REVIEW

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Myelination and support of axonal integrity by glia

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The myelination of axons by glial cells was the last major step in the evolution of cells in the vertebrate nervous system, and white-matter tracts are key to the architecture of the mammalian brain. Cell biology and mouse genetics have provided insight into axon–glia signalling and the molecular architecture of the myelin sheath. Glial cells that myelinate axons were found to have a dual role by also supporting the long-term integrity of those axons. This function may be independent of myelin itself. Myelin abnormalities cause a number of neurological diseases, and may also contribute to complex neuropsychiatric disorders.

Glial cells outnumber neurons in the human brain and are involved in almost all neural functions, but for decades they received relatively little scientific attention. This is both a cause and a consequence of the poor understanding of what glial cells do. New technologies available to neurobiologists have now provided unexpected insight into glial-cell function, and have greatly expanded research.

A unique specialization of glia in vertebrates is the deposition of myelin. The ability of oligodendrocytes in the central nervous system (CNS) and Schwann cells in the peripheral nervous system (PNS) to wrap long segments of axons with a multilayered sheath of extended cell membrane (Box 1), and to assemble a complex seal with the axon surface that defines the nodes of Ranvier between long axon segments with myelin (termed 'internodes'), leads to one of the most spectacular and intimate cell–cell interactions in the nervous system (for recent reviews, see refs 1–4).

Myelin was first understood to enable 'saltatory' impulse propagation in axons more than 60 years ago (before it was recognized by electron microscopists to be a specialized outgrowth of glia[5]), and this function is a key concept of neurophysiology. Other functions of glial cells are still not completely understood. We do not even know, at a morphological descriptive level, how myelin is deposited. This will be resolved only with the use of new genetic tools and imaging techniques.

I will begin this Review with a look at myelin evolution and the unique physiology of a myelinated brain, before coming to the unexpected functions of myelinating glia in axon support. This will lead to a discussion of myelin diseases, and the possible role of myelination in higher brain functions. In separate boxes, I will summarize knowledge of the molecular architecture of the axon–myelin unit in the CNS, and the molecular mechanism by which axonal signals control myelination, which is, so far, better understood in the PNS.

From axon-associated glia to myelination

The myelination of axons was the last true 'invention' of vertebrate evolution in the cellular architecture of the nervous system, thought to have occurred in placoderms[6,7] — that is, fish with a hinged jaw. Axons with larger diameters allow more rapid impulse propagation, but it is difficult to increase these diameters when the axons are contained in bone. To overcome this, vertebrates achieved rapid impulse propagation by myelinating small-diameter axons. Improved muscle control became the basis for the development of complex predatory and escape behaviour, which ultimately drove body size and vertebrate evolution.

Myelin-like ensheathments of axons evolved independently in Annelida (ringed worms), Arthropoda (arthropods) and Chordata (vertebrates and invertebrates with a hollow dorsal neural tube)[8], but they are morphologically distinct. Glial cells that engulf axons without myelinating them are a feature of almost all nervous systems. The physical separation of electrically active axons may limit crosstalk. However, as discussed below, axon-engulfing glia also exert a trophic support that relates to neuronal development, problems associated with axon length, or both.

Myelination follows the basic wiring of the nervous system, and largely occurs postnatally in mammals[9]. Thus, even severe developmental defects of myelin are not lethal to embryos, but instead are a cause of disease.

In the simpler PNS, non-myelinating Schwann cells, or Remak cells, coexist with myelin-forming Schwann cells and engulf multiple small-calibre C-fibre axons (which convey, for example, pain signals) in so-called Remak bundles[10]. Why do we have Remak cells that may represent an ancestral type of axon-associated glia? The functional perturbation of Remak cells in transgenic mice causes progressive C-fibre degeneration and sensory neuropathy[11], suggesting that the cells are required to maintain the integrity of axons. This is presumably a function of all axon-associated glial cells[12].

Oligodendrocytes — which myelinate several axons simultaneously — and Schwann cells — which restrict myelination to one axonal segment — solve similar tasks with an overlapping, but not identical, set of genes. This is a result of some 300 million years of parallel evolution, which is thought to have begun with a glial cell similar to those in unmyelinated fish, such as lamprey. Although the mechanism that led to the evolution of myelin in such jawless fish may never be known, it is intriguing that overexpression of a single axonal growth factor turns non-myelinating into myelinating Schwann cells[13].

The CNS contains no equivalent to Remak cells. Oligodendrocytes arise from a large population of oligodendrocyte precursor cells, which are morphologically complex, unlike stem cells (Box 1). They can be defined by expression of the proteoglycan protein NG2, and have been considered a 'fourth' class of glia in the brain[14]. In retrospect, it is astounding that it took neurobiologists so long to recognize the abundance of these oligodendrocyte lineage cells. The finding that NG2-

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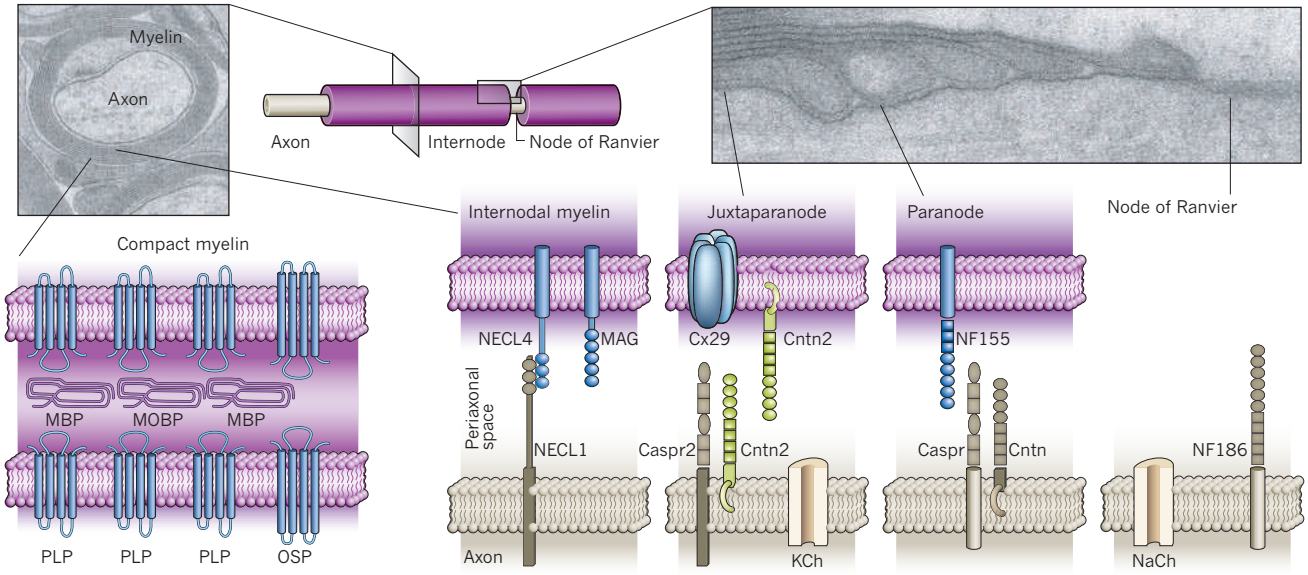
BOX 1

Oligodendrocytes and the axon myelin unit

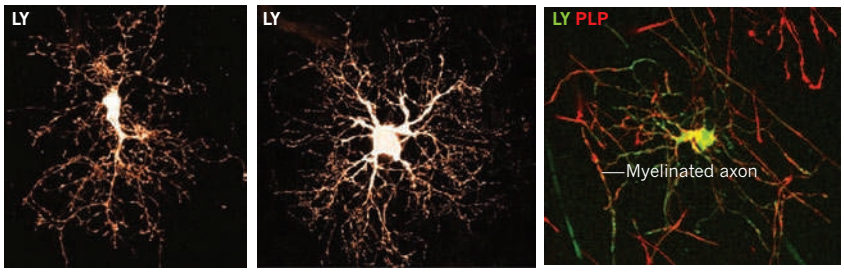


In the rodent central nervous system (CNS), myelin is formed by oligodendrocytes that are derived from morphologically complex precursor cells (oligodendrocyte precursor cells or NG2 cells); the function of these is not well understood[14,83]. Successive stages of oligodendrocyte precursor cell (OPC) differentiation can be visualized *in situ* following the injection of lucifer-yellow dye (LY; see bottom image, adapted from ref. 84).

Mature oligodendrocytes make myelin by wrapping axons with their own cell membrane in a spiral shape, which eventually becomes a multilayered sheath covering a long segment of axon. Although oligodendrocytes are morphologically distinct from the Schwann cells in the peripheral nervous system, axon–myelin units are similar and have been illustrated in the top image as a 'canonical' myelin sheath. Compact myelin is shown by electron microscopy to have a periodic ultrastructure (the inset shows a myelinated optic-nerve axon in cross section). The compaction requires the abundant expression of structural proteins, such as proteolipid protein (PLP) and myelin basic protein (MBP), in the CNS. The functions of most myelin-associated proteins, which have only recently been identified by proteomics[85], are not well understood. A fraction of these proteins may reflect intracellular biogenesis and transport of myelin components that have a slow turnover rate. Myelin membranes are very rich in lipids. Cholesterol, specifically, is rate-limiting for myelin biogenesis[86].

The myelinated axon segments are flanked by nodes of Ranvier, the sites at which Na^+ channels are concentrated and action potentials generated. Here, a specialized axon–glia contact zone (paranodal junction) also seals the internodal periaxonal space from the outside milieu. The molecular architecture of the zone is reminiscent of synaptic junctions, and builds on a battery of glia and axonal adhesion proteins that are linked by axonal scaffolding proteins (not shown) to Na^+ channels and K^+ channels (in the juxtaparanodal region). For details, see ref. 4.

Caspr, contactin-associated protein; Cntn, contactin (Cntn2 is also known as Tag1); Cx29, connexin 29 kDa; KCh, fast potassium channels; MAG, myelin-associated glycoprotein; MBP, myelin basic protein; MOBP, myelin oligodendrocyte basic protein; NaCh, voltage-gated sodium channels; NECL, nectin-like protein/synCAM; NF155/186, neurofascin 155 kDa/186 kDa; OSP, oligodendrocyte-specific protein; PLP, proteolipid protein.



OPC / NG2 cell | Pre-oligodendrocyte | Mature oligodendrocyte

expressing cells also express glutamate receptors and receive transient synaptic input from unmyelinated axons[15] fits earlier observations that neuronal activity modulates myelination. One laboratory has even reported that a subset of NG2 cells can fire action potentials[16], blurring the distinction between neurons and glia.

The benefit of myelinated axons

In the PNS, where neuron–glia interactions are simpler, neurons control glia remotely for their own advantage. The survival, proliferation and terminal differentiation of Schwann cells, Remak cells and their common precursors are largely controlled by one axonal growth factor, termed neuregulin-1 type III (ref. 17). In the CNS, the proliferation and differentiation of oligodendrocyte lineage cells is controlled by further growth factors and cytokines, such as platelet-derived growth factor, brain-derived neurotrophic factor, ciliary neurotrophic factor (CNTF) and leukaemia inhibitory factor. However, not all of these factors are neuronal, and there is no known axonal signal that drives myelination of the very axon that presents it (Box 2).

Neurons benefit from the myelination of their axons in two ways. First, in electrically active but unmyelinated fibres, the restoration of ion gradients by the Na^+, K^+-ATPase consumes a large fraction of available ATP. Myelination strongly reduces this energy consumption,

because action potentials and ion currents are restricted to less than 0.5% of the axon's surface. Second, the up to 100-fold increase in conduction velocity (the actual factor depends on the axon diameter) for myelinated neurons allowed complex yet compact higher nervous systems to evolve.

Increasing the resistance (and lowering the capacitance) of axonal membranes is not the only function of oligodendrocytes and Schwann cells. There is growing awareness that myelinating glia communicate lifelong with axons, and that glia are required for the long-term integrity and survival of axons[18–22]. This vital function, which may have a neurotrophic component, is independent of myelin itself and relevant to a broad spectrum of human myelin diseases (see 'Myelin diseases leading to axonal degeneration').

Axon–glia interactions beyond signalling

To understand axon–glia interactions, one must consider cell size. Neurons are extremists, as is shown by a scaled up model. The 1-μm axon of a cortical neuron, projecting 100 cm into the corticospinal tract, can be compared to a 4-m-wide subway tube that is 4,000 km long. To extend the metaphor, fast axonal transport (of mitochondria, at 5 μm s^{-1}) is analogous to a train travelling at 70 km h^{-1}, whereas slow axonal transport (of proteins, at 2 mm day^{-1}) is, by analogy, slower than a pedestrian (0.5 km h^{-1}). Neurons with long axons, therefore, present a logistical problem, and are a vulnerable bottleneck for the entire nervous system. Axon dimensions may even limit the sizes of the largest vertebrates[23]. Neurological diseases that are known to have a primary origin in the glia cause length-dependent axon loss (see 'Myelin diseases leading to axonal degeneration'), showing that long axons profit from the intimate interaction with local glial cells[24].

Axons and the ensheathing glia interact bidirectionally and throughout life. The finding that PNS axons in dysmyelinated trembler mice, which have a mutation in the peripheral myelin protein 22 (*Pmp22*) gene, are reduced in calibre[25] was early evidence for glia-to-axon (glia–axon) signalling. Similarly, dysmyelinated axons in the CNS of shiverer mice (which lack expression of myelin basic protein, MBP) are thinner than in wild-type mice[26]. Hypophosphorylated neurofilaments suggest that abnormal activity of kinases and/or phosphatases underneath immature myelin further tightens the axonal bottleneck.

The glial signals that modulate axon size are not well defined. One candidate is myelin-associated glycoprotein (MAG), a non-compact myelin protein and a member of the immunoglobulin superfamily[27]. The protein can be shed by proteolytic cleavage, and has been studied as an inhibitor of axonal regeneration. MAG-deficient mice are fully myelinated but show decreased axon calibres and neurofilament spacing, which are probable causes of progressive axonal loss[22]. MAG-mutant mice are more sensitive to the poorly understood neurotoxin acrylamide than are the wild type, and soluble recombinant MAG reduces axon damage in cellular models[28]. The axonal receptor for this protective function is unrelated to the neurite outgrowth inhibitor A (NogoA) receptor complex, which mediates growth-cone collapse.

Cytokines derived from Schwann cells, such as CNTF[29] and erythropoietin[30], also enhance axon survival, at least in experiments of nerve regeneration. Thus, glial signalling molecules provide a line of endogenous neuroprotection. In early development, signalling between neurons and Schwann cells is even more vital. Death of the Schwann cells in embryos, caused by disrupted expression of glial neuregulin-1 type III receptors (ErbB3)[31], leads to secondary loss of motor neurons and most dorsal-root ganglia neurons, resulting in perinatal death in mice.

Axonal integrity requires more than glia signalling molecules. Myelin assembly seems to be normal in *Plp1*-null mice, which lack expression of proteolipid protein (PLP), an abundant tetraspan membrane protein in CNS myelin, whereas natural *Plp1* mutants, such as jimpy and rumpshaker mice, exhibit dysmyelination caused by the toxicity of a misfolded protein[32]. Except for minor ultrastructural abnormalities of myelin and reduced physical stability[33], the PLP-null mutants develop normally and are long-lived. In contrast to dysmyelinated shiverer mutants, the myelinated axons even exhibit normal neurofilament spacing and are developmentally mature. At 3 months of age, however, axons in almost all white-matter tracts in PLP mutants develop swellings ('spheroids') filled with membranous organelles and phosphorylated neurofilaments[18] (similar to those in Fig. 1a, b). As swellings enlarge, the myelin sheath often retracts and is lost over swollen regions. Later, many affected axons in *Plp1*-null mice undergo distal Wallerian degeneration. Within a few months, mice develop a progressive ataxia and die prematurely, without obvious myelin loss but with signs of severe neurodegeneration[18]. Small-calibre axons, which may have the lowest intra-axonal energy reserves, are predominantly affected. Before axonal degeneration there is perturbation of fast axonal transport[19], with possible consequences for brain function as discussed in 'Myelin plasticity and higher cognitive functions'.

It is intriguing that shiverer mice exhibit no axonal degeneration, although they are severely dysmyelinated[18]. More importantly, axonal swellings recur in *Mbp Plp1* double mutants, an observation that points to a myelin-independent role of PLP in axon support. The first functional insight into the mechanism came with an observation that other myelin proteins are less abundant in, or absent from, PLP-deficient myelin[34]. This lack is a failure of post-translational transport into the myelin compartment. The near-absence of nicotinamide adenine dinucleotide-dependent deacetylase sirtuin-2 (SIRT2), a protein expressed by oligodendrocytes and Schwann cells[34–36], is most striking. Although the physiological targets of this enzyme are not known, the phenotype of SIRT2-mutant mice suggests that it has a vital function in neuroprotection (B. Kasapoglu, H. Werner, L. Guarente and K.-A.N., unpublished observations). Recent reports that acetylation regulates the key steps of intermediate metabolism[37] are compatible with SIRT2 having a role in adapting the metabolism of glia.

Specific genetic targeting can be expected to deliver direct insight into the role of the oligodendroglial intermediate metabolism. For example, peroxisomes, which are abundant in oligodendrocytes, are involved in fatty-acid β-oxidation and are crucial for axon function. Conditional mutants have been created, in which oligodendrocytes lack peroxisomal targeting signal 1 receptor (PEX5)-mediated protein import into peroxisomes[38]. During development, these mice assemble myelin that seems normal. However, at about 2 months of age, they exhibit signs of premature neurodegeneration in white-matter tracts and die within one year. Notably, this primary defect of oligodendrocytes causes a secondary neurodegeneration that exceeds demyelination pathology, and is most advanced in the electrically most active subcortical-fibre tracts of the forebrain[38] (Fig. 1c).

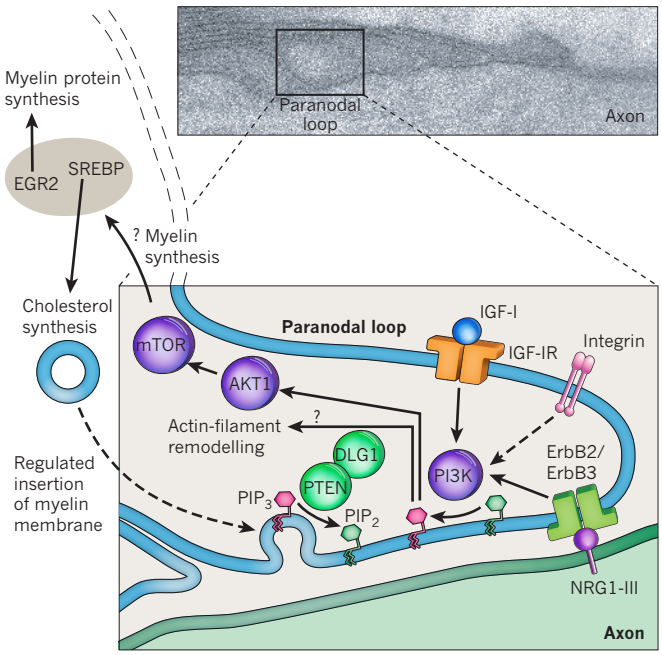
More than one gene is responsible for the support of axons by myelinating glia. For example, the oligodendrocyte-specific protein 2',3'-cyclic nucleotide phosphodiesterase (CNP), which resides in non-compact myelin[39], is thought to bind to RNA and tubulin, and to contribute to oligodendroglial process dynamics *in vitro*[39,40]. Like PLP, CNP is not essential for myelination, but is required for axonal integrity[20] (Fig. 1a, b). *Cnp1*-mutant mice are more severely affected than are *Plp1*-null mice, with the first degenerating axons detected after a just few weeks[21]. Moreover, swellings of the inner tongue emerge very early in life[21]. These point to the perturbation of transport processes within the myelin sheath that could also depend on intact tubular tracts.

I have argued that myelination itself necessitates the support of glia, because for long axons the physical insulation decreases rapid and unlimited metabolic exchange with the extracellular milieu[24]. However, non-myelinating Schwann cells also protect the survival of sensory axons, in line with the hypothesis that axonal support is myelin-independent. Proof of this principle is the phenotype of transgenic mice that express truncated ErbB4 receptors in Remak cells[11], which develop a progressive sensory neuropathy with the loss of numerous unmyelinated C-fibre axons.

BOX 2

Axon–glia signalling and phosphatidylinositol-(3,4,5)-trisphosphate as a nodal point of myelin growth

In the peripheral nervous system, myelination is under the strict control of axons. Among several growth factors, membrane-bound neuregulin-1 type III (NRG1-III) regulates almost all steps of Schwann-cell differentiation[17], including the control of myelin-sheath thickness[87], which is a function of axon size. It is thought that signalling between NRG1-III and the epidermal growth factor receptor (ErbB) family of proteins occurs at the glia–axon interface and activates several second-messenger cascades, including phosphatidylinositol-3-kinase (PI3K) and mitogen-activated protein kinase pathways, focal adhesion kinase, and Ca^{2+} (reviewed in ref. 88). Depicted here is a schematic magnification of paranodal loops with glial ErbB receptors and the sequential activation of PI3K–serine-threonine-specific protein kinase AKT/PKB (AKT1)–mammalian target of rapacin (mTOR) kinases, leading to the activation of myelin-associated genes in the Schwann-cell nucleus. Extracellular matrix components and converging integrin-mediated signalling[88] are not shown. Lipid synthesis is the primary transcriptional response following NRG1-III stimulation *in vitro*[89] and *in vivo* (M. Schwab and K.-A.N., unpublished observations).



The formation of phosphatidylinositol-(3,4,5)-trisphosphate (PIP_3) by PI3K polarizes Schwann cells and stimulates cellular RhoGTPases, actin dynamics and process outgrowth, all of which might be required for membrane protrusions and spiral wrapping of axons[90]. The formation of PIP_3 as a lipid second messenger and nodal point of myelination is tightly controlled and antagonized by the phosphatase and tensin homologue (PTEN) protein. Associated with a scaffolding protein (mammalian discs large homolog 1, DLG1), this lipid phosphatase acts as a brake on myelin growth, preventing hypermyelination and pathological outfoldings[90,91]. In adult nerves, Schwann cells require axons to express the prion protein to prevent demyelination and neuropathy[92].

Oligodendrocytes are different to Schwann cells; they differentiate well in the absence of axonal signals (at least *in vitro*). The effect of neurotrophins on myelination by oligodendrocytes is also distinct from the effect on Schwann cells[93]. *In vivo*, NRG1 and ErbB signalling is largely dispensable for myelination in the central nervous system (CNS)[94], prompting a search for alternative axonal signals. Insulin-like growth factor 1 (IGF-1) and astroglial leukaemia inhibitory factor (LIF) stimulate CNS myelination[95,96], but are not associated with specific axons. AKT and mTOR drive hypermyelination in both Schwann cells and oligodendrocytes[90,97], and transgenic NRG1 overexpression in CNS neurons stimulates some hypermyelination[94]; these observations support a signalling system similar to NRG1. On the other hand, oligodendrocytes in culture can wrap even chemically fixed axons[98]. Thus, neither complex instructive signals nor electrical activity seems to be essential for myelination. This leaves room for the idea that oligodendrocytes are stimulated by a plethora of unconfined growth factors to myelinate by default, but are locally restricted by inhibitory cues, such as polysialylated neural cell adhesion molecule (NCAM)[99].

BACE, β-site amyloid precursor protein-cleaving enzyme 1; EGR2, early growth response protein 2 (also known as Krox20); ErbB2/ErbB3, heterodimeric NRG1 receptor tyrosine kinases; IGF-1R, IGF-1 receptor; PIP_2, phosphatidylinositol-4,5-bisphosphate; SREBP, sterol regulatory element binding protein. Dashed lines indicate pathways that are not well-established.

Some myelin defects trigger inflammation

Mild overexpression of wild-type *Plp1* in transgenic mice causes a combination of dysmyelination and demyelination in the CNS, leading to premature death[41,42]. The disease mechanism exceeds endoplasmic-reticulum stress and includes lipid-trafficking abnormalities[43]. PLP overexpression models a frequent subform of the human *PLP1* disease (see Pelizaeus–Merzbacher disease below) and causes late-onset axonal degeneration[44]. The mechanism of axon loss is unclear, but a secondary inflammation (Fig. 1d), including microgliosis and T-cell infiltration, clearly contributes to the severity of the disease[45]. Invading $CD8^+$ T cells are not just bystanders, because on a recombinant activating gene-1 mutant background (that is, in the absence of functional B and T cells) a significant amelioration of pathology is seen. *Plp1* transgenic mice with T cells lacking the proteins perforin or granzyme B also fail to show the full-blown phenotype[46]. In the optic nerve of *Plp1* transgenics, it is striking that axonal segments at the already demyelinated (retinal) end are less visibly affected by swellings than are the distal axonal segments, which are associated with residual myelin and inflammation[47]. Thus, with respect to axon function, 'no myelin' may be better than 'bad myelin', with inflammation posing an extra burden for axonal metabolism.

Although T-cell infiltration is a feature of other neurodegenerative conditions, oligodendrocyte dysfunction may be of specific relevance for inflammation. The strongest secondary immune response was observed in the white matter of conditional *Pex5*-mutant mice (Fig. 1c), including activated and clonally expanded $CD8^+$ T cells and perivascular B cells (ref. 38 and B. Barrette, C. Kassmann and K.-A.N., unpublished data). Myelin-lipid turnover creates arachidonic acid and eicasonoids, which include lymphocyte chemoattractants that are degraded in peroxisomes[48]. Thus, abnormal myelin turnover and the failure to degrade inflammatory mediators may contribute to neuroinflammation.

In these myelin mutants, microgliosis and the recruitment of $CD8^+$ T cells by genetically perturbed (but live) oligodendrocytes may trigger a vicious cycle of degeneration and inflammation. This is a working hypothesis relevant to human neurological disease.

Myelin diseases leading to axonal degeneration

The differentiation of myelinating glia largely occurs postnatally. Thus, even major genetic defects result in a developmental disorder rather than death of the embryo. The clinically most important disorders are acquired demyelinating diseases, which present during adolescence and in adult life.

Multiple sclerosis

Multiple sclerosis (MS) is the prototype of immune-mediated demyelination[49], but its trigger and the primary cause of autoimmunity remain unknown. Lymphocytes and monocytes cross the blood–brain barrier and invade the brain. Focal areas of inflammation and immune attacks destroy oligodendrocytes and myelin sheaths, but rarely dissect axons directly. Instead, they lead to lesions in white matter, detectable by magnetic resonance imaging (MRI), that turn into oedematous plaques. There is also major loss of myelinated fibres in cortical grey matter; this loss has been underestimated, because it does not have the same degree of cellular infiltration[50]. Only a fraction of MS lesions become clinically apparent. Often, the acute signs result from axonal conduction blocks, but are reversible as inflammation and oedema resolve, sodium channels reorganize and remyelination occurs. After years of 'relapsing–remitting' MS, most patients enter the secondary phase: 'progressive' MS, characterized by increasing disability without acute attacks or remissions[49]. Although immune modulators, such as β-interferon, are given to reduce the rate of relapse, there is no similar therapy against secondary, progressive MS. It is thought that, at this stage of disease, axon degeneration causes persistent disability[51]. Although old lesions are never free of inflammation, the correlation with the swelling and loss of axons becomes weaker. MS is probably heterogeneous and triggered in susceptible individuals by the late consequence of an early infection that turns into a vicious cycle of inflammation and neurodegeneration. In some MS patients, progressive neurodegeneration may be a distinct disease mechanism[51].

Research into the mechanism of axon loss as the final common pathway in MS is hampered by the absence of true animal models. In mice with experimental allergic encephamyelitis, disease progression is driven by autoreactive $CD4^+$ T cells, which model only one aspect of neuroinflammation. Also in the genetic models, the infiltration of activated $CD8^+$ T cells is insufficient to trigger MS-like lesions. It is likely that a combination of inflammation and demyelination creates a high risk of axon loss; the lack of oligodendroglial support occurs when axons require that support the most. Demyelination and new axonal Na^+ channels reduce the axonal energy balance. Inflammation generates reactive oxygen species — such as nitric oxide — and glutamate-mediated excitotoxicity, which further perturbs residual mitochondrial functions. Once ATP is so low that the axonal membrane cannot be repolarized, a 'threshold' is reached that leads to abnormal calcium entry, proteolysis and axonal destruction[52].

Leukodystrophies

Leukodystrophies in the CNS comprise a heterogeneous group of rare inherited disorders of dysmyelination and demyelination, in which oligodendrocytes fail to assemble or to maintain myelin, respectively. Children with perturbed myelination experience a severe delay in reaching basic milestones of motor–sensory and cognitive development. People with leukodystrophies who survive into adolescence develop a secondary degenerative course of disease, which points to irreversible axon loss. The underlying mechanisms are currently being studied in mouse models, and the search concentrates on the possible role of abnormal glia–axon signalling, toxic insults and perturbed metabolic support.

Disease classifications, originally based on histopathology, biochemical markers and MRI, have shifted to genetic criteria. A large proportion of human leukodystrophy genes have now been identified. However, each of the known leukodystrophies covers a broad clinical spectrum, in which disease severity is determined by the specific mutation. Thus, defects in the same gene can result in early-infantile or late-adult onset, owing to complex combinations of gain- and loss-of-function effects, in combination with modifier genes and epigenetic differences. The dual role of oligodendrocytes in myelination and axonal support becomes most obvious in the late-onset forms.

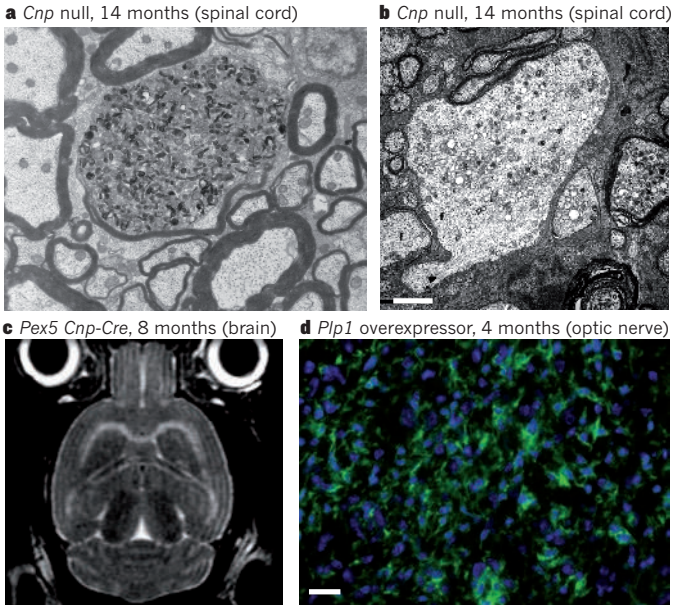


Figure 1 | Oligodendrocyte defects causing axonal degeneration in the central nervous system. **a**–**d**, Electron microscopy (**a**, **b**), magnetic resonance imaging (MRI; **c**) and anti-CD45 immunostaining (**d**) of mouse mutants, defined by abnormal expression and (conditional) mutations of oligodendroglial genes. *Cnp*, 2',3'-cyclic nucleotide 3' phosphodiesterase; *Cnp-Cre*, Cre-recombinase glial driver line; *Pex5*, peroxisomal biogenesis factor 5; *Plp1*, proteolipid protein 1. Although myelination appears relatively normal in these mutants, axonal transport — mostly of small-calibre axons — is perturbed, leading to Wallerian degeneration and premature death. Swellings contain vesicular cargo and organelles (**a**) and/or neurofilament aggregates (**b**). In more severely affected models[20,38,47], neurodegeneration is associated with monocyte and lymphocyte infiltration (**d**). One model, lacking oligodendroglial peroxisomes, eventually loses most of the subcortical white matter, as visualized by MRI hyperintense signals (**c**). Images are taken from (or related to) refs 20 (**a**), 82 (**b**), 38 (**c**) and 47 (**d**). Ages are indicated. Scale bars, 2 μm (**b**) and 20 μm (**d**).

A prototype of the hypomyelinating leukodystrophies (HLD) is Pelizaeus–Merzbacher disease (PMD or HLD1, Online Mendelian Inheritance in Man (OMIM) accession 312080), which is caused by mutations or duplications of the X chromosome-linked *PLP1* gene[53]. Most mutations cause a misfolding of PLP. The degree to which the polytopic membrane protein escapes endoplasmic-reticulum retention determines the extent of an unfolded protein response, apoptotic oligodendrocyte death and CNS dysmyelination. Clinically, *PLP1*-related disorders span a broad spectrum of disease expression, from early lethality in the connatal forms to the mildest course of disease, pure spastic paraplegia (SPG2). The latter is clinically distinct (OMIM 312920), with relatively few myelin abnormalities. These different phenotypes of *PLP1* diseases have been successfully modelled in natural *Plp1* point mutations, *Plp1* transgenic mice and *Plp1*-null mutants[54].

A 'PMD-like' HLD (HLD2, OMIM 608804)[55] has been defined by mutations in a gap junction protein gene, which encodes the protein connexin 47 (Cx47). This developmental disorder demonstrates a requirement of efficient coupling by gap junctions between oligodendrocytes (with Cx47, Cx32) and astrocytes (Cx43, Cx30), possibly for the transport of metabolites during myelinogenesis[56]. The adult forms (SPG44, OMIM 613206) also demonstrate that pan-glia coupling has an important role in axonal preservation[57].

That astrocytes are important for myelination and for preventing demyelination is demonstrated by Alexander's disease[58] (AXD; OMIM 203450) and mutations of the glial fibrillary acidic protein gene, which encodes an astrocyte-specific intermediate filament. The onset of AXD is variable, and detailed disease mechanisms are unknown. The structural integrity of astrocytes, which provide a link between oligodendrocytes and the blood–brain barrier, seems to be critical for myelin preservation and axonal support.

Leukodystrophy genes do not encode only the proteins specific to glial-cell function. For example, 'vanishing white matter' disease (VWM; OMIM 603896) can be attributed to mutations affecting eukaryotic translation initiation factor (EIF2B) subunits, which comprise a housekeeping protein and translational-initiation factor[59]. Mouse models can be used to explore whether it is the role of EIF2B in the efficient generation of astrocytes[60] or the inability of oligodendrocytes to fine-tune membrane-protein translation (thereby causing endoplasmic-reticulum stress) that explains the clinical and pathological similarities of VWM to AXD.

Some leukodystrophies are degenerative disorders that manifest later in life, affecting white matter that has developed normally. For example, in X-linked adrenoleukodystrophy (X-ALD; OMIM 300100), loss of a peroxisomal transporter protein (ABCD1) interferes with the degradation of very-long-chain fatty acids and causes an inflammatory demyelination[61]. Although the gene is widely expressed, only oligodendrocytes and adrenal cells are affected; this may reflect their unusual degree of lipid metabolism. *Abcd1*-mutant mice fail to show the X-ALD phenotype within a normal lifespan. However, targeting peroxisomal import in myelinating glia[38] creates a very good phenocopy (Fig. 1c). This suggests that inflammatory demyelination and axon loss might be caused by a secondary peroxisomal defect and by organelle dysfunctions, which accumulate over time and only in *ABCD1* mutant oligodendrocytes.

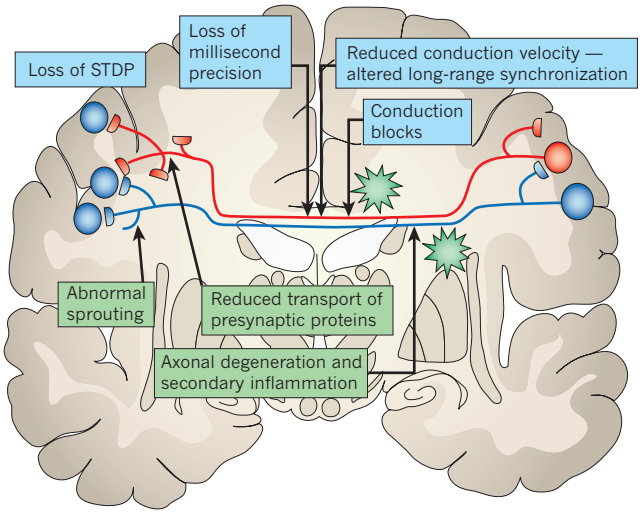


Figure 2 | Oligodendrocyte defects may lead to cognitive impairment. A hypothetical model pointing to possible consequences of reduced myelination, altered axonal diameters, and/or fast axonal transport, when caused by oligodendroglial dysfunction (blue boxes). In this schema, transcallosal cortical projections are myelinated and can establish and maintain long-range oscillations between cortical subfields. Spike-timing-dependent plasticity (STDP) requires millisecond precision, which is myelin dependent. Perturbed fast axonal transport may alter the protein composition of presynaptic terminals. More severe oligodendroglial perturbations, as caused by inflammations (green star-like cells) and demyelination, lead to axonal defects (green boxes), such as conduction blocks and/or irreversible axon loss that clearly disrupt long-range connectivity. Poor intracortical myelination might also trigger abnormal axon sprouting and/or interfere with memory consolidation.

Demyelinating neuropathies

As in the CNS, genetic defects in making or maintaining myelin in the PNS comprise a heterogeneous group of diseases. These are collectively referred to as 'demyelinating' Charcot–Marie–Tooth (CMT) neuropathies, and have been reviewed elsewhere[62,63]. Genetically, there is surprisingly little overlap with leukodystrophies, but the abnormal expression of membrane proteins, such as myelin protein zero (MPZ) and PMP22, in Schwann cells leads to endoplasmic-reticulum stress, followed by dysmyelination and demyelination. Hypertrophic myelin growth is a unique feature of CMT disease. Here, tomacula and myelin outfoldings originate at Schmidt–Lantermann incisures and at para-nodal loops, the latter disrupting the sites of axon–glia interactions. Most neuropathies have been modelled in mutant or transgenic mice.

The true absence of myelin is rare; more frequent are moderate dysmyelinating and demyelinating conditions in which the decrease of nerve-conduction velocity is clinically silent. All relevant symptoms, such as distally pronounced muscle weakness and sensory loss, are attributable to progressive and length-dependent degeneration of axons[62,63]. The role of Schwann cells in axonal integrity, as with that of oligodendrocytes, can be uncoupled from myelination. Rare point mutations in *MPZ* that cause a late-onset axonal form of CMT disease (OMIM 607736), which does not affect conduction velocity and myelination but does cause sensory defects including hearing loss, are proof of this principle[64]. What makes these *MPZ* mutations different from those in patients with the demyelinating form of CMT is not known.

Myelin plasticity and higher cognitive functions

Because brain evolution entailed an increase in the amount of subcortical white matter, one would assume that myelination is necessary for higher cognitive functions. However, except for case reports of psychosis in MS and adult-onset leukodystrophy, myelin diseases have not been studied well with respect to psychiatric phenotypes. An unbiased search for transcriptional changes in post-mortem brains of schizophrenics has revealed a significant decrease in abundance of RNAs for oligodendrocyte-specific proteins[65]. Although these changes affected the intracortical oligodendrocytes, MRI also revealed the loss of subcortical white matter in patients with schizophrenia, depression and bipolar disorder[66]. Unfortunately, MRI lacks the spatial resolution to distinguish between changes in axon number and myelin thickness. The mechanisms by which oligodendrocytes might contribute to psychiatric disorders such as schizophrenia are not known, and are probably complex (Fig. 2).

There are several reasons why myelination ought to be required for higher brain function. Myelination of cortical association fibres in humans continues into the third decade of life, paralleling cognitive maturation[9]. Even in adults, the acquisition of fine motor skills, such as professional piano playing, has been associated with substantial changes in the white matter in corresponding areas of the motor cortex[67].

Myelination itself shows some plasticity, as was first recognized in electric fish that change myelin-sheath thickness to control the velocity of the axons that trigger electrical discharges (these nerves have differing lengths, but their input to electrocytes must be synchronized with millisecond precision). Adaptations of conduction velocity to synchronize neural activity are also found in mammals, but whether these involve alterations of myelin is unclear. Earlier work has shown that Schwann-cell differentiation is regulated in response to the spiking frequency of associated axons[68], and works through an activity-dependent release of ATP from axons that is sensed by P2 receptors. Similarly, electrical activity of the optic nerve increases the number of oligodendrocyte precursors present in the nerve[69], possibly in response to the release of adenosin[70].

Oligodendrocytes stimulate the regional growth of axonal diameter independently of myelination[71]. This is intriguing, because axon calibre is a major variable in conduction velocity. Because the

electrical activity of axons is detected by glia[70], it is worth exploring whether back-signalling from glia to axons can modulate axon size, for example by neurofilament phosphorylation[72]. Such an adaptation of conduction velocity would be faster and more dynamic than slow changes in myelin-sheath thickness. But how can oligodendrocytes perceive the electrical activity of the axons that they ensheath? In addition to the study of adenosin and P2 receptors[70], much recent work has been devoted to the role of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) and NMDA (*N*-methyl-D-aspartate) type glutamate receptors on NG2 cells and myelinating oligodendrocytes[73–75]. These could enable the oligodendrocytes to sense the release of glutamate, possibly as a function of spiking activity. The downside to glutamate responsiveness could be a sensitivity of mature oligodendrocytes to excitotoxic injury[76].

Focal myelin loss in the adult brain is followed by remyelination; this plasticity may reflect a physiological function in adult brains. Myelin could stabilize the wiring of axonal terminals — a property that is associated with functional plasticity. This property has been demonstrated in mice lacking the neuronal receptor (NGR) for Nogo, MAG and oligodendrocyte myelin glycoprotein; that is, myelin proteins that inhibit axonal sprouting and regeneration. NGR mutants exhibit a longer critical period, in which ocular dominance columns can be reshaped in the visual cortex[77]. Thus, myelination consolidates specific neural circuitry of the cortex. Indirect evidence suggests that abnormal Nogo and NGR signalling is a risk factor for schizophrenia[78].

Hypomyelination and reduced conduction velocity in long axons limit the distance over which cortical neurons can fire in synchrony[23]. The absence of long-range γ-oscillations between cortical subfields could cause attention deficits[79]. Myelin defects in long axons would also perturb spike-timing-dependent plasticity (STDP), which underlies synaptic strengthening or weakening (long-term potentiation or long-term depression) and possibly long-range circuit refinements[80]. For example, unmyelinated axons that have transcallosal conduction times of about 0.5 s will not maintain the temporal precision in the 10–20 ms range[23] that is critical for STDP.

Degeneration of cortical axons in the presence of apparently normal myelin — for example, that assembled by oligodendrocytes lacking PLP or CNP — has obvious consequences for brain function. The axonal degeneration is preceded by significant perturbation of fast axonal transport[19]. This raises the intriguing possibility that oligodendroglial support is required for the timely delivery of presynaptic components, such as nuclear-encoded enzymes and proteins that control the fast calcium-regulated neurotransmitter release. For example, a 50% gene dosage of Munc18 (mammalian uncoordinated 18 or syntaxin binding protein 1), which encodes a mediator of synaptic vesicle docking, is sufficient to reduce the readily releasable pool size in various synapses[81] and to cause hyperactivity, a behaviour related to schizophrenia in mice. Little is known about how the steady state of this or other presynaptic proteins is controlled in the terminals of long axons, but the effect of reduced transport rates is probably equivalent to that of reduced expression rates.

Conclusion

As in all facets of neurobiology, the myelin field has made unexpected progress in the past few decades, following several breakthroughs in molecular cell biology and mouse genetics. Research on myelin has always been interdisciplinary, with a strong focus on neurological diseases, and is likely to include more psychiatric disorders in the future. Having reached a better understanding of glial-cell development and myelin diseases, fascinating new questions on the complex nature of axon–glia interactions have emerged, and will shape myelin research in the future. The morphogenesis of myelin, a three-dimensional problem, is yet to be unravelled, and will require adaptation of high-resolution time-lapse imaging techniques. Myelin proteomics has revealed hundreds of new players, whose parts in myelin synthesis and maintenance remain unknown. We are only at the beginning of understanding the dynamics of protein–protein interactions at the axon–glia interface and in mature myelin. For the CNS, the interdependence of oligodendrocytes with both axons and astrocytes needs to be explored; this may hold a key to understanding the metabolic relationship between neurons and glial cells. We have learned that oligodendrocytes and Schwann cells support survival of the axons that they ensheath. It is important to find out how they do this, as the knowledge may lead to new therapies in neuropsychiatric diseases. ■

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