



Expanding the function of oligodendrocytes to brain energy metabolism




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Abstract

Oligodendrocytes are best known for wrapping myelin, a unique specialization that enables energy-efficient and fast axonal impulse propagation in white matter tracts and fibers of the cortical circuitry. However, myelinating oligodendrocytes have additional metabolic functions that are only gradually understood, including the regulated release of pyruvate/lactate and extracellular vesicles, both of which are in support of the axonal energy balance. The axon-supportive functions of glial cells are older than myelin in nervous system evolution and implicate oligodendrocyte dysfunction and loss of myelin integrity as a risk factor for progressive neurodegeneration in brain diseases.

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Introduction

A major driving force of nervous system evolution has been the increase of axonal propagation speed by myelin. Myelin not only enabled enhanced escape reflexes in lower vertebrates, but also contributed to the gradual evolution of the powerful brain architecture. Myelin is the spiral ensheathment of axons by a lipid and cholesterol-rich glial cell membrane [1] that reduces the capacitance and increases the resistance of the axonal membrane (Figure 1a, b). The intricate structure of myelin is also a feat that is possible due to the specific localization of myelin proteins, primarily myelin basic protein (MBP), which allows myelin membrane leaflets

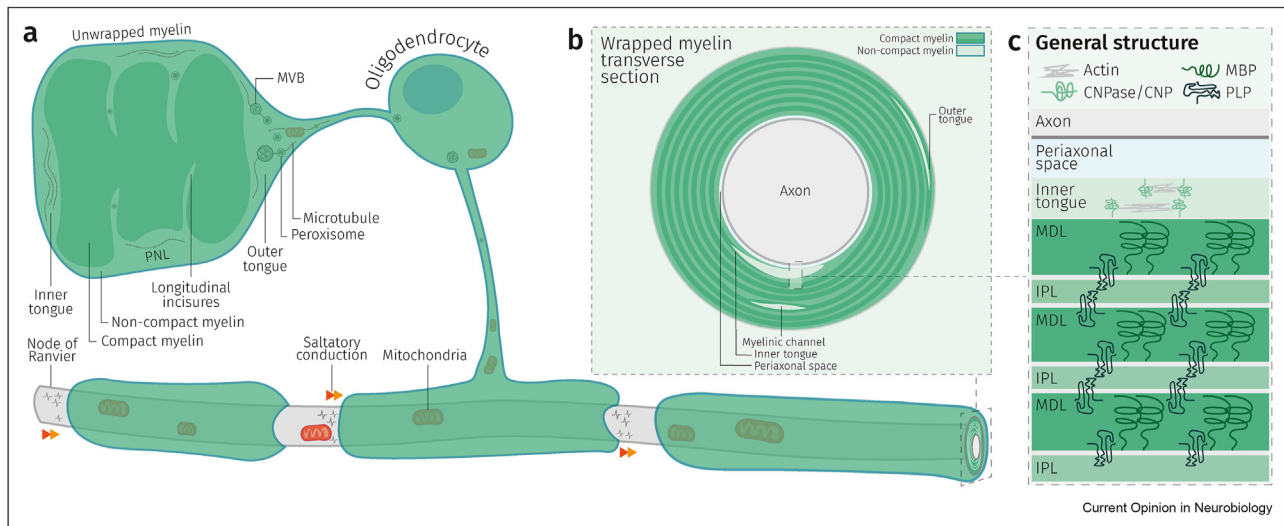
to be tightly zipped together (Figure 1c). This allows the well-known saltatory propagation of action potentials from one node of Ranvier to the next, with axonal ion currents also involving the periaxonal cytoplasmic space in oligodendrocytes [2]. Axonal myelination speeds up nerve conduction velocity as a function of axon diameter [3]. Thus, myelin was particularly relevant for the evolution of large vertebrates that require fast axonal conduction over long distances. Vertebrate myelin occurred relatively late in the phylogenetic timeline, but glial ensheathments of axons have been observed in almost all other phyla [4]. Axon ensheathing glial cells are also thought to prevent “ephaptic coupling” between neighboring axons, i.e. unspecific activation by close contact. In vertebrates, this may be relevant for large axonal tracts that run in parallel [5], such as those in optic nerve, corpus callosum, or spinal cord, but experimental support for this hypothesis is difficult to obtain.

While myelination proceeds rapidly after birth in the peripheral nervous system, central myelination is a spatially and temporally more regulated process. Basic motor-sensory functions that require myelination of spinal cord and cerebellum are rapidly acquired after birth, whereas myelination of the mammalian forebrain and of intracortical fibers is significantly delayed, specifically in humans with cortical myelination still active in adult life [6]. Ongoing myelination of the human brain has been documented at up to 40 years of age [7]. This late myelination in the adult cortex is followed by the exhaustion of oligodendrocyte precursor cells (OPC) with senescence [8,9] and a gradual loss of myelin integrity in the aging brain [10]. This raises the question whether myelin defects contribute to late-onset neurodegenerative diseases.

Oligodendrocytes in central nervous system energy metabolism

The brain is well known for its high energy demands, specifically in gray matter areas. In white matter tracts, the energy consumption is lower [11,12], but myelination poses a unique challenge for the axonal energy generation [13]. In white matter tracts, myelin sheaths cover more than 95% of the axonal surface areas and thereby physically impede rapid access of the ensheathed axons to energy-rich metabolites of the

Figure 1



Oligodendrocytes in axonal energy metabolism. (a) Schematic drawing of a myelin forming oligodendrocyte with one sheath conceptually unwrapped (upper left), exposing compacted myelin (dark) and non-compacted (light) myelin compartments. Oligodendrocytes are functionally connected to the axon by “myelinic channels”, the continuous cytoplasmic space including oligodendrocyte process, inner and outer tongue of myelin, and the connecting paranodal loops (PNL). The cytoplasmic compartment contains microtubules (MT) for directed transport of cargo, peroxisomes (Px) and multivesicular bodies (MVB, thought to give rise to exosomes). (b) Scheme of a myelinated axon in transverse section with compacted myelin (dark) and the myelinic channel compartments (light). (c) Depiction of compacted myelin membranes forming the inner major dense line (MDL) and the outer interperiod line (IPL), with help of myelin basic protein (MBP) and proteolipid protein (PLP), respectively. Cyclic nucleotide phosphodiesterase (CNP) lines the inner tongue and interacts with actin, which prevents hypercompaction and channel collapse.

extracellular milieu. Importantly, the axonal Na^+/K^+ ATPases are largely localized in internodal regions underneath myelin [14], which indicates where ATP is mostly consumed. For a review on mitochondrial docking and transport in axons, which may differ in CNS and PNS, see also ref. Mandral and Rerup [15].

Oligodendrocytes help support axonal integrity, a discovery that began with mouse mutants carrying oligodendrocyte-specific gene defects. These had no major impact on myelination but led to axonal swellings and progressive axonal degeneration, often weeks and months after birth [16–19]. Also, the clinical phenotype of these mice reflected increasing axonal conduction blocks, ataxia and paraparesis, leading to premature death. This is in marked contrast to the clinical presentation of the myelin deficiency phenotype, such as in the mouse mutant *shiverer*. Here, the lack of MBP causes the near complete absence of CNS myelin, with tremors and seizures at an early age [20] but no axonal degeneration.

The lack of proteolipid protein (PLP) from myelin and the associated axonal degeneration phenotype [16] correlate with a reduced energy balance of the myelinated axons, which was shown much later with the help of axonal ATP sensors [21]. However, when studied *ex vivo* and at rest, ATP deficits of optic nerve axons were not severely decreased, suggesting that ATP is an important

set point. Reduced metabolic support may also be developmentally compensated by an increased volume of myelinic channels and some astrogliosis [21].

One line of evidence for direct metabolic support of myelinated axons by oligodendrocytes was the characterization of conditional mouse mutants of the *COX10* gene, encoding a farnesyl-transferase required to assemble complex IV in mitochondria. In these mutants, oligodendrocytes survive well in the absence of mitochondrial oxidative phosphorylation, and without signs of myelin loss, cell death, neurodegeneration or secondary inflammation [22]. By magnetic resonance spectroscopy of anesthetized mice (using isoflurane, which unspecifically inhibits mitochondrial respiration in neurons and glia), brain lactate levels were well detectable and higher in mutants than in controls. However, upon washout of isoflurane, brain lactate levels fell to undetectable levels in mice of either genotype. Thus, glycolysis products of oligodendroglial origin are readily metabolized in axonal mitochondria that are genetically wild-type [22].

The proposed mechanism is reminiscent of the astroglial “lactate shuttle” at the synapse [23], a concept that is still controversially debated [24–26]. Herein, glutamatergic activation is met by an astrocytic response of increasing glucose utilization to provide

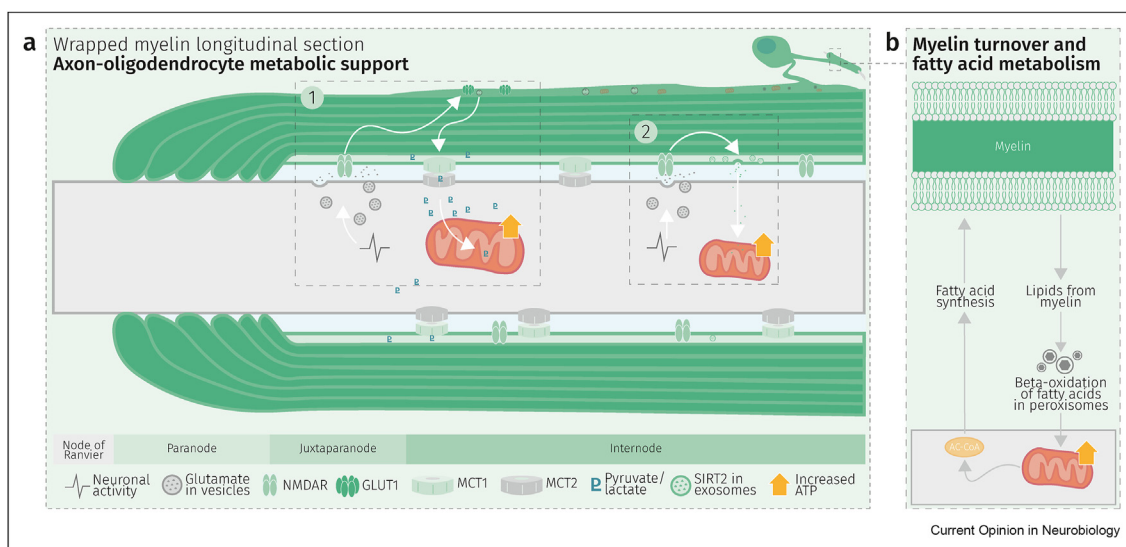
neurons with lactate in the extracellular space to meet the neuronal energy demands. In nervous system evolution, the metabolic support of long axons by associated wrapping glia must be an ancestral feature, because virtually the same mechanisms were identified with the help of genetic mutations in *Drosophila* [27].

In oligodendrocytes, one requirement for the transfer of the pyruvate/lactate to axons is monocarboxylate transporters [28,29]. At the innermost myelin layer, monocarboxylate transporter 1 (MCT1) faces the nm-wide periaxonal space, whereas its homologue MCT2 resides mostly on the axonal membrane (Figure 2a). Indeed, genetics revealed that MCT1 is critical for axonal integrity, because heterozygous mutants develop a late onset axonal degeneration [29], with axonal pathology similar to that of PLP-deficient mutants. However, MCT1 is also expressed by astrocytes which harbor glycogen granules and can support neuronal metabolism via the “lactate shuttle” [30]. Thus, the demonstration that silencing MCT1 expression in oligodendrocytes of adult mice, using a viral strategy, is sufficient to cause axonal damage was important [29]. When acutely isolated optic nerves from wild-type mice were studied *ex vivo*, the glycolytic support was only required by fast-spiking axons. Using mice with genetically encoded ATP sensors expressed in the neuronal and axonal compartment, both resting and spiking optic nerves were stimulated in the presence of glucose and specific MCT1

inhibitors. Surprisingly, these inhibitors affected axonal conduction and ATP levels only at a higher stimulation frequency [31], suggesting that oligodendroglial metabolic support is critical for the larger and faster-spiking myelinated axons [32] that also have a higher density of mitochondria. However, the higher surface:volume ratio of small caliber axons makes thinner axons more vulnerable to energy deprivation.

Surprisingly, a constitutive but oligodendrocyte-specific mutation of the same gene is well tolerated with axonal degeneration only detectable at advanced age [33]. It thus appears that MCT1 transporters, if deleted early in oligodendrocyte development, are functionally compensated. Candidates are MCT2 or gap junction proteins that couple oligodendrocytes to astrocytes [34]. Indeed, for the thalamus, it has been shown how oligodendrocytes and astrocytes can form a “panglial” network that supports neurons with metabolites [35]. Oligodendrocytes may also be able to deliver glucose directly to the axonal compartment. This is suggested by experiments with brain slices, in which compound action potentials of the corpus callosum are maintained even in glucose-free media if the gap-junction coupled oligodendrocytes are intracellularly filled with glucose [36]. In the same setup, the filling of oligodendrocytes with lactate did not support axonal conduction, but the horizontal spread of glucose and lactate may not be the same. However, the hypothesis that glial metabolic

Figure 2



Oligodendrocytes providing metabolic support. (a) Myelin shielding restricts the access of axons to energy-rich metabolites in the extracellular milieu to the Node of Ranvier. Spiking axons receive additional metabolic support via myelinic channels and monocarboxylate transporters MCT1 and MCT2. Neuronal activity causes the axonal release of glutamate (by vesicular exocytosis or sodium transients reverting the direction of glutamate transporters) followed by oligodendroglial NMDA receptor signaling leading to surface expression of glucose transporter GLUT1 and an increased glycolytic flux, resulting in the production of pyruvate/lactate that can be supplied to the axon via MCT. Glutamate signaling also stimulates the release oligodendroglial exosomes including the transfer of SIRT2 to the axonal compartment, where the deacetylase stimulates mitochondrial ATP generation. (b) Continuous myelin turnover and fatty acid metabolism can help myelinated nerves to overcome a transient loss of glucose supply thereby providing a metabolic reserve. For references see text.

support might be regionally different deserves further attention.

An essential requirement for the direct transfer of energy-rich metabolites from oligodendrocytes to the myelinated axonal compartment is “myelinic channels” within the myelin sheath. This term refers to regions of non-compacted myelin, which comprises a tube-like cytoplasmic space spanning from the oligodendrocyte soma, along the outer lip and through the paranodal loops of myelin to the inner periaxonal space underneath the compacted myelin sheath [37]. In these myelinic channels, the membrane-associated protein CNP has the function of a “strut” that keeps the cytosolic space open by preventing an abnormal degree of MBP-mediated myelin compaction and a local channel collapse [38]. Lack of CNP thus causes swellings of the myelinic channels, described twenty years earlier [17], presumably reflecting ongoing transport processes within this compartment. Importantly, with respect to metabolic support, perturbations of myelinic channels are not only slowing the diffusion of metabolites, but also blocking the vesicular transport of MCT1 and its normal turnover in the oligodendroglial cell membrane. Indeed, in purified myelin from brains of adult CNP mutant, MCT1 is hardly detectable (Goebbels and Nave, unpublished). This might explain why axons affected by abnormal myelin first show signs of pathology with a delay of weeks to months. While axonal swellings are in principle reversible [39], impaired mitochondrial transport and turnover might further perturb axonal integrity and contribute to axonal degeneration with a long delay. Interestingly, the heterozygous loss of CNP leads to a later onset of axonal degeneration, with myelin abnormalities and low-grade inflammation, reminiscent of white matter abnormalities in wild-type mice at a very old age. Thus, *Cnp* mutant mice are a good model of premature white matter aging [40]. In all myelin mutants studied so far, axonal degeneration and secondary inflammation virtually coincide, leaving the causal relationship between the two phenotypes unclear. While axon degeneration is known to trigger inflammation, it is possible that the recently discovered feature of oligodendrocyte expressing immune genes in disease [41,42] is a direct trigger of neuroinflammation independent of axon loss. Finally, oligodendrocytes that fail to properly deliver their glycolysis products to myelinated axons may instead release glycolysis products into the extracellular milieu where acidic pH or lactate itself could affect the behavior of microglia.

Adapting oligodendroglial metabolic support

The brain meets fluctuating energetic needs for neuronal communication with spiking rates of myelinated axons that can differ widely. Thus, a continued excess of pyruvate/lactate release above that what axonal ATP generation requires might lead to tissue acidification and

secondary problems. Here, the nervous system has developed mechanisms that help match glucose utilization to ATP consumption. The finding that spiking axons can release trace amounts of glutamate to associated glial cells [43], in particular to oligodendroglial α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-Methyl-D-aspartic acid (NMDA) type glutamate receptors localized at the innermost layer of myelin, supports the concept of the “axo-myelinic synapse” [44]. Spiking axons release glutamate into the narrow periaxonal space, yielding locally elevated glutamate concentrations that are sufficient to induce calcium influx into the myelin compartment [45]. When cultured oligodendrocytes were treated with glutamate receptor agonists, NMDA induced an unexpected translocation of the glucose transporter (GLUT1) into the oligodendroglial plasma membrane (similar to insulin stimulation of GLUT4 expressing cells) which was followed by increased lactate release [46]. Optic nerves from oligodendrocyte-specific NMDA receptor deficient mice, challenged *ex vivo* with transient oxygen-glucose deprivation (OGD), showed reduced functional recovery when re-exposed to oxygen and glucose. In contrast, with oxygen and lactate in the medium the recovery from OGD was normal. In vivo, the conditional mutants showed axonal degeneration at older age. This led to a working model that oligodendroglial glutamate receptor signaling matches -with some temporal delay-the glycolytic flux and pyruvate/lactate export to axonal energy demands [46]. Whereas the translocation of GLUT1 to the glial cell surface takes 10–20 min in monolayer cultures, such translocation from a submembrane compartment of the myelin sheath *in vivo* may be much faster. The delay time is clearly within the 30 min window that astroglial glycogen stores can buffer the energy demands of spiking axons [47]. An additional layer of regulation and much faster increase of lactate release by oligodendrocytes is seen in response to the potassium transients that are invariably associated with high-frequency spiking of myelinated axons [48].

Recent evidence suggests that oligodendrocytes are even critical for the axonal signaling to pericytes on capillaries in white matter tracts. The vascular response to fast-spiking axons, which leads to an increased supply of oxygen and glucose, has been termed “axo-vascular coupling” and is considerably slower than neurovascular coupling on the cortex [49]. Axonal glutamate release is again involved since the oligodendrocyte-specific NMDA receptor deficient mice lack normal axo-vascular coupling.

Glycolytic oligodendrocytes also connect to CNS neurons that control food intake. Mice lacking the oligodendroglial G-protein-coupled receptor GPR17 in oligodendrocytes exhibit the activation of protein kinase A (PKA) with upregulated expression of pyruvate dehydrogenase kinase 1 (PDK1), leading to enhanced lactate release. This triggers in hypothalamic neurons

the AKT/STAT3-dependent expression of proopiomelanocortin (POMC) and suppression of agouti-related peptide (AGRP), with reduced food intake and abnormally lean phenotypes even in mice maintained on a high-fat diet [50].

In PLP-deficient mice, an unexplained finding was the complete lack of sirtuin 2 (SIRT2) from myelin, a nicotinamide adenine dinucleotide- (NAD-)dependent protein deacetylase that does not directly bind to PLP but is an abundant component of the myelin proteome [51]. In development, SIRT2 contributes to the differentiation of oligodendrocyte precursor cells [52], but its role in myelin has remained unclear. SIRT2 null mutant mice are well myelinated, but in the absence of this protein the degenerative phenotype of 2',3'-Cyclic-nucleotide 3'-phosphodiesterase (CNP) mutant mice is severely enhanced (Kusch and Nave, unpublished), similar to mice lacking both CNP and PLP, whereas the phenotype of PLP null mice is unaltered by the loss of SIRT2. Thus, in PLP null mice, the observed axonal degeneration is owed in part but not exclusively to the concomitant lack of SIRT2 from myelin.

Oligodendroglial SIRT2 is also contained in myelin-derived exosomes. These are extracellular vesicles (EV) that are presumably derived from multivesicular bodies in the myelinic channels and generated in the course of myelin membrane turnover. Myelinic EV contain a subset of oligodendroglial proteins and are taken up by the underlying axon, contributing to axonal integrity [53]. Upon the loss of CNP, myelinic channels are perturbed [34] and this has been shown to impair the release of myelinic EV [50]. Similar to glycolytic support, the release of myelinic EV is stimulated by oligodendroglial NMDA receptor signaling [54]. SIRT2 in myelin-derived EV is thus transferred to the axonal compartment where it was shown to deacetylate the mitochondrial enzyme ANT (adenine nucleotide translocase). This facilitates ATP production [55].

The interactions of oligodendrocytes and myelin with the underlying axon are complex and exceed the transfer of energy-rich metabolites. Oligodendroglial exosomes also contain a ferritin-heavy chain which acts as an iron chelator that prevents a toxic iron build-up in the aging white matter [56]. Interestingly, these recently discovered axon-supportive glial mechanisms were rediscovered in *Drosophila* and are thus highly conserved, preceding the evolution of myelin in the vertebrate lineage. This includes recent findings that lipid droplets are an energy reserve in *Drosophila* glial cells that respond to starvation with lipolysis, fatty acid beta-oxidation and the local generation of ketone bodies for the metabolic support of neuronal compartments [57]. Unmyelinated nervous systems have lipid droplets in axon-associated glial cells, as also studied in the lamprey

[58], that appear “lost” with the evolution of myelinating glia. This led to a speculation that myelin membranes may have evolved as a smart way of storing lipids as both, an energy reserve and a means to increase axonal conduction speed [59]. Indeed, myelin is a lipid-rich cellular compartment that remains dynamic throughout life [60,61]. The continuous turnover of myelin membranes by lipid degradation and fatty acid beta-oxidation in mitochondria and peroxisomes leads to recycling of acetate residues by fatty acid synthesis and membrane biogenesis (Figure 2b). When the mouse optic nerve (a model white matter track) is transiently “starved” *ex vivo* under low glucose conditions, ongoing fatty acid metabolism and transfer of metabolites (possibly ketone bodies) supports axonal integrity and mitochondrial ATP generation in neuronal and glial compartments [62]. Thus, under starvation conditions lipids of the white matter are a potential energy reserve like lipid droplets in the *Drosophila* nervous system.

Disease relevance

A number of neuropsychiatric diseases have been associated with myelin abnormalities, from various CNS myelin diseases, notably leukodystrophies and multiple sclerosis (MS), to neurodegenerative disorders like Amyotrophic Lateral Sclerosis (ALS) and Alzheimer's disease (AD). One bottleneck of neuronal survival is the integrity of the long axons where myelinating glial cells are the closest bystanders. While the etiologies of MS and AD, for example, are complex and very different from each other, recent experiments in mouse models suggest that the reduced metabolic support by oligodendrocytes could be directly involved in both of them.

In human MS and its animal model myelin oligodendrocyte glycoprotein-experimental autoimmune encephalomyelitis (MOG-EAE), the acute inflammatory demyelination is followed by axonal degeneration in lesion sites that is mechanistically not fully understood [63,64]. It is widely thought that demyelination and the lack of an axon-protective myelin sheath in the presence of numerous inflammatory mediators are the main causes of axon loss [65]. Thus, a direct comparison of MOG-EAE in mice with wild-type myelin and mice with a partly dysmyelinated spinal cord was surprising. It revealed that unprotected “naked” axons improve rather than worsen the overall clinical phenotype of EAE mice which exhibited the same degree of autoimmunity [66]. Thus, “bad myelin is worse than no myelin” because MS-relevant myelin injuries [67] perturb the integrity of myelinic channels and metabolic support. Dysfunctional or injured oligodendrocytes that do not allow for compensation by any other cell types turn the affected myelin ensheathment into a burden of the underlying axonal energy metabolism which causes irreversible axon loss.

In human AD, the major risk factor is age and advanced brain aging of non-human primates has been associated with progressive deterioration of the myelin ultrastructure [10]. These changes include myelin delamination, myelin membrane out-foldings and clogging of myelinic channels with large multivesicular bodies, all of which can be predicted to deteriorate the function of myelinic channels, myelin integrity and oligodendroglial metabolic support of axons.

Recently, established transgenic AD models (5xFAD and *App*^{NLGF}) were cross-bred to mouse mutants with oligodendrocyte-specific defects (*Cnp*, *Plp1*). The latter exhibit features of white matter aging, i.e. ultrastructural myelin defects, axonal degeneration and neuroinflammation at a much younger age (see above). In the resulting double mutant mice, amyloidosis was significantly enhanced, which made it possible to propose a causal relationship [68]. Structural myelin defects emerged as upstream “drivers” of neuronal APP processing and the Aβ plaque load in the mouse cortex. Interestingly, secondary neuroinflammation also added to the disease burden in these mice. When studied at the single-cell level, microglia that had engaged with dysfunctional myelin showed a major change of their transcriptional phenotype. Morphologically, they were visibly “distracted” from phagocytosing Aβ plaques [68].

Conclusion

Our view on oligodendrocytes, once thought to be mere providers of insulating myelin sheaths for saltatory axonal impulse propagation, has dramatically changed. Myelin is a dynamic compartment in the mature brain that uses energy-rich metabolites and EV-mediated protein transfer to maintain the functional integrity of axons that are otherwise deprived of vital access to the extracellular milieu. The experimental finding in disease models that “no myelin is better than bad myelin” leads to the insight that any loss of myelin integrity, as seen acutely in demyelinating disorders or more gradually in the aging brain, becomes a risk factor for irreversible neurodegeneration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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