage, including axonal loss, in some persistently demyelinated lesions. Recently, [^{11}C]Pittsburgh Compound B PET myelin imaging established criteria for MS patients with high and low propensity to remyelinate and demonstrated an inverse relationship of remyelination efficiency and clinical disability (64). However, it should be noted that axonal loss in MS is not restricted to focal demyelinated lesions (150, 472, 580), and axonal loss in the normal-appearing white matter does not correlate with focal demyelinated lesions (150, 172), adding to the complexity of understanding the molecular relationship between lack of myelin and axonal degeneration in MS. A more thorough understanding of a potentially widespread disturbance of oligodendrocyte-myelin-axon interactions in MS, which is not limited to focal demyelinated plaques, will further aid in designing rational neuroprotective and pro-remyelinating therapies.

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4. Neuroaxonal damage and disease progression

Apart from the striking and obvious focal myelin pathology, MS is characterized by neuroaxonal damage that accumulates over the years and occurs at least in part independently of focal demyelinated lesions (150, 173), thus placing it near to neurodegenerative disorders (631). Pathological studies in patients with late-stage disease indicate a substantial loss of axons reaching up to 80% in the spinal cord and other brain regions, aggravated by focal lesions, but not entirely explained by them (172, 200, 472). Similarly, neuronal loss that occurs to a relatively minor degree, compared with classical neurodegeneration, in many brain regions, including the cerebral and cerebellar cortex, hippocampus, spinal cord, and deep grey matter especially the thalamus, ranges between 20 and 30% in most studies. It is not closely associated with focal demyelination (106, 124, 370, 457, 654). In addition, the substrates of neuronal connectivity, presynaptic boutons and postsynaptic structures, are reduced in most brain regions studied so far, which seems equally independent of focal demyelination (11a, 457, 653, 661). With regard to the pronounced reduction in dendritic spines observed in the cerebral cortex of demyelinated as well as normal-appearing cortex of patients with MS, animal models suggest that reductions in spine density may reflect the impact of inflammatory cytokines on neurons (287, 324, 376). However, in experimental models of cortical autoimmune inflammatory demyelination, spine density recovers within a short period of time (287). In contrast, in progressive MS, reductions in synaptic density are substantial, notwithstanding a still observable synaptic reorganization (11a). In line with the pronounced microscopic pathology in the grey matter, rates of grey matter atrophy detected by MRI are, on a group level, the best predictor for disease progression (187). Most recently, deep grey matter atrophy has been linked to the accumulation of disability, and regional grey matter atrophy may spread with disease evolution (29, 170, 171).

Continuous low-grade inflammatory activity and long-lasting disease duration may contribute to the dysfunction and loss of neural structures in the human disease (553). Along this line, a disruption of axonal energy supply is currently considered to contribute to axonal demise. Mitochondrial dysfunction, most likely aggravated by inflammation, may lead to a state of "virtual hypoxia," a dysfunction of ion channels, ionic imbalance, axonal transport disturbance, and ultimately necrosis (372, 632). In human tissue, mitochondrial DNA deletions and cytochrome *c* oxidase (COX)-negative neurons were observed in the cortex of patients with long-standing disease, supporting the hypothesis of a failure to allocate sufficient energy to the neuroaxonal compartment in chronic disease (103, 371). However, in experimental models, the local inflammatory milieu including oxidative damage does not lead to mitochondrial dysfunction and a lack of local energy supply (436, 585), hinting towards a more complex pathophysiology in the human disease. The concept of an insidious, slowly progressive neuroaxonal dysfunction is well in line with the progressive deterioration of clinical symptoms that is characteristically observed in MS, but not in a phenotypically similar autoimmune disease, NMO, despite its more destructive lesion pathology (672). Thus the chronic intrathecal inflammatory process inherent to MS may induce a vicious circle of neuroaxonal energy deficits that is aggravated by the focal loss of myelin and oligodendrocytes, which further reduces the availability of metabolic substrates (404).

The above-mentioned chronic active and smoldering lesions that are characteristic of progressive MS and not readily seen in other disease conditions have yet to be reproduced in experimental models. They reflect ongoing, low-grade disease activity and contribute to progressive neuroaxonal damage (193).

Data from MRI as well as pathology support the concept of MS as a "whole brain disease" and indicate that apart from the conspicuous focal demyelinated lesions, disease-specific changes may occur in the so-called normal-appearing white matter (13, 173, 196, 329). In addition to tissue alterations occurring around focal demyelinated lesions and along white matter tracts, indicative of Wallerian degeneration (163, 579, 580), diffuse abnormalities in the normal-appearing white matter include (416) scattered T lymphocyte infiltrates, microglia activation in part in the form of microglial nodules, APP-positive axonal profiles, and reactive astrogliosis. These evidence a disease process not solely restricted to or emanating from focal demyelinated lesions (13, 329, 560). Recent work identified swelling of myelinated axons in MS patients with little focal cerebral demyelination in the pathologically, but not radiologically, normal-appearing white matter as a pathological feature independent of demyelination. This finding underlines the close, but not yet fully understood, interplay between axons and myelin/oligodendrocytes in the disease (633).

B. Acute Disseminated Encephalomyelitis

In contrast to MS, acute disseminated encephalomyelitis (ADEM) is a clinicopathological entity that shows demyelination limited to the perivenous tissue and lacks the progressive neurodegeneration typical of MS. This points at fundamentally different disease mechanisms in the two entities and underlines the relevance of CNS-intrinsic factors for MS pathogenesis, most likely the long-term exposure of a foreign (or altered self) antigen. A closer understanding of the mechanisms of myelin damage in ADEM is thus instrumental to develop testable concepts of MS lesion pathogenesis.

Clinically, ADEM is characterized by the sudden onset of multifocal neurological symptoms, frequently accompanied by encephalopathy and usually characterized by rapid recovery (692). Children and young adults are typically af-

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fected (for review, see Refs. 480, 618). MRI typically shows large, ill-defined lesions on T2-weighted MRI, frequently involving more than one brain lobe as well as the brain stem and spinal cord. Contrast enhancement is frequently seen, although usually not in all lesions (692; for review, see Ref. 239). Severe brain edema may develop and worsen the otherwise generally favorable prognosis (148, 230, 240, 313). Pathologically, ADEM is characterized by multiple, strictly perivenular demyelinated sleeves, often occurring focally accentuated in specific brain regions. If multiple neighboring vessels are affected by demyelination, coalescence may occur, but large, confluent lesions typical for MS should detract from a diagnosis of ADEM (258, 491, 692). In small biopsy samples, however, perivascular demyelinated sleeves in MS may be confounded with ADEM (692). The perivascular inflammatory infiltrate in ADEM consists of T cells, foamy macrophages, and, at least in early lesion stages, granulocytes, including eosinophils (240, 510, 692). Deposits of immunoglobulins and activated complement components may also be found (332). In contrast to MS, perivascular demyelination in ADEM is characterized by a similar stage of lesion evolution in all demyelinated lesions (148, 692). ADEM frequently occurs after exposure to antigens, e.g., through an upper respiratory or gastrointestinal infection or after immunization. This supports the hypothesis that molecular mimicry is crucial to the pathogenesis of the disease (672). Correspondingly, experimental models induced by immunization with myelin antigens, leading to perivascularly accentuated brain and spinal cord inflammation, are frequently considered more as models for ADEM than for MS (362, 523; for review, see Refs. 337, 592, 599).

1. Mechanisms of myelin pathology in ADEM

The mechanism of demyelination in ADEM very likely involves antibody reactivities against myelin proteins (442). Accordingly, ~40% of pediatric patients with ADEM and ~20% of adult patients show serum antibodies against myelin oligodendrocyte glycoprotein (MOG) [80, 331, 442; for review, see Ramanathan et al. (502)]. MOG antibody disease has recently been identified as a distinct demyelinating disease entity with a range of clinical presentations, including ADEM, optic neuritis, and transverse myelitis (229, 280, 288). Also, part of the patients clinically classified as NMOSD may present with anti-MOG instead of anti-AQP4 antibodies (281, 308, 494). Recently, anti-MOG serum antibodies derived from patients with relapsing optic neuritis produced perivenous and subpial demyelination when injected into T cell-transferred rodents (590).

Mechanisms of myelin destruction in ADEM most likely involve a T cell-mediated opening of the blood-brain barrier and antibody-mediated myelin destruction **(FIGURE 6)**. Antibody-dependent phagocytosis, complement-dependent myelin lysis, and antibody-dependent cellular cytotoxicity (ADCC) may play a role (466, 590). Importantly, apart from the classic monophasic disease with a mostly favorable outcome, multiphasic and recurrent disease variants also exist, particularly in MOG-positive patients, whose underlying immune mechanisms still must be elucidated (268, 352). In children, a positive MOG-antibody serostatus predicts a reduced risk of developing MS (228, 300). In summary, antibody-mediated demyelination in ADEM leads to a clinically fulminant, mostly self-limiting disorder with demyelination that is spatially limited to the perivenous CNS tissue. Although axonal damage is substantial during acute demyelination in ADEM, no progressive neuroaxonal degeneration is found in the disease.

C. NMOSD With Anti-AQP4 Serum Autoantibodies

NMOSD with anti-AQP4 antibodies are primary astrocytopathic diseases with secondary oligodendrocyte and myelin damage (458). Apart from classic NMO, a number of clinical syndromes have been attributed to AQP4 serum autoantibodies (671). NMO is characterized by a predominant affection of optic nerves and spinal cord leading to blindness and paralysis (for review, see Ref. 664). Due to clinical and pathological similarities, NMO has long been considered a variant of MS until NMO-Ig was identified as a disease-specific serum autoantibody (347). NMO-Ig was later found to target AQP4, the main water channel of the CNS expressed at high density on astrocytic foot processes abutting the brain capillaries (346). Expression is not restricted to the CNS but also found in other organs, such as the kidney, lungs, and placenta (for review, see Ref. 424). The high antigen density in grey matter regions such as the central spinal cord and the dorsal medulla may render these areas particularly vulnerable to lesion formation (531). The pathogenic potential of anti-AQP4 antibodies was demonstrated by transferring purified serum antibodies from NMO patients into experimental models (74, 305). Similarly, human recombinant monoclonal anti-AQP4 antibodies from NMO patients, injected intravenously or intracerebrally, were shown to reproduce most of the pathological features of NMO lesions (679). Apart from pericapillary astrocytes, astrocytes at the external glial limiting membrane, ependymal cells, and choroid plexus epithelial cells all express AQP4 in the CNS. Anti-AQP4 antibody-mediated cell damage to these barrier sites facilitates further entry of pathogenic antibodies into the cerebrospinal fluid and the CNS parenchyma, triggering the formation of periventricular and subpial lesions (226). The circumventricular organs, CNS areas without the protection of the blood-brain barrier such as the dorsal medulla, are also predilection sites for lesion formation (412, 531). In patients with NMO, autoantibodies against glucose-regulated protein 78 (GRP78) were recently detected that bind to their target on brain endothelial cells and contribute to the disruption of the BBB, thus facilitating entry of astrocyte-damaging anti-AQP4 antibodies (568). In line with the

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highest antigen expression and in contrast to MS, the frequently longitudinally extensive lesions in the spinal cord typically involve the central grey matter (427, 490). Patients with NMO recuperate less well from disease attacks compared with MS patients, but the slowly progressive accumulation of disability, typical for later MS stages, is not seen in NMO (282, 672).

1. Lesion pathology and pathogenesis of myelin damage in NMO

Recently formed NMO lesions are characterized by massive astrocyte loss and some residual astrocytes with features of cell damage and death, i.e., condensed cytoplasm, fragmented processes, and nuclear condensation, mostly located at the lesion edge (413, 458). Characteristically, the reduction in AQP4 immunoreactivity in lesion areas exceeds that observed for glial fibrillary acidic protein (GFAP), indicating a downregulation and/or internalization of AQP4 in a proportion of astrocytes (253, 255, 410, 411, 413, 531). Oligodendrocytes and OPC are strikingly reduced in early NMO lesions (86, 679). Apoptotic and in part activated caspase-3 positive oligodendrocytes are a frequent finding in newly formed, astrocyte-depleted lesions (413, 458) **(FIGURE 6)**. Aside from abundant foamy macrophages, some T cells and occasional B and plasma cells, and depending on the lesion stage, also scattered neutrophilic and eosinophilic granulocytes can be observed (86, 361, 410, 413, 458, 531). Perivascular deposition of IgG, IgM, and the C9neo antigen identifies perivascular astrocyte processes as primary targets of the antibody-mediated immune attack (361, 458, 531). In relation to the timing and intensity of the immune attack as well as the prevailing immune effector mechanisms, different pathological patterns can be observed in patients with anti-AQP4 autoimmunity (413). Besides antibody and complement-mediated astrocyte lysis, ADCC executed by granulocytes or NK cells may play a role (476, 509, 540, 679, 697). Independent of antibody-triggered immune effector mechanisms, direct effects of anti-AQP4 antibody binding to its target may lead to channel dysfunction, internalization, and downregulation, contributing to tissue damage and edema (255). In addition, AQP4 forms a macromolecular complex with the excitatory amino acid transporter EAAT2, and downregulation of EAAT2 accompanies antibody binding to AQP4, thus leading to a reduction in glutamate scavenging in the lesions (254).

The mechanisms involved in rapid oligodendrocyte depletion after astrocyte death have not yet been fully elucidated; experimental models suggest excitotoxicity (377) and bystander deposition of activated complement components on oligodendrocytes (627). In line with the pronounced toxicity to oligodendrocytes observed in early NMO lesions, LFB staining for myelin phospholipids is only reduced, but not completely absent (74, 410, 413, 458). Intramyelinic edema is distinct (255, 458). Concomitantly, immunoreactivity for proteins of compact myelin such as MBP and PLP may still be seen in degenerating, vacuolized myelin while macrophages initiate myelin resorption (86, 458). In contrast, immunoreactivity for proteins of noncompact myelin such as MAG and CNP is substantially reduced in early lesions, corresponding to secondary myelin degeneration after oligodendrocyte demise (2, 86, 277, 413). Similar to what can be observed in patients, electron microscopic studies in a model of focal NMO showed an early vacuolization of the inner tongue of the myelin sheath and ensuing MBP degradation (663). Experimental models based on the intracerebral injection of recombinant human anti-AQP4 antibodies with complement reproduce the sequence of astrocyte, oligodendrocyte, and myelin loss observed in the human disease (539, 679). The near-complete astrocyte and oligodendrocyte depletion in early NMO lesions apparently does not support oligodendrocyte regeneration and myelin repair. Although uni- and bipolar GFAP-positive cells, reflecting astrocyte repopulation, are regularly found in NMO lesions, evidence for oligodendrocyte replenishment and remyelination is scarce (458). In contrast, Schwann cell remyelination of CNS axons may be extensive in NMO lesions (226, 270, 276). Early NMO lesions are characterized by a preservation of axons, but acute axonal transport disturbance may be observed in experimental lesions as well (244, 410, 413, 458, 679). However, in the chronic disease stage, axonal loss and spinal cord atrophy are frequently severe, exceeding that observed in MS (276, 375). Noteworthy, whereas NMO is characterized by a stepwise, attack-related accumulation of disability, the gradual disease progression frequently seen in MS is not observed (282, 672). In summary, demyelination in NMO is instigated by an immune-attack against the astrocyte, a cell that is on first glance unrelated to the axon-myelin unit, thus serving as a paradigmatic disease to highlight the interdependence and close physical interaction between glial cells in the CNS.

D. Leukodystrophies

Although inflammatory demyelinating diseases are most prevalent, much of the fundamental insights into primary oligodendrocyte/myelin pathology and the role of other CNS-intrinsic cell populations in myelin disease has emerged from the study of inherited white matter disorders collectively referred to as leukodystrophies. Depending on classification criteria, more than 90 diseases are recognized, and with the advent of next-generation sequencing, an increasing number of entities is being defined (645, 651).

Reflecting the diversity of the underlying genetic alterations, leukodystrophies exhibit variable age of onset, radiological presentation, and clinical course. Although leukodystrophies have been understood as genetic defects leading to hypomyelination or demyelination, only a few of the affected genes are oligodendrocyte-specific (651). Novel classification systems thus put forward the

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primary involvement of any cell population in the white matter by classifying myelin disorders in primary oligodendrocyte/myelin defects, astrocytopathies, leuko-axonopathies, microgliopathies, and leukovasculopathies (639) **(FIGURE 8)**.

The shift of classification systems towards pathophysiology highlights the complex cellular interdependencies of the CNS and their contributions to disease development. For instance, the role of the glial syncytium in myelin pathology is underscored by mutations in genes coding for astrocytic

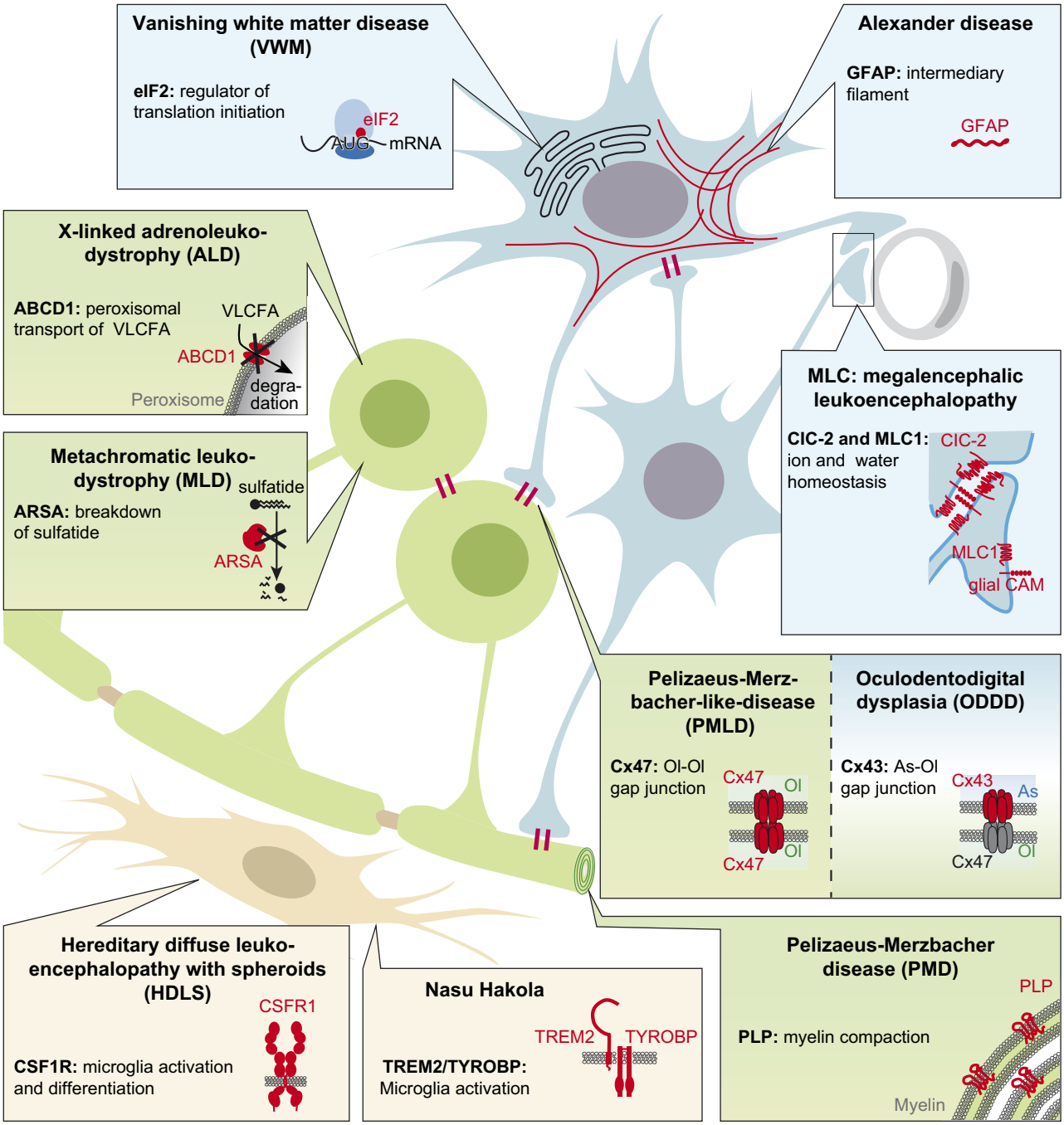

FIGURE 8. Leukodystrophies: pathways and cellular populations involved in demyelination. Genetic defects primarily affecting astrocytes (As: blue), oligodendrocytes (Ol: green), or microglia (brown) can all manifest as hereditary demyelinating disease. Distinct molecular pathways leading to demyelination in selected leukodystrophies illustrate the broad spectrum of pathophysiological mechanisms and subcellular localization of the affected molecules (red) and range from imbalances in water homeostasis in megalencephalic leukoencephalopathy (MLC), defects in structural proteins in Pelizaeus-Merzbacher disease (PMD), to defects in membrane receptors involved in microglia activation and differentiation in hereditary diffuse leukoencephalopathy with spheroids (HDLS) and Nasu Hakola disease, among others.

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or oligodendroglial connexins (Cx) in which loss of function of the astrocytic Cx43 in oculodentodigital dysplasia (ODDD) or the oligodendroglial Cx47 in Pelizaeus Merzbacher-like disease (PMLD) are associated with myelin loss (3). Also, mutations leading to functional defects in glial cell adhesion molecule (GlialCAM), megalencephalic leukoencephalopathy with subcortical cysts-1 (MLC1), and the chloride voltage-gated channel 2 (CLCN2), all proteins related to ion and water homeostasis of astrocytes, are associated with megalencephalic leukoencephalopathy with subcortical cysts (MLC), a disease causing white matter swelling and myelin vacuolation (638). Surprisingly, mutations in primarily microglial genes such as the colony stimulating factor 1 receptor (CSF1R) in hereditary diffuse leukoencephalopathy with spheroids (HDLS), or the triggering receptor expressed on myeloid cells-2 (TREM2) and its adaptor protein TYROBP in Nasu Hakola disease lead to late-onset demyelination through mechanisms that are not yet fully understood (499, 611) **(FIGURE 8)**.

In the following section we discuss pathophysiological aspects of leukodystrophies based on exemplary diseases with primary oligodendrocyte, astrocyte, and microglial defects. For a general overview and discussion of specific disease groups, the reader is referred to recent reviews (114, 315, 639).

E. Mutations in Oligodendrocyte and Myelin-Related Genes

Mutations in genes enriched in oligodendrocytes can manifest pathologically as diseases associated with hypomyelination, dys-/demyelination, or myelin swelling (639). Affected genes are functionally heterogeneous, ranging from genes coding for proteins with structural function to enzymes involved in specific metabolic pathways. Prominent examples are PLP1, Cx47 (GJC2), and the lysosomal enzyme arylsulfatase A (ASA), which will be discussed in the following section.

F. Mutations in the Myelin Membrane Protein PLP/DM20

1. Pelizaeus Merzbacher Disease/X-linked severe spastic paraplegia 2 (SPG2)

Pelizaeus Merzbacher disease (PMD) and *X*-linked severe spastic paraplegia 2 (SPG2) are inherited myelin disorders caused by mutations in the *PLP1* gene, coding for the structural myelin protein PLP and its splice variant DM20. The most common genetic alteration in PMD is *PLP1* duplication, which occurs in ~60–70% of the patients followed by missense or point mutations (15–20%), insertions, and deletions (625).

As expected from its abundant expression in the CNS and its role in the apposition of myelin sheaths, defects in PLP show a strong genotype-phenotype correlation. In general, *PLP* duplications cause classical PMD, which manifests in the first 5 years of life, while missense mutations result in a severe variant with connatal onset. Deletions and null mutations give rise to SPG2 and null PMD syndrome, milder clinical forms with later age of onset (114, 639). The specific genetic defects lead to different pathophysiological mechanisms with considerable overlap in the presentation of these different disorders is observed (435). Patients with classic PMD show hypomyelination in the cerebral and cerebellar white matter with relative preservation of the grey matter (238, 561). Ultrastructurally, myelin sheaths display swellings, constriction, and abnormal foldings; occasionally abnormally thick myelinated fibers are seen (338).

A striking histological feature is the almost complete absence of mature oligodendrocytes due to increased cell death (314, 570), possibly as a result of gain-of-toxic function caused by PLP. Indeed, in PLP overexpressing transgenic mice, dys-/demyelination is observed and disease severity correlates with the amount of PLP expressed (19, 289, 512). Why abnormal levels of PLP cause cell death is unknown, but altered ratios of myelin membrane components might lead to a build-up of toxic material within the cell. Accumulation of PLP and associated lipids occurs in oligodendrocyte cell body where abnormal lysosomes and autophagic vacuoles are observed (46, 73, 294, 572). Contrary to point mutations (see below), PLP duplication does not lead to prominent ER accumulation. Therefore, activation of the unfolded protein response (UPR), a cellular adaptive response to stress triggered by ER sequestration of proteins that may lead to apoptosis (245, 349), seems to play a less important role in oligodendrocyte death in PLP duplication. However, both activation and inhibition of stress responses in human induced pluripotent stem cell-derived oligodendrocytes harboring *PLP* duplications can lead to prolonged cellular stress relief, allowing the reestablishment of normal oligodendrocyte morphology (435).

PLP null mutations are also associated with hypomyelination, but myelin loss is less severe compared with patients with *PLP* duplication. When evaluated with histochemical methods, diffuse myelin loss with preservation of U-fibers can be observed, yet when immunohistochemistry for myelin proteins such as MBP is used, the white matter seems to be well myelinated (201, 570). Ultrastructural analysis reveals a great variation in the degree of myelination of individual fibers, with areas showing normal myelin interspersed with thinly myelinated fibers and myelin dissolution (338). However, in spite of the overall relative normal appearance of myelin, axonal swellings and Wallerian degeneration are frequently observed (201, 570). Similar findings have been reported in PLP-null mice in which myelin ultrastructure is well preserved, but axonal degeneration is prominent (225). As with other white matter pathologies, these results highlight the pivotal role of proper myelin

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function in securing axonal survival (reviewed in Refs. 50, 432).

Finally, several point mutations in *PLP1* have been described that also lead to demyelination and oligodendrocyte loss. However, variable clinical phenotypes associate with specific mutations and range from mild to severe connatal forms (100, 265). In mouse models harboring PMD-related mutations, abnormal PLP structure and apoptosis of fully differentiated MBP-expressing oligodendrocytes were observed (219). In culture, truncated or misfolded PLP forms failed to be transported to the plasma membrane, showed accumulation in the endoplasmic reticulum/Golgi, and associated with oligodendrocyte death (155, 218, 219, 588, 606). Expression of mutant PLP in culture systems led to the expression of stress markers and in particular the nuclear expression of CHOP, an effector protein of the ER stress response associated with apoptosis (588). Moreover, CHOP localization to the oligodendrocyte nucleus was also demonstrated in human PMD (588).

G. Mutations in the Oligodendrocyte-Specific Connexin Cx47

1. PMLD

Highlighting the important role of gap junctional communication in myelin maintenance and development, mutations in the *GJC2* gene, encoding the oligodendrocyte-specific Cx47 (309, 388) (see sect. III*A5*) lead to a demyelinating disease referred to as PMLD (243, 635).

Several recessive mutations in the coding and promoter regions of *GJC2* have been described and include frameshift, nonsense, and missense mutations (90, 129, 217, 243, 635, 657). Clinically, PMLD patients show a rather homogeneous phenotype with early onset (90, 243, 635), while in patients with mutations in promoter regions, the clinical manifestations are more variable (3). MRI changes suggestive of abnormal myelination are observed in the cerebral white matter with relative sparing of corticospinal tracts (545, 635, 674). The cerebellar white matter may be affected, whereas the basal ganglia appear normal in the majority of patients (44).

The relatively narrow clinical phenotype and the recessive inheritance suggest a loss of Cx47 function in PMLD (3). When expressed in culture, Cx47 with PMDL-associated mutations is unable to form functional oligodendrocyte/oligodendrocyte or oligodendrocyte/astrocyte gap junctions (156, 449, 450). In contrast to PLP-null mutants, Cx47 knockout mice show prominent myelin vacuolation with large vacuoles surrounded by few layers of compact myelin (388, 443). No overt demyelination is observed, probably owing to a compensatory effect of Cx32. In Cx47/Cx32 double knockout mice, however, dys- and demyelination with oligodendrocyte apoptosis and axonal damage occur (388, 443). Altogether, these observations suggest that demyelination in PMLD is likely the result of loss of function of gap junctional communication in mature oligodendrocytes, oligodendrocyte apoptosis, and impaired myelin development and maintenance, which seems less redundant in humans than in mice.

H. Defects in Lipid Metabolism

1. Metachromatic leukodystrophy

Several leukodystrophies have been described, in which the causing mutation affects genes related to lipid metabolism. Probably one of the best studied examples is metachromatic leukodystrophy (MLD), an autosomal recessive leukodystrophy caused by mutations in the *ARSA* gene, which encodes for the lysosomal protein arylsulfatase A (ASA), or in the *PSAP* gene encoding for prosaposin B, an activator of ASA (107, 649). ASA plays a crucial role in the metabolism of sulfatides, lipids enriched in myelin, but is also present in astrocytes, neurons, and peripheral organs (164). Therefore, defects in sulfatide degradation result in intralysosomal accumulation of lipids in the CNS and PNS as well as in visceral organs such as gallbladder, liver, pancreas, intestines, and kidney (164).

The age of onset and severity correlate with residual enzyme activity. Disease manifestation occurs when activity drops below ~10–15% of normal levels (208). Homozygosity and compound heterozygosity for alleles that do not allow synthesis of functional enzyme result in the severe early-childhood form with age of onset before 3 yr and rapid psychomotor regression leading to weakness, areflexia, and death (209, 649). In the juvenile form, patients have residual enzymatic activity and therefore progress slower, but eventually also decline (208). Finally, in the adult variant, with onset after the age of 16 yr, enzyme levels are higher, and neurological deficits with cognitive and behavioral changes and neuropathy occur later (208, 328).

Diffuse myelin loss with regions of myelin sparing, so-called radiating stripes, is found in the cerebral white matter (115, 578, 646, 650). The disease is characterized histologically by metachromatically stained granules, which are found within neurons, glial cells, and macrophages and also outside of cells (316, 646). Axonal destruction is severe. The main ultrastructural features in demyelinated areas are accumulation of myelin degradation products within phagocytes. In MLD, demyelination is thought to be the direct consequence of lipid accumulation leading to oligodendrocyte death followed by myelin destruction (209, 316). However, at the lesion borders in the subcortical white matter, myelin sheaths display milder abnormalities with dissociation of myelin lamellae and dysjunction from the axolemma (224, 227). The pathophysiological contribution

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of such subtle myelin abnormalities and widespread metabolic alteration involving axonal dysfunction is unclear.

I. Mutations Affecting Microglia

1. Hereditary diffuse leukoencephalopathy with spheroids and Nasu Hakola disease

Microglia are the resident macrophages of the CNS, yet besides their role in immune surveillance, they have a wide range of developmental and homeostatic functions. For instance, microglia guide the construction, maturation, and function of neuronal networks. Also, they interact directly with the periphery and react to specific signals influencing the CNS microenvironment (reviewed in Refs. 302, 493, 617). Microglia may also play a role in myelin homeostasis and development, which has become evident with the discovery of hereditary demyelinating diseases caused by mutations in microglial genes such as hereditary diffuse leukoencephalopathy with spheroids (HDLS) and Nasu Hakola disease (NHD).

In both diseases, the affected genes are key regulators of macrophage/microglial activation and inflammatory pathways. In HDLS, mutations lead to defective kinase activity of the colony-stimulating factor 1 receptor (CSF1R), which is required for macrophage/microglia differentiation, maintenance, and activation (10, 117, 365, 499, 501, 593, 659). NHD is caused by loss-of-function mutations in either of two interacting molecules, the extracellular receptor (TREM2) and its intracellular interaction partner DNAX-activating protein of molecular mass 12 kDa (DAP12) also known as TYRO protein kinase-binding protein (TYROBP) (311, 454, 455). Trem2/DAP12 plays an important role in microglia polarization as receptor activation allows microglia to convert from a homeostatic to an activated state (298, 318).

Both diseases have a similar clinical presentation with onset in the fourth or fifth decade of life and psychiatric alterations followed by neurological symptoms and death (58, 453, 593). Changes suggestive of progressive demyelination and axonal damage are observed and occur initially in the frontal lobe (58, 603). Demyelination and axonal loss, with a particular regional distribution also involving brain stem and cerebellum, are a common feature in all patients (30, 526, 642). Numerous axonal swellings and spheroids, often with accompanying myelin vacuolization, are found in demyelinated areas and occasionally in the grey matter. These changes are accompanied by widespread astrogliosis (17, 28, 30, 453, 526, 642). Interestingly, tau-positive neurites were observed in the cortex of both HDLS and NHD (453, 526).

The exact mechanisms linking microglial dysfunction and demyelination are unclear. However, in HDLS, there is evidence that axonal damage precedes demyelination (16, 603). Late disease onset, extensive axonal damage, and expression of CSF1R in neurons and neural progenitor cells (NPCs) suggest that demyelination might arise as a consequence of primary neuroaxonal damage and microglia dysfunction (10, 117, 365, 501, 659). Nonetheless, CNS abnormalities such as ventricle dilation, cortical atrophy, reduced microglial colonization and reduced density of NPCs, mature neurons and oligodendrocytes in CSF1R knockout and older haploinsufficent *Csf1r*$^{+/-}$ mice point towards an important developmental component (116, 169, 428). However, conditional deletion of CSF1R in NPCs did not show cortical atrophy, or microglia or oligodendrocyte reduction, suggesting that CSFR1 deficiency in microglia contributes to disease manifestation (116, 169, 428). The notion that white matter pathology can arise from a primary microglial phenotype is further supported by NHD, since *TREM2* and *DAP12* are primarily (perhaps exclusively) expressed in microglia in the CNS (59, 621). Whether microglia dysfunction can directly trigger demyelination and oligodendrocyte death is unclear. A direct interaction between myelin and microglia has been demonstrated in the process of age-related myelin clearance, where microglia actively strips off damaged myelin (542). Also, OPC homeostasis appears to depend on microglia function (233), as treatment with the microglia-depleting compound CSF1-R inhibitor BLZ945 was associated with a significantly reduced number of OPCs (233). The exact molecular pathways by which microglia sustain OPC survival is not clear, but soluble growth factors or mitogens such as IGF-1 may be involved (233, 246, 259). In addition, in a toxic demyelination model, TREM2-deficient mice failed to expand the number of microglia, leading to impaired myelin clearance and persistent demyelination (104, 482), suggesting that impairment of microglial function additionally contributes to lesion progression in NHD.

J. Mutations in Primarily Astrocytic Genes

1. Vanishing white matter disease (VWM) and Alexander disease

Astrocyte physiology is traditionally associated with homeostasis, for example, by maintaining blood-brain barrier integrity and modulating synaptic activity through regulation of extracellular neurotransmitter and ion concentrations (584). However, during the last decade it has become clear that astrocytes serve more specialized roles in physiological as well as pathological situations (463, 584). Astrocytes are known to modulate synaptic plasticity, formation, and maturation and to contribute to functional regeneration after injury. Moreover, astrocytes show variable and often disease-specific contributions in neuropathology ranging from protective effects to pathological modifications leading to the release of neurotoxic factors and exacerbation of tissue damage (463).

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Little is known about the role of astrocytes in oligodendrocyte/myelin pathology, development, and maintenance, yet myelin disorders in which the causal mutations affect primarily astrocytic function suggest a tight interaction between these two cellular populations.

Alexander disease is an autosomal dominant disorder caused by mutations in the GFAP gene, an intermediate filament protein that is expressed predominantly in astrocytes. Although GFAP expression is found in other cell types, symptoms are restricted to the CNS (77, 78). Based on clinical presentation and radiological findings, Alexander disease has been classified as type I with early onset and predominantly frontal leukoencephalopathy (496) and type II with later, variable age of onset and predominant posterior fossa and spinal cord localization (393, 496). The histopathological hallmark of Alexander disease is the presence of astrocytic cytoplasmic inclusions (12), usually known as Rosenthal fibers, owing to their first description by Rosenthal in an old glial scar (534, 673). Rosenthal fibers arise as a consequence of GFAP overexpression and consist of GFAP associated with other proteins such as cyclin D2, the filament binding protein plectin, and the small heat shock proteins alphaB-crystallin and Hsp27, among others (279, 286, 587).

Demyelination is usually severe in early-onset forms and can be mild or even absent in late-onset pathology. In the former, oligodendrocytes are severely reduced and macrophages are usually not increased in areas of demyelination. Moreover, macrophages do not contain myelin degradation products, suggesting a defect in myelin formation, rather than active demyelination. On the other hand, in childhood- and adult-onset cases, when demyelination is present, lipid-laden macrophages can be found (68, 483, 626).

Current concepts regarding the pathogenesis of Alexander disease suggest a gain-of-toxic function of GFAP. GFAP overexpressing mice, carrying a human GFAP (hGFAP) transgene under the control of its own promoter, showed markedly hypertrophic astrocytes containing Rosenthal fibers. Moreover, the life span of the animals inversely correlated with GFAP dosage, suggesting that GFAP overexpression exerts a primary pathological effect (394). Nevertheless, transgenic mice expressing the Alexander disease-associated GFAP-R76H and -R236H mutations also developed Rosenthal fibers and elevated levels of total GFAP, but the animals had a normal life span without behavioral abnormalities (231). Mutant monomers assemble to form aberrant large oligomers that inhibit the proteasome system (612). In addition, GFAP accumulation has been shown to alter cytoskeletal dynamics (118), increase autophagy (613, 614), and interfere with glutamate/potassium buffering, calcium signaling, and gap-junctional coupling (544, 586, 623) as well as reducing cell proliferation and promoting apoptosis (118).

Although astrocytic dysfunction can partly explain select clinical features of Alexander disease, the exact mechanisms linking astrocyte dysfunction to demyelination remain elusive. Olabarria and Goldman propose three mechanisms that might contribute to demyelination. First, the increased expression of CXCL10 in astrocytes in Alexander disease (232, 446, 447) may exert direct effects on oligodendrocytes or influence the immune reaction promoting demyelination (446). Second, the loss of gap junctional communication and the resulting alterations in the buffering capacity of astrocytes may lead to intramyelinic edema (586, 623). Finally, extracellular deposition of hyaluronan, a protein that is produced by astrocytes and accumulates in the extracellular space in other demyelinating diseases, might inhibit OPC differentiation (60, 92).

Recently, a mechanism independent of astrocytic dysfunction has been proposed. As GFAP is also expressed in neural progenitor cells, mutated or increased GFAP levels may also interfere with cellular development and OPC differentiation (215).

Another leukodystrophy where astrocytes have been widely implicated is vanishing white matter disease (VWM), a recessively inherited disorder caused by mutations in any of the five subunits of eukaryotic translation initiation factor 2B, *eIF2B* (345, 641). The eIF2B protein plays a central role as regulator of translation initiation, specifically for RNA/ribosome assembly, and modulates the overall rate of protein synthesis (1). There are several VWM-associated *eIF2B* mutations, the majority of which consist of missense mutations (91) leading to loss of eIF2B complex structure and reduction of complex activity (1). The lack of reported homozygous nonsense or frameshift mutations indicates that eIFB2 is essential for survival (91, 643).

Clinical presentation ranges from fatal pre- and neonatal variants to the rapidly progressive classical form, with onset in early childhood (643), to milder phenotypes with onset in adolescence or middle age (189, 640, 643, 644). The classical form of VWM is characterized by progressive neurological deterioration in which episodes of febrile infection and even mild head trauma might result in unexplained coma and prompt severe and rapid progression (552, 637). In later onset disease, the initial clinical presentation often consists of dementia, seizures, and psychiatric or motor symptoms (643).

Typically, the entire cerebral white matter shows hyperintense T2-weighted signals in MRI that develop into cystic lesions (637, 640). Cystic degeneration is less complete in late-onset forms and in the cerebellum (643). Histologically, myelin is severely reduced and shows extensive vacuolation and cystic changes in particular in frontotemporal regions (21, 85, 637, 640). Axonal density is variable in

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demyelinated areas with mild vacuolation, but clearly reduced in areas with cystic degeneration. Astrocytes show a characteristic dysmorphy with coarse, blunt cell processes (85, 643).

Within cavitated areas and in their immediate vicinity, cellularity is reduced with marked oligodendrocyte loss (85). In areas with relative tissue preservation, an increase in oligodendrocyte density is observed. These so-called "foamy" oligodendrocytes show characteristic enlarged nuclei and abundant granular cytoplasm (529, 637, 640, 647, 678).

Surviving oligodendrocytes in lesion areas as well as in areas of ongoing demyelination express proliferative as well as pro- and anti-apoptotic markers (85, 647), the coexpression of which might promote cell death (647). Also, nuclear changes characteristic of apoptosis suggest that demyelination might ultimately be a consequence of oligodendrocyte loss (85). eIF2b is ubiquitously expressed, and abnormal eIF2b subunits may also have a direct effect on oligodendrocyte survival. In fact, increased levels of phosphorylated PERK, p-eIF2α, ATF4, and CHOP in VWM oligodendrocytes (646, 648) could be the result of an adaptive response to eIF2b mutations (291, 349).

Abnormal oligodendrocyte function and demise may hence occur, at least partly, as a direct consequence of defective eIF2b, yet developmental abnormalities may also be at play. In a transgenic mouse model harboring the R132H mutation of eIF2b, an increased OPC density, myelin abnormalities, and an increased amount of small-diameter axons with low myelin content were observed (205). Increased OPC numbers could occur as a consequence of maturation failure, which might in part be mediated by astrocyte dysfunction. In mutant astrocyte/mutant OPC coculture systems, defective eIF2B led to a maturational arrest of OPCs which could be rescued by coculture of mutant OPCs with wild-type astrocytes, indicating a direct role for astrocytes in OPC maturation (159).

It remains unclear why mutations in a ubiquitously expressed principal regulator of protein synthesis manifests primarily as a neurological disease affecting glia. It has been speculated that glial cells show a relatively low constitutive eIF2B activity as compared with other cells and are therefore particularly vulnerable to further reductions in its activity (643). Also, the increased stress response observed in VWM could prove especially harmful to glial cells (643). Finally, eIF2B might have yet unidentified functions especially relevant for glial cell physiology (1). Altogether, myelin pathology in VWM may occur as a consequence of defective OPC maturation, likely mediated by astrocyte dysfunction, and of demyelination due in part to oligodendrocyte death, as a direct effect of abnormal eIF2b. It is plausible that the aberrant astrocytic function may also lead to osmotic and metabolic imbalances further contributing to lesion progression.

K. Viral Infection Leading to Demyelination

1. Progressive multifocal leukoencephalopathy

Demyelination represents a hallmark of several viral CNS infections in humans and other mammals. The mechanisms often involve oligodendrocyte apoptosis and/or lysis as well as disruption of the intracellular machinery responsible for myelin biosynthesis.

One of the best studied examples is progressive multifocal leukoencephalopathy (PML), a usually fatal demyelinating disease caused by CNS infection with the double-stranded DNA polyomavirus JC. Latent infection with JC virus (JCV) is highly prevalent in humans, while lytic CNS infection is almost exclusively found in the context of immunosuppression (373).

Demyelination is typically multifocal, confluent, and located in the cerebral hemispheres (25, 56, 296, 297, 518). Oligodendrocytes show enlarged nuclei, and astrocytes frequently demonstrate bizarre nuclear morphology suggestive of neoplasia (25, 518). Cortical lesions are a common finding in PML autopsies with reported frequencies ranging from 57 to 100% (415, 681). PML is one of the few CNS pathologies besides MS where cortical demyelination has been recognized as a prominent feature (415).

In accordance with the association between PML and immunosuppression, inflammatory infiltration frequently is sparse in PML lesions and consists mostly of CD8 T-lymphocytes, with only a few B cells (680). Interestingly, an increase in B cells, plasma cells, and T cells with a CD8 predominance has been reported in the context of the PML-associated immune reconstitution inflammatory syndrome (PML-IRIS), where PML becomes clinically apparent or worsens with the recovery of the immune system, mostly in MS patients treated with natalizumab and in HIV patients (379, 395).

The most widely accepted mechanism of demyelination in PML implicates oligodendrocyte and astrocyte infection by JCV followed by lytic oligodendrocyte death with local virus spread and subsequent demyelination.

The JCV genome contains early and late transcribing portions separated by a noncoding control region. The early region is transcribed before DNA replication and consists of large, small, and splice variants of T antigen. The late portion codes for agnoprotein and capsid proteins VP1, VP2, and VP3, of which VP1 represents the principal capsid component (178). Immunohistochemically, both VP1 and T-antigen can be observed in oligodendrocytes, suggesting that

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oligodendroglia contribute to productive viral infection (204, 223, 273, 285). Additionally, ultrastructural changes compatible with viral adsorption, penetration, and intracellular transport in oligodendrocytes have been demonstrated in PML (383).

Besides oligodendrocyte lysis, several studies suggest a prominent role for apoptosis in PML (391, 517, 684), which might depend on the p53 pathway (22, 595). Given the highly selective human tropism of JCV, and thus its inability to replicate productively in non-human hosts, good animal models of PML are lacking (667). Nevertheless, complex chimeric studies in transgenic animals in which myelin-deficient, immunosuppressed mice were engrafted with human glial progenitor cells showed extensive oligodendrocyte apoptosis triggered by viral T antigens. In this model, JCV infection induces an aberrant reentry of oligodendrocytes in the cell cycle, leading to an arrest in G_2 with subsequent apoptotic death (317).

In PML lesions, oligodendrocytes and astrocytes express the apoptosis inhibitor survivin (479). It has been proposed that the virally induced expression of anti-apoptotic proteins allows a longer time period for JCV to replicate and complete its lytic cycle (149). It remains unclear whether these infected, longer-surviving oligodendrocytes ultimately undergo cellular lysis and necrotic cell death. Also, the relative contribution of specific mechanisms of oligodendrocyte death to the extent of demyelination and virus propagation remain unknown.

The distribution of infected oligodendrocytes suggests that demyelination progresses mainly through sequential, productive JCV infection and lysis of oligodendrocytes, resulting in radial lesion expansion (278, 301, 415, 569, 670) **(FIGURE 6)**. However, the radiological manifestations of PML indicate that lesions can also spread along white matter tracts, suggesting that in addition to local virus spread after lysis of infected cells, further mechanisms of local and distant virus propagation may exist (563). In particular, it has been proposed that virions disperse locally in an intracellular manner and that distant virus propagation is likely to occur extracellularly along white matter tracts (666). Indeed, viral particles are not only observed in the cytoplasm and cell processes of oligodendrocytes at the demyelinating lesion border (278, 666), but also at the intraperiod line between the myelin lamellae in the extracellular space (383).

In addition to oligodendrocytes, JCV infection of astrocytes and neurons has been documented (25, 223, 373, 562, 675, 681). Astrocytes are not considered to contribute significantly to productive infection (354), but the presence of infected astrocytes in areas without overt demyelination has led some authors to postulate that viral propagation might begin in astrocytes and then spread to neighboring oligodendrocytes (26, 317, 562). However, next to their potential role in virus propagation, it is unknown how infected astrocytes contribute to demyelination. JCV-infected neurons are found in about half of the patients with lesions in the gray matter and only 11% in areas not associated with demyelination (160, 681), but their contribution to myelin pathology is unknown.

VII. CONCLUSION

In this review we have discussed our current knowledge in the biology of myelin and its implications for disease. We highlighted advances in our understanding of myelin formation, its plasticity, and the reciprocal interactions of oligodendrocytes with the axons they ensheath. Oligodendrocytes are embedded in a vast network of interconnected glial and neuronal cells, in which oligodendrocytes actively provide metabolic support to neurons, regulate ion and water homeostasis, and adapt to activity-dependent neuronal signals (575). Novel insights into molecular mechanisms governing the interactions between cellular populations of the nervous system have influenced current pathophysiological thinking about myelin disorders. These recent advances showing the cellular interdependence indicate that myelin dysfunction should be understood in the broader context of nervous system pathophysiology. We demonstrate this by discussing how specific interactions between astrocytes, oligodendrocytes, and microglia might contribute to demyelination in hereditary white matter pathologies. In addition, we summarized the mechanisms of lesion formation and myelin damage in inflammatory demyelinating diseases, taking as an example multiple sclerosis, the most frequent acquired demyelinating disease of the CNS, which is increasingly recognized as a "whole-brain" disease. We believe that the interdependence of the cellular partners has the potential to explain how pathological alterations can expand throughout the nervous system and is also important for our understanding of how focal MS lesions develop over time. Also, evidence is accumulating that dysfunction of myelin is not restricted to neurological diseases, but affects a wide range of psychiatric disorders, including schizophrenia, bipolar disorder, and obsessive-compulsive disorders (181). Even if much progress has been made and the role of myelin in health and disease is expanding, fundamental questions remain to be solved. Among those are: How do oligodendrocytes know which axons to myelinate? What is the function of myelin beyond saltatory nerve conduction? Does myelin contribute to neuronal plasticity? How is myelin functionally coupled to other cells? In the context of inflammatory myelin diseases, apart from the specific role of immune cell subsets and humoral factors for disease initiation and progression, the antigenic targets of the immune response and the specific environmental triggers of autoimmunity, the interactions between axons, myelin, and oligodendrocytes in MS are only beginning to be appreciated. Also, the interactions of astrocytes and axons

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to support axonal conductance and lesion repair, especially in chronic demyelinated MS lesions, are not well understood. In addition, the role of microglia within the glial syncytium might be worth a deeper look.

While there is an expanding knowledge about the mechanisms of lesion formation in leukodystrophies, the mechanisms of lesion repair are largely unexplored. In the majority of leukodystrophies it is unknown whether, how, and at which time point after lesion onset, a correction of the underlying genetic defect would result in effective tissue recovery and whether this would translate into clinical benefit. Is a functional pan-glial syncytium a prerequisite for lesion repair? For instance, in diseases with primary astrocyte dysfunction or loss, it is not known whether astrocyte repopulation is required for remyelination, OPC survival, and axonal maintenance. Which compensatory mechanisms make up for defective/absent astrocyte function? What is the role of the immune system in the repair process? Clearly, further work will be necessary to elucidate the mechanisms and the molecules that mediate communication in the glio-neuronal network in health and disease.

ACKNOWLEDGMENTS

We thank Simon Hametner and Franziska van der Meer for critical reading of the manuscript, Anne Winkler and Jan Ficner for help with graphical illustration, Cynthia Bunker for language editing, and Carolin Dreyer for manuscript editing.

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GRANTS

The work was supported by grants from the German Research Foundation (SI 746/12-1; TRR128-2, SyNergy Excellence Cluster; STA-1389/2-1), an ERC-Consolidator Grant (to M. Simons), the Tschira-Stiftung (to M. Simons), the Adelson Foundation (to M. Simons), the Gemeinnützige Hertie Foundation (to C. Stadelmann), the German MS Society (DMSG) (to C. Stadelmann), and the National MS Society of the USA (NMSS) (to C. Stadelmann). A. Barrantes-Freer was partly funded by the MWK Kolleg für translationale Medizin (Niedersächsisches Ministerium für Wissenschaft und Kultur).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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