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Structural properties of proteins specific to the myelin sheath

Review Article

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Summary. The myelin sheath is an insulating membrane layer surrounding myelinated axons in vertebrates, which is formed when the plasma membrane of an oligodendrocyte or a Schwann cell wraps itself around the axon. A large fraction of the total protein in this membrane layer is comprised of only a small number of individual proteins, which have certain intriguing structural properties. The myelin proteins are implicated in a number of neurological diseases, including, for example, autoimmune diseases and peripheral neuropathies. In this review, the structural properties of a number of myelin-specific proteins are described.

Keywords: Myelin – Membrane protein – Unstructured protein – Post-translational modification – Protein domain – Protein structure

Abbreviations: P0, myelin protein zero; MAG, myelin-associated glycoprotein; MOG, myelin/oligodendrocyte glycoprotein; MBP, myelin basic protein; MOBP, myelin/oligodendrocyte basic protein; CaM, calmodulin; P2, peripheral myelin protein 2; CNS, central nervous system; PNS, peripheral nervous system; OMgp, oligodendrocyte/myelin glycoprotein; CNPase, 2′,3′-cyclic nucleotide 3′-phosphodiesterase; FABP, fatty acid binding protein; PnK, polynucleotide kinase; Ig, immunoglobulin

Introduction

The rapid transduction of nerve impulses is required for the normal functioning of the vertebrate nervous system. The fast 'saltatory' travel of the impulse along the axonal membrane is promoted by the presence of a thick layer of glial plasma membrane that intimately wraps around the axon. This multilayered membrane called myelin is formed by oligodendrocytes in the central nervous system (CNS) and Schwann cells in the peripheral nervous system (PNS). Both CNS and PNS myelin can be roughly divided into two compartments, based on morphological features: compact and non-compact myelin. Interestingly, these compartments both carry a well-defined subset of myelin-specific proteins.

In compact myelin, the extracellular space is only about 2 nm thick, while the cytoplasmic leaflets of myelin membrane from consecutive turns are practically fused, excluding cytoplasm from the compartment. This very tightly packed structure implies that the specific set of proteins in compact myelin have intimate interactions with the myelin membrane, regardless of whether they are cytosolic or transmembrane proteins with both intra- and extracellular domains.

Non-compact myelin, on the other hand, is less densely packed, the extracellular space generally being in the order of 12–14 nm. The intracellular pocket is large enough to hold significant amounts of cytoplasm and cytoskeletal assemblies. Thus, in addition to specific proteins of non-compact myelin, also ubiquitous cytoplasmic proteins are present in high concentrations. Regions of non-compact myelin include Schmidt-Lanterman incisures, the abaxonal and adaxonal membranes, and the segment near the nodes of Ranvier.

When discussing proteins of the myelin sheath, it is necessary to keep in mind the extraordinary environment in which these proteins must function during the life of an individual. There is little, if any, cytoplasm, and the negatively charged inner membrane of myelin is in close contact even with the cytoplasmic myelin proteins. The myelin sheath is also enriched in zinc, and not surprisingly, several myelin proteins have been shown to bind zinc ions. Several authors have proposed a role for zinc cations in the compaction of the mature myelin sheath

(Inouye and Kirschner, 1984; Earl et al., 1988; Riccio et al., 1995; Tsang et al., 1997).

Why would one be specifically interested in the structural properties of myelin proteins? In principle, there are two reasons above others. Firstly, the formation and maintenance of the myelin sheath, which is a highly specialised subcellular structure, is an intriguing biological question. By studying the structures of specific myelin proteins, we can better understand the processes that drive the formation of myelin and contribute to its stability and other properties. Secondly, a number of myelin-specific proteins are implicated in diseases of the nervous system. Such diseases include, for example, autoimmune diseases, in which the immune system attacks proteins of the myelin sheath. This occurs e.g. in multiple sclerosis (Sospedra and Martin, 2005). Several inherited peripheral neuropathies diseases also exist that involve mutations in myelin proteins (Shy, 2004). Thus, by obtaining accurate 3-dimensional models of myelin proteins, we can also begin to understand the reasons for neurological diseases at the molecular level.

General structural properties of myelin-specific proteins

In myelin, a number of structural classes of proteins are present. Some proteins are extremely hydrophobic membrane-embedded polypeptides, some integral membrane proteins have a single transmembrane domain and clearly defined extra- and intracellular domains, and some of the myelin proteins are cytosolic; however, they are often intimately associated with the myelin membrane.

Some of the myelin proteins, belonging to the family of tetraspanins, are amongst the most hydrophobic proteins known. One of these proteins is the proteolipid protein. This group of proteins is most poorly characterised structurally, and will not be discussed in this review.

A number of type I transmembrane proteins are present in myelin. A common denominator for these proteins is that their extracellular domains are formed of one or more immunoglobulin (Ig) domains, and they are glycosylated. On the other hand, the cytoplasmic domains of these proteins generally are short, and bear no significant overall homology to other proteins. Usually, the cytoplasmic domains are also predicted to be unfolded, and have an overall positive charge. From the point of view of structure determination, such proteins are generally tackled domain by domain instead of using the full-length protein.

Several proteins are specifically expressed in the cytoplasmic compartment of myelin. In general, these proteins are highly basic and soluble, and often they have large disordered regions. They are able to interact with membrane surfaces, and often bind small-molecule ligands, such as ions or lipids.

In the following paragraphs, a number of the structurally best characterised myelin proteins are discussed.

Selected examples of myelin-specific proteins with interesting structural features

Myelin protein zero

Myelin protein zero (P0) is an abundant membrane protein in compact PNS myelin, representing over 50% of total PNS myelin protein (Everly et al., 1973). It has a molecular weight of 30 kDa, and it comprises a glycosylated extracellular Ig domain, a transmembrane helix, and a small cytoplasmic domain (Eichberg, 2002).

The crystal structure of the extracellular domain of P0 from rat has been determined (Shapiro et al., 1996). The domain is an Ig domain of the variable type; from the packing of the crystal, conclusions have also been drawn as to the packing of P0 in native myelin. According to this view, P0 is present in the membrane as tetramers (Fig. 1), and these tetramers from opposing myelin membranes interact with each other, promoting myelin compaction. The tetrameric nature of P0 has been proven in a number

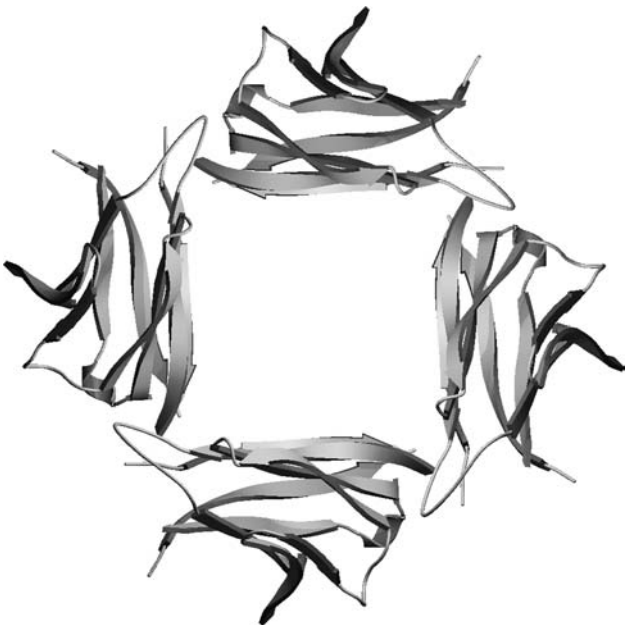

Fig. 1. The crystal structure of the extracellular domain of P0 (Shapiro et al., 1996). The tetrameric packing within the crystal, also suggested to occur in myelin, is shown. All figures of 3-dimensional structures were prepared using Molscript (Kraulis, 1991) and POV-Ray (www.pov-ray.org)

of studies (Shapiro et al., 1996; Inouye et al., 1999; Thompson et al., 2002). Disease-linked mutations in the P0 extracellular domain have been identified that can be analysed in detail based on the crystal structure (Shy et al., 2004).

The extracellular domain harbours a single N-linked glycosylation site at Asn93 (Sakamoto et al., 1987). The glycan attached to P0 at this site carries the HNK-1 epitope, a carbohydrate moiety also found on other myelin proteins (Shy et al., 1986). The detailed structure of the epitope on P0 has been determined by NMR methods (Voshol et al., 1996).

The 64-residue P0 cytoplasmic domain is predicted to be formed of two α helices (Combet et al., 2000), with several predicted and proven phosphorylation sites. The cytoplasmic domain of P0 is highly basic, having an overall pI of 11, which most likely is important for its ability to interact with the inner leaflets of the myelin membrane. It is important to note that the P0 cytoplasmic domain indeed is tightly sandwiched between two membranes, since there is very little, if any, cytoplasm in compact myelin.

Peripheral myelin protein 2

Peripheral myelin protein 2 (P2) is a small folded protein having a high degree of homology to members of the fatty acid binding protein (FABP) family (Chmurzynska, 2006). It is expressed in the cytoplasmic face of compact myelin in the PNS (Eylar et al., 1980; Trapp et al., 1984), and its lipid-binding activity suggests it may serve important functions in generating and maintaining the unique lipid composition of the myelin membrane (Uyemura et al., 1984). P2 is possibly one of the autoantigens in the human disorder Guillain-Barre syndrome (Rostami, 1997; Hughes et al., 1999; Hughes and Cornblath, 2005), which is an autoimmune disease of the peripheral nervous system.

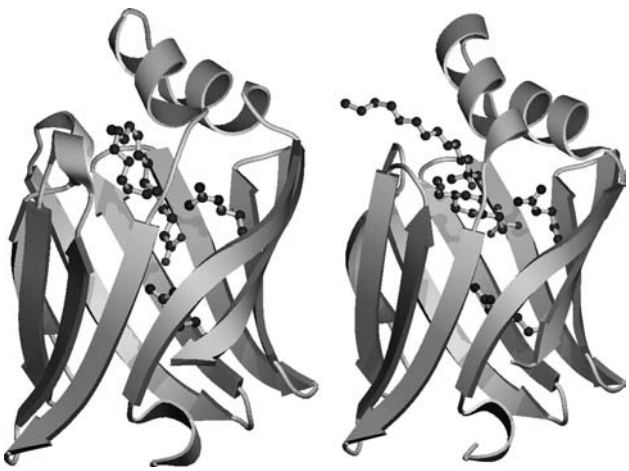

Fig. 2. Crystal structures of bovine (left) and equine (right) P2 (Jones et al., 1988; Hunter et al., 2005). The two arginine residues inside the ligand-binding cavity are shown in ball-and-stick mode, as are bound ligands in the crystal structures

The crystal structure of P2 has been determined from both bovine (Jones et al., 1988) and equine (Hunter et al., 2005) sources (Fig. 2). As expected from sequence homology, the folding of P2 closely resembles that of the other FABPs. The structure is formed mainly of an antiparallel 10-stranded β-sheet barrel; in addition, one loop forms two short helices that cover the lipid-binding pocket.

Inside P2, a large cavity exists for lipid binding. Comparing the internal cavity to that seen in FABP1 (PDB entry 2F73), it can be seen that in P2, the walls of the cavity are much more polar than those in FABP1. This may be important for binding of myelin-specific lipids by P2. Two arginine residues, Arg106 and Arg1126, play a key role in interacting with negatively charged groups on bound lipids (Fig. 2). Crystallisation of P2 in complex with lipids has been reported (Sedzik et al., 2003), but the resulting structures have not been published.

2′,3′-cyclic nucleotide 3′-phosphodiesterase

2′,3′-cyclic nucleotide 3′-phosphodiesterase (CNPase) is an enzyme specifically expressed in myelin, where it is localised in the cytoplasm of non-compact myelin. The reaction it catalyses, the phosphodiester hydrolysis of 2′,3′-cyclic nucleotides to generate 2′-nucleotides (Drummond et al., 1962), is well-characterised, but its physiological relevance, or the actual physiological substrate, has not been clarified. Structurally, CNPase belongs to the family of 2H phosphodiesterases (Mazumder et al., 2002). Both crystal (Sakamoto et al., 2005) and NMR (Kozlov et al., 2003) structures have been determined for the catalytic fragment of CNPase (Fig. 3), while a structure of the full-length enzyme has not been determined.

The catalytic mechanism of CNPase has been suggested to be related to that of RNase A (Sakamoto et al., 2005). It is possible that the function of CNPase is related to RNA metabolism; in this respect, it is interesting to note that mRNAs for some myelin proteins are transported to the myelin sheath and the peripheral processes of the myelinating cell (Boccaccio and Colman, 1995; Holz et al., 1996; Ainger et al., 1997; Carson et al., 1997; Carson et al., 1998). It is clear that the evaluation of the function of CNPase would greatly benefit from the availability of the structure of full-length CNPase.

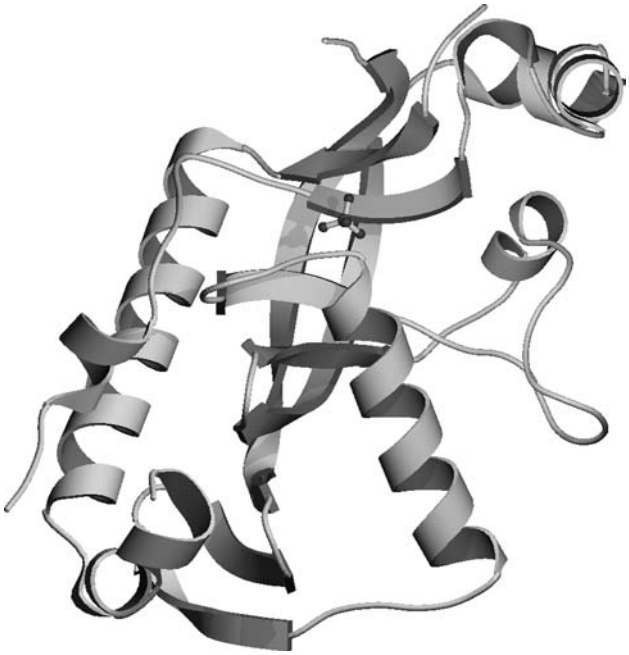

Fig. 3. The crystal structure of the catalytic fragment of human CNP (Sakamoto et al., 2005). A phosphate ion is bound in the predicted active site

For example, the N-terminal domain of CNPase, not present in either of the determined structures, contains a P-loop motif around residue 60, which is probably involved in ATP binding (not shown). The ATP-binding region is most homologous to that seen in Bcl-3 binding protein (Watanabe et al., 2003).

3D-PSSM (Kelley et al., 2000) search with the N-terminal sequence of CNPase suggests highest structural homology to the N-terminal kinase domain of T4 polynucleotide kinase (PnK) (Wang et al., 2002), an enzyme with a function in RNA repair. Interestingly, this domain in PnK dimerises. Evidence also exists for the dimerisation of CNPase (Muller et al., 1981; Muller, 1982). However, the residues related to PnK dimerisation are the least conserved between PnK and CNPase, likely excluding the possibility of similar dimerisation for CNPase to that seen in PnK.

Myelin-associated glycoprotein

The myelin-associated glycoprotein (MAG) is one of the few myelin-specific proteins expressed by myelinating glia in both branches of the nervous system (Quarles et al., 1973; Figlewicz et al., 1981), suggesting a crucial role in myelin formation and maintenance. In the CNS, MAG is enriched exclusively in the periaxonal membrane of myelin internodes (Sternberger et al., 1979), while in the PNS, it is found in the periaxonal membrane, paranodal loops, Schmidt-Lanterman incisures, and the inner and outer mesaxons (Sternberger et al., 1979; Trapp and Quarles, 1982; Martini and Schachner, 1986; Trapp et al., 1989). In other words, MAG is present in the non-compacted membranes of the myelin sheath.

The structural properties of MAG have been reviewed earlier (Kursula, 2003); the main features putatively related to its function will be discussed here. MAG is a type I transmembrane protein, with its 5 N-terminal Ig domains in the extracellular space and one of 2 alternative cytoplasmic domains inside the cell. It is specifically expressed in non-compact myelin both in the CNS and PNS, where it amounts to 0.1–1% of total myelin protein. MAG has an overall molecular weight of

Fig. 4. The predicted structure of MAG Ig domains 1–2. Arg118, crucial for binding sialic acid, is shown. The 3 disulfide bridges, one in domain 1, one in domain 2, and one between domains 1 and 2, are also indicated

Table 1. Direct interactions between MAG cytoplasmic domains and other compounds

Isoform	Interaction partner	Characteristics	Reference
L-MAG	S100B	Ca^{2+}-dependent, Inhibits PKA phosphorylation	Kursula et al. (1999b, 2000)
	Protein kinase C	Ser phosphorylation	Kirchhoff et al. (1993) and Kursula et al. (2000)
	Protein kinase A	Ser and Thr (Thr607) phosphorylation	Kursula et al. (2000)
	Fyn kinase	Phosphorylation at Tyr620	Jaramillo et al. (1994)
	Phospholipase Cγ	Binds to Tyr-phosphorylated L-MAG	Jaramillo et al. (1994)
	L-MAG	dimerisation	Kursula (2000)
	Src kinases	Phosphorylation	Afar et al. (1990)
S-MAG	Zn^{2+}	Becomes more hydrophobic upon binding	Kursula et al. (1999a)
	tubulin	Binds tubulin and microtubules	Kursula et al. (2001)
	Protein kinase C	Ser phosphorylation	Kirchhoff et al. (1993) and Kursula et al. (2000)

100 kDa, of which approximately 30% is carbohydrate (Frail and Braun, 1984).

The MAG extracellular domain is formed of 5 heavily glycosylated Ig domains, of which the N-terminal one is of the variable type, and Ig domains 2–5 are of the constant type. Immunoglobulin domains 1 and 2 (Fig. 4) are linked via an interdomain disulfide bridge (Pedraza et al., 1990). The conformation of the isolated extracellular domain has been studied by biophysical methods (Attia et al., 1993; Fahrig et al., 1993), but no high-resolution structural information is available. The isolated extracellular domain is rod-like, with a maximum length of slightly under 20 nm (Fahrig et al., 1993), indicating it must be tightly packed between extracellular membrane leaflets. Molecular modeling (Kursula, 2001) suggests that the variable-type Ig domain 1 has high structural similarity to the sialic-acid binding domain of sialoadhesin (May et al., 1998), the crystal structure of which has been determined. A central residue for sialic acid binding is Arg118 (Tang et al., 1997), which interacts *via* a salt bridge with the acidic group on sialic acid, being a conserved residue within the sialoadhesin family.

As the result of alternative mRNA splicing, two MAG isoforms are produced, differing only by their carboxy-terminal segments (Lai et al., 1987). The expression of the two MAG isoforms is differentially regulated during development. L-MAG is found exclusively in the periaxonal membrane, where it may serve a signaling role, while S-MAG may have a structural function in all non-compacted myelin membranes. The MAG isoforms share a common cytoplasmic domain of 36 amino acids, which is followed by the isoform-specific carboxy-terminal domains of 10 or 54 amino acids for S- and L-MAG, respectively. At the primary sequence level, neither one of the MAG cytoplasmic domains shares clear homology with other proteins. Experimental data and secondary structure predictions indicate that while the S-MAG cytoplasmic domain does not have secondary structure in solution, the L-MAG cytoplasmic domain most likely comprises a folded domain and dimerises (Kursula, 2000). A number of studies have been carried out to identify the binding partners of the MAG cytoplasmic domains. The current data concerning the interactions between the cytoplasmic domains of MAG and other molecules are briefly summarised in Table 1. For example, the cytoplasmic domain of S-MAG binds zinc, which induces a conformational change that makes the protein surface more hydrophobic (Kursula et al., 1999a), and it also binds to tubulin and microtubules in vitro (Kursula et al., 2001). The unstructured nature of the S-MAG cytoplasmic domain, also observed for other tubulin-binding proteins, could play a role in its interactions.

Myelin-associated oligodendrocytic basic protein

The myelin-associated oligodendrocytic basic protein (MOBP) is a small protein present in oligodendrocytes (Yamamoto et al., 1994). It is localised to compact myelin (Yamamoto et al., 1994) where it has been suggested to play a role in myelin compaction and the formation of the so-called radial component (Yamamoto et al., 1999; Yoshikawa, 2001). MOBP is a highly basic soluble protein, which is expressed in a number of forms that share a common N-terminus of approximately 70 residues (Yamamoto et al., 1994; McCallion et al., 1999). No homology to other known proteins has been detected for MOBP, although in many instances, it has been suggested that its sequence and properties are similar to another protein present in compact myelin, the myelin basic protein (MBP). MBP is intrinsically unstructured, which has hampered attempts to study its 3-D structure-function relationships (Harauz et al., 2004).

The two main isoforms of MOBP are approximately 70 and 180 residues long, and differences in expression and

Fig. 5. Sequence alignment between MOBP and MyRIP. The main encephalotogenic epitope of MOBP, residues 15–36, is highlighted in light gray, and the putative Zn-coordinating residues are shown in dark gray. The conserved hydrophobic loop contains residues 29–33. The figure was made with ESPript (Gouet et al., 1999)

function between these isoforms have been suggested. Mice deficient in MOBP are viable and their myelin seems normal, but certain effects have been attributed to the loss of MOBP. Firstly, although myelin seems to compact normally, treatment with the demyelinating drug hexachlorophene showed that the structure is not as tight as in wild-type animals (Yamamoto et al., 1999; Yoshikawa, 2001). Secondly, the so-called radial component, a structure found only in CNS myelin, is abnormal (Yamamoto et al., 1999; Yoshikawa, 2001). The relation of these findings and other functional results to MOBP structure has been unclear, since it has generally been accepted that MOBP could be unstructured like MBP.

The cloning of the MyRIP protein (El-Amraoui et al., 2002) allows to detect a strong homology between the N-terminus of MOBP and MyRIP (Fig. 5). Furthermore, similarity to other proteins with homology to MyRIP, such as melanophilin and rabphilin 3A, the crystal structure of which has been determined (Ostermeier and Brunger, 1999), can also be detected. The homology is in the region of the double zinc-finger FYVE domain (Stenmark et al., 1996), and ends at the beginning of the proline-rich region (see below) of MOBP. Searches for sequence homologues of MOBP have probably been distracted by the fact that the characteristic locations of the conserved Zn-coordinating Cys and His residues have slightly shifted in MOBP (Fig. 5). However, in 3-dimensional space, the Cys and His residues of MOBP are predicted to cluster at the two Zn-binding sites (not shown). It has been suggested that such FYVE domains act as non-specific membrane anchors via a conserved hydrophobic loop. While this loop inserts into the hydrophobic environment of the membrane, basic residues at its vicinity interact with negatively charged lipidic headgroups.

A number of studies have proposed a role for MOBP in the etiology of multiple sclerosis (Maatta et al., 1998; Holz et al., 2000; Kaye et al., 2000; de Rosbo et al., 2004). The suggested main encephalitogenic epitopes of MOBP lie completely within the predicted FYVE domain. The peptide mostly suggested to be involved in multiple sclerosis, residues 15–36 (de Rosbo et al., 2004), comes from the predicted first Zn-binding site and the hydrophobic membrane-anchoring loop.

The longer isoform of MOBP has, in addition to the FYVE domain, a 100-residue proline-rich region which has a high positive charge. This region has no homology to other proteins, and its structure is most probably randomly extended due to the large number of proline residues. MOBP is localised in the cytoplasmic compartment of compact myelin, in which practically no cytoplasm is present due to the tight packing of the membranes. It is likely that the tail region runs along the inner plasma membrane surface. Proline-rich regions are often mediators of protein-protein interactions (Zarrinpar et al., 2003). No binding partners for MOBP are known, however.

Myelin contains a high concentration of zinc, most of which is protein-bound. In fact, zinc is the most abundant trace element in myelin (Berlet et al., 1994). Zinc deficiency causes alterations in myelin, both in vivo and in vitro. Zinc favours myelin compaction (Inouye and Kirschner, 1984) and inhibits the release of MBP from myelin (Earl et al., 1988). In Zn-deficient rats, less myelinated nerve fibers are found and the myelin sheaths are thinner than usual (Gong and Amemiya, 2001). Although some myelin proteins, namely MBP (Tsang et al., 1997) and S-MAG (Kursula et al., 1999a), bind zinc, the exact binding mode of zinc to these proteins is poorly understood, since they do not have conserved Zn-binding domains. It has been assumed that the interactions zinc makes with the membranes and MBP are charge-mediated and rather unspecific in nature. The putative specific Zn-binding FYVE domain of MOBP helps us better understand the role of zinc in maintaining normal myelin structure. It is likely that some of the effects zinc is known to have on myelin structure are mediated by MOBP. Thus, MOBP is a good candidate for structural studies, since it has a conserved folded domain with functional implications. Future studies on MOBP should primarily focus on structure determination of the FYVE domain and the characterisation of its metal- and membrane-binding properties.

Myelin basic protein

MBP comprises a major part of the cytosolic protein of compact myelin. It is present both in the CNS and PNS,

and presents a variety of isoforms generated by alternative splicing and a large selection of different post-translational modifications. MBP also is a major autoantigen in multiple sclerosis, and is crucial for the formation and maintenance of normal myelin.

The structural properties of MBP have recently been excessively reviewed (Harauz et al., 2004; Tzakos et al., 2005; Boggs, 2006; Harauz and Musse, 2006); thus, it will be only briefly discussed here. MBP is a highly basic small protein, which is though to mediate adhesion between myelin membranes via electrostatic interactions.

Using electron microscopy, a C-shaped folded structure for MBP has been detected upon adsorption to a lipid monolayer (Beniac et al., 1997; Ridsdale et al., 1997). In addition, small-angle X-ray scattering has indicated that upon lipid binding, MBP has a compact structure (Haas et al., 2004). MBP has, on the other hand, been characterised as being unstructured in solution; however, several regions of MBP have propensity to fold into secondary structure, and folding – at least locally – is likely to occur upon binding to ligand molecules. Biophysical and computational methods have been excessively used for MBP characterisation, and short peptides of MBP can be found in a number of crystal structures in the PDB; however, none of these are in complex with physiological myelin ligands. Rather, MBP peptides are seen in complexes with immune system molecules, relevant for autoimmune disease, and as substrate mimics in protein kinase structures.

Experiments on full-length MBP and large fragments of it have indicated that structural studies, especially by X-ray crystallography, are unlikely to be successful (Sedzik and Kirschner, 1992). Thus, during recent years, it has become clear that one major way to obtain 3-D structural information of MBP is to use peptide fragments of it, possibly bound to a suitable ligand molecule. One such ligand for MBP is calmodulin (CaM) (Polverini et al., 2004), which is a ubiquitous calcium sensor, also localised in noncompact myelin (Mata and Fink, 1988). Current evidence suggests the presence of two CaM binding sites for CaM in MBP (Libich et al., 2003).

Periaxin

Periaxin is a protein of noncompact myelin in the PNS (Gillespie et al., 1994), which has two isoforms generated by alternative mRNA splicing (Dytrych et al., 1998). A number of apparent loss-of-function mutations have been described and linked to both autosomal recessive Dejerine-Sottas neuropathy (Boerkoel et al., 2001) and demyelinating Charcot-Marie-Tooth disease (Guilbot et al., 2001; Kijima et al., 2004; Niemann et al., 2006).

The two human periaxin isoforms, S- and L-periaxin, have in common the first 127 residues, and are 147 and 1461 residues in size, respectively (Boerkoel et al., 2001). The domain common to S- and L-periaxin is predicted to fold into a PDZ domain. PDZ domains are modular protein domains capable of recognising and binding the carboxy termini of their target proteins, which are ofter receptors or channels. The target proteins of periaxin in the myelin sheath have not been identified.

The non-PDZ part of periaxin is only approximately 50 residues in S-periaxin. In L-periaxin, on the other hand, several additional domains are present: a highly basic domain functioning as a nuclear localiastion signal, a long repeat domain, and an acidic domain. The repeat region has homology to the large repeat domain of the giant 700-kDa nucleoprotein AHNAK, also called desmoyokin (not shown). It is unclear whether any of the further domains in periaxin are folded; thus, at the moment, structural studies are focusing on the PDZ domain.

Myelin/oligodendrocyte glycoprotein

The myelin/oligodendrocyte glycoprotein (MOG) is a transmembrane protein present in CNS myelin, and it is also one of the main autoantigens in multiple sclerosis (Iglesias et al., 2001). The crystal structure of the extracellular variable-type Ig domain of MOG has been determined (Clements et al., 2003), as has the structure of its complex with the Fab fragment of a demyelinating MOG-specific antibody, 8-18C5 (Breithaupt et al., 2003). These structures are shown in Fig. 6. The structure of human MOG, however, has not been determined.

Oligodendrocyte/myelin glycoprotein

The oligodendrocyte/myelin glycoprotein (OMgp) is a 120-kDa, 440-amino-acid, glycosylated extracellular molecule, linked to the myelin membrane via a glycosylphosphatidylinositol linkage. It is expressed in myelin of both developing and adult CNS (Vourc'h et al., 2003a). In addition, it is expressed in neurons. In addition to MAG and Nogo, OMgp is also involved in the myelin-related inhibition of axonal regeneration (Vourc'h et al., 2003b).

The structural properties of OMgp have been recently reviewed (Vourc'h and Andres, 2004). The bulk of the OMgp structure is predicted to form of a leucine-rich repeat domain, such as that seen in the Nogo receptor.

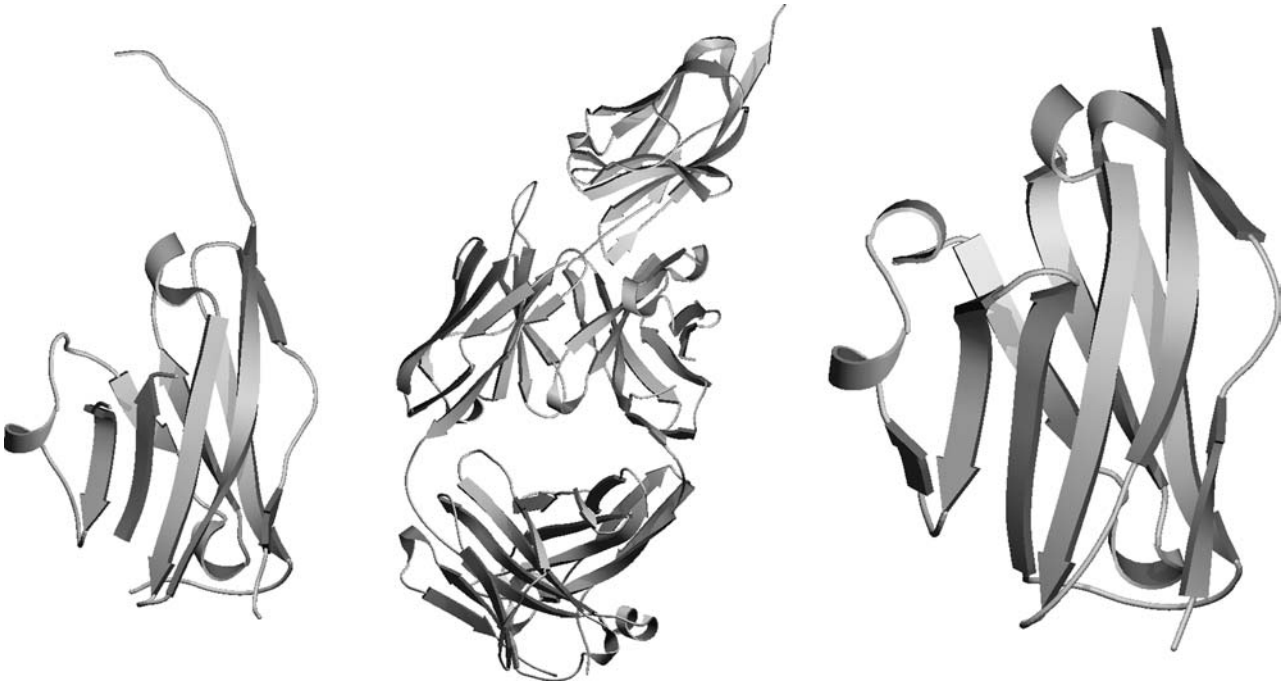

Fig. 6. The crystal structures of the extracellular domain of MOG (Breithaupt et al., 2003; Clements et al., 2003). Shown are the structures of rat MOG alone (left) and complexed with the mouse monoclonal antibody (middle), as well as mouse MOG (right). In the antibody complex, MOG sits on the top in this view

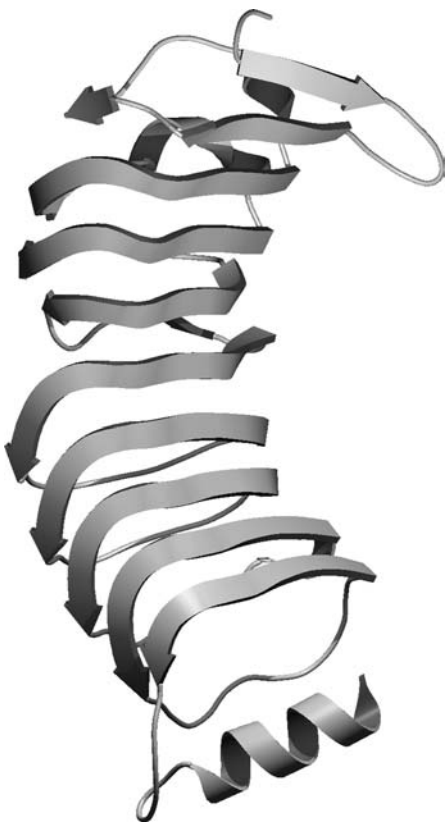

Fig. 7. A model of the leucine-rich repeat domain of OMgp, based on its homology to platelet glycoprotein 1Bα

A molecular model for this domain has also been presented (Vourc'h and Andres, 2004). In Fig. 7, a model based on the homology between OMgp and the N-terminal domain of human platelet receptor glycoprotein 1bα (Varughese et al., 2004) is shown. C-terminal to the leucine-rich repeat, OMgp has a serine/threonine rich domain, and in its N-terminus, it harbors a cysteine-rich domain.

Concluding remarks

Even though thousands of studies have been published on the myelin proteins, their localisation, and their function, relatively little is still known about their accurate 3-dimensional structures and their structure-function relationships. It is clear that further experimental structural studies, for example by X-ray crystallography and complementary methods, should be carried out on the myelin proteins in order to elucidate the molecular mechanisms of myelin formation and maintenance. Many myelin proteins are also implicated in human disease; knowledge of their 3-dimensional structures would greatly facilitate our understanding of myelin-related neurological disease etiology. The author's laboratory is currently actively working to solve 3-dimensional structures of several myelin proteins, domains thereof, and the complexes between myelin proteins and their ligands.

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