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Myelin Biogenesis: Sorting out Protein Trafficking

Myelin biogenesis is a complex process involving coordinated exocytosis, endocytosis, mRNA transport and cytoskeletal dynamics. Recent studies indicate that soluble neuronal signals may control the surface expression of proteolipid protein, a process that involves reduced endocytosis and/or increased transport carrier recruitment from an intracellular pool.

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Myelin is a dynamic, multilamellar membrane which ensheathes axons, providing the structural basis for saltatory nerve conduction which allows for increases in the speed of action potential propagation and dramatic savings in both energy consumption and space requirements; without myelin, neurons would have to have significantly larger diameters to achieve the same conduction speed [1–3]. The myelin sheath also participates in bidirectional communication with both its partner axons and the environment [1–3]. For example, myelin regulates axon diameter and is a key player in ion channel clustering at nodes of Ranvier [4]. Myelin-associated glycoprotein can inhibit neurite outgrowth during axonal regeneration; reciprocally, neurons regulate myelin gene expression, oligodendrocyte survival [1] and, as recently reported by Trajkovic *et al.* [5], myelin proteolipid protein recruitment to the membrane. Loss or damage of myelin results in serious neurological disorders such as multiple sclerosis [1]. Remyelination is limited to a few lamellae, restoration of function is generally poor, and therapies remain suboptimal. The interdependence of myelin and axons takes on increasing importance with recognition of axonal degeneration in demyelinating disease.

Myelin biogenesis is a major part of brain development. As oligodendrocytes enter terminal differentiation, coordinated myelin gene expression is initiated, oligodendrocyte processes interact with axons, and myelin is produced as a specialization of the oligodendrocyte plasma membranes on a remarkable scale of approximately 5–50 x 10^3 μm^2 membrane per cell per day [2,3]. Although myelin-like membranes are synthesized in culture without neuronal contact, *in vivo* the quantity and stability of myelin is strongly enhanced by oligodendrocyte–neuron interactions [2,3]. While myelin has a relatively simple pattern of major proteins, there are myriad quantitatively, though certainly not functionally, 'minor' proteins [6], some of which have been implicated in demyelinating diseases [7]. Further, myelin has multiple domains: myelin basic protein and proteolipid protein are found abundantly in compact internodal myelin; oligodendrocyte specific protein is localized to junctions that spiral through the myelin sheath; neurofascin-155 is concentrated at paranodes; and myelin-associated glycoprotein and myelin oligodendrocyte protein are concentrated in periaxonal and outer lamellae, respectively [2,4].

This asymmetric distribution of proteins provides myelin with the potential for functional diversity and compartmentalization of activity. However, with the long distances myelin membrane components may need to travel along oligodendrocyte processes to reach their target membranes, this also imposes additional burdens on the biosynthetic and trafficking mechanisms. One would therefore expect that molecules that regulate and coordinate the trafficking and recruitment of transport carriers to the plasma membrane and cytoskeletal dynamics would be essential for oligodendrocyte differentiation and myelin biogenesis. For example, mRNA molecules encoding myelin basic protein are transported to compact myelin in granules that contain specific components of the translation and transport machineries [2]. Exocytic transport regulators, such as Rab3a, the exocyst components Sec8 and Sec6, and the exocyst regulator RalA, are expressed at high levels in myelin; Rab3a and the v-SNARE synaptobrevin-2 are up-regulated during maturation of oligodendrocytes; and Sec8 is central for oligodendrocyte process growth and arborization [2,8,9]. A recent genetic screen in zebrafish [10] showed that N-ethylmaleimide sensitive factor, a protein critical for membrane fusion, is required for correct expression of myelin basic protein and formation of nodes of Ranvier.

Current hypotheses suggest that recycling endosomes play central roles in protein sorting and trafficking, both during plasma membrane recycling and as an intermediate step during cargo transport from the trans-Golgi network to the plasma membrane [11] (Figure 1). Trajkovic *et al.* [5] investigated how axonal signals might control myelin biogenesis,

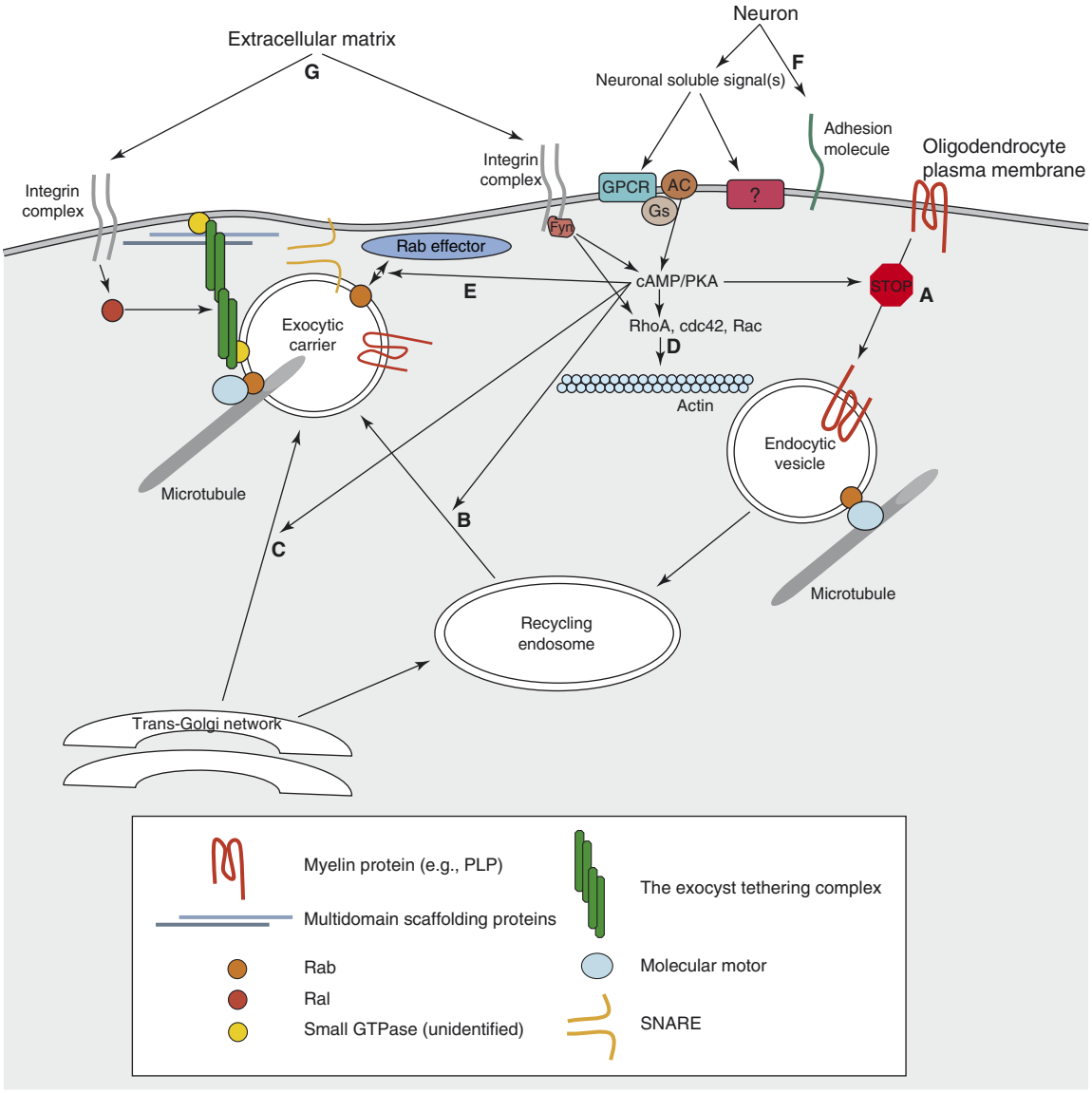

Figure 1. A model for the regulation of myelin protein trafficking.

Soluble signals derived from neurons activate receptors on the surface of oligodendrocytes, such as G-protein-coupled receptors (GPCR) which activate adenylate cyclase (AC), stimulating cAMP synthesis and leading to PKA activation. The activation of intracellular signaling pathways, such as cAMP/PKA: (A) decreases membrane recycling; (B,C) enhances vesicle recruitment from (B) recycling endosomes and/or (C) the exocytic compartment; (D) modulates cytoskeleton dynamics via Rho GTPases; and/or (E) augments vesicle docking, for example via Rab activation. (F) Neurons may also signal via surface adhesion molecules. (G) Integrins on the oligodendrocyte membrane modulate cytoskeleton dynamics via Rho GTPases, and the recruitment of trafficking carriers to the membrane via transport regulators, such as Rab, Ral and the exocyst.

obtaining results that suggest that late endosomes/lysosomes may contribute to this process. For this, they used first primary oligodendrocytes, and then, more extensively, two cell lines with some of the characteristics of oligodendrocytes. They concentrated on the major myelin protein proteolipid protein, the biosynthesis and transport of which coincide with the induction of myelination [12]. It is noteworthy that perturbations in the transport and or degradation pathways for protein proteolipid are associated with major myelin pathologies [1].

Taking advantage of the fact that, in one of the cell lines (Oli-neu), proteolipid protein is normally detected at minimal levels on the plasma membrane, Trajkovic *et al.* [5] showed that the amount of proteolipid protein on the cell surface increased in the presence of neurons or neuron-conditioned medium. This could in principle be due to reduced proteolipid protein endocytosis and/or increased proteolipid protein trafficking to the cell surface. Using another cell line (OLN-93) that does express proteolipid protein on the surface, they showed that neuronal signals reduced the internalization of surface proteolipid protein in a clathrin-independent process that involved the actin cytoskeleton and RhoA,