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G protein-coupled Receptors in Myelinating Glia

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Abstract

The G protein-coupled receptor (GPCR) super-family represents the largest class of functionally selective drug targets for disease modulation and therapy. GPCRs have been studied in great detail in central nervous system (CNS) neurons, yet these important molecules have been relatively understudied in glia. In recent years, however, exciting new roles for GPCRs in glial cell biology have emerged. Here, we focus on key roles for GPCRs in a specialized subset of glia, myelinating glia. We highlight recent work firmly establishing GPCRs as regulators of myelinating glial cell development and myelin repair. These advancements expand our understanding of myelinating glial cell biology and underscore the utility of targeting GPCRs to promote myelin repair in human disease.

Keywords

G protein-coupled receptor (GPCR); myelination; Schwann cell; oligodendrocyte; remyelination

An overview of G protein-coupled receptors in the nervous system

The G protein-coupled receptor (GPCR) super-family of seven transmembrane (7TM) receptors comprises the largest class of cell membrane receptors [1]. GPCRs are activated by myriad stimuli including peptides, hormones, light, proteolytic processing of their N-termini, small molecules, and more traditional protein ligands [2,3]. GPCRs have emerged as major pharmacological drug targets due to their key roles in a variety of physiological functions in disease and health, and GPCR modulators represent at least one-third of all clinically marketed drugs [4]. GPCRs can be classified into five families using the phylogenetically based GRAFS system: glutamate, rhodopsin, adhesion, frizzled, and secretin [5]. Glutamate is a major excitatory neurotransmitter in the nervous system, and

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Conflict of interest statement

The authors declare no competing conflicts.

accordingly, glutamate receptors have been studied in great detail with regard to their key roles in synaptic transmission, synapse formation, axon guidance, and development of neuronal circuits [6,7]. The rhodopsin family has by far the greatest number of GPCRs, and members are involved in photoreception and neurotransmission [5]. Frizzled GPCRs are activated by wingless/int (Wnt) proteins and control numerous cellular processes including neural crest development, patterning and adult neurogenesis [8]. Secretin receptors are classic hormone receptors, some of which have neuroprotective functions in the central nervous system (CNS) [9]. Finally, adhesion GPCRs represent the second largest GPCR family, with 33 human orthologs. Adhesion GPCRs play key developmental roles in many tissues, and recent work has highlighted their roles in nervous system development and disease [10,11].

Despite their roles in various nervous system functions, there is a relative paucity of knowledge regarding GPCRs in myelinating glia. Myelin is the multilayered membrane formed by the spiral wrapping of specialized glial cells around axons in the vertebrate nervous system; myelin insulates axons and allows for the rapid propagation of action potentials, and myelinating glia also provide trophic support to neurons. Schwann cells form myelin in the peripheral nervous system (PNS), while oligodendrocytes are responsible for forming myelin in the CNS. The importance of myelin in normal nervous system function is perhaps best underscored by the fact that myelin loss and inefficient remyelination cause devastating symptoms in many diseases including Charcot-Marie-Tooth disease in the PNS and multiple sclerosis (MS) in the CNS. Recent studies investigating GPCR function in myelinating glial cell development, myelination, and myelin repair have uncovered new therapeutic targets for myelin-related diseases. In this review, we discuss our current understanding of key roles played by GPCRs in PNS and CNS myelinating glia.

GPCRs in Schwann cell development and myelination

Schwann cell development

Schwann cells, which myelinate axons in the PNS, originate from a subset of neural crest progenitor cells during development. At early stages, proliferative Schwann cell precursors migrate along growing axons; once migration ceases, immature Schwann cells remain proliferative and are arranged around bundles of axons. In a process called radial sorting, immature Schwann cells interdigitate cytoplasmic projections into axon bundles. Following radial sorting, axon segments to be myelinated are associated with a single promyelinating Schwann cell. Promyelinating Schwann cells terminally differentiate into myelinating Schwann cells by spiraling their membrane around the axon segment many times, ultimately generating the myelin sheath (Figure 1) [12,13].

To date, roles for three different GPCRs have been described in Schwann cells: Gpr126/Adgrg6 (also previously called VIGR [Vascular-inducible GPCR] and DREG [Developmentally regulated GPCR]), Gpr44 (also called Prostaglandin D2 receptor 2), and LPA1 (Lysophosphatidic acid receptor 1, also called Vzr [Ventricular zone gene]-1 and Edg [Endothelial differentiation gene]-2). Gpr126/Adgrg6 belongs to the adhesion GPCR family, while Gpr44 and LPA1 are rhodopsin family members.

Gpr126/Adgrg6 in Schwann cell development and myelination

As an adhesion GPCR, Gpr126/Adgrg6 is characterized by an extremely long N-terminus that contains the GPCR autoproteolysis-inducing (GAIN) domain, which encompasses the highly conserved GPCR proteolytic site (GPS). Many adhesion GPCRs undergo autoproteolysis at the GPS motif, resulting in a protein that is separated into an N-terminal fragment (NTF) and a C-terminal fragment (CTF) [10,14]. Gpr126/Adgrg6 was discovered to be essential for Schwann cell myelination by a forward genetic screen in zebrafish [15,16], and subsequent work has firmly demonstrated that the CTF of Gpr126/Adgrg6 couples to Gs proteins, elevates 3', 5'-cyclic adenosine monophosphate (cAMP) levels, activates protein kinase A (PKA), and initiates transcription of key regulators (*e.g.*, Oct6/Pou3f1) of terminal Schwann cell differentiation in zebrafish as well as mammals [16-22]. In mammals, *Gpr126* mutants also present with limb contracture defects [17]; importantly, human mutations in *GPR126/ADGRG6* as well as *Adenylate cyclase gene 6 (ADCY6*, which encodes a cAMP-synthesizing protein) cause limb and myelination defects, highlighting the conserved and critical function of this pathway in the human PNS [23,24].

What activates Gpr126/Adgrg6 to elevate cAMP? Recent work has demonstrated that receptor autocleavage generates a cryptic tethered agonist ligand termed the *Stachel* sequence [20]. *Stachel*-mediated activation of the Gpr126/Adgrg6 CTF potently elevates cAMP, and mutational analysis in zebrafish suggested that signaling via the *Stachel* sequence is both necessary and sufficient for myelination *in vivo* [20]. However, the *Stachel* sequence is predicted to be deeply buried within the GAIN domain of Gpr126/Adgrg6, and it is unclear how this agonist might be exposed to the CTF [14]. In the case of Schwann cells, it is likely that interactions between Gpr126/Adgrg6 and extracellular matrix (ECM) proteins modulate the NTF such that the *Stachel* sequence can activate the CTF. To date, two Schwann cell-derived ECM binding partners have been defined for the N-terminus of Gpr126/Adgrg6: collagen IV and laminin-211 [21,22]. An emerging concept is that ECM proteins mechanically modulate signaling properties of adhesion GPCRs [11,22,25], and in the future it will be interesting to understand how different ECM signals converge to control Gpr126/Adgrg6 signaling. In humans, mutations in *LAMA2*, encoding the $\alpha 2$ chain of Laminin-211, cause merosin-deficient congenital muscular dystrophy (MDC1A) with dysmyelination [26-28], suggesting that modulation of GPR126/ADGRG6 might be efficacious in these patients. Intriguingly, a third binding partner for Gpr126/Adgrg6 in Schwann cells has also been described: axonally-derived Prion protein (PrP^c) [29]. Whereas infectious prions consist of a misfolded form of a normal protein called PrP^c, the natural functions of PrP^c are not fully understood. Previously, loss of PrP^c in neurons was shown to non-cell-autonomously cause a demyelinating neuropathy in aged mice [30]. Recent work demonstrates that PrP^c binds Gpr126/Adgrg6 and elevates cAMP in Schwann cells and suggests that this signaling axis may be required for long-term axon-Schwann cell interactions. Whether PrP^c plays a role in early Schwann cell development (*e.g.*, radial sorting) and whether collagen IV and laminin-211 signaling via Gpr126/Adgrg6 are required for maintenance in the PNS remain to be determined.

All known Gpr126/Adgrg6 binding partners modulate cAMP levels, but this adhesion GPCR may also have cAMP-independent functions in Schwann cells. First, genetic analysis of an

allelic series of zebrafish mutants suggests that the NTF of Gpr126/Adgrg6 can drive radial sorting independently of the CTF [22]. Second, Gpr126/Adgrg6 can couple to G_i proteins as well as G_s proteins [19,20], and the $\beta\gamma$ -dimers of G_i-coupled GPCRs are known to activate Rac1 via PI3K [31]. Given that radial sorting defects and aberrant cytoplasmic protrusions are shared phenotypes between *Rac1* and *Gpr126/Adgrg6* mutant Schwann cells [19,32], this may be a fruitful area of future research. Additionally, low levels of cAMP promote proliferation of Schwann cells, while high levels of cAMP promote Schwann cell differentiation [33]. Together, by interacting with both G_i- and G_s-proteins and by integrating signals from other essential pathways, Gpr126/Adgrg6 could precisely regulate the concentration of cAMP required for a given stage of Schwann cell development.

GPCRs in Schwann cells that relay signals from axons

While Gpr126/Adgrg6 can be activated in autocrine (collagen IV, laminin-211) and paracrine (PrP^c) fashions, other GPCRs in Schwann cells are thought to be activated solely by axonal ligands. One of the best known axonal molecules essential for Schwann cell development is Neuregulin 1 (NRG1) type III [34,35]. Axonal NRG1 type III is cleaved extracellularly, and in the PNS, one consequence of this cleavage event is induction of prostaglandin D2 synthase (PGDS), which then catalyzes production of the hormone prostaglandin D2 (PGD2) [36]. PGD2 is a known ligand for the GPCR Gpr44, previously reported to be involved in cell-cell interactions during inflammatory responses [37,38]. Recently, this PGD2-Gpr44 signaling axis was demonstrated to play a key role in Schwann cell development: neuronal L-PGDS is secreted, which catalyzes the production of PGD2. PGD2 then binds to Gpr44 on Schwann cells, and Gpr44 activation dephosphorylates the transcription factor NFATc4 [36]. Dephosphorylation of NFATc4 allows for nuclear translocation and transcription of genes that promote Schwann cell differentiation [39]. Loss of *Gpr44* or of PGDS enzymatic activity causes hypomyelination in mouse models. Furthermore, genetic and pharmacologic inhibition of PGDS leads to myelin maintenance disruptions, suggesting that PGD2/Gpr44 signaling is also important in the mature PNS [36].

As noted above, LPA1 is another GPCR present on Schwann cells; this molecule, like Gpr44, is thought to receive axonal signals that regulate Schwann cell development. The LPA1 ligand, lysophosphatidic acid (LPA), is produced by neurons and is a potent survival and migration factor for Schwann cells in culture [40,41]. Analysis of *Lpa1* knockout mice demonstrate that this receptor is required for Schwann cell survival, radial sorting, and proper myelination *in vivo* [40,41]. The role of axon-Schwann cell GPCR signaling in controlling radial sorting also likely extends to other players, given that neuronally-derived Wnt and Respondins may also signal via Lgr receptors and Lrp/Frizzled receptor complexes on Schwann cells [42]. The identity of additional GPCRs that function in Schwann cell development as well as analysis of GPCRs in PNS repair and remyelination remain to be determined.

GPCRs in oligodendrocyte development and myelination

Oligodendrocyte development

There are similarities and important differences in the development of myelinating glia in the peripheral vs. central nervous systems. In the CNS as in the PNS, oligodendrocyte development is a multistep process characterized by expression of distinct molecular markers and dramatic changes in cell morphology (Figure 2). Oligodendrocyte precursor cells (OPCs) migrate remarkable distances to populate the entire CNS. Recent work shows that OPC migration can occur along blood vessels and is coordinated by morphogens and ECM proteins [43–45]. Once migration ceases, a subset of OPCs transition into pre-myelinating oligodendrocytes, which extend numerous processes and ensheath multiple axon segments. Pre-myelinating oligodendrocytes then terminally differentiate and iteratively wrap their associated axonal segments to generate the myelin sheath [46,47]. While the molecular mechanisms that govern CNS myelin development are not completely understood, recent advances implicate several GPCRs as regulators of proliferation, migration, and maturation during oligodendrocyte development.

Wnt and chemokine receptors during early OPC development

OPC proliferation and migration are energy-taxing processes requiring vascular access for sufficient oxygenation [48]. A recent live-imaging study of cortical slices from embryonic mice revealed that OPCs migrate along vascular scaffolds, and faulty endothelium-OPC interactions lead to abnormal OPC clustering around the blood vessels as well as halting OPC differentiation [43]. Interestingly, frizzled and chemokine GPCRs have been implicated in these early stages of oligodendrocyte development.

Frizzled GPCR receptors are activated by Wnt ligands, leading to signaling via canonical or noncanonical downstream pathways. In the canonical Wnt pathway, β -catenin translocates to the nucleus and facilitates activation of TCF/LEF transcription factor target genes. In zebrafish, knockdown of a Frizzled 8 (Fzd8) ortholog or pharmacologic activation of the canonical Wnt pathway block oligodendrocyte maturation [49]. Similarly, in mouse, OPC-specific genetic activation of canonical Wnt signaling is inhibitory to OPC maturation and leads to aberrant aggregates of these cells along the blood vessels, indicating that the Wnt pathway is crucial for timely OPC differentiation and proper OPC-vasculature interactions [43,50]. Whether these functions are mediated by the canonical Wnt effector Tcf712 (Tcf4) may vary by CNS region and developmental stage [51,52]. Future studies can investigate whether OPC-vasculature interactions are mediated via Tcf712 and if Fz8 or a different frizzled GPCR plays a role in Wnt-mediated signaling in oligodendrocytes.

What mechanisms might mediate OPC-vasculature interactions? Transcriptomic profiling revealed that the chemokine GPCR Cxcr4 is highly enriched in Wnt-activated OPCs [43]. The secreted chemokine Cxcl12 (also known as Sdf-1) is the only known ligand for the chemokine receptor Cxcr4. Cxcl12 is expressed by vascular endothelial cells during OPC migration, and pharmacologic inhibition of Cxcl12 signaling disrupts OPC-vascular interactions [43], consistent with previous studies implicating Cxcr4 in OPC migration [53,54] and underscoring a crucial role for the Cxcr4/Cxcl12 signaling axis in early OPC

development. Cxcr4 couples to $G\alpha_i$ proteins following activation by Cxcl12 [55]. Cxcl12, however, does not solely bind to Cxcr4: this chemokine ligand can also activate the GPCR Gpr17 [56], another key regulator of oligodendrocyte development.

Gpr17 and Gpr37 in oligodendrocyte differentiation

Gpr17 is a rhodopsin family GPCR enriched in cells of the oligodendrocyte lineage [57]. *Gpr17* is expressed in OPCs, abundant in pre-myelinating oligodendrocytes, and is not detectable in mature oligodendrocytes [57,58]. Genetic analyses in mouse demonstrate that loss of Gpr17 leads to precocious oligodendrocyte maturation, while overexpression inhibits oligodendrocyte development and myelination [57]. Although the *in vivo* endogenous binding partner(s) for Gpr17 in oligodendrocyte development are not known, this GPCR can bind uracil nucleotides, cysteinyl leukotrienes, and oxysterols [59,60], and work *in vitro* with small molecule agonists suggests that Gpr17 can signal through $G\alpha_{i/o}$, G_s , and G_q proteins [61,62]. *In vitro*, $G\alpha_{i/o}$ protein signaling inhibits adenylyl cyclase signaling and subsequent OPC differentiation [62], consistent with previous reports implicating cAMP in the promotion of oligodendrocyte development [63]. In the future, it will be interesting to determine if Gpr17 function *in vivo* is dependent on Cxcl12 as a ligand, either directly or via Gpr17/Cxcr4 heterodimers [56].

In addition to Gpr17, another rhodopsin family GPCR, Gpr37, has also been recently described as a key regulator of oligodendrocyte development [64], though there are key differences between these two GPCRs in CNS myelination. In contrast to Gpr17, Gpr37 expression in the oligodendrocyte lineage begins later, at the pre-myelinating oligodendrocyte stage, and Gpr37 levels are maintained in mature oligodendrocytes. Additionally, loss of *Gpr37*, but not *Gpr17*, causes hypermyelination throughout development and adult stages. While Gpr17 and Gpr37 act at different stages, importantly, both GPCRs negatively regulate oligodendrocyte development: as in *Gpr17* mutants, loss of *Gpr37* leads to precocious oligodendrocyte differentiation [59]. Moreover, Gpr37, like Gpr17, can couple to $G\alpha_{i/o}$ proteins [65], cAMP levels are accordingly elevated in *Gpr37*^{-/-} brains and cultured oligodendrocytes, and pharmacological experiments implicate increased Epac/Raf/ERK signaling downstream of cAMP when Gpr37 function is lost [59]. Although prosapinin has been identified as a ligand for Gpr37 [65], this glycoprotein may not function in Gpr37-mediated oligodendrocyte development [64]. Thus, identification of binding partner(s) for Gpr37 in oligodendrocyte lineage cells is an important area of future research.

Adhesion GPCRs in oligodendrocyte development

Like Gpr17 and Gpr37, the adhesion GPCR Gpr56/Adgrg1 is a third inhibitory GPCR important for oligodendrocyte development. Gpr56/Adgrg1 belongs to the same adhesion GPCR subfamily as Gpr126/Adgrg6 [10]. In the CNS, *Gpr56/Adgrg1* is expressed in several cell types including OPCs, where this adhesion GPCR functions cell autonomously as an evolutionarily conserved regulator of OPC proliferation and differentiation [66,67]. In zebrafish and mouse *Gpr56/Adgrg1* loss-of-function mutants, OPCs precociously differentiate before the full cohort of these cells are established such that hypomyelination is observed in later development. That human patients with *GPR56/ADGRG1* mutations

present with white matter defects underscores the clinical importance of this adhesion GPCR in CNS myelination [68]. Gpr56-dependent OPC proliferation is mediated by $G\alpha_{12/13}$ -RhoA signaling [66,67], although the activating ligand for Gpr56/Adgrg1 in OPCs is currently unknown. In other cellular contexts, Gpr56/Adgrg1 can bind the ECM proteins tissue transglutaminase (TG2) and collagen III [69,70], and in the future it will be interesting to determine if either of these molecules activates Gpr56/Adgrg1 in OPCs. Moreover, Gpr56/Adgrg1, like Gpr126/Adgrg6, possesses an agonistic *Stachel*-sequence [71], and the receptor may also be mechanically activated [11]; future work can determine if these interesting adhesion GPCR mechanisms are at play for Gpr56/Adgrg1 function in OPCs.

At later stages of development, the adhesion GPCR Gpr98/Adgrv1 (also previously called Very large GPCR-1 [Vlgr1]) is enriched in myelinating oligodendrocytes [72]. In cultured oligodendrocytes, loss of Gpr98/Adgrv1 decreases while overexpression of Gpr98/Adgrv1 increases levels of Myelin-associated glycoprotein (MAG), and MAG levels are also decreased in the CNS of *Gpr98/Adgrv1* mutant mice [72]. These functions are thought to be mediated by Gpr98/Adgrv1's $G\alpha_s$ and $G\alpha_q$ G protein coupling abilities in response to extracellular calcium [72]. In all, recent work has firmly established several GPCRs as key regulators of oligodendrocyte development and CNS myelination.

GPCRs and activity-dependent myelination

While the aforementioned GPCRs mediate cell-cell and cell-matrix interactions during myelinating glial cell development, it is important to note that glial cell development and myelination can also be modulated by neuronal activity via neurotransmitters, including glutamate [reviewed in [73,74]]. While much attention has been paid to ionotropic AMPA and NMDA glutamate receptors [75,76], metabotropic glutamate (mGlu, *e.g.*, GPCRs) receptors are also expressed in oligodendrocyte lineage cells [77,78], and activation of mGlu4 accelerates OPC differentiation *in vitro* [78]. How else might mGlu receptors directly regulate oligodendrocyte development, myelination, and myelin plasticity and how do metabotropic and ionotropic glutamate receptors interact in these processes? This is an important area of future research given that understanding mechanisms mediating myelin plasticity are likely to be key for stimulating myelin repair in the mature CNS.

Pharmacological implications of GPCRs in myelin diseases

GPCRs are excellent therapeutic targets [4] and are therefore attractive for drug development to stimulate remyelination after injury and in myelin disorders. For example, GPR126/ADGRG6 could be targeted in the PNS, perhaps by a modified *Stachel*-sequence peptide [20], to promote myelination in MDC1A, as these patients lack functional laminin-211 ligand but should possess GPR126/ADGRG6 in Schwann cells. In the CNS, Gpr17 has been explored as a potential therapeutic target in remyelination either by inhibiting Gpr17 via antagonists or by activating the reserve pool of Gpr17-expressing OPCs to maturation [79,80]. As *Gpr17* is enriched in white matter plaques of MS patients and in rodent models of MS, antagonism of Gpr17 or other inhibitory GPCRs may indeed be efficacious in future treatment strategies [57,64,66,67]. Additional GPCRs have been implicated in CNS myelin repair including Cxcr4, Gpr30, endothelin receptors, and sphingosine 1-phosphate receptors

[81-85], underscoring the importance of this receptor super-family in myelin health and disease.

Excitingly, high-throughput *in vitro* screens for small molecules and compounds that promote myelination have uncovered several molecular targets of GPCRs, some which have been further validated *in vivo* [86-90]. For example, starting with a chemical screen for compounds that affect oligodendrocyte differentiation, the Chan lab identified κ -opioid receptor (KOR) agonists as promoters and KOR antagonists as inhibitors of oligodendrocyte differentiation [90]. Accordingly, genetic deletion of *KOR* delays developmental myelination *in vivo* [90], and pharmacologic activation of this GPCR accelerates repair following demyelination in several rodent models [89,90]. Future work elucidating the molecular mechanisms by which GPCRs control developmental myelination and remyelination in both the CNS and PNS will provide invaluable resources for identifying new therapeutic targets in injury and disease.

Concluding Remarks

Myelin disruptions can lead to permanent neuron loss, significant pain, morbidity, and ultimately paralysis. Currently, no treatments exist to prevent demyelination or to enhance remyelination, partly because of our incomplete understanding of the genetic and molecular details of myelination. GPCRs are emerging as key regulators of myelinating glial cell development and myelin repair, yet many discoveries remain to be made (See Outstanding Questions Box). To date, functions for only a handful of GPCRs in Schwann cells and oligodendrocytes have been described. In addition to obvious questions regarding ligand discovery for the known receptors and uncovering other GPCRs present in myelinating glia, understanding how glial GPCRs interact – at the level of receptor multimerization at the cell surface as well as downstream signaling cross-talk and integration – is of fundamental importance. In the future, it will also be very interesting to explore “non-traditional” modes of GPCR function in myelinating glia, including endosomal receptor signaling and biased agonism. Moreover, given the unparalleled pharmacologic potential of targeting GPCRs, understanding the mechanisms mediated by these receptors that underlie glial cell development and remyelination at the cellular and molecular levels has a therapeutic potential to enhance myelin repair and functional recovery in patients.

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Outstanding Questions

- Multiple GPCRs are expressed in the same cell types; what GPCRs are present in myelinating glial cells throughout development and adulthood and what crosstalk might exist between receptors?
- To date, most studies of GPCRs in myelinating glia have focused on traditional ligand-mediated G protein signaling and downstream effectors. What role might other facets of GPCR signaling, including β -arrestins, G protein $\beta\gamma$ complexes, and endosomal-bound GPCRs, play in Schwann cell and oligodendrocyte development?
- Can multiple GPCRs be activated by the same ligand? Conversely, are there distinct ligands that modulate individual GPCR signaling at different stages of glial cell development or remyelination?
- What is the best way forward to translate discoveries of GPCR function in myelin repair to new therapies in the clinic?

Trends box

- G protein-coupled receptors (GPCRs) represent the largest class of therapeutic drug targets.
- GPCRs have essential and diverse functions in the nervous system, yet have only recently been implicated in myelinating glial cell biology.
- GPCRs, their ligands, and downstream signaling effectors are emerging as key regulators of myelination both the peripheral and central nervous systems.
- Insights from GPCR biology in myelinating glia can define new therapeutic targets to promote remyelination in disease and after injury.

Figure 1. GPCRs in Schwann cells (SCs). From left to right, neural crest-derived SC precursors (SCPs) migrate along growing axons. Immature SCs surround axons and perform radial sorting by inserting processes into axon bundles. After sorting a single axon segment, promyelinating SCs iteratively wrap around the axons to make myelin, and myelin must be maintained throughout the life of an organism. GPCRs known to regulate given stages of development are shown. Insets show putative localization of GPCRs and ligands (if known) at a given developmental stage. Neurons and axons are blue, and SCs are orange.

Figure 2.

GPCRs in oligodendrocytes (OLs). From left to right, neural precursor-derived OL precursor cells (OPCs) proliferate and migrate throughout the developing CNS. OPCs then transition into pre-myelinating OLs, which extend exploratory cytoplasmic processes towards axons. Following terminal differentiation, mature OLs wrap around and myelinate multiple axonal segments. These myelin sheaths can be damaged in disease or injury, and remyelination may occur if OPCs are stimulated to remyelinate. Insets show putative localization of GPCRs and ligands (if known) at a given stage. Axons are blue, and OLs are orange. Cross-section cartoons are adapted from [93].

Table
GPCRS in myelinating glia and known binding partners

GPCR	Family (GRAFS classification system)	Endogenous ligand(s) for myelinating glia	Endogenous ligand(s) in other physiological contexts	Citation(s)
Schwann cell development				
Gpr126/ Adgrg6	Adhesion	collagen IV		(21)
		laminin-211		(22)
		Prion protein Prp ^C		(29)
Gpr44/ Ptgdr2	Rhodopsin	Prostaglandin D2		(36)
LPA1	Rhodopsin	Lysophosphatidic acid	Oleoyl phosphate derivatives	(40,41,91)
Oligodendrocyte Development				
Cxcr4	Rhodopsin	C-X-C chemokine 12/ Stromal cell-derived factor 1		(55)
Gpr17	Rhodopsin	unknown	Cxcl12/Sdf1	(56)
			Cysteinyl-leukotrienes	(59)
			Uracil nucleotides	
			Oxysterols	(60)
Gpr37	Rhodopsin	unknown		
Gpr56/ Adgrgl	Adhesion	unknown	Tissue transglutaminase 2	(69)
			Collagen III	(70)
Gpr98/ Adgrv1/Vlgr1	Adhesion	unknown		
mGlu4	Glutamate	presumably Glutamate		(76)
Gpr30	Rhodopsin	unknown	Estrogen	(82)
Endothelin Receptor type B	Rhodopsin	Endothelin		(83)
Sphingosine 1-phosphate receptors	Rhodopsin	unknown	Sphingosine-1-phosphate	(92)
K-opioid receptor	Rhodopsin	Dynorphin B		(90)