Glia in mammalian development and disease

J. Bradley Zuchero* and Ben A. Barres

ABSTRACT

Glia account for more than half of the cells in the mammalian nervous system, and the past few decades have witnessed a flood of studies that detail novel functions for glia in nervous system development, plasticity and disease. Here, and in the accompanying poster, we review the origins of glia and discuss their diverse roles during development, in the adult nervous system and in the context of disease.

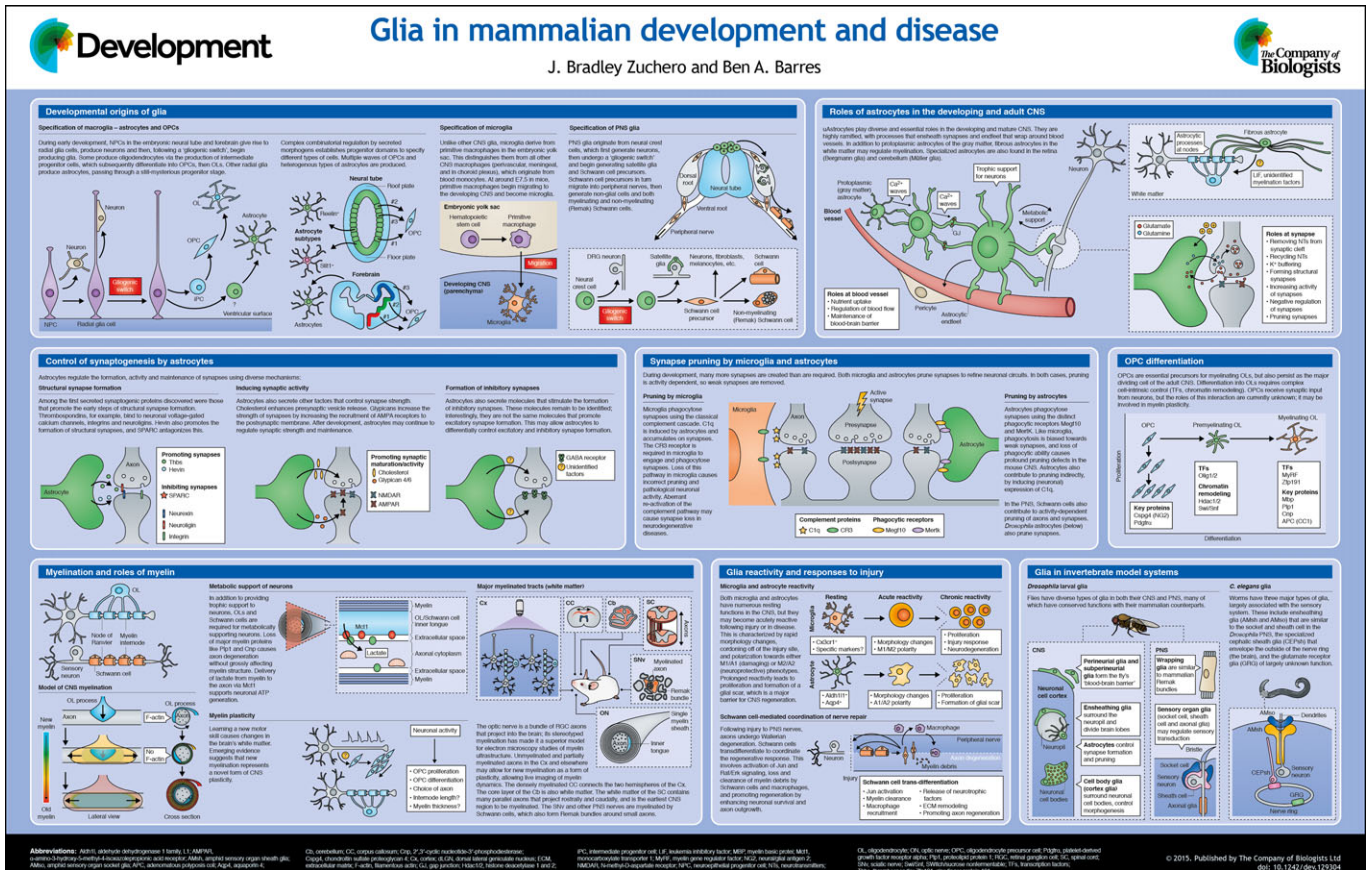KEY WORDS: Astrocyte, Glia, Microglia, Myelination, Nervous system, Oligodendrocyte

Introduction

Since their discovery over a century ago, glia were thought for a long time to function only to support neurons passively. We now appreciate that glia function as master regulators of the nervous

Department of Neurobiology, Stanford University, School of Medicine, Stanford, CA 94305, USA.

*Author for correspondence (brad.zuchero@gmail.com)

system, controlling numerous aspects of nervous system development, plasticity and disease (Barres, 2008; Fields et al., 2015). Here, we provide an overview of these many functions. We first briefly introduce the origins and specification of glia during development. We then discuss emerging roles for each glial cell type (astrocytes, oligodendrocytes, Schwann cells and microglia) in regulating the development and plasticity of the nervous system. We focus on vertebrate glia, but also refer to roles for glia in invertebrate model systems. Astrocytes, the most abundant cell type in the vertebrate central nervous system (CNS), have perhaps the most diverse roles among glia. We review their contributions to promoting neuronal survival, synaptogenesis and synapse pruning, and roles related to their close interaction with the vasculature. Oligodendrocytes (OLs) and Schwann cells are the myelinating glia of the CNS and the peripheral nervous system (PNS), respectively. We review how they create myelin to electrically insulate axons and control conduction velocity in novel forms of plasticity, and how they also metabolically support neurons (Bercury and Macklin, 2015). Microglia, the resident immune cells in the CNS, have been studied extensively with regard to their roles in inflammation and disease, but less is known about

their functions in the developing and adult brain (Casano and Peri, 2015). We focus on their role in synapse pruning, and direct readers interested in their other functions to recent reviews (Kettenmann et al., 2011; Casano and Peri, 2015). Finally, we highlight exciting recent work that supports a key role for glia in regeneration and diverse diseases of the nervous system.

Origins and specification of glia

Macroglia – astrocytes and the oligodendrocyte lineage – arise from neuroepithelial progenitor cells (NPCs) in the embryonic neural tube and forebrain (Rowitch and Kriegstein, 2010). At around embryonic day (E) 9 in mice, NPCs transform into radial glia, which are the primary progenitor cells for both neurons and macroglia during embryogenesis. After radial glial cells generate neurons, a 'gliogenic switch' occurs and they begin differentiating into astrocytes or oligodendrocyte precursor cells (OPCs, also called NG2 glia). During this time, numerous secreted signals – notably Sonic hedgehog (Shh), fibroblast growth factors (FGFs), Wnts, Notch/Delta, bone morphogenetic proteins (BMPs) and cytokines – act together to control cell fate spatially and temporally, leading to the presence of specific domains that selectively generate either astrocytes or OPCs (Rowitch and Kriegstein, 2010; Zuchero and Barres, 2013). Key transcription factors involved at this time include Sox9, nuclear factor I and serum response factor for general gliogenesis, and Olig1/Olig2 for OPC production (Rowitch and Kriegstein, 2010; Lu and Ramanan, 2012). Interestingly, astrocytes generated in distinct regions have important functional differences that are just beginning to be revealed (reviewed by Molofsky and Deneen, 2015). Although multiple waves of OPC production occur during development from different regions, it remains to be determined whether these different populations also have distinct functions (Richardson et al., 2006). It is also largely unknown how astrocytes are specified separately from OPCs, and whether there are discrete, transcriptionally distinct stages during astrocyte maturation (similar to the differences between OPCs and myelinating OLs).

In contrast to astrocytes and oligodendrocytes, microglia are mesodermal in origin and are generated in the yolk sac during embryogenesis, at E7.5 in the mouse (Aguzzi et al., 2013; Ginhoux and Prinz, 2015; Casano and Peri, 2015). First, hematopoietic stem cells in the yolk sac become primitive macrophages, and then these primitive macrophages migrate to the developing CNS and become microglia. Resting microglia are highly ramified cells and occupy the entire CNS parenchyma. Other (non-parenchymal) CNS macrophages are also present and are derived from blood monocytes that originate in the bone marrow; microglia are thus unique in their yolk sac origin. An important goal for the future is to determine the signals that promote microglia identity and renewal in the CNS.

All glial cells within the PNS, by contrast, originate from neural crest cells, with gliogenesis starting at E11 in the mouse embryo (reviewed by Jacob, 2015). Analogous to the stepwise specification of CNS neurons and glia from NPCs, neural crest cells first generate sensory neurons of the dorsal root ganglia (DRG) before generating glia. Neural crest cells give rise directly to two populations of glia: Schwann cell precursors and satellite glia. Satellite glia remain in PNS ganglia and ensheath the somata of neurons, and they may metabolically support neurons or even contribute to information processing (Huang et al., 2013). By contrast, Schwann cell precursors migrate out of the ganglia into peripheral nerves, where they differentiate into either myelinating Schwann cells or the nonmyelinating Schwann cells that form Remak bundles around small caliber axons. In addition, Schwann cell precursors can also

give rise to melanocytes, parasympathetic neurons, endoneurial fibroblasts, or mesenchymal stem cells (Jacob, 2015). Key extrinsic signals that promote the generation of Schwann cell precursors include neuregulin, Notch/Delta and FGFs; by contrast, BMP and Wnt signaling are pro-neural and must be antagonized to allow for gliogenesis. In addition, transcription factors – especially Sox10 and Pax3 – and Hdac1/2 histone deacetylases, which regulate chromatin remodeling, work in concert to promote the formation of Schwann cell precursors from neural crest cells (Jacob, 2015). Neural crest cells also give rise to enteric glial cells in the gastrointestinal tract (Coelho-Aguiar et al., 2015) and olfactory ensheathing cells that reside in both the PNS and the olfactory bulb in the CNS (Barraud et al., 2010). The functions of these and their precise mechanisms of specification are still being worked out, and it will be interesting to determine similarities and differences compared with Schwann cell precursors.

Roles of astrocytes in CNS development and function

Work over the past decade has overwhelmingly demonstrated that astrocytes, which were once thought to function only as supporting cells for neurons, play diverse and essential regulatory roles in the developing and adult CNS (reviewed by Allen, 2014). Astrocytes are the most abundant cell type in the vertebrate CNS, and are classified as protoplasmic (gray matter) or fibrous (white matter). Specialized forms of astrocytes include Müller glia in the retina and Bergmann glia in the cerebellum (Barres, 2008). Protoplasmic astrocytes of the gray matter are highly ramified, containing endfeet that contact blood vessels, as well as terminal projections that ensheath synapses. A single mouse astrocyte can ensheath more than 100,000 synapses, and a human astrocyte may ensheath many more.

What do astrocytes do? An essential function of astrocytes, and one that has made it difficult to study their other roles in the CNS, is promotion of neuronal survival. The loss of astrocytes *in vivo* causes neuronal death, and in most culture models neurons require astrocytes for survival. Their dual interactions with neurons and the vasculature allow them to take up nutrients from the blood and provide metabolic support to neurons (Pellerin et al., 2007). Astrocytes also play a crucial role in neurovascular coupling, and they stimulate increased blood flow to brain regions with active neurons in response to neurotransmitter release (Attwell et al., 2010). Astrocytes may also contribute to a CNS analog of the lymphatic system, the 'glymphatic' system, by regulating the flow of cerebral spinal fluid (Jessen et al., 2015b).

At synapses, astrocytes have long been known to enhance the fidelity of synaptic transmission, by removing and recycling neurotransmitters from the synaptic cleft and buffering extracellular potassium. More recently, it has become apparent that astrocytes also powerfully control the formation, strength and turnover of synapses. Since the first demonstrations nearly two decades ago that astrocytes are required for the formation of functional synapses in retinal ganglion cells, there has been great progress in identifying the numerous proteins released by astrocytes that control excitatory synapse formation and function (reviewed by Clarke and Barres, 2013; Allen, 2014). These include astrocyte-secreted proteins that trigger the formation of postsynaptically silent synapses (e.g. thrombospondins, hevin), make synapses active by recruiting AMPA glutamate receptors to the postsynaptic membrane (e.g. glypicans), or enhance presynaptic vesicular release (e.g. cholesterol). Astrocytes also release molecules that can antagonize pro-synaptic signals (e.g. Sparc), and they can also prune synapses by phagocytosis (see below). Inhibitory synapse formation is also

controlled by astrocytes, by different and still unidentified secreted factors. Finally, it has been noted that astrocytes *in vivo* and in culture respond strongly to neuronal activity with calcium waves, which may allow for control of local synaptic activity as well as coordinating activities over greater distances throughout the CNS. The precise mechanisms underlying these diverse functions are still debated, and clearly this will remain an exciting focus for future studies (Haydon and Nedergaard, 2015).

Synapse pruning by glia

During the development of the nervous system, more synapses form than are ultimately required, and remodeling is thus required to achieve precise wiring. Synapse remodeling refers to the elimination (or 'pruning') of unnecessary synapses and the strengthening of remaining synapses. Extensive work in the last decade has revealed that both microglia and astrocytes are essential players in the elimination of CNS synapses during development, and that Schwann cells eliminate excess axons and synapses in the developing PNS (Allen, 2014; Schafer and Stevens, 2015). Importantly, in all cases, synapse elimination by glia has been found to be activity dependent; that is, weak synapses are selectively pruned, and strong synapses are spared.

How do glia prune synapses? Early insight came from work in *Drosophila*, where it was found that glia phagocytose degenerating axonal debris during development, in both the CNS and PNS. However, a role in clearing degenerating axons did not necessarily indicate an active role in controlling remodeling, so the discovery that vertebrate microglia prune individual synapses was groundbreaking (Schafer and Stevens, 2015). The local control of synapse elimination by microglia relies on the deposition of complement proteins such as C3 and C1q, which are expressed on neurons in an astrocyte-dependent manner, to tag synapses for phagocytosis (Stephan et al., 2012). More recently, it was discovered that astrocytes also directly phagocytose synapses, in both *Drosophila* and vertebrates, utilizing the Megf10/Draper and Mertk phagocytic receptors (Freeman, 2015; Chung et al., 2015). Mice lacking C1q, or those with astrocytes that lack Megf10 and Mertk, have severe defects in developmental synapse pruning. Strikingly, the phagocytosis of synapses by both microglia and astrocytes is strongly dependent on neuronal activity; synapses of neurons silenced with tetrodotoxin (TTX, a potent neurotoxin) are selectively engulfed. Current work aims to understand how widespread glial pruning of synapses is throughout the nervous system, how it contributes to plasticity in the adult, and whether synapse elimination by glia is aberrantly activated in neurodegenerative diseases.

Mechanism and novel roles of myelination

The myelination of axons – by OLs in the CNS, and Schwann cells in the PNS – forms an electrical insulator that allows rapid signal transmission, and its evolution in vertebrates has allowed for a small yet incredibly powerful nervous system. Myelination begins embryonically in the rodent PNS and spinal cord, and this is followed by myelination in the brain and optic nerve in the first few postnatal weeks. To myelinate axons, OPCs exit the cell cycle and differentiate into pre-myelinating OLs, and then begin expressing major myelin proteins (e.g. Mbp, Cnp, Plp1). Much work in the past few decades has focused on understanding how differentiation occurs, and has revealed crucial roles for chromatin remodeling (e.g. histone acetylation/deacetylation, remodeling by SWI/SNF enzymes), transcription factors (Olig1/2, Sox10, MyRF, Zfp191), and microRNAs (Zuchero and Barres, 2013; Emery and Lu, 2015).

Once differentiation begins, OLs undergo complex morphological changes to extend numerous processes, each of which can encounter and ensheath an axon, then spirally wrap around the axon while extending longitudinally along it to form a mature myelin internode. Myelination has been studied in earnest for half a century, but the geometry of the wrapping and the cellular (cytoskeletal) mechanisms driving these morphology changes were only recently elucidated (Snaidero and Simons, 2014; Nawaz et al., 2015; Zuchero et al., 2015). Combined with quantitative gene expression data from multiple stages of myelination (Zhang et al., 2014) and numerous gene knockouts affecting myelination, the stage is set to fully unravel the cellular and molecular mechanisms that drive myelination during development, and to understand why remyelination often fails in demyelinating diseases such as multiple sclerosis (MS; Franklin and Goldman, 2015).

Schwann cells constitute ~80% of all cells in peripheral nerves and use many of the same transcriptional and signaling pathways to myelinate PNS axons as do OLs, although numerous important differences have been observed (Salzer, 2015). Morphologically, a single Schwann cell forms one myelin internode (in contrast to the dozens formed by an OL), and its myelin is often far thicker than CNS myelin. Pre-myelinating Schwann cells also form Remak bundles in which a single Schwann cell surrounds numerous small caliber axons. In contrast to OLs, Schwann cells transdifferentiate following peripheral nerve injury to clear cellular debris and coordinate the repair process (Brosius Lutz and Barres, 2014; Jessen et al., 2015a).

With the evolution of myelin came a new problem: myelinated axons are completely surrounded by myelin membranes and thus may have limited access to nutrients in the extracellular space. However, work in the last decade has shown that both OLs and Schwann cells solve this problem by metabolically supporting neurons, for example by providing lactate to neurons for ATP generation (Saab et al., 2013; Simons and Nave, 2015) and by regulating angiogenesis during development (Yuen et al., 2014). In fact, several of the most highly expressed proteins found in myelin are dispensable for myelination but are required in OLs/Schwann cells for axonal health. OL–axon interactions also organize Nodes of Ranvier, allowing for saltatory conduction (Normand and Rasband, 2015).

Emerging work also indicates that changes in myelination might represent a novel form of plasticity in the CNS (reviewed by Fields, 2010; Bercury and Macklin, 2015). It has long been appreciated that humans or rodents learning a new motor activity exhibit structural changes in their white matter (myelinated tracts), but the nature and role of these changes have been unknown. It was recently determined that OPCs continue to produce myelinating OLs in the adult brain, and that numerous axons, especially in the adult gray matter, remain unmyelinated. Intriguingly, inducing motor activity in mice, by optogenetic stimulation of the motor cortex or teaching a mouse a complex motor task, induces the rapid local proliferation and subsequent differentiation of OPCs (Gibson et al., 2014; McKenzie et al., 2014). In these studies, blocking the ability of new OLs to differentiate and express myelin proteins severely inhibits motor learning. Together, these studies illustrate that myelination is sensitive to neural activity and can respond by altering myelin structure to affect behavior. Remaining questions include how activity induces OPCs to proliferate and generate new myelin, and to what extent activity also regulates ultrastructural changes in pre-existing myelin (e.g. myelin thickness).

Central roles of glia in injury, regeneration and disease

With the realization that glia are essential regulators of most, if not all, functions of the nervous system has come the ever increasing

awareness of their important contributions to disorders of the nervous system. The importance of OLs in the pathology of demyelinating diseases such as MS is easily appreciated, as myelin loss directly affects nerve transmission. More broadly, the dysregulation of OL-mediated metabolic support of neurons might contribute to neuronal death in multiple neurodegenerative diseases, including MS and amyotrophic lateral sclerosis (ALS; Saab et al., 2013), as well as contributing to psychiatric disorders (Fields, 2008). Similarly, many diseases of the PNS are due primarily to pathologies of Schwann cells and a subsequent loss of neurons.

An important function of both astrocytes and microglia is to respond to injury, a complex change known as reactive gliosis (Burda and Sofroniew, 2014). Similar to microglia, which are traditionally thought to enter a negatively acting 'M1' phenotype following neuroinflammatory insult, astrocytes are polarized to an 'A1' phenotype, which is characterized by the upregulation of many factors involved in the classical complement cascade (Zamanian et al., 2012). A major future goal is to understand the signals that drive astrocytes and microglia towards neuroprotective forms of gliosis (i.e. A2/M2 phenotypes) rather than harmful (i.e. A1/M1) phenotypes, to prevent damage caused by reactive gliosis following injury and in disease (Aguzzi et al., 2013). Both astrocytes and microglia have also been implicated in numerous neurological and psychiatric diseases (e.g. ALS, Alzheimer's disease and Parkinson's disease; Phatnani and Maniatis, 2015; Ginhoux and Prinz, 2015). In most cases, it is incompletely understood whether their contributions to these diseases are due to toxic gain of functions (e.g. A1/M1 forms of reactivity) or loss of normal, neuroprotective functions. Intriguingly, complement proteins that mediate synapse elimination by microglia are upregulated in many CNS diseases, and this precedes neuron death and synapse loss, suggesting that aberrant activation of this pathway might contribute broadly to neurodegeneration (Stephan et al., 2012).

Another role of glia in the adult the nervous system is to serve as stem cells, both for normal function and to promote regeneration in injury and disease. For example, radial glia function as stem cells in the adult CNS to allow for neurogenesis, which is crucial for memory (Kempermann et al., 2015). Some populations of astrocytes might also serve as neural stem cells in the adult CNS, and be able to generate neurons in response to injury (Kriegstein and Alvarez-Buylla, 2009; Péron and Berninger, 2015). There is also evidence that OPCs function as stem cells in the adult CNS, beyond their ability to mature into OLs (Crawford et al., 2014). This ability might someday allow for the transplantation of OPCs or other stem cells to be used as a therapy for demyelination and other neurodegenerative diseases (Franklin and Goldman, 2015). Alternatively, it might be possible to reprogram glia *in vivo* directly into neurons to promote regeneration (Péron and Berninger, 2015).

Conclusions

Glia are increasingly being appreciated as essential components for all functions of the CNS and PNS. They play key roles in the development and proper wiring of the nervous system, in the survival and metabolic support of neurons, and in complex cell-cell interactions that can regulate information flow and plasticity in numerous ways over multiple scales, from synapse to circuits. As we learn more about the normal functions of glia, their importance in disorders of the nervous system becomes increasingly appreciated.

What does the next decade hold for the glial field? Elucidation of the gene expression profiles of glia in different regions of the CNS, at different developmental stages, and in humans will continue to

increase our mechanistic understanding of glial function and heterogeneity in development and in adults. The presence of diverse types of glia in invertebrate model organisms opens up the possibility of using powerful genetic approaches for gaining further mechanistic insight (Freeman, 2015; Shaham, 2015). The continued improvement of vertebrate genetic tools to specifically modify glia *in vivo* (e.g. astrocytes without also targeting neurons, discriminating between microglia and macrophages) will allow the field to characterize fully the developmental roles of glia as well as their contributions to diseases of the nervous system. Finally, additional studies on the role of glia as stem cells might enable therapies for promoting regeneration following injury, and in disease. It remains an exciting time for those of us studying the roles of glia, cells that are inarguably master regulators of the nervous system.

Development at a Glance
A high-resolution version of the poster is available for downloading in the online version of this article at http://dev.biologists.org/content/142/22/3805/F1.poster.jpg

References
Aguzzi, A., Barres, B. A. and Bennett, M. L. (2013). Microglia: scapegoat, saboteur, or something else? *Science* **339**, 156-161.

Allen, N. J. (2014). Astrocyte regulation of synaptic behavior. *Annu. Rev. Cell Dev. Biol.* **30**, 439-463.

Attwell, D., Buchan, A. M., Charpak, S., Lauritzen, M., MacVicar, B. A. and Newman, E. A. (2010). Glial and neuronal control of brain blood flow. *Nature* **468**, 232-243.

Barraud, P., Seferiadis, A. A., Tyson, L. D., Zwart, M. F., Szabo-Rogers, H. L., Ruhrberg, C., Liu, K. J. and Baker, C. V. H. (2010). Neural crest origin of olfactory ensheathing glia. *Proc. Natl. Acad. Sci. USA* **107**, 21040-21045.

Barres, B. A. (2008). The mystery and magic of glia: a perspective on their roles in health and disease. *Neuron* **60**, 430-440.

Bercury, K. K. and Macklin, W. B. (2015). Dynamics and mechanisms of CNS myelination. *Dev. Cell* **32**, 447-458.

Brosius Lutz, A. and Barres, B. A. (2014). Contrasting the glial response to axon injury in the central and peripheral nervous systems. *Dev. Cell* **28**, 7-17.

Burda, J. E. and Sofroniew, M. V. (2014). Reactive gliosis and the multicellular response to CNS damage and disease. *Neuron* **81**, 229-248.

Casano, A. M. and Peri, F. (2015). Microglia: multitasking specialists of the brain. *Dev. Cell* **32**, 469-477.

Chung, W.-S., Allen, N. J. and Eroglu, C. (2015). Astrocytes control synapse formation, function, and elimination. *Cold Spring Harb. Perspect. Biol.* **7**, a020370.

Clarke, L. E. and Barres, B. A. (2013). Emerging roles of astrocytes in neural circuit development. *Nat. Rev. Neurosci.* **14**, 311-321.

Coelho-Aguiar, J. d. M., Bon-Frauches, A. C., Gomes, A. L. T., Veríssimo, C. P., Aguiar, D. P., Matias, D., Thomasi, B. B. d. M., Gomes, A. S., Brito, G. A. d. C. and Moura-Neto, V. (2015). The enteric glia: identity and functions. *Glia* **63**, 921-935.

Crawford, A. H., Stockley, J. H., Tripathi, R. B., Richardson, W. D. and Franklin, R. J. M. (2014). Oligodendrocyte progenitors: adult stem cells of the central nervous system? *Exp. Neurol.* **260**, 50-55.

Emery, B. and Lu, Q. R. (2015). Transcriptional and epigenetic regulation of oligodendrocyte development and myelination in the central nervous system. *Cold Spring Harb. Perspect. Biol.* **7**, a020461.

Fields, R. D. (2008). White matter in learning, cognition and psychiatric disorders. *Trends Neurosci.* **31**, 361-370.

Fields, R. D. (2010). Change in the brain's white matter. *Science* **330**, 768-769.

Fields, R. D., Woo, D. H. and Basser, P. J. (2015). Glial regulation of the neuronal connectome through local and long-distant communication. *Neuron* **86**, 374-386.

Franklin, R. J. M. and Goldman, S. A. (2015). Glia disease and repair – remyelination. *Cold Spring Harb. Perspect. Biol.* **7**, a020594.

DEVELOPMENT

Freeman, M. R. (2015). Drosophila central nervous system glia. *Cold Spring Harb. Perspect. Biol.* **7**, a020552.

Gibson, E. M., Purger, D., Mount, C. W., Goldstein, A. K., Lin, G. L., Wood, L. S., Inema, I., Miller, S. E., Bieri, G., Zuchero, J. B. et al. (2014). Neuronal activity promotes oligodendrogenesis and adaptive myelination in the mammalian brain. *Science* **344**, 1252304.

Ginhoux, F. and Prinz, M. (2015). Origin of microglia: current concepts and past controversies. *Cold Spring Harb. Perspect. Biol.* **7**, a020537.

Haydon, P. G. and Nedergaard, M. (2015). How do astrocytes participate in neural plasticity? *Cold Spring Harb. Perspect. Biol.* **7**, a020438.

Huang, L.-Y. M., Gu, Y. and Chen, Y. (2013). Communication between neuronal somata and satellite glial cells in sensory ganglia. *Glia* **61**, 1571-1581.

Jacob, C. (2015). Transcriptional control of neural crest specification into peripheral glia. *Glia* **63**, 1883-1896.

Jessen, K. R., Mirsky, R. and Lloyd, A. C. (2015a). Schwann cells: development and role in nerve repair. *Cold Spring Harb. Perspect. Biol.* **7**, a020487.

Jessen, N. A., Munk, A. S. F., Lundgaard, I. and Nedergaard, M. (2015b). The glymphatic system: a beginner's guide. *Neurochem. Res.* (in press).

Kempermann, G., Song, H. and Gage, F. H. (2015). Neurogenesis in the adult hippocampus. *Cold Spring Harb. Perspect. Biol.* **7**, a018812.

Kettenmann, H., Hanisch, U.-K., Noda, M. and Verkhratsky, A. (2011). Physiology of microglia. *Physiol. Rev.* **91**, 461-553.

Kriegstein, A. and Alvarez-Buylla, A. (2009). The glial nature of embryonic and adult neural stem cells. *Annu. Rev. Neurosci.* **32**, 149-184.

Lu, P. P. Y. and Ramanan, N. (2012). A critical cell-intrinsic role for serum response factor in glial specification in the CNS. *J. Neurosci.* **32**, 8012-8023.

McKenzie, I. A., Ohayon, D., Li, H., Paes de Faria, J., Emery, B., Tohyama, K. and Richardson, W. D. (2014). Motor skill learning requires active central myelination. *Science* **346**, 318-322.

Molofsky, A. V. and Deneen, B. (2015). Astrocyte development: a guide for the perplexed. *Glia* **63**, 1320-1329.

Nawaz, S., Sánchez, P., Schmitt, S., Snaidero, N., Mitkovski, M., Velte, C., Brückner, B. R., Alexopoulos, I., Czopka, T., Jung, S. Y. et al. (2015). Actin filament turnover drives leading edge growth during myelin sheath formation in the central nervous system. *Dev. Cell* **34**, 139-151.

Normand, E. A. and Rasband, M. N. (2015). Subcellular patterning: axonal domains with specialized structure and function. *Dev. Cell* **32**, 459-468.

Pellerin, L., Bouzier-Sore, A.-K., Aubert, A., Serres, S., Merle, M., Costalat, R. and Magistretti, P. J. (2007). Activity-dependent regulation of energy metabolism by astrocytes: an update. *Glia* **55**, 1251-1262.

Péron, S. and Berninger, B. (2015). Reawakening the sleeping beauty in the adult brain: neurogenesis from parenchymal glia. *Curr. Opin. Genet. Dev.* **34**, 46-53.

Phatnani, H. and Maniatis, T. (2015). Astrocytes in neurodegenerative disease. *Cold Spring Harb. Perspect. Biol.* **7**, a020628.

Richardson, W. D., Kessaris, N. and Pringle, N. (2006). Oligodendrocyte wars. *Nat. Rev. Neurosci.* **7**, 11-18.

Rowitch, D. H. and Kriegstein, A. R. (2010). Developmental genetics of vertebrate glial–cell specification. *Nature* **468**, 214-222.

Saab, A. S., Tzvetanova, I. D. and Nave, K.-A. (2013). The role of myelin and oligodendrocytes in axonal energy metabolism. *Curr. Opin. Neurobiol.* **23**, 1065-1072.

Salzer, J. L. (2015). Schwann cell myelination. *Cold Spring Harb. Perspect. Biol.* **7**, a020529.

Schafer, D. P. and Stevens, B. (2015). Microglia function in central nervous system development and plasticity. *Cold Spring Harb. Perspect. Biol.* **7**, a020545.

Shaham, S. (2015). Glial development and function in the nervous system of Caenorhabditis elegans. *Cold Spring Harb. Perspect. Biol.* **7**, a020578.

Simons, M. and Nave, K.-A. (2015). Oligodendrocytes: myelination and axonal support. *Cold Spring Harb. Perspect. Biol.* **7**, a020479.

Snaidero, N. and Simons, M. (2014). Myelination at a glance. *J. Cell Sci.* **127**, 2999-3004.

Stephan, A. H., Barres, B. A. and Stevens, B. (2012). The complement system: an unexpected role in synaptic pruning during development and disease. *Annu. Rev. Neurosci.* **35**, 369-389.

Yuen, T. J., Silbereis, J. C., Griveau, A., Chang, S. M., Daneman, R., Fancy, S. P. J., Zahed, H., Maltepe, E. and Rowitch, D. H. (2014). Oligodendrocyte-encoded HIF function couples postnatal myelination and white matter angiogenesis. *Cell* **158**, 383-396.

Zamanian, J. L., Xu, L., Foo, L. C., Nouri, N., Zhou, L., Giffard, R. G. and Barres, B. A. (2012). Genomic analysis of reactive astrogliosis. *J. Neurosci.* **32**, 6391-6410.

Zhang, Y., Chen, K., Sloan, S. A., Bennett, M. L., Scholze, A. R., O'Keeffe, S., Phatnani, H. P., Guarnieri, P., Caneda, C., Ruderisch, N. et al. (2014). An RNA-sequencing transcriptome and splicing database of glia, neurons, and vascular cells of the cerebral cortex. *J. Neurosci.* **34**, 11929-11947.

Zuchero, J. B. and Barres, B. A. (2013). Intrinsic and extrinsic control of oligodendrocyte development. *Curr. Opin. Neurobiol.* **23**, 914-920.

Zuchero, J. B., Fu, M.-M., Sloan, S. A., Ibrahim, A., Olson, A., Zaremba, A., Dugas, J. C., Wienbar, S., Caprariello, A. V., Kantor, C. et al. (2015). CNS myelin wrapping is driven by actin disassembly. *Dev. Cell* **34**, 152-167.