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Visions & Reflections

Exploring oligodendrocyte guidance: 'to boldly go where no cell has gone before'

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Abstract. Oligodendrocytes, the myelinating cells of the central nervous system (CNS), originate early in the formation of the brain in specific foci, and migrate throughout the parenchyma. The instructional cues guiding the migration of these progenitor cells must be encoded into their developing environment. Soluble factors as well as membrane-bound cues most likely synergize to create a complex thoroughfare needed to sculpt and organize the brain into a functional organ with white and gray matter. Classically, the focus of many guidance related studies in the CNS has been limited to neuron physiology. However, It is becoming increasingly clear that their lifelong partners, oligodendrocytes, express both ligands and receptors able to both present and respond to these classical cues. In this short review, some recent findings in the Semaphorin and Eph fields will be presented with respect to oligodendrocyte expression and function.

Key words. Oligodendrocyte; Semaphorin; Neuropilin; Eph; ephrin; guidance.

Introduction

Oligodendrocytes (OLs), are neural tube-derived cells that have the potential to form myelin, a compact lamellar wrapping found on relatively large fiber axons, thus facilitating nerve conduction. The myelin degenerates, and OLs die during the human neurological autoimmune disease Multiple Sclerosis (MS), leaving uninsulated axonal segments that functionally short circuit. The result of this demyelination is reflected in the disease etiology of MS, whereby patients have, at the very least, unsteady gait and muscle weakness. Generally, the mature OL can be identified by its immunoreactivity to the monoclonal antibodies O4 (sulfatide/seminolipid), and O1, which recognizes galactocerebroside (fig. 1) [1, 2]. *In vivo*, this stage broadly represents the point where myelination can occur. The mature OL is derived from a transient Pro-OL, which appears as an O4 immunoreactive cell [1], while OL progenitors can be distinguished via single immunostaining with A2B5, a monoclonal antibody recognizing tetrasialogangliosides [3]. From their neural tube origins to their myelinating roles, OLs are influenced in a variety of ways by both soluble and membrane-bound signals. Some signals will regulate their cell division, or differentiation, while others will help govern their dispersal within the brain parenchyma to the presumptive white matter. These latter signals, also known as guidance cues, are simply messages imparted to a cell by the surrounding environment to help designate migratory choices. Autocrine cues may also exist. These cues can be soluble, matrix bound or displayed on the cell surface, and may exist in gradients. These signals may not themselves be chemotactic and cause migration, but direct the movement of growth cones of stationary or migrating cells.

Understanding the guidance cues that regulate oligodendrocyte function through their developmental program involves understanding the milieu into which they originate, divide, migrate and finally myelinate. These same

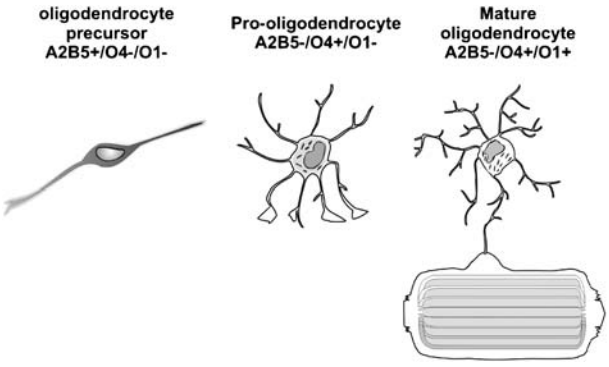

Figure 1: Developmental progression of cultured rat brain oligodendrocytes.Oligodendrocyte progenitors (left) can be identified using A2B5 monoclonal antibody and should appear bipolar. Pro-oligodendrocytes (center) similarly loose A2B5 immunoreactivity and adopt O4 reactivity. Mature oligodendrocytes (right) sustain expression of O4, while now adopting expression of galactocerebroside, as recognized by O1 monoclonal antibody.

guidance cues that map out the pathways progenitor cells use are most likely the same that inhibit remyelination when improperly expressed during neurological disease [4]. Signals that regulate (re)myelination will not be discussed here. However, it is important to note that those same signals may also have co-incidental effects on the development and migration of oligodendrocytes [5, 6].

Exploring the signals that regulate oligodendrocyte biology, insight into their genomics – more specifically, a time-resolved analysis of their gene expression patterns from their neural stem cell origins, to lineage-specified progenitors, to the committed but immature pro-oligodendrocyte and finally to the terminally differentiated myelinating phenotype – will begin to reveal answers of how oligodendrocytes 'get there from here'. The changing genomics of the other elements of the brain, such as radial glia, pre-existing and co-developing neurons, astrocytes, microglia and even vasculature, should also be considered when trying to understand the regional development and migration of oligodendrocyte progenitors. This review will summarize some of the findings in the field of oligodendrocyte guidance cues, focusing on the Semaphorin/Neuropilin [7–15] and Eph/ephrin [16–21] families, which have been classically associated with neuron-related guidance. Since this field is in its infancy, with no oligodendrocyte-specific knockout or overexpression animal models to address the roles of these gene families *in vivo*, culture or explant-based systems have been used. The interpretation of these results may be simplified, and should be taken with caution, as there are most likely several redundant systems co-functioning simultaneously *in vivo*. Other important cues, such as in the Nogo/Nogo receptor family will not be mentioned, as they are discussed at length in several recent reviews [22–30].

Semaphorin-neuropilin-plexin superfamily

The Semaphorins are a family of secreted, transmembrane or membrane associated ligands, which in vertebrates span through several classes named 3–7 [7–15, 31–34]. Class 3 ligands are secreted, 4–6 are membrane spanning, while class 7 are glycerophosphatidyl myo-inositol (GPI) linked (fig. 2, adapted from [34]). Classically, the Sema 3 class ligands associate with their two cognate receptors, the Neuropilins [35, 36], while others from classes 4–7 are thought to interact with Plexins [9, 12, 15, 31, 37]. It is important to note that although signaling through these partners is somewhat defined, multiple pathways is affected, and it is difficult to tease out the involvement of a single pathway. Therefore, much is needed to understand the biological relevance of these systems in neurons as compared to oligodendrocytes, which serve particularly different purposes *in vivo* (fig. 2).

We originally detected the presence of Semaphorins and Neuropilins in oligodendroglia using a shotgun microarray approach followed by confirmatory methodologies [38]. Using cytometry-sorted acutely isolated total rat brainstem oligodendrocytes, and highly purified cultures, we observed a broad spectrum of expression of Semaphorin ligands from classes 3–7, and specific isoforms of the 2 Neuropilin receptors. Further, we demonstrated that solid-phase immobilized recombinant Sema 3 class ligands [35, 36], presumably binding through the two Neuropilin receptors, inhibited the process outgrowth of oligodendrocyte progenitors. Earlier, Ricard and colleagues [39, 40] also observed similar results with soluble Sema 3A, and further characterized the expression of several collapsing response mediator proteins (CRMPs) known to be mediators of Semaphorin signaling, in oligodendroglia. Recently, Spassky and co-workers found similar results with respect to the inhibitory role of Sema 3A using an elegant explant-based system derived from a transgenic mouse embryonic optic nerve. Likewise, they observed that oligodendrocyte progenitors expressed both Neuropilin-1 and -2 [41]. In contrast, their results with Sema 3F suggested a trophic effect, while 3C and 3E had no observable effect on the migration of mouse OLPs. The differences in our results may arise from origin of the tissue, brain versus optic nerve, species differences or even isolated cells versus a less well defined explant-based culture system. The important aggregate observation is that Semaphorins can and do alter the trajectory of migrating OLPs.

In our studies, we also observed the expression of Sema 4D in OLs, and that soluble recombinant Plexin B1, its presumptive receptor [31], bound their cell surface. Similarly, Moreau-Fauvarque and co-workers [42] recently demonstrated in mouse CNS that Sema 4D was co-localized to OLs and their myelin sheaths. Further,

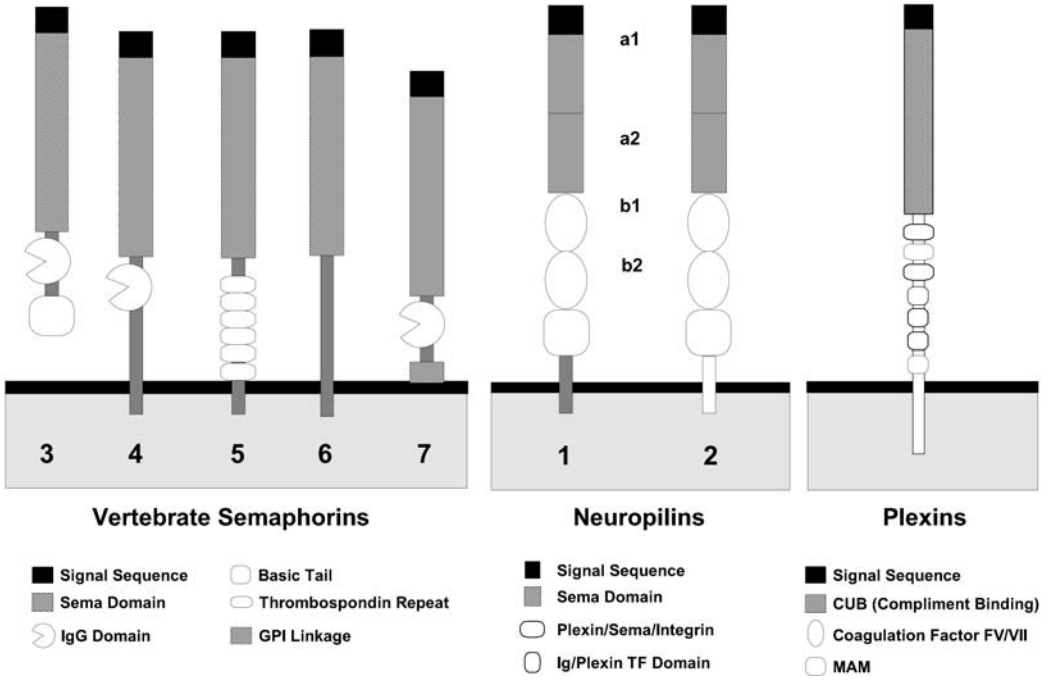

Figure 2. Graphical representation of extracellular motifs in the semaphorin, neuropilin and plexin superfamilies. These diagrams were adapted from the review paper of Huber et al. [34], and others.

this expression, which was positively regulated with OL development, was further, albeit, transiently upregulated following spinal cord injury for 1 month. Interestingly, Giraudon and colleagues demonstrated the reverse, where T-cell-supplied CD100 caused process collapse in OLs, and even death to neural precursor cells [43]. The mechanism whereby T cells mediated this response is not clear, but may be through non-Plexin-associated pathways, as no description of Plexin expression in OLs has been previously reported.

Semaphorins supplied by OLs may also prove to be an important regulatory signal for developing or regenerating neurons. As mentioned above, Moreau-Fauvarque and co-workers observed a transient overexpression of OL-supplied Sema 4D in the injured spinal cord. They went on to show using a standard stripe assay that Sema4D was a strong inhibitor of postnatal sensory and cerebellar granule cell axon outgrowth. Their findings strongly intimated a role of this OL-supplied cue as an inhibitor of axon regeneration [42]. Evidence for this hypothesis was further cemented by recent findings of Goldberg and co-workers [44]. They also observed the expression of multiple Semaphorins in optic nerve, with Sema 5A being specific for the OL lineage. In contrast, Sema 5A was not present in the peripheral nervous system (PNS) glia, reminiscent of differential expression of members of the Nogo family [45, 46]. Their results demonstrated that, in part, Sema 5A-derived from OLs could play a role in the inhibition of regeneration of retinal ganglion cells (RGC) in the injured optic nerve. Taken together, OLs seem able to both respond to and express members of the semaphorin family, suggesting that they may be able to regulate their own guidance in a homologous way and still respond to other cells in a heterologous manner.

These few studies indicate a strong role for this gene family in regulating neuron-glial interactions. More investigation into developmental and disease models should reveal further relevant functional roles.

Eph-Ephrin superfamily

Similar to our above-mentioned findings in the Semaphorin/Neuropilin family, we also observed expression of members belonging to the Eph/ephrin receptor tyrosine kinase/ligand superfamily (fig. 3, adapted from [47]).

Eph, the receptors and ephrin, their cognate ligands, comprise a large family of receptor tyrosine kinases and membrane-spanning or tethered ligands [10, 16–18, 20, 21, 32, 34, 37]. The 15 Eph receptor genes are separated into two major families containing full-length, truncated splice variants. The A and B class receptors, with the exception of EphB6, have functional tyrosine kinase domains and are complemented by two classes of ligands capable of signal transduction. In reductionist Eph/ephrin-signaling vernacular, ‘forward signaling’ is defined as signal transduction through cells expressing Eph receptors, while ‘reverse signaling’ refers to intracellular

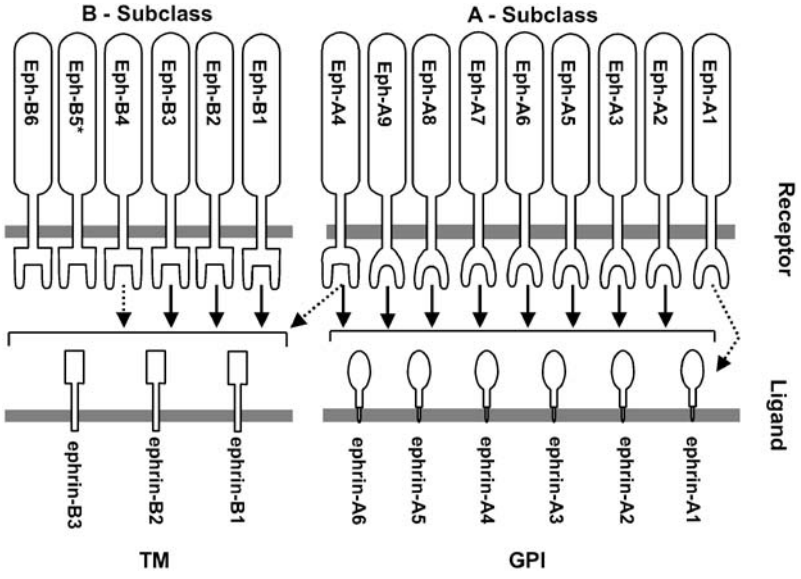

Figure 3. Graphical representation of Eph and ephrin superfamily. These diagrams were adapted from the review paper of Flanagan and Vanderhaeghen [47] and others.

cascades activated in ligand-expressing cells. The A class ligands are GPI linked, while the B class ligands have a short intracellular domain. The A class GPI ligands are thought to transduce reverse signaling through tight associations with partners in microraft domains, which may involve kinases, such as src and fyn [16–18, 20, 21]. Conversely, the B class ligands have a short intracellular domain and interact with PDZ binding proteins to propagate their signaling cascades. [16–18, 20, 21]. Suffice to say, the major role of this receptor-ligand interaction in the nervous system is to define patterns of neural pathways [10, 16, 17, 19–21, 32].

Studies analyzing Eph/ephrin expression and/or their roles in glia are lacking. Our unpublished results [R. I. Cohen and K. J. Chandross], demonstrated a wide expression of both A and B class receptors and ligands which appeared to be negatively regulated with their coincident differentiation (data not shown). We focused our studies on the roles of EphB receptors, i.e. forward signaling, in oligodendroglia, and found that ephrin-B-Fc ligands, in a modified stripe assay, restricted the migratory path of rat brain-derived OLPs in culture (fig. 4) [R. I. Cohen and K. J. Chandross, unpublished results]. Conversely, Prestoz and co-workers found OLPs can also propagate reverse signaling. Using optic nerve-derived embryonic mouse OLPs, they observed specific expression of ephrinA5, ephrinB2 and ephrinB3 and that striped EphB2-Fc appeared to be more adhesive than that of EphA6-Fc. This decrease in apparent migration may hint at a role in regulating OLP function during development. Thus, EphB2 may act as a neuron-derived regulator of OLP infiltration. Aside from these limited findings, little else is known about the role of the Eph/ephrin system in oligodendroglia.

Relevance to neurological disorders

Findings of both Miranda and co-workers [48–50] and Bundesen and colleagues [51] strongly suggest a role for the Eph/ephrin receptor-ligand interactions in the inhibition of regeneration in rodent models of spinal cord Injury. Recently, Sobel and co-workers [Sobel, R.A., Brain Path. Jan 2005, in press] revealed the aberrant expression of several EphA class receptors and ligands in reactive astrocytes surrounding white matter lesions in pathological samples from patients affected with MS. However, in the models cited above, the disease-associated component due to expression of Ephs or ephrins by oligodendrocytes or response to signaling through these systems remains to be elucidated. Similarly, the upregulation of Sema 3A in spinal cord injury [52, 53] appears to indicate a role in preventing regeneration. Therefore, one must appreciate that multiple receptor-ligand pathways, in addition to the above-mentioned gene family members, can co-operate to form a highly efficient molecular barrier to nerve regeneration. Thus, teasing out a single downstream signaling pathway that covers a broad spectrum of inhibitors may be the only avenue to effectively neutralize enough inhibitors to facilitate neural repair [4, 54–56].

Summary

These seminal studies uncovered a new approach examining neuron-glial interactions, and revealed that developing oligodendroglia can and do express classically neuron-associated guidance genes. Albeit interesting, their roles remain unclear with respect to development or during

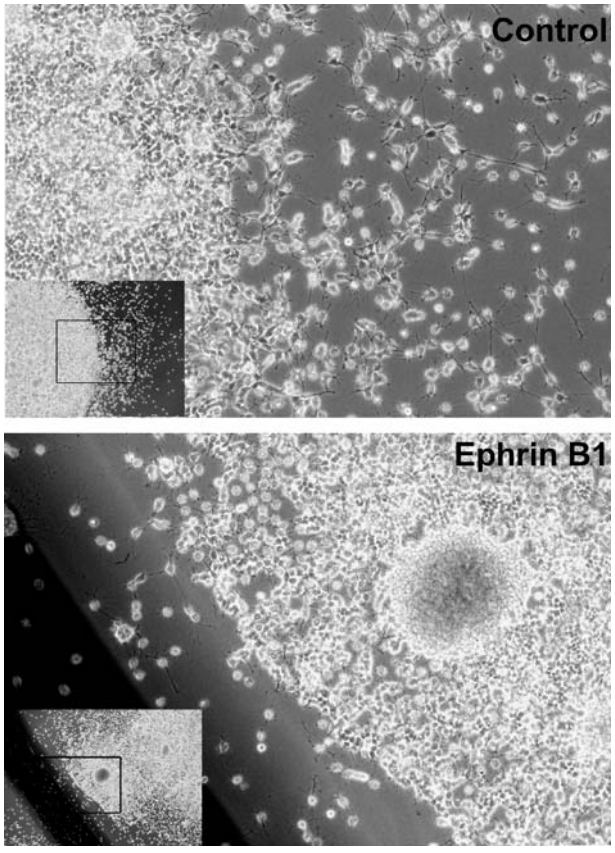

Figure 4. Ephrin B class ligands inhibit oligodendrocyte outgrowth. Oligodendrocyte progenitors (OLPs) were aggregated overnight on non-tissue-culture-treated plastic. The aggregates were plated at high density adjacent to a stripe of ephrin B class ligand (bottom panel), or buffer (top panel). The inset is a lower magnification showing gross radial migration of OLPs from the respective treatments. The cells were allowed to grow for several days, following which they were photographed. The dark stripe in the ephrin B1-Fc (lower) panel is a mark on the reverse of the culture dish indicating the area adjacent to the striped ligand. Note that the ephrin-B1-Fc prevents the majority of OLPs from entering the striped area.

regeneration in disease states. What are the roles of these molecules? Do they help define white and gray matter? Do these families regulate the guidance of OLPs into the right compartment? Are they overexpressed by reactive elements in disease states? These and more questions remain to be addressed before we can fully appreciate the oligodendroglial lineage cell types in neuron-glia interactions. Paradigms that will remove these genes, or neutralize their expression in a specific manner such as in a CRE-lox oligodendrocyte-specific system [57–60], will help flesh out the roles of these molecules in this cell type. Importantly, *in vitro* assays can now begin to address the signaling cascades and potentially hint at the roles of the Semaphorin and Eph/ephrin systems in using stripe assays and time-lapse videography in pure or co-culture techniques.

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