

NEURAL CAMS AND THEIR ROLE IN THE DEVELOPMENT AND ORGANIZATION OF MYELIN SHEATHS

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1. ABSTRACT

Myelination of axons is a prerequisite for the rapid propagation of nerve impulses, and thus for the proper functioning of the nervous system. Phenotypic analysis of genetically engineered mice has provided evidence that cell adhesion molecules are critically involved in the interaction of myelin-forming glial cells with axons, the formation of regularly spaced myelin internodes along axons and the organisation of paranodes and the myelin-free gaps separating the internodes, the nodes of Ranvier. This review will focus on three members of the immunoglobulin-superfamily, the myelin-associated glycoprotein (MAG), the neural cell adhesion molecule (NCAM) and the neural adhesion molecule L1 and will discuss studies on transgenic mice that have analyzed the role of these cell adhesion molecules in the initiation of myelination, formation of structurally intact myelin sheaths and/or maintenance of myelin and axon integrity.

2. INTRODUCTION

Myelin in the central nervous system (CNS) and peripheral nervous system (PNS) consists of the extended plasma membranes of oligodendrocytes and Schwann cells, respectively. The myelin formed by these two types of glial cells electrically insulates axons and thus restricts the generation of action potentials to the nodes of Ranvier, which represent myelin-free regions between myelin segments where voltage-gated sodium channels are aggregated. As a result, nerve impulses are rapidly propagated along myelinated fibers. The formation and maintenance of myelin sheaths around axons is the result of reciprocal interactions between myelinating glial cells and axons. Axons destined to become myelinated have to be

recognized by myelin-forming glial cells, glial cell processes have then to enwrap these axons, and cytoplasm has to be extruded from the glial processes to form the multilayered and tightly packed compact myelin with its alternating major dense lines and intraperiod lines (Figure 1 and 9a). Only small domains of myelin sheaths remain uncompacted, including the periaxonal cytoplasmic collar, the paranodal loops, or the Schmidt-Lanterman incisures (for reviews, see 1 - 3). While myelination is thought to be initiated by axonal signals (4 - 6), myelinating glial cells in turn influence the axon. This is exemplified, for instance, by the induction of a significant radial growth of axons accompanied by a reorganization of the axonal cytoskeleton (7 - 11) or the regulation of expression and targeting of sodium channels (12 - 17).

The complex and reciprocal interactions between myelinating glial cells and axons are, in part, mediated by cell adhesion molecules. The present review will focus on the role of the myelin-associated glycoprotein (MAG), a member of the immunoglobulin- (Ig) superfamily of cell adhesion molecules, in the initiation of myelination, formation of normal myelin sheaths, and maintenance of myelin and axon integrity. It will also briefly summarize the functions of two other members of the Ig-superfamily, the neural cell adhesion molecule (NCAM) and the neural adhesion molecule L1 in axon-glia interactions and the formation and maintenance of myelin. Other cell adhesion molecules that mediate interactions between myelinating glial cells and axons or are involved in the formation and maintenance of myelin internodes or the organization of nodal and paranodal regions of myelinated fibers are discussed in a number of excellent recent reviews (18 - 27).

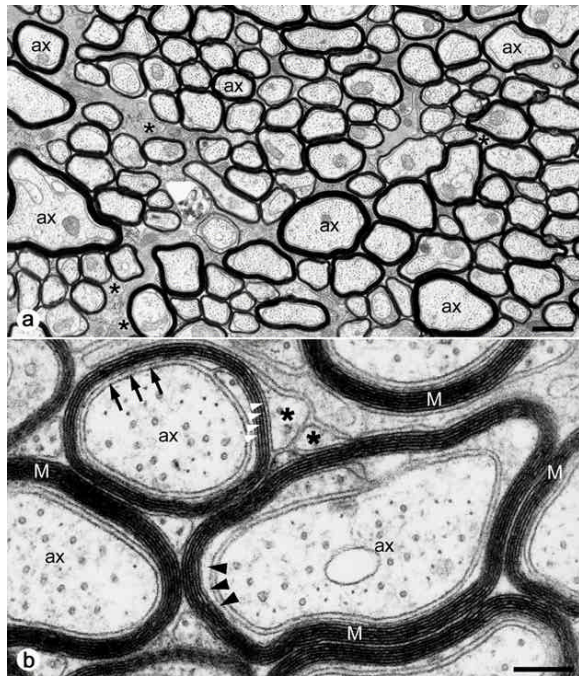


Figure 1. Myelinated axons in the optic nerves of wild-type mice. Virtually all axons in the optic nerve of adult wild-type mice are surrounded by a myelin sheath (a). The few unmyelinated retinal ganglion cells axons (some labeled with asterisks in a) are of small calibre. The axon and the myelin sheath are separated by a small gap, the periaxonal space (arrows in b). The myelin sheath consists of alternating, regularly spaced major dense lines (appositions of the inner leaflets of the oligodendrocyte plasma membrane; white arrowheads in b) and intraperiod lines (appositions of the outer leaflets of the oligodendrocyte plasma membrane; b). The innermost loop of most CNS myelin sheaths contains cytoplasm (“periaxonal cytoplasmic collar”; black arrowheads in b). Cytoplasm on the outside of CNS sheaths is confined to the external tongue process (some labeled with asterisks in b). ax, axon; M, myelin. Bar in (a): 1 μ m; in (b): 0.2 μ m.

3. DISCUSSION

3.1. Myelin-associated glycoprotein (MAG)

Myelin-associated glycoprotein (MAG) is a member of the Ig-superfamily. The protein consists of five Ig-like domains, a single transmembrane domain and a short cytoplasmic tail and shares significant homology with the neural cell adhesion molecule (NCAM) (28 - 30). MAG is quantitatively a minor protein constituent of CNS and PNS myelin and is exclusively expressed by myelinating glial cells, oligodendrocytes and Schwann cells (31-33). Two MAG isoforms, which after deglycosylation have molecular masses of 67 kD (also termed S-MAG) and 72 kD (also termed L-MAG), result from the alternative splicing of the primary MAG transcript (29, 34). S- and L-MAG are identical in their extracellular and transmembrane domains, but differ in their cytoplasmic domains and are differentially expressed during development (35; see below).

Experiments with function-blocking antibodies have demonstrated that MAG mediates oligodendrocyte-oligodendrocyte and oligodendrocyte-axon adhesion *in vitro* (36), and MAG incorporated into liposomes or MAG-Fc fusion proteins have been shown to bind to the cell surface of neurons (36 - 41). Furthermore, depending on the type and developmental age of the nerve cell, MAG either enhances or inhibits neurite elongation (37, 42 - 48). MAG is also critical for the maintenance of myelin and axon integrity *in vivo* (see below). Finally, in myelinating glial cells, MAG is associated with the tyrosine kinase Fyn and cross-linking of MAG with antibodies stimulates kinase activity (49; see below). Since nerve cells do not express MAG, these adhesive and signal transducing activities are mediated by heterophilic interactions of MAG with neuronal receptors or ligands.

Within the Ig-superfamily, MAG belongs to the sialoadhesins or siglecs. Sialoadhesins are sialic-acid binding integral membrane proteins with an extracellular domain consisting of an amino-terminal V-set Ig-like domain followed by a variable number of C2-set Ig-like domains (50 - 53). Sialylated glycoconjugates are thus potential neuronal receptors for MAG, and binding of MAG to nerve cells or MAG-mediated inhibition of neurite elongation has indeed been demonstrated to be sialic acid-dependent (46, 50, 54).

Binding of MAG to gangliosides, sialic acid-containing cell surface glycosphingolipids and the most abundant sialylated glycoconjugates in the nervous system, is well documented in a number of studies (55 - 59). Remarkably, mice lacking complex gangliosides because of a targeted disruption of the gene encoding GM2/GD2 synthase, a key enzyme in complex ganglioside biosynthesis, display reduced expression of MAG and pathological features in the CNS and PNS (60) that are highly reminiscent of those observed in MAG-deficient mice (see below). Furthermore, neurons from GM2/GD2 synthase-deficient mice or wild-type neurons pharmacologically depleted of glycosphingolipids are less susceptible to MAG-mediated inhibition of neurite elongation (54). Finally, the inhibitory effect of MAG on neurite elongation is mimicked by antibody cross-linking of gangliosides GD1a or GT1b on neuronal cell surfaces (54, 59). The inhibitory effect of MAG on neurite elongation involves activation of Rho GTPase (61), and neurite inhibition induced by antibody cross-linking of GT1b is reversed by blocking Rho kinase (59). Interestingly, the neurotrophin receptor p75 has recently been demonstrated to transduce the inhibitory signal of MAG in neurons via activation of Rho GTPase and to associate with GT1b, indicating that GT1b and p75 form a receptor complex for MAG (62). The combined observations thus indicate that gangliosides serve as physiological axonal receptors for MAG.

Interactions of MAG with sialoglycoproteins are indicated by the observation that binding of MAG to nerve cells is trypsin-sensitive (46). Furthermore, the majority of MAG binding sites on N2A neuroblastoma cells has been identified as sialylated N-glycans of glycoproteins (63), and

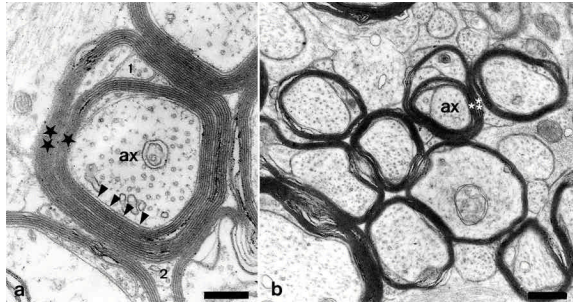


Figure 2. Ultrastructural abnormalities of myelin sheaths in the optic nerves of MAG null mutant mice. Compact myelin in the optic nerve of MAG-deficient mice displays a normal ultrastructure (a, b), and axons and myelin sheaths are separated by a periaxonal space of normal width (arrowheads in a). Note, however, that most myelin sheaths lack a well-developed periaxonal cytoplasmic collar (a, b). Note also the presence of doubly myelinated axons (labeled with ax in a and b). The inner myelin sheaths (labeled with a single asterisk in a and b) are spiraling clockwise, whereas the outer myelin sheaths (labeled with a pair of asterisks in a and b) are spiraling counterclockwise. The outer tongue process of the inner and outer myelin sheath in (a) is labeled with (1) and (2), respectively. Ax, axon. Bar in (a): 0.2 μm ; in (b): 0.5 μm . Reproduced with modifications from (85).

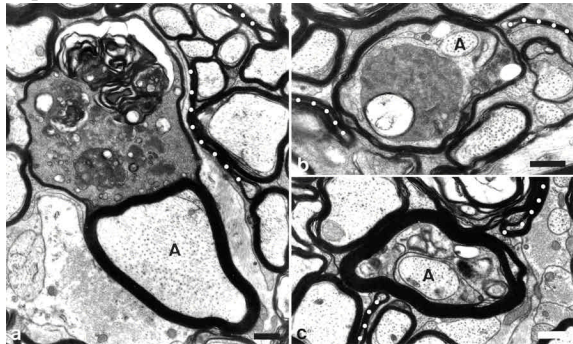


Figure 3. Dying-back oligodendrogliopathy in the optic nerve of MAG-deficient mice. Degenerative alterations of distal oligodendrocyte processes start within compact myelin (a) or periaxonally (b, c) and are characterized by the presence of membranous inclusions, vesicles and osmiophilic material. Note the normal ultrastructure of corresponding axons. Note also the presence of redundant myelin (labeled with white dots in a-c). A, axon. Bars (in a-c): 0.5 μm . Reproduced with modifications from (33).

affinity precipitation experiments have demonstrated sialic acid-dependent interactions of MAG with several glycoproteins on neuronal cell surfaces (39, 63). These studies, however, did not yet succeed to identify a distinct sialoglycoprotein as a neuronal cell surface receptor for MAG. Instead, interactions of MAG with several constituents of the extracellular matrix have been described, including tenascin-R (64), different types of collagen (65 - 67), and fibronectin (68). Knowledge about the functional relevance of these interactions is, however, still limited.

A recent study has shown binding of MAG to a neuronal phosphorylated isoform of microtubule-associated

protein 1B (MAP1B) (41). Evidence has been presented that MAP1B is a transmembrane glycoprotein and that MAG-positive cells induce elevated expression and phosphorylated MAP1B in cultivated neurons (41). The interaction of MAG with MAP1B might thus be a mechanism through which MAG modulates the axonal cytoskeleton. Binding of the cytoplasmic domain of S-MAG to tubulin, on the other hand, potentially links the axonal surface with the cytoskeleton of myelinating glial cells (69).

Oligodendrocytes and Schwann cells start to express MAG at early stages of myelination, and MAG is detectable on actively myelinating oligodendrocyte processes and turning loops of myelinating Schwann cells. When myelination is completed, MAG becomes restricted to the myelin-axon interface and to non-compacted regions of myelin, the paranodal loops, the Schmidt-Lanterman incisures and the outer cytoplasm-containing aspects of Schwann cells (70 - 74). Abnormal alterations of the periaxonal space and periaxonal cytoplasmic collar of myelinated fibers in the PNS of the *quaking* mutant were confined to MAG-negative regions of myelin sheaths, suggesting a role of the protein in the formation and maintenance of these structures (71). Furthermore, elevated and reduced expression of MAG in Schwann cells resulted in an acceleration or retardation, respectively, of the myelination of co-cultured dorsal root ganglion neurons. This points to a pivotal function of MAG at the onset of myelination (75, 76). Based on all these observations MAG has been implicated in essentially all steps of myelin formation, including axon-glia recognition, the initiation of myelination, the formation of structurally normal myelin and the stabilization of axon-myelin contacts (31 - 33, 77).

3.1.1. Delayed myelination and defective myelin sheaths in the CNS of MAG-deficient mice

Mice deficient in MAG were generated to study its functions *in vivo* (78, 79). Consistent with the early expression of MAG on actively myelinating oligodendrocyte processes (72, 74), formation of myelin sheaths in optic nerves of young MAG mutant mice was significantly delayed (79). Impaired initiation of myelination in the absence of MAG was also reflected by an increased number of small-sized unmyelinated axons in optic nerves of adult MAG mutant mice compared to age-matched wild-type mice (Figure 6) (80, 81). However, the number of unmyelinated axons in optic nerves of adult MAG mutant mice decreased with increasing age of the animals, indicating a continuing slow progression of myelination in the adult (Figure 6) (80).

Compact myelin was not detectably affected in the CNS of MAG mutant mice (Figures 2 and 3) (78, 79), in line with the restriction of MAG expression to non-compacted myelin. MAG is expressed periaxonally and was implicated in the formation and maintenance of the periaxonal cytoplasmic collar of myelinating glial cells and the periaxonal space (71). The most frequent defect in the CNS of MAG mutant mice was an abnormal oligodendrocyte periaxonal cytoplasmic collar, which was either absent or reduced in length (Figures 2 and 3) (78,

79). The periaxonal cytoplasmic collar of ~75% of myelin sheaths in wild-type mice, but only of ~5% of myelin sheaths in MAG mutant mice spanned more than half of the axonal circumference (79). While some studies found a reduced periaxonal spacing in some CNS myelin sheaths (78, 82), others reported no detectable alterations of the periaxonal space (Figure 2a) (79, 83). However, in double mutant mice lacking MAG and in addition galactolipids as a result of a targeted disruption of the gene encoding the enzyme UDP-galactose:ceramide galactosyltransferase (84), many more myelinated axons with reduced periaxonal spacing or periaxonal splitting were observed than in single galactolipid mutant mice. This suggests a role of MAG in mediating periaxonal cell-cell interactions and in stabilizing axon-myelin contacts (82). Formation of redundant compact myelin that extends away from the axon and is often tightly associated with neighbouring myelin sheaths was another frequent abnormality in the CNS of MAG mutant mice (Figure 3) (78, 81, 85). Furthermore, a recent study reported a delayed maturation of nodal regions in the absence of MAG (82). About 20% of paranodal regions in young MAG mutant mice exhibit a disorganised appearance with paranodal loops not adhering, but facing away from the axon. In addition, transverse bands, electron dense structures spanning the periaxonal space between the paranodal loops and the axon and thought to represent sites of adhesive axon-glia contact, were absent in young, but present in older MAG mutant mice (82). The ultrastructural defects were paralleled by diffuse or abnormal locations of contactin-associated glycoprotein (Caspr) or paranodin, normally located in the paranodal region, and Caspr2 and the delayed rectifier potassium channel Kv1.1, normally enriched in the juxtaparanodal region. This emphasizes the importance of normal interactions between myelinating glial cells and axons in organizing the molecular domain structure of myelinated axons. Diffuse location of the oligodendroglial 155kD isoform of neurofascin, which is normally clustered in the paranodal axo-glial junction, also indicates a delayed maturation of nodal regions in MAG mutant mice (82).

Another defect in the CNS of MAG mutant mice was the presence of oligodendrocyte cytoplasm in compact myelin (Figure 2). Interestingly, oligodendrocyte cytoplasm was often confined to terminal oligodendrocyte processes and was found in compact myelin of ~10% of all myelin sheaths (78, 79). In some cases, the presence of terminal oligodendrocyte processes within compact myelin correlated with a change in the spiralling direction of myelin (79), which is indicative for the presence of two or more myelin sheaths concentrically surrounding the same axon (Figure 2). Subsequent studies confirmed the presence of doubly or multiply myelinated axons in the CNS of MAG mutant mice (81, 85). Myelination of already myelinated axons in the absence of MAG supports the view that MAG functions as an adhesion molecule that mediates glia-axon interactions.

3.1.2. Degenerative alterations of oligodendrocytes in the absence of MAG

Degenerative alterations of distal oligodendrocyte processes, but not of proximal processes or cell bodies,

were noticed in an ultrastructural analysis of the CNS of adult MAG-deficient mice (Figure 3) (86). Pathological changes affected periaxonal (Figure 3b, c), as well as intramyelinic (Figure 3a) oligodendrocyte processes and were characterized by the presence of multivesicular bodies, the accumulation of mitochondria, and the deposition of granular or paracrystalline inclusions and lipofuscin granules, a condition previously described as “dying-back” oligodendrogliopathy in a mouse model of cuprizone-induced demyelination (87). Axons associated with affected internodes appeared normal (Figure 3) (86). Reduced levels of 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNPase), the 120 kD isoform of NCAM, β -tubulin and the Na^+, K^+ -ATPase in myelin fractions from MAG-deficient mice are consistent with pathological changes in oligodendrocytes (88).

Degenerative alterations of distal oligodendrocyte processes have also been observed at early stages of cuprizone-induced demyelination (87), in Theiler's virus-induced encephalomyelitis (89) and in some acute multiple sclerosis plaques (90, 91). All these pathologies are characterized by a significant demyelination. In contrast, there is no evidence for acute and pronounced demyelination in the CNS of MAG mutant mice (80, 86, 88). This also includes aged (i.e. 1.5 years old) animals (Susanne Bartsch, Malte Raether, Melitta Schachner and Udo Bartsch, unpublished observations). Instead, only a few axons were observed that were surrounded by unusually thin myelin sheaths (86). While these findings suggest that some de- and remyelination has occurred, they also demonstrate that oligodendrocyte dystrophy progresses at a very low rate in the MAG mutant mouse model.

A “dying-back” oligodendrogliopathy in the absence of MAG is consistent with the periaxonal location of MAG (70, 72, 74) and suggests that the integrity of oligodendrocytes depends on MAG-mediated signalling from the axon. Decreased levels of MAG-immunoreactivity at the periphery of some demyelinating lesions of different pathogenesis might precede loss of myelin or reduced expression of other myelin proteins (92 - 96), also suggesting that oligodendrocyte integrity and normal MAG expression are closely associated.

3.1.3. Normal formation, but impaired maintenance of myelinated fibers in the PNS of MAG-deficient mice

Investigations of peripheral nerves of the *quaking* mutant and cell culture experiments have suggested pivotal functions of MAG for myelin formation in the PNS (71, 75, 76). It thus came as a surprise that myelin formation by MAG-deficient Schwann cells was not compromised, neither in young mutant mice *in vivo* (79), nor *in vitro* (Figure 4) (97). The only abnormalities observed in the PNS of mutant mice were a dilated periaxonal space or a reduced periaxonal spacing and a lack of the periaxonal collar in some fibers (78). In contrast, these pathological features were not observed in a different study (79). Ultrastructural analysis of peripheral nerves of older MAG mutant mice, however, revealed degeneration of myelin and axons, demonstrating a role of MAG in the maintenance of myelin and axon integrity (98 - 102) (see

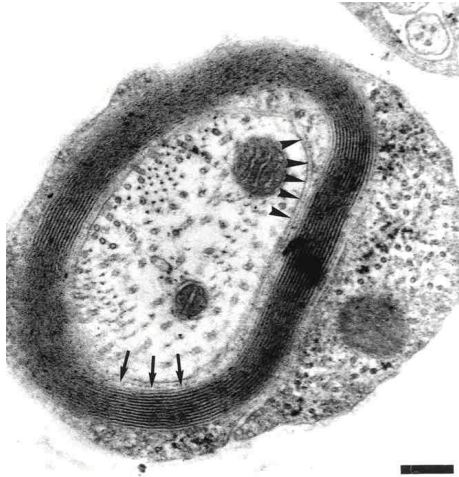


Figure 4. Myelination of dorsal root ganglion neurons by MAG-deficient Schwann cells *in vitro*. MAG-deficient Schwann cells form morphologically intact myelin sheaths around neurites of co-cultured dorsal root ganglion neurons, with a normal periodicity of major dense and intraperiod lines and a well developed periaxonal Schwann cell cytoplasmic collar (arrows). Note that the myelin sheath and the axon are separated by a periaxonal space of normal width (arrowheads). Bar: 0.2 μ m. Reproduced from (33).

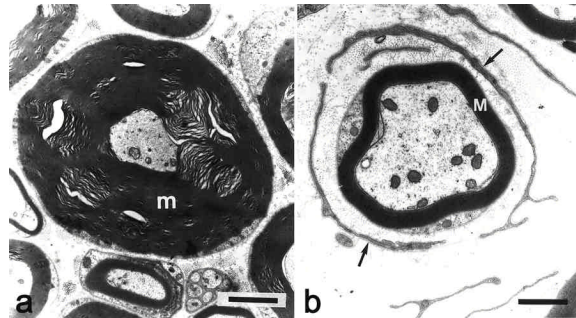


Figure 5. Pathological alterations in peripheral nerves of MAG/NCAM double mutant mice. (a) A relatively small axon surrounded by thick myelin (m) in the quadriceps nerve of a one-month-old MAG/NCAM mutant (a). Note the densely packed neurofilaments within the axon (a). (b) An onion bulb formation in the quadriceps nerve of a 26-week-old MAG/NCAM mutant consisting of an axon that is surrounded by a relatively thin myelin sheath and supernumerous Schwann cells (arrows). m, myelin; M, myelin. Bar (in a): 2 μ m; (in b): 1 μ m. Reproduced from (100).

Figure 5 for MAG-specific defects in MAG/NCAM double mutant mice). Onion bulbs, i.e. circumferentially oriented supernumerary Schwann cells surrounding axons with thin myelin sheaths and indicative of demyelination-induced proliferation of Schwann cells (103), were frequently encountered in the PNS of old MAG mutant mice (98). Myelin tomacula, i.e. abnormally thick myelin segments, were another pathological feature of MAG-deficient

peripheral nerves and were preferentially found in paranodal regions of myelinated fibers (100, 101).

Since axons surrounded by hypertrophic myelin often showed signs of degeneration, it has been suggested that myelin tomacula might be the cause of axonal degeneration in MAG mutant mice. Specifically, it has been hypothesized that the excessive myelin might mechanically constrict the axons, thereby interfering with axonal transport and ultimately causing axonal degeneration (100). A different explanation for the axonal pathology in MAG mutant mice is based on the presence of reduced calibers of myelinated axons, which is accompanied by a reduced phosphorylation and spacing of neurofilaments (101). Phosphorylation of neurofilaments is thought to increase the lateral extension of neurofilament sidearms, thereby increasing neurofilament spacing and axon caliber (8, 10, 104). These data suggest that MAG in the adaxonal membrane of myelinating Schwann cells serves as a signal that modulates the axonal cytoskeleton and consequently axonal caliber. Axonal atrophy in the absence of MAG is particularly pronounced in paranodal regions. A collapse of the myelin sheath as a result of axonal shrinkage is thus a likely explanation for the formation of paranodal tomacula in MAG-deficient mice (101). Remarkably, reduced neurofilament spacing has recently been reported in patients with anti-MAG paraproteinaemic demyelinating peripheral neuropathies (105), also suggesting a role of MAG in modulating axonal properties.

Electrophysiological studies have corroborated the progressive morphological phenotype of MAG-deficient peripheral nerves. While electrophysiological characteristics of peripheral nerves of young MAG mutant mice is indistinguishable from those of wild-type mice (79, 83), a moderate but significant decrease in conduction velocity was reported for aged MAG mutant mice (102) and was suggested to be related to the reduced calibre of peripheral axons (see above).

The combined observations demonstrate a role of MAG for the long-term maintenance of peripheral myelin and axons. While an axonal pathology has not been described in the CNS of MAG-deficient mice, it is of potential interest that axonal degeneration in the CNS of mice deficient in proteolipid protein (106) is accelerated by the additional inactivation of the *Mag* gene (83).

3.1.4. A subtle role for the neural cell adhesion molecule (NCAM) in maintaining the integrity of axon and myelin in the absence of MAG

The subtle phenotypes in MAG mutant mice and in particular the normal initiation of myelination and the formation of morphologically normal myelin sheaths in the PNS was an unexpected observation and prompted the search for compensatory and/or functionally redundant molecules, which might substitute, at least partially, for the lack of MAG in the null mutant. The neural cell adhesion molecule (NCAM), like MAG a member of the Ig-superfamily, was among the candidate molecules.

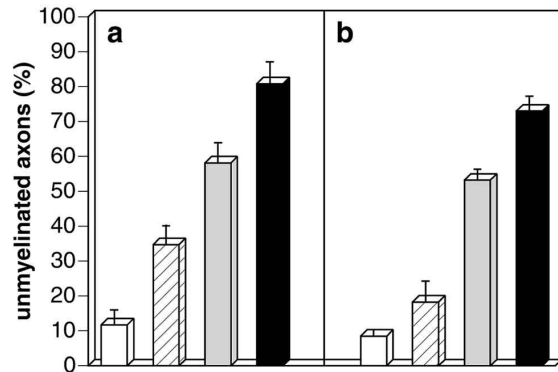


Figure 6. The percentage of unmyelinated axons in the optic nerves of mice with different genotypes. The percentage of unmyelinated axons was determined in optic nerves of two- (a) and nine-month-old (b) wild-type (open bars), MAG- (hatched bars), Fyn- (grey bars) and MAG/Fyn- (filled bars) deficient mice. Note the similar values for each genotype at both developmental ages. Note also that the percentage of unmyelinated axons in optic nerves of MAG/Fyn double mutants is significantly increased when compared to Fyn mutants ($p < 0.0001$ according to the unpaired t test). Each bar represents the mean value \pm SD from six animals. Reproduced with modifications from (120).

NCAM is expressed by myelin-forming oligodendrocytes and Schwann cells, is detectable in CNS and PNS myelin, supports oligodendrocyte survival and formation of myelin-like membranes *in vitro* and has been implicated in the formation of myelin (e.g., 73, 107 - 113). Furthermore, a compensatory function of NCAM in the PNS of MAG knock-out mice was suggested by the up-regulation of NCAM in myelinating Schwann cells at the mRNA, as well as at the protein level (79). Remarkably, the expression of NCAM was elevated in the periaxonal region and on the outer surface of myelinating Schwann cells, both regions of myelinated fibers that are normally MAG-immunoreactive (79). Mice deficient in MAG (79) and NCAM (114) were generated to test for a potential compensatory function of NCAM in the MAG mutant mouse model.

Analysis of the CNS (our unpublished observations) or the PNS (100) of NCAM mutant mice revealed no evidence for a role of NCAM in myelination. However, large-sized unmyelinated axons or thinly myelinated axons were found in the CNS of some aged (i.e., older than one year) MAG/NCAM double mutant mice, but not in the CNS of age-matched single mutant mice (our unpublished observations). Furthermore, degeneration of myelin and axons in the PNS of MAG/NCAM double mutant animals (Figure 5) started ~4 weeks earlier than in the PNS of MAG single mutant mice (100). The combined results thus suggest a subtle role for NCAM in the maintenance of CNS myelin and of myelinated fibers in the PNS. This function, however, only becomes apparent in the absence of MAG.

3.1.5. Differential functions of MAG isoforms in CNS versus PNS

The small (S-MAG) and large (L-MAG) isoforms of MAG, generated by alternative splicing of the primary MAG transcript, are identical in their extracellular and transmembrane domains but differ in their cytoplasmic domains. L-MAG is the predominant MAG isoform during active myelination and associates with fyn, a non-receptor type tyrosine kinase, which is known to be critical for the initiation of myelination in the CNS (49, see below). In comparison, S-MAG is the predominant MAG isoform in the adult (29, 34, 115, 116). In order to functionally characterize the different MAG isoforms, a mutant mouse was generated by introducing a stop codon into the last exon of the *Mag* gene (35). This mouse strain expresses a truncated form of L-MAG, which is predicted to be four amino acids shorter than S-MAG. Immunoblot analysis of the mutant line confirmed the expression of S-MAG and of a truncated L-MAG protein. However, levels of total MAG protein were reduced by approximately 50% compared to wild-type animals. Interestingly, phenotypic analysis of the CNS of L-MAG mutant mice revealed striking similarities with MAG null mutant animals, including the formation of redundant compact myelin, the presence of doubly or multiply myelinated axons and indications of a delayed myelination (see above). Since heterozygous MAG null mutant mice display a similarly reduced level of MAG expression (79) as L-MAG mutant mice, yet lack a detectable phenotype (35), it is unlikely that the defects observed in the CNS of the L-MAG mutant line result from reduced levels of total MAG protein. Myelination of peripheral axons was not affected in the L-MAG mutant mouse model and, more remarkably, there was no evidence for degeneration of myelin and axons in aged animals (35). Although it is presently unknown, whether all the pathological features seen in the CNS of MAG null mutant animals are also present in L-MAG mutant mice, these data identify the cytoplasmic domain, which is unique to L-MAG, as the functionally important MAG domain for myelin formation in the CNS. They also indicate that the extracellular domain, which is common to S- and L-MAG, is sufficient to maintain the integrity of myelinated fibers in the PNS.

3.1.6. The tyrosine kinase Fyn is critical for the initiation of myelination in the CNS

The cytoplasmic domain, which is unique to L-MAG, contains a tyrosine phosphorylation site and associates with Fyn, a non-receptor-type tyrosine kinase of the src family (49, 117). Furthermore, crosslinking of L-MAG, but not of S-MAG, with anti-MAG antibodies stimulates Fyn tyrosine kinase activity in cotransfected COS cells (49). These data thus identify Fyn as a signalling molecule downstream of MAG. Severe hypomyelination of the CNS of adult Fyn mutant mice (118) with a reduction of the myelin content of about 50% demonstrates a critical role of Fyn for normal myelination (49). Subsequent studies using independently generated Fyn mutant mice (119) confirmed a severe hypomyelination of the CNS in the absence of Fyn (Figure 6 and 8b) (120, 121). In addition, similarly impaired myelin formation was observed in mutant mice, which express full-length Fyn

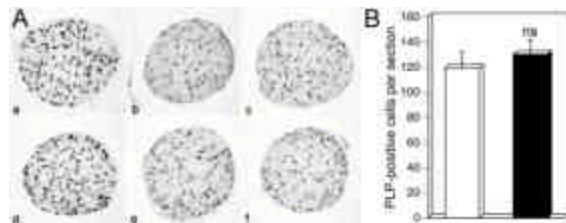


Figure 7. Normal numbers of oligodendrocytes in optic nerves of MAG/Fyn-deficient mice. (A) Oligodendrocytes were visualized in cross-sectioned optic nerves from adult wild-type (a-c) and MAG/Fyn-deficient (d-f) mice by *in situ* hybridization using cRNA probes specific to proteolipid protein/DM-20 (a,d), proteolipid protein (b,e) and myelin oligodendrocyte glycoprotein (c,f). Note the similar numbers of labeled cells in optic nerves of both genotypes. (B) Quantitative analysis confirmed the presence of similar numbers of proteolipid protein-positive oligodendrocytes in wild-type (open bar) and MAG/Fyn-deficient (filled bar) optic nerves. Each bar represents the mean value \pm SD from six animals. (ns: not significantly different according to the unpaired *t* test).

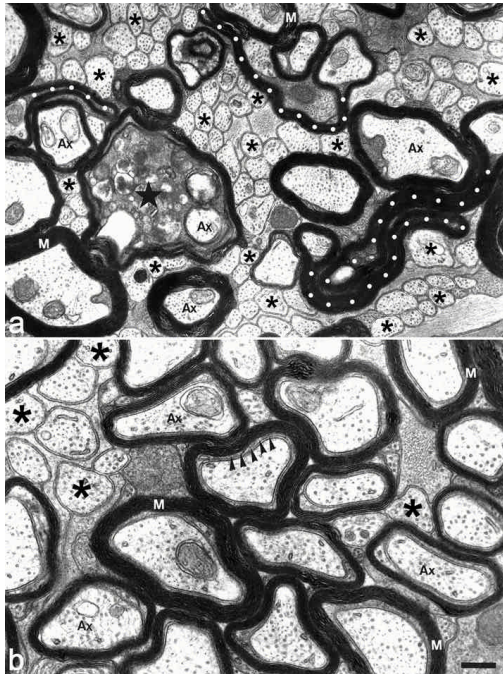


Figure 8. MAG, but not Fyn is essential for the formation of normal myelin sheaths in the CNS. Myelin sheaths in the optic nerve of adult MAG/Fyn-deficient mice (a) lack a well developed periaxonal cytoplasmic collar, and some sheaths elaborate redundant myelin (white dots in a) or display degenerative alterations (large asterisk in a). Note the presence of numerous unmyelinated and small-sized axons in the MAG/Fyn-deficient optic nerve (some labeled with small asterisks in a). Myelin sheaths in the optic nerve of adult Fyn mutants (b), in contrast, display a normal morphology with a well developed periaxonal cytoplasmic collar (arrowheads in b). Note that many axons are unmyelinated and of small caliber (some labeled with asterisks in b). Ax, axon; M, myelin. Bar in (b): 0.5 μ m for (a); 0.25 μ m for (b). Reproduced from (120).

with a missense mutation that abolishes kinase activity (121).

While one study suggested that the phenotype of Fyn mutant mice is related, in part, to reduced numbers of oligodendrocytes (121), another study reported normal numbers of oligodendrocytes in the severely hypomyelinated optic nerve of MAG/Fyn double mutant animals (Figure 7) (120). Impaired morphological maturation of oligodendrocytes, instead of oligodendrocyte loss, is a possible explanation for the pronounced hypomyelination of the CNS of Fyn mutant mice. In fact, inactivation of Fyn kinase activity in cultivated oligodendrocytes by either kinase inhibitors or by the expression of a dominant-negative variant of Fyn interfered with the formation of cell processes (122). The cytoskeletal protein Tau has recently been identified as a downstream target of Fyn and was shown to interact with the SH3 domain of Fyn. Expression of a mutant variant of Tau, which lacks the microtubuli interaction domain, impairs process formation of cultured oligodendrocytes without, however, affecting kinase activity (123). Impaired morphological maturation of oligodendrocytes might not only explain the hypomyelination in the CNS of Fyn (or MAG/Fyn) mutant mice, but also the regional variability in the severity of this defect. Hypomyelination in Fyn (or MAG/Fyn) mutant animals is pronounced in fiber tracts containing predominantly small-sized myelinated axons, such as the optic nerve, corpus callosum or corticospinal tract, but is mild or not apparent in fiber tracts containing predominantly large-sized myelinated axons, such as the fasciculus gracilis and cuneatus or the ventral funiculus of the spinal cord (120, 121). In tracts with small-sized axons, a single oligodendrocyte myelinates many axons and thus has to extend numerous processes. In contrast, in tracts with large-sized axons oligodendrocytes myelinate only a few axons or oligodendrocyte cell bodies are directly associated with axons without elaborating interconnecting processes (2).

Since Fyn is not only expressed in oligodendrocytes and their precursors (122, 124), but also at high levels in nerve cells (125 - 127), it is possible that a neuronal deficit contributes to the impaired myelination in Fyn mutant animals. However, abnormal development of oligodendrocytes from Fyn-deficient mice in the absence of nerve cells *in vitro* (128) and extensive myelination of MAG/Fyn-deficient axons by oligodendrocytes derived from grafted wild-type neural stem cells *in vivo* (129) suggests that the phenotype of Fyn (and MAG/Fyn) mutant mice is caused by a cell autonomous defect in oligodendrocytes and argues against a significant involvement of a neuronal component.

Hypomyelination in the CNS of Fyn null mutant mice is more pronounced than in MAG mutants and is most severe in MAG/Fyn double mutants (Figures 6 and 8) (120). In the optic nerve of two-month-old animals, for instance, ~30% of ganglion cell axons are unmyelinated in MAG mutant mice, ~60% in Fyn mutant animals and ~80% in MAG/Fyn double mutant individuals compared to ~10% unmyelinated axons in wild-type mice (Figure 6) (120). A

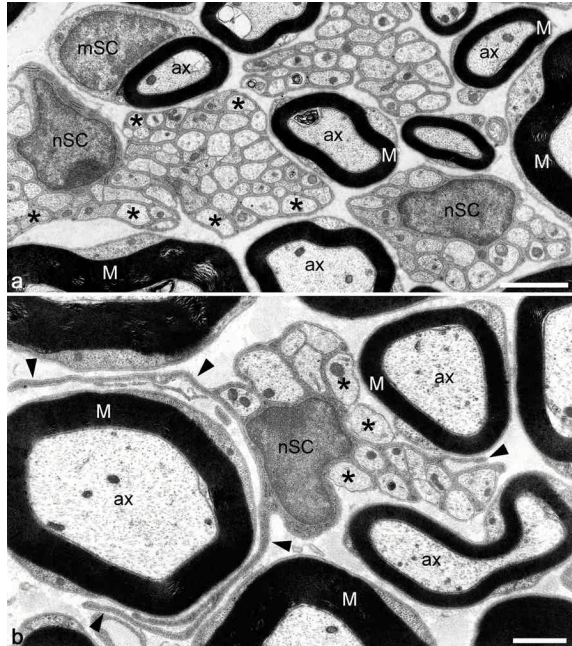


Figure 9. Pathological alterations in peripheral nerves of L1-deficient mice are confined to unmyelinated fibers. Each myelinating Schwann cell (mSC) in peripheral nerves of wild-type mice (a) engages with a single axon (ax) and forms a single internodal myelin segment. Nonmyelinating Schwann cells (nSC) ensheath several unmyelinated axons in separate cytoplasmic troughs (a). Note that most unmyelinated axons in wild-type nerves (some labeled with asterisks in a) are completely surrounded by the Schwann cell. Myelinated fibers in sciatic nerves of two-month-old L1-deficient mice (b) display a normal morphology. Note, however, the low number of axons associated with one nonmyelinating Schwann cell (nSC in b). Note also the redundant processes of the nonmyelinating Schwann cell (arrowheads in b) and the presence of axons (labeled with asterisks in b) that are only incompletely ensheathed by Schwann cell processes. M, myelin. Bar in (a): 2 μ m; in (b): 1 μ m.

possible interpretation of these results is that MAG and Fyn act independently to initiate myelination and that the severe phenotype in the double mutant line simply stems from a combination of the phenotypes of the respective single mutant animals. However, compensatory mechanisms might also explain the different severity of the MAG, Fyn and MAG/Fyn phenotypes. In the absence of Fyn, other signalling pathways might be activated more strongly by MAG. *Vice versa*, in the absence of MAG, Fyn might be activated more strongly by other oligodendrocyte cell surface molecules. Simultaneous elimination of MAG and Fyn would disrupt these hypothetical compensatory pathways and result in a phenotype of the double mutant mouse that is more severe than that of each single mutant line. An L-MAG-associated kinase activity in Fyn mutant mice at early stages of myelination (49) and the association of the 120kD isoform of the neural cell adhesion molecule (NCAM) or the cell adhesion molecule F3/F11/contactin with Fyn in detergent-insoluble glycosphingolipid-rich

microdomains of oligodendrocytes and myelin (124) is of potential interest in this context.

Analysis of the Fyn mutant mouse generated by Yagi and colleagues (118) revealed an abnormal ultrastructure of myelin (130, 131), while investigations of a different Fyn mutant line (119) demonstrated the presence of ultrastructurally intact myelin sheaths (Figure 8b) (120, 121). The reasons for these discrepant observations are unknown, but it is possible that the defects in the former mutant line are related to the expression of a truncated Fyn protein in fusion with β -galactosidase (118). Furthermore, in the PNS of Fyn-mutant mice neither the formation, nor the maintenance of myelinated fibers is affected (120). MAG-related signalling pathways that mediate the formation of morphologically normal myelin sheaths in the CNS or maintain the integrity of myelinated fibers in the PNS thus remain to be elucidated.

3.2. The neural adhesion molecule L1 mediates axon-Schwann cell interactions

The neural adhesion molecule L1 consists of six Ig-like domains, five fibronectin type III domains, a single trans-membrane domain and a highly conserved cytoplasmic domain (132). The protein performs important functions during neural development and has been implicated in the migration and survival of neurons, in the elongation, fasciculation, pathfinding and regeneration of axons, as well as in synaptic plasticity and myelination. L1 is believed to perform its functions mainly by homophilic (i.e. L1-L1) interactions, but heterophilic interactions with a variety of ligands have also been described (133, 134). The identification of L1 mutations as the cause for severe neurological syndromes in humans including HSAS (hydrocephalus due to stenosis of the aqueduct of Sylvius), MASA (mental retardation, aphasia, shuffling gait, adducted thumbs), SP-1 (spastic paraplegia type-1) and ACC (agenesis of corpus callosum) confirms a critical role of L1 for normal brain development (135 - 138).

In the CNS L1 is present on unmyelinated axons, whereas glial cells lack detectable expression of the protein (74, 139). In the PNS the protein is present on unmyelinated axons and nonmyelinating Schwann cells. L1 is also expressed by myelinating Schwann cells at the onset of myelination, but disappears as the Schwann cell process has formed about 1.5 loops around the axon (73). A possible involvement of L1 in the myelination of peripheral axons is indicated by the failure of cultured Schwann cells to ensheath and myelinate neurites of co-cultured dorsal root ganglion neurons in the presence of anti-L1 antibodies (140, 141).

Mice with a targeted disruption of the *L1cam* gene (142, 143) display a variety of defects, which are also seen in human patients with L1 mutations. These include increased mortality, hypoplasia of the corticospinal tract, pathfinding errors of corticospinal axons, hypoplasia of the corpus callosum, and hydrocephalus (e.g. 142 - 146). The PNS of mutant mice is also affected. Abnormalities in peripheral nerves are restricted to unmyelinated fibers, whereas the onset of myelination and the formation of morphologically normal myelin sheaths is not affected (compare Figure 9a with 9b)

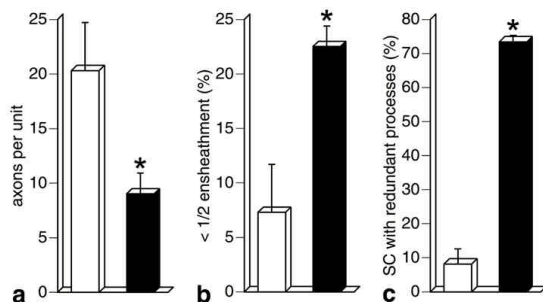


Figure 10. Quantitative analysis of unmyelinated fibers in the PNS of L1-deficient mice. Unmyelinated fibers in sciatic nerves of two-month-old wild-type mice (open bars) and age-matched L1 mutants (filled bars) were analyzed at the ultrastructural level. The number of axons associated with one nonmyelinating Schwann cell is significantly decreased (a), and the percentage of incompletely ensheathed axons (b) and of Schwann cells extending redundant processes into the endoneurial space (c) is significantly increased in the mutant compared to the wild-type (*: $p < 0.01$ according to the Mann-Whitney-test). Each bar represents the mean value \pm SD from six animals. SC, Schwann cell.

(142, 147, 148). Nonmyelinating Schwann cell processes extend into the endoneurial space without associated axons. A fraction of unmyelinated axons is either incompletely ensheathed by Schwann cell processes or not at all and the number of axons that are associated with one nonmyelinating Schwann cell is significantly reduced (compare Figure 9a with 9b; Figure 10) (142, 147, 148). Since initial formation of unmyelinated fibers is normal in L1-deficient mice, L1 is important for maintaining axonal ensheathment and possibly also for supporting axonal survival (147). In transplantation experiments, impaired ensheathment of axons was only observed when wild-type Schwann cells were grafted to sciatic nerves of L1 mutant animals, but not when L1-deficient Schwann cells were grafted to sciatic nerves of wild-type animals. The maintenance of normal axonal ensheathment is thus mediated by heterophilic interactions between axonal L1 and a yet unknown ligand on Schwann cells, rather than by homophilic L1-L1 interactions (147).

Double mutant animals, which are deficient for L1 and MAG, were generated to examine the possibility of a functional redundancy of both proteins in myelination. This would potentially explain the normal myelin formation in the PNS of each of the single mutant lines. However, neither the onset of myelination, nor the formation of morphologically normal myelin sheaths is impaired in these double mutant animals (147). L1 and MAG are thus dispensable for the formation of peripheral myelin, but essential for maintaining the integrity of unmyelinated and myelinated fibers.

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