Oligodendrocyte Development and Plasticity

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Oligodendrocyte precursor cells (OPCs) originate in the ventricular zones (VZs) of the brain and spinal cord and migrate throughout the developing central nervous system (CNS) before differentiating into myelinating oligodendrocytes (OLs). It is not known whether OPCs or OLs from different parts of the VZ are functionally distinct. OPCs persist in the postnatal CNS, where they continue to divide and generate myelinating OLs at a decreasing rate throughout adult life in rodents. Adult OPCs respond to injury or disease by accelerating their cell cycle and increasing production of OLs to replace lost myelin. They also form synapses with unmyelinated axons and respond to electrical activity in those axons by generating more OLs and myelin locally. This experience-dependent "adaptive" myelination is important in some forms of plasticity and learning, for example, motor learning. We review the control of OL lineage development, including OL population dynamics and adaptive myelination in the adult CNS.

Oligodendrocytes (OLs), the myelin-forming cells of the central nervous system (CNS), develop from glial progenitor cells, known as "oligodendrocyte precursor cells" (OPCs), which arise from several parts of the ventricular germinal zones of the embryonic neural tube. OPCs proliferate and migrate away from these zones into developing gray and white matter before differentiating into myelin-forming OLs. However, unlike most progenitors, OPCs remain abundant in the adult CNS, where they retain the ability to generate new OLs that allow rapid regeneration of myelin that might be lost through normal aging or disease, as well as changing the pattern of myelination in response to life experience. These cells have been under intense scrutiny since their first discovery (Raff et al. 1983) because it was soon recognized that understanding the cell and developmental biology of OPCs would be key to understanding how to control myelin production and regeneration in CNS diseases and injuries in which myelin destruction is a major cause of pathology and disability. OPCs have also been referred to as "NG2 cells" (because they express the NG2 proteoglycan on their surface) or "polydendrocytes" (because they have multiple processes); for simplicity, we refer to them as OPCs. Here, we provide an overview of the mechanisms that specify OPC generation, their physiological properties, and the pathways that influence their behavior during development. We also consider their role in the adult CNS, with a focus on myelin plasticity.

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VENTRAL AND DORSAL ORIGINS of OLs IN MAMMALIAN SPINAL CORD

OPCs can be identified in fixed CNS tissue by immunohistochemistry and/or in situ hybridization for NG2 or the platelet-derived growth factor receptor (α-subunit, Pdgfra), together with the transcription factors Olig2 and Sox10. NG2 and Pdgfra are down-regulated rapidly when OPCs start to differentiate into OLs, but Sox10 and Olig2 continue to be expressed in mature OLs. OPCs can first be detected in the ventricular germinal zones (VZs) of the brain and spinal cord around midgestation in rodents. In transverse sections of cervical spinal cord small clusters of ($Olig2^+$, $Sox10^+$, $Pdgfra^+$), OPCs appear in the ventral VZ near the floor plate around embryonic day 12.5 (E12.5) in mice, E14 in rats, E6–E7 in chicks, or gestational week 6.5 (~E45) in humans (Fig. 1A–D) (Pringle and Richardson 1993; Timsit et al. 1995; Hajihosseini et al. 1996; Orentas and Miller 1996). They presumably arise by division of radial stem cells (radial glia) in the VZ, one of the daughters retaining contact with the ventricular and pial surfaces and the other daughter (the OPC) losing those contacts, in much the same way that migratory neuronal progenitors are generated, although time-lapse imaging has not been performed to confirm this sequence of events. Soon after they appear, these ventrally derived OPCs proliferate rapidly and migrate in all directions, becoming evenly distributed through the cord in both gray and white matter by ~E15 in mice (Pringle and Richardson 1993).

The ventral "clusters" of OPCs described above are, in fact, cross-sectional views of narrow columns of cells that run all along the length of the spinal cord into the hindbrain and midbrain. The position of the OPCs, close to but not in contact with the floor plate, corresponds to the "pMN" progenitor domain that, just before OPC production, generates motor neurons (MNs). Speculations on the evolutionary significance of this close developmental relationship between MNs and OLs can be found elsewhere (Richardson et al. 1997; Li and Richardson 2008). The molecular mechanisms that cause MNs and OPCs to be generated sequentially from the same progenitor domain, presumably from a common set of radial stem cells, are discussed below (see section Determinants of OPC Specification and Neuron-OPC Fate Switching).

After the initial production of OPCs from the pMN domain in the ventral spinal cord, a second wave of OPC production begins in the dorsal cord at ~E15.5 (Cai et al. 2005; Fogarty et al. 2005; Vallstedt et al. 2005; Tripathi et al. 2011). These dorsally derived OPCs transdifferentiate from radial glia as they retract their apical processes from the central canal toward the pial surface (Fig. 1E,F) (Fogarty et al. 2005). Most radial glia transform into white- and gray-matter astrocytes, but a subset starts to express OPC markers Olig2, Sox10, and Pdgfra. Their endfeet remain attached to the pial undersurface during this process, and, presumably because of this, dorsally derived OPCs do not migrate as widely as ventrally derived OPCs, most of them remaining in the dorsal half of the cord where they gradually displace their ventrally derived counterparts from dorsal axon tracts (Tripathi et al. 2011). Dorsally derived OPCs ultimately make up ~20% of all OPCs in the mouse spinal cord, the remaining ~80% coming from the pMN domain (Fig. 1G) (Tripathi et al. 2011).

Shortly before birth (~E18.5 in mice), some OPCs in the spinal cord start to generate differentiated OLs that express myelin genes, including myelin basic protein (MBP) and the myelin proteolipid protein (PLP); these OLs first appear in the ventral and dorsal funiculi (developing white matter) where they associate with axons and start to elaborate myelin. OL production throughout the white and gray matter gathers pace after birth, reaching a maximum ~2–4 wk postnatal in mice, but continuing for at least 8 postnatal months, although at an ever-decreasing rate (Rivers et al. 2008). The function of the late-born OLs and the myelin they produce is considered later in this review.

VENTRAL VERSUS DORSAL ORIGINS OF OLs IN THE BRAIN

An analogous series of events plays out in the telencephalon (embryonic precursor of the forebrain). OPCs first appear in the ventral VZ of the medial ganglionic eminence ([MGE] ter-

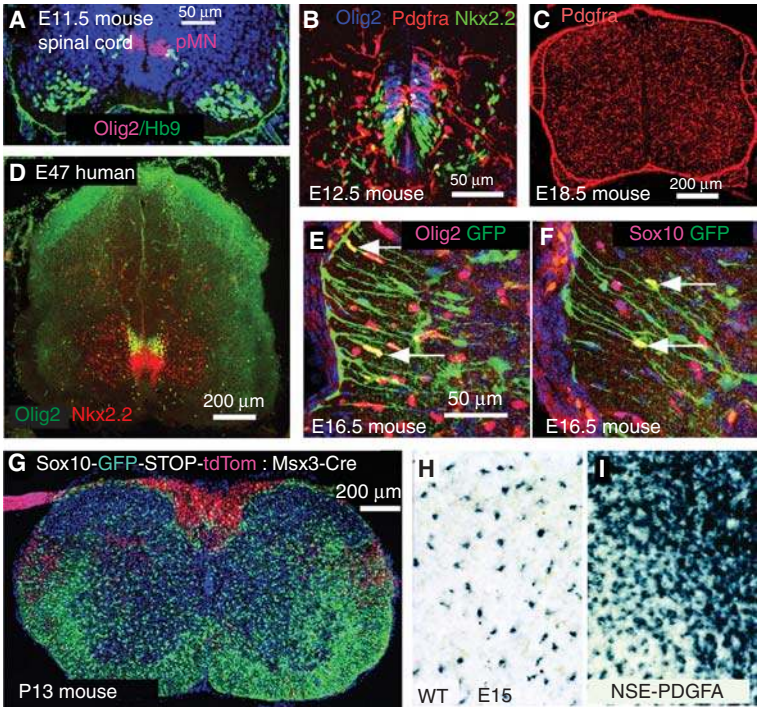

Figure 1. Specification and proliferation of OPCs in the developing spinal cord. (*A*) Neural stem cells in the pMN domain of the embryonic spinal cord near the floor plate express Olig2 (magenta) and make MNs (marked by expression of transcription factor HB9) from ~E9–E12 in mouse. (*B*) Starting on ~E12.5, the pMN stem cells switch to making OPCs, which express Pdgfra (red). The Nkx2.2$^+$ nuclei outside the VZ are mostly interneurons. Pdgfra$^+$ OPCs start to express Nkx2.2 as they migrate away from the midline and up-regulate its expression as they differentiate into OLs. (Images *A* and *B* provided by Dr. Raquel Taveira-Marques.) (*C*) Pdgfra$^+$ OPCs migrate throughout the developing cord and become evenly distributed in future gray and white matter before birth on ~E18.5. (*D*) Specification of OPCs in the ventral human spinal cord follows a similar pattern as mouse; Olig2$^+$ (green) neural stem cells in the pMN domain generate migratory OPCs. Many OPCs at the edges of the VZ coexpress Nkx2.2 (red) in humans. (Image kindly provided by Dr. Pantelis Tsouflas, University of Miami.) (*E*,*F*) Starting ~E16.5 in mouse, some radial glia in the intermediate and dorsal spinal cord start to express OL lineage markers Olig2 and Sox10 (arrows) and transdifferentiate into OPCs. Here, green fluorescent protein (GFP) is expressed under the control of Dbx1, which is expressed in the VZ at the dorsoventral boundary of the cord. (From Fogarty et al. 2005; adapted, with permission, from the investigators). (*G*) A two-color reporter *Sox10-GFP-STOP-tdTom* (tandem-duplicated Tomato), when combined with a dorsally expressed Cre transgene *Msx3-Cre*, labels pMN-derived OPCs/OLs green and dorsally derived OPCs/OLs red. Dorsally derived OL lineage cells are ~20% of the total and mainly populate dorsal and intermediate axon tracts (Tripathi et al. 2011). (*H*) OPCs in the gray matter of the wild-type postnatal cord are evenly spaced. (*I*) In *NSE-Pdgf-A* transgenic mice (which greatly overproduce Pdgf-A in neurons), OPCs (Pdgfra$^+$) proliferate more than normal and pile up in tumor-like masses (van Heyningen et al. 2001). Pdgf-A overexpression also increases OPC numbers in adulthood (Woodruff et al. 2004). WT, wild type.

ritory marked by expression of transcription factor Nkx2.1) ~E12.5 in mice; soon afterward, they begin to be generated from the lateral ganglionic eminence ([LGE] Gsx2 territory) (Fig. 2A–C) (Kessaris et al. 2006). They migrate laterally and dorsally from the MGE and LGE, many as far as the developing cerebral cortex, which they invade in a lateral-to-medial direction from ~E16. Soon after birth, another wave of OPC production starts from the cortical VZ (Emx1 territory) (Kessaris et al. 2006). After birth, MGE-derived OPCs are gradually elimi-

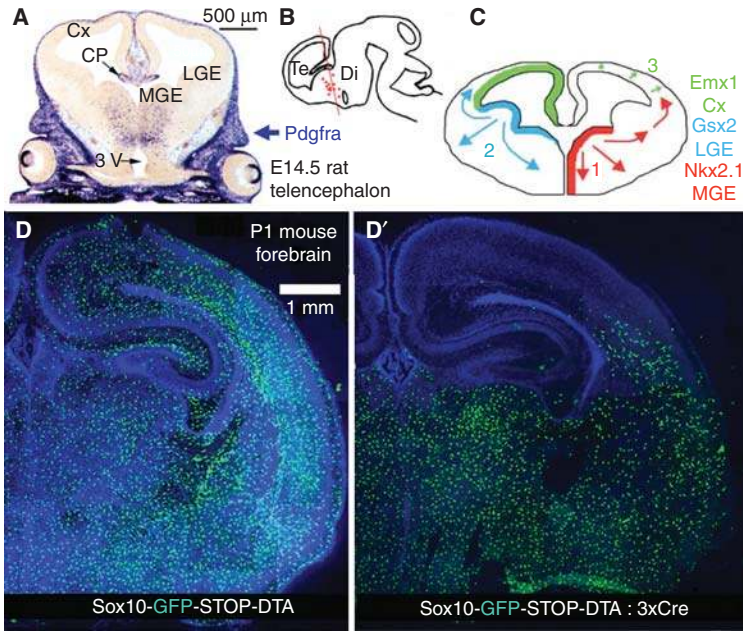

Figure 2. Development of the OL lineage in the forebrain. (*A*) In situ hybridization reveals that the first *Pdgfra*$^+$ precursor cells appear in the ventral VZ (MGE) of the rat telencephalon (forerunner of the forebrain) ~E13.5 (~E12.5 in mice); some of these are OPCs that migrate through the developing forebrain, reaching the cortex (Cx) after ~E17 (~E16 in mice) (Tekki-Kessaris et al. 2001). Note that *Pdgfra* is expressed in many cells and tissues outside the CNS. (*B*) Lateral view of the developing rodent brain, indicating the plane of the section and the position of the *Pdgfra*$^+$ cells in *A*. (*C*) After the first OPCs appear in the MGE (Nkx2.1 territory), a second "wave" of OPCs arises in the LGE (Gsx2 territory) and, after birth, a third wave within the cortical VZ (Emx1 territory). Cortically derived OPCs settle within the cortex and comprise ~80% of all OPCs in the adult cortex (Tripathi et al. 2011). (*D*) A Sox10-driven green fluorescent protein–diphtheria toxin A chain (GFP–STOP-DTA) reporter illustrates the near-uniform distribution of OPCs in the perinatal mouse forebrain (very few OLs are present in the brain at birth). (*D′*) When the same Sox10 reporter is combined with three Cre transgenes (3xCre; Emx1-Cre, Gsx2-Cre, Nkx2.1-Cre), diphtheria toxin A chain (DTA) is expressed and kills the developing OPCs. (Images *D* and *D′* from Iannarelli 2014.) Despite the fact that practically all telencephalic OPCs are eliminated at their source, the ventral forebrain is rapidly repopulated by OPCs that migrate forward from the diencephalon. At birth, the cortex is still almost devoid of OPCs, but is repopulated within the first 2 postnatal weeks; the mice survive and reproduce normally, although their body size is slightly reduced. Cx, cortex; MGE, medial ganglionic eminence; LGE, lateral ganglionic eminence; 3 V, third ventricle; CP, choroid plexus; Te, telencephalon; Di, diencephalon.

nated from the cortex by an unknown mechanism; hence, OPCs in the adult mouse cortex (motor area) are derived mainly from the cortical VZ with an ~20% contribution from the LGE (Tripathi et al. 2011). It is unclear whether OPCs are produced uniformly from all parts of the cortical VZ or preferentially from some regions, for example, the lateral edges of the cortical VZ (Ivanova et al. 2003; Nakahira et al. 2006) and/or the dorsal aspect of the postnatal subventricular zone (SVZ) (Levison and Goldman 1993; Tsoa et al. 2014).

NONMAMMALIAN VERTEBRATES

Early development of OPCs in the avian spinal cord and brain follows a similar pattern as in rodents. For example, (Sox10$^+$, Pdgfra$^+$) OPCs first appear in the ventral VZ of the chick thoracic spinal cord ~E6 (Hamilton–Hamburger stage 29) and migrate from there throughout the cord (Ono et al. 1995). In the chick forebrain, OPCs originate in the ventral telencephalon and disperse from there throughout the ventral and dorsal developing forebrain (Olivier et al. 2001).

It has also been shown that OPCs, destined for chick optic nerves, originate in the VZ at the ventral midline of the diencephalon underneath the third ventricle (Ono et al. 1997). It is likely that this and perhaps other local "oligogenic" zones exist in mammals too, but have yet to be described. These chick studies emphasize ventral origins of OPCs; it is not clear whether the dorsal sources of OPCs described in the mouse spinal cord and forebrain also exist in birds (Olivier et al. 2001). Attempts to address this question for the spinal cord using chick–quail chimeras led to conflicting conclusions for reasons of methodology and interpretation (discussed in Richardson et al. 2006). However, both ventral and dorsal sources have been shown to exist in the embryonic chick midbrain (Fu et al. 2003) and hindbrain (Davies and Miller 2001).

Although some OL lineage markers are common to all vertebrates, the timing of their appearance can vary among species. In the chick spinal cord, for example, monoclonal antibody O4 labels all OPCs from the time of their first appearance in the ventral VZ until after they differentiate into OLs (Ono et al. 1995), whereas, in rats and mice, O4 is not expressed until the early differentiating (premyelinating) stage after Pdgfra is down-regulated (Hall et al. 1996; Bansal and Pfeiffer 1997). Similarly, antibody A2B5, which has been useful for labeling all OPCs (along with other neural precursors) in rats (Raff et al. 1983; Baracskay et al. 2007), labels only a subset of OPCs in mice (Fanarraga et al. 1995). Moreover, zebrafish OPCs appear to lack Pdgfra expression (Park et al. 2002; Mora 2005). These observations illustrate the obvious point that care is needed when generalizing across species—even among different mammals. The remainder of this review deals with mouse development, unless stated otherwise.

DETERMINANTS OF OPC SPECIFICATION AND NEURON–OPC FATE SWITCHING

Development of the ventral spinal cord is directed by diffusible signals, including Sonic hedgehog (Shh) from the notochord and floor plate at the ventral midline, modulated by bone morphogenetic proteins (Bmps) and Wnts from the roof plate at the dorsal midline. This includes specification of OPCs in the pMN progenitor domain (Orentas and Miller 1996; Poncet et al. 1996; Pringle et al. 1996; Mekki-Dauriac et al. 2002; Agius et al. 2004; Miller et al. 2004). Shh, acting through its downstream mediators, the Gli proteins, activates transcription of different sets of lineage-determining genes (primarily transcription factors) at different distances from the floor plate (different concentrations of Shh) (Briscoe and Ericson 2001). In the pMN domain, Shh induces the basic helix–loop–helix (bHLH) transcription factor Olig2, which is absolutely required for sequential generation of MNs and OPCs; in *Olig2* null spinal cords, the pMN is missing, so MNs and OPCs are absent and the animals die at birth (Lu et al. 2002; Takebayashi et al. 2002; Zhou and Anderson 2002). How can this one transcription factor be responsible for two quite different cell types? In wild-type mice, Olig2 is phosphorylated on serine 147 ($Olig2^{S147}$) at early times during and before MN production, but is rapidly dephosphorylated at the time pMN switches to OPC production (Li et al. 2011). This causes Olig2 homodimers to fall apart and, instead, to favor heterodimerization with related bHLH proteins, including neurogenin 2 (Ngn2), altering the activity of Olig2 (e.g., by affecting DNA binding) and contributing to the switch of cell fate (Li et al. 2011).

The Notch signaling pathway collaborates with Shh for OPC specification. Notch and its ligands of the Delta/Jagged family participate in cell contact–mediated signaling to induce and maintain differences between developing cells in many parts of the embryo. In the zebrafish ventral neural tube, Notch signaling between committed neuronal precursors and radial glia keeps the latter in a stem-like state, thereby preserving the pool of precursors available to generate OPCs later; inhibiting Notch signaling globally with the drug DAPT leads to a glut of MNs at the expense of OPCs (Park and Appel 2003; Kim et al. 2008). The phenotypes of zebrafish *Notch3* loss-of-function mutations are consistent with this interpretation (Zaucker et al. 2013). Experiments in chicks and mice also support this general model and indicate

that *Jagged2* is a key Notch ligand responsible for holding back OPC production until the time of the MN–OPC switch (Rabadan et al. 2012). Perhaps Notch-Jagged2 signaling, acting via the transcriptional inhibitor Hes5 (Rabadan et al. 2012), regulates the expression or activity of the phosphatase(s) responsible for dephosphorylating Olig2^{S147}. Notch signaling also plays an important role later during development, when OPCs are maturing to OLs and elaborating myelin (Wang et al. 1998; Hu et al. 2003).

There is no floor plate in the forebrain, but Shh is expressed from early times (E10.5 onward in mice) by precursor/stem cells of the MGE and LGE, in which it auto-induces expression of Olig2 and the closely related Olig1 (Nery et al. 2001; Tekki-Kessaris et al. 2001). The Olig-expressing stem cells generate OPCs that migrate throughout the forebrain after ~E12.5. Olig-positive stem cells also generate neurons, although the lineage relationship among OPCs and forebrain neurons is not well understood. Cholinergic projection neurons, which settle in the ventral forebrain (Furusho et al. 2006), and inhibitory (γ-aminobutyric acid, GABAergic) interneurons, which migrate dorsally to populate the cerebral cortex (He et al. 2001; Yung et al. 2002; Petryniak et al. 2007), are known to descend from Olig-expressing precursors along with OPCs. It is not known whether the phosphorylation state of Olig2^{S147} plays a role in neuron–OPC switching in the forebrain, as it does in the ventral spinal cord.

Fibroblast growth factor (Fgf) signaling also plays an important role in OPC specification in the ventral telencephalon. There are four Fgf receptors (Fgfr1–4), of which Fgfr1–3 are expressed in the developing CNS. Conditional knockout of either *Fgfr1* or *Fgfr2* (but not *Fgfr3*) in the ventral forebrain from ~E10.5, using *Foxg1-Cre*, resulted in a reduction in the number of *Sox10*$^+$, *Pdgfra*$^+$ OPCs in the ventral telencephalon from E12.5–E16; in *Fgfr1/2* double knockouts, OPCs were almost completely absent (Furusho et al. 2011). The expression and activity of Shh were not affected, judging by the continued presence of messenger RNAs (mRNAs) encoding *Shh* and its receptor *Patched* (*Ptc*) (which is transcriptionally activated by Shh) in the ventral telencephalon of the *Fgfr1/2* mutants. Inhibitors of either Hedgehog or Fgf signaling block OPC production in cultures of embryonic forebrain cells, pointing to an obligatory collaboration between Shh and Fgf signaling (Kessaris et al. 2004; Furusho et al. 2011). It is known that Fgf and Hedgehog pathways interact in other contexts (reviewed by Stecca and Ruiz 2010).

Both Shh and Fgf function by inducing *Olig* expression in the neural stem cells on which they act. Olig2 is absolutely required for OPC specification in the spinal cord (Lu et al. 2002; Takebayashi et al. 2002). *Olig1* mRNA, although coexpressed with *Olig2* in the VZ from before E11, is not translated into protein until ~E18.5 (Fu et al. 2009), so Olig1 does not contribute to OPC specification in the spinal cord. However, Olig1 can partially compensate for loss of Olig2 in the embryonic brain because some OPCs are generated in the brains of *Olig2* null mice, but none are generated in *Olig1/Olig2* double knockouts (Lu et al. 2002; Zhou and Anderson 2002).

There is agreement that Olig1 is not required for OPC specification, provided Olig2 is present, but there has been uncertainty over whether Olig1 might play an essential role in later stages of OL development (Lu et al. 2002; Xin et al. 2005). The balance of evidence now suggests that Olig1 is dispensable for OL development and myelination (Paes de Faria et al. 2014), although it appears to be needed for remyelination of demyelinated lesions in the adult CNS (Arnett et al. 2004; also see Emery and Lu 2015).

ARE VENTRALLY AND DORSALLY DERIVED OLs FUNCTIONALLY DISTINCT?

It is likely that ventral sources of OPCs are specified primarily by Shh, but the signals that specify OPCs in the dorsal spinal cord and brain are less well understood. Small numbers of OPCs are produced in the dorsal spinal cord of *Nkx6.1/Nkx6.2* double-null mice, in which Shh signaling in the ventral cord is disrupted (Cai et al. 2005; Vallstedt et al. 2005). OPCs also develop in cultures of Shh null embryonic spinal cord (Cai et al. 2005). These and other experi-

ments (Chandran et al. 2003; Kessaris et al. 2004) point to a Shh-independent pathway for OPC specification in the spinal cord, possibly an Fgf family member, but which one or from which cells is unknown.

That dorsally and ventrally derived OPCs are generated independently, by different signals, raises the question of whether the ventral and dorsal "lineages" might produce OPCs that are functionally distinct. This is a potentially important question to answer because it has implications for the design of future cell-based therapies for repair of demyelinating damage. Different morphological subclasses of OLs have been described that myelinate either many small-diameter axons or only one or a few larger-diameter axons (Bjartmar et al. 1994; Butt et al. 1998a; Anderson et al. 1999). Specialized subsets of OLs have also been suggested on the basis of molecular differences (Butt et al. 1998b; Kleopa et al. 2004). However, a link between OL heterogeneity and developmental origin has not been established. In fact, they appear to be interchangeable. When one group of OPCs was ablated at their site of origin using a Cre-inducible diphtheria toxin (DT) transgene targeted to different regions of the embryonic neuroepithelium with *Nkx2.1-Cre*, *Gsh2-Cre*, or *Emx1-Cre* (Kessaris et al. 2006), OPCs from neighboring regions invaded the targeted area and proliferated to fill the void, ultimately achieving a normal distribution of OPCs and mice that were phenotypically normal. Even when practically all telencepalic OPCs were ablated (in mice carrying all three Cre transgenes plus inducible DT), mice recovered within a few weeks after birth, apparently by forward migration of OPCs from the diencephalon (Fig. 2D) (Iannarelli 2014). This illustrates the remarkable developmental plasticity of OL lineage cells and argues against intrinsic differences among OPCs from different embryonic origins.

An equivalent genetic ablation experiment has not been performed in spinal cord because of a lack of suitable Cre lines. However, experiments with mouse reporters, which distinguish dorsal and ventral lineages, have shown that dorsally derived OPCs displace their ventrally derived counterparts from dorsal axon tracts in the spinal cord during postnatal development (Tripathi et al. 2011a) and have a greater propensity to remyelinate demyelinated lesions during adulthood (Zhu et al. 2011a). It is not known whether this is because the dorsal and ventral lineages are intrinsically specialized for different tasks or the dorsal cells are generated slightly later during development and, hence, remain more "youthful" and better able to compete for limiting mitogens or other extracellular signals. It has, so far, not been possible to distinguish dorsally and ventrally derived OPCs by their antigenic or electrophysiological properties (Tripathi et al. 2011; Clarke et al. 2012). Ultimately, genome-wide screens of expressed genes (e.g., by RNA sequencing) in purified populations of dorsal versus ventral OL lineage cells might determine whether different OL subtypes are linked to their developmental origins.

CONTROL OF OL DEVELOPMENT BY POLYPEPTIDE GROWTH FACTORS

When they first appear in the VZ, mammalian and avian OPCs express Pdgf receptors (α-subunit, Pdgfra) and they survive and proliferate in response to Pdgf-AA secreted from neighboring cells (neurons and astrocytes) (Noble et al. 1988; Raff et al. 1988; Richardson et al. 1988; Hart et al. 1989; Pringle et al. 1992). The Pdgf family comprises four related subunits, Pdgf-A, -B, -C, and -D, encoded by separate genes. Active Pdgf is a dimer with the structure AA, BB, AB, CC, or DD; Pdgfra can bind to and be activated by all of these except Pdgf-DD (Reigstad et al. 2005). In *Pdgf-A* null mice, OPC development is affected more or less severely, depending on the region. The most severely affected areas are optic nerve and spinal cord, in which OPC numbers are reduced $>$ 99% and ~88% at birth; the cerebral cortex and brainstem are less affected (~80% and ~60% reduction, respectively) (Fruttiger et al. 1999). Pdgf-BB and/or Pdgf-CC might be responsible for the residual mitogenic activity in regions less affected by loss of Pdgf-A; for example, *Pdgf-C* is expressed in the developing cerebral cortex (Hamada et al. 2002), although its role in OPC development has not been tested. Pdgf does not act alone,

but requires the coparticipation of extracellular matrix (ECM) molecules and their receptors (integrins) for its mitogenic activity; relevant ECM components include the NG2 proteoglycan (Nishiyama et al. 1996) and Tenascin-C (Garcion et al. 2001), and the key integrin combination appears to be αvβ3, which is phosphorylated and becomes mitogenically active in its own right following physical association with ligand-bound Pdgfra (Baron et al. 2002, 2005).

Fgf family members are also mitogenic for OPCs in culture, particularly in cooperation with Pdgf. When cultured in defined medium containing Pdgf-AA, OPCs divide and differentiate into OLs on a similar pattern as in vivo. A fraction of the daughters of cell divisions survive as OPCs, whereas the remainder differentiate into OLs (Raff et al. 1988; Tang et al. 2000). When cultured in Pdgf-AA (or -AB) and basic Fgf (Fgf2), they continue to divide without differentiating for an extended period (Bögler et al. 1990; McKinnon et al. 1990), expanding OPC numbers seemingly indefinitely. Despite this striking effect in vitro, conditional deletion of Fgf receptors has revealed very little involvement of Fgf in controlling OPC proliferation in vivo (see below).

The repertoire of Fgfr's expressed by OL lineage cells changes as OPCs mature and differentiate in vitro (Fortin et al. 2005). Fgfr1 and Fgfr3 are both expressed by purified primary OPCs in culture; signaling through Fgfr1 (e.g., by Fgf2) stimulates proliferation, whereas signaling via Fgfr3 (e.g., by Fgf8) does not affect DNA synthesis or cell division, but inhibits terminal differentiation to OLs (Butt and Dinsdale 2005; Fortin et al. 2005). Despite these findings, conditional deletion of *Fgfr1* or *Fgfr2* in the ventral telencephalon (using *Foxg1-Cre*) did not affect OPC proliferation rate in vivo (Furusho et al. 2011). Germline knockout of *Fgf2* (expression of which normally increases in the CNS in the second postnatal week) also did not affect OPC proliferation in the developing spinal cord, but increased the number of differentiated OLs, suggesting that signaling through Fgfr1 in OPCs normally inhibits OL differentiation (Murtie et al. 2005). Deletion of both *Fgfr1* and *Fgfr2* in differentiated OLs (using *Cnp-Cre* or *Olig1-Cre*) resulted in reduced activity of the mitogen-activated protein kinase (MAPK) pathway, inhibition of myelin protein synthesis, and thinner myelin sheaths over the long term (Furusho et al. 2012), suggesting that Fgf signaling normally stimulates myelin synthesis by differentiated OLs.

Fgfr3 is strongly expressed by neural stem cells and astrocytes, so that in situ hybridization for *Fgfr3* or recombination of a reporter transgene by *Fgfr3-CreER* preferentially marks those cells, not OPCs (Pringle et al. 2003; Young et al. 2010). Fgfr1/2 (but not Fgfr3/4) are also highly expressed by many neurons, so alteration of Fgf signaling in these cells might indirectly affect OL lineage cells in vivo. Clearly, Fgf signaling in the normal CNS is very complex and could be further modulated by disease or injury in ways that are difficult to predict, and experimentally challenging to investigate, because of the large number of Fgf family members that could potentially be involved (22, at least 18 of which are expressed in the CNS) (Ford-Perriss et al. 2001). The role of FGF signaling in CNS pathology, for example, in the impairment of OL differentiation, which is believed to occur in chronic multiple sclerosis (MS) lesions, is an important research area that warrants further attention.

Epidermal growth factor (Egf) has a profound effect on the production of OPCs in vivo, greatly increasing numbers of OPCs when Egf is delivered into the intact adult CNS and significantly improving the repair of demyelinating damage caused by gliotoxin injection or perinatal ischemia (Cantarella et al. 2008; Scafidi et al. 2014). In this context, Egf is likely to act by steering SVZ stem cells away from their default fate (generation of olfactory interneurons) toward production of glial cells, including OPCs (Sun et al. 2005; Cantarella et al. 2008; Gonzalez-Perez and Alvarez-Buylla 2011). In keeping with this interpretation, SVZ stem cells express high levels of the Egf receptor (Egfr, ErbB1), whereas OPCs do not (Chojnacki and Weiss 2004; Sun et al. 2005; Cahoy et al. 2008), and Egf has been reported not to stimulate proliferation of OPCs or other neural cells outside of the SVZ in slice culture (Hill et al. 2013).

A large number of other polypeptides and their receptors have been reported to influence proliferation, differentiation, and/or survival of OL lineage cells. These include members of the transforming growth factor (Tgf)-β/bone morphogenetic protein (Bmp) family (See and Grinspan 2009; Dutta et al. 2014; Palazuelos et al. 2014), insulin-like growth factor-1 (McMorris et al. 1986; D'Ercole and Ye 2008), neuregulins (Canoll et al. 1996; Vartanian et al. 1999; Fernandez et al. 2000; Carteron et al. 2006; Brinkmann et al. 2008; Taveggia et al. 2008; Ortega et al. 2012), Wnts (Shimizu et al. 2005; Fancy et al. 2009; Ye et al. 2009; Langseth et al. 2010; Dai et al. 2014), neurotrophin-3 (Barres et al. 1993; Cohen et al. 1996), chemokines (Robinson et al. 1998; Dziembowska et al. 2005; Göttle et al. 2010), ciliary neuronotrophic factor (Barres et al. 1993), brain-derived neurotrophic factor (Vondran et al. 2010; Wong et al. 2013), transferrin (Silvestroff et al. 2013), erythropoetin (Sugawa et al. 2002), thyroid hormone (TH; triiodothyronine) (Walters and Morell 1981; Barres et al. 1994; Ahlgren et al. 1997; Rodriguez-Pena 1999), retinoic acid (Barres et al. 1994; Noll and Miller 1994), and others. Most of these factors influence the differentiation of OLs and/or their subsequent survival including, perhaps especially, during demyelination and remyelination. Apart from diffusible or contact-mediated signals such as these, there has been an explosion of interest in the regulatory roles played by electrical signals between neurons and OL lineage cells. This is discussed in detail below (see section Axoglial Synaptic Signaling and Development).

OL POPULATION DYNAMICS AND HOMEOSTASIS IN VIVO

OPCs proliferate when cultured in defined medium containing Pdgf. If passaged in medium lacking TH, they proliferate for many generations without differentiating (Barres et al. 1994), but if TH is present, cell division and differentiation occur simultaneously, apparently recapitulating OL lineage development in vivo (Tang et al. 2000). When single OPCs are cultured on their own with Pdgf and TH, they divide a predictable number of times before all progeny differentiate into OLs (Temple and Raff 1985). The younger the tissue from which OPCs are isolated, the more divisions they undergo before differentiating, giving rise to the idea that OPCs have an intracellular timer that determines when they should stop dividing and differentiate (Temple and Raff 1986; Durand and Raff 2000). This timer apparently requires Pdgf to keep it running and TH to trigger differentiation at the allotted time (Barres et al. 1994; reviewed by Durand and Raff 2000). However, clonal analysis in mixed cell cultures (Zhang and Miller 1995; Ibarrola et al. 1996) or live mice (Zerlin et al. 2004; Kang et al. 2010; Zhu et al. 2011) shows that the progeny of a given proliferating OPC do not necessarily differentiate synchronously as they do in single-cell culture; clones of OL lineage cells frequently contain both cycling OPCs and myelinating OLs. Temporal and spatial control of differentiation in vivo is complex; the cell-intrinsic timing program in OPCs is presumably controlled and modified by signals from neighboring cells. What is the nature of those signals?

When Pdgf is withdrawn from OPC cultures that contain TH in the medium, all OPCs stop dividing together and differentiate into OLs (Durand and Raff 2000). This is accompanied by rapid down-regulation of Pdgfra, but the latter is thought to be a consequence of differentiation, not the trigger (Hart et al. 1989). Nevertheless, it could be diminishing activity of the Pdgf signaling pathway upstream of or downstream from the receptor that leads OPCs to exit the cell cycle and differentiate in vivo. The cell division rate of OPCs declines during embryonic development, cell-cycle time increasing from ~24 h in the E12.5 mouse spinal cord to >100 h at E17 (van Heyningen et al. 2001), and this seems to be a consequence of declining Pdgf signaling because the cell cycle of E17 OPCs is accelerated by placing them in dissociated cell culture with saturating concentrations of Pdgf (van Heyningen et al. 2001). Overexpressing Pdgf-A in transgenic mice under the control of an astrocyte or a neuron-specific promoter (astrocytes and neurons are normal

sources of Pdgf-A) leads to an increase in the population density of OPCs in the white or gray matter, respectively (Fig. 1H,I) (Calver et al. 1998; Fruttiger et al. 2000; van Heyningen et al. 2001). Moreover, in *Pdgf-A*$^{+/-}$ embryos, the density of OPCs is reduced to ~50% of normal (van Heyningen et al. 2001), showing that the normal density of OPCs in vivo (at least in the spinal cord) is determined by the Pdgf supply, not solely by cell-intrinsic mechanisms. Remarkably, the cell-division rate of OPCs, at steady state, was found to be the same in different transgenic lines with different levels of Pdgf-A expression (Calver et al. 1998; van Heyningen et al. 2001). This led to the proposal that the population density of OPCs is determined by the balance between the rate of provision of Pdgf (by neurons and/or astrocytes) and the rate of consumption by OPCs themselves, that is, the OPC population expands until the rate at which it removes Pdgf from the system by receptor binding and internalization matches the rate of supply. At that point, any further increase in the number of OPCs reduces the Pdgf concentration below the limit required to prevent OPCs from exiting the cell cycle; some OPCs then differentiate, down-regulating Pdgfra and reducing demand for Pdgf. This, in turn, allows Pdgf to rise above the threshold for cell division, and so on, leading to a stable steady state (van Heyningen et al. 2001).

Although this "supply and demand" model can explain why the cell cycle slows down as the number of OPCs increases during embryonic development, it does not explain what causes OPC proliferation to continue slowing during postnatal life while the OPC number remains roughly constant (Rivers et al. 2008; Young et al. 2013). For example, the cell cycle of OPCs in the corpus callosum slows from ~3 d at P21, to ~10 d at P60, to >100 d at P240 (Psachoulia et al. 2009; Young et al. 2013). If, for example, there was a diminishing rate of Pdgf synthesis and secretion with age of the animal, then, according to the supply-and-demand model, there should be a decline in the number of OPCs per unit volume, but ultimately no change in division rate. The persistent slowing could be explained by a diminishing mitogenic responsiveness of OPCs to Pdgf, and a parallel reduction in their rate of differentiation (or they would all differentiate and the OPC population would be depleted). This returns us to the idea of a cell-intrinsic timer, not one that triggers synchronous differentiation after a fixed time, but one that controls cell-cycle transition probabilities, from $G_1 \rightarrow S$ and from $G_1 \rightarrow G_0$. There might be a steady accumulation with age of intracellular activities that inhibit cell-cycle progression, such as the inhibitory proteins $p27^{Kip1}$ and $p57^{Kip2}$ (Durand et al. 1998; Durand and Raff 2000; Dugas et al. 2007), coupled with diminishing activity of differentiation-inducing or -permissive pathways (Tokumoto et al. 2001; Billon et al. 2004).

OPCs assume a bipolar shape and migrate radially and tangentially into the developing spinal cord and brain as they exit their germinal zones. The factors that promote their dispersion are not well understood, but are likely to involve contact-mediated interactions using molecules similar to those that guide neuronal migration, including Netrin/DCC/Unc5, Semaphorin/Neuropilin, and Ephrin/Eph (de Castro and Bribian 2005). For example, in the embryonic spinal cord, Netrin-1 is secreted by the floor plate, whereas OPCs express the Netrin-1 receptors DCC and UNC5. Netrin-1 repels OPCs in vitro (Tsai et al. 2003) and mice deficient in Netrin-1 show impaired dorsoventral migration of OPCs (Jarjour et al. 2003). OPCs also express the Neuropilin 1 receptor and its ligand Sema3A repels OPCs in vitro (Sugimoto et al. 2001; Spassky et al. 2002; Syed et al. 2011); they also express Neuropilin 2, and its ligand Sema3F attracts OPCs. Nevertheless, persistent OPC migration deficits have not been observed in mice lacking these individual components, suggesting that there may be several redundant pathways that regulate their early migration. Growth factor availability and repulsion brought about by increases in OPC density also influence their dispersion. In Pdgfra null mice, the proliferation of OPCs is inhibited and dispersion is reduced, resulting in profound deficits in myelination in most regions of the CNS (Fruttiger et al. 1999). This suggests that Pdgf not only promotes proliferation, but also enables cell

movement, perhaps by forcing repulsive interactions (see below).

Gray matter OPCs show a radial morphology, extending highly ramified processes ~25 μm into the surrounding neuropil, whereas, in white matter, their processes are oriented parallel to traversing axons. Time-lapse imaging of fluorescently labeled OPCs in the upper layers of the cortex using two-photon microscopy has revealed that these cells are not static, but continuously reorient their processes and move through the brain parenchyma at an average rate of 2 μm/d (Hughes et al. 2013). Each OPC process is studded with numerous filopodia, which extend and retract on a timescale of seconds, and dynamic growth cones are visible at the leading edge of extending processes. This behavior is reminiscent of the scanning behavior shown by microglia (Davalos et al. 2005; Nimmerjahn et al. 2005) and suggests that OPCs actively survey their local environment. When a filopodium makes contact with an adjacent process on the same cell, or on a neighboring cell, it invariably retracts. This powerful self-inhibition provides a means for OPCs to maintain discrete territories despite their active growth. By analogy to amacrine cells in the retina, which show a similar radial morphology and tiling, these repulsive cues might not only control cell spacing, but might also establish and maintain nonoverlapping, radially oriented processes on each cell (Kay et al. 2012). Expression profiling has revealed that OPCs express transcripts for proteins implicated in controlling dendritic spacing and cell body position in neurons (Cahoy et al. 2008), but the repulsive cues used by OPCs, whether secreted or membrane bound, remain to be determined.

OPCs IN THE ADULT CNS: ROLES IN HEALTH AND DISEASE

A large population of Pdgfra$^+$, NG2$^+$ OPCs persists beyond perinatal development into adulthood when they comprise ~5% of all neural cells; these are distributed nearly uniformly throughout the brain and spinal cord in both white and gray matter (Fig. 3A) (Pringle et al. 1992; Chang et al. 2000; Dawson et al. 2003). This was initially a surprise and "adult OPCs" came under scrutiny as a novel glial cell type in their own right (Berry et al. 2002; Butt et al. 2002; Greenwood and Butt 2003). When encountered by physiologists, they were often confused with astrocytes, and they referred to them as "complex astrocytes" or "GluR astrocytes." OPCs are the major proliferating cell type in the mature CNS (Dawson et al. 2003), yet their numbers remain more-or-less constant during postnatal life (Rivers et al. 2008), raising the question of what becomes of their excess progeny. The answer must be that half of the daughters of each OPC cell division, on average, either differentiate or die. The realization that there are dividing multipotent stem cells in the adult SVZ and hippocampus fueled speculation that OPCs might be yet another population of stem cells with broad differentiation potential. However, genetic lineage-tracing experiments in mice (using tamoxifen-inducible CreER) indicate that OPCs are lineage restricted and overwhelmingly generate OLs in adulthood (Fig. 3B,C) (Dimou et al. 2008; Rivers et al. 2008; Kang et al. 2010; Zhu et al. 2011b). Following injury or disease, the situation might change slightly, as several studies indicate that adult OPCs can expand to include some astrocytes (glial fibrillary acidic protein [GFAP] expressing) and also myelinating Schwann cells (Dimou et al. 2008; Barnabé-Heider et al. 2010; Tripathi et al. 2010; Zawadzka et al. 2010; Komitova et al. 2011), although the majority of differentiated progeny are still OLs (reviewed by Richardson et al. 2011; Franklin and Goldman 2015). A notable exception is a report (Tatsumi et al. 2008) that Olig2$^+$ OPCs generate exclusively protoplasmic astrocytes following freeze–thaw damage to the cerebral cortex. This result might be explained if Olig2 function was compromised somehow (e.g., by cold) because inactivating *Olig2* in OPCs using *NG2-Cre* has been shown to cause cortical OPCs to develop into protoplasmic astrocytes rather than OLs (Zhu et al. 2012).

The in vivo fate-mapping experiments described are something of a setback for the hope that OPCs might represent a distributed pool of multipotent stem cells that can potentially be

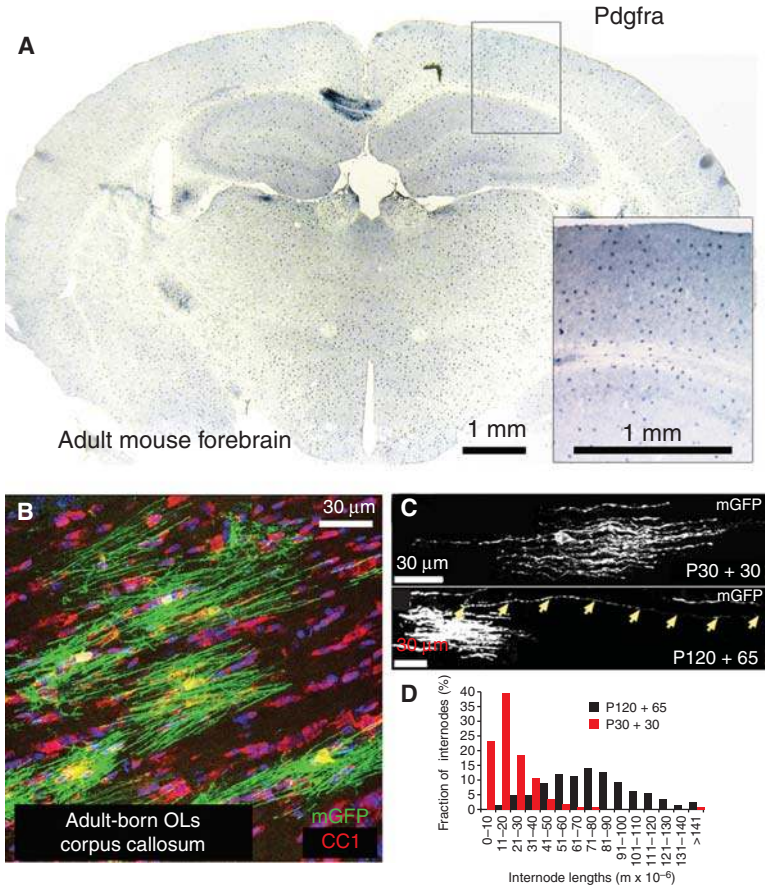

Figure 3. OPCs persist in the adult CNS. (*A*) In situ hybridization for *Pdgfra* reveals many OPCs scattered more or less uniformly throughout the adult brain (~20-μm section). The *inset* shows a region of the cortex (marked by a rectangle) at higher magnification. (*B*) These adult OPCs continue to divide and generate myelinating oligodendrocytes (OLs) in the gray and white matter throughout at least the first year of life in mice (newborn OLs visualized in *Pdgfra-CreER*^{T2}*: Tau-mGFP* transgenic mice, recombination induced by tamoxifen injection on P60 and analyzed 1 mo later. (Image kindly provided by Dr. Sarah Jolly.) (*C*) Adult-born (after P120, *lower* panel) OLs in the optic nerve have shorter internodes, but many more of them than OLs born earlier (e.g., after P30, *upper* panel). Tamoxifen was injected at P30 or P120 and the animals analyzed after 30 or 65 d, respectively. Adult-born OLs frequently also have one or two very long internodes (yellow arrows), which might represent first-time myelination of the very small number of unmyelinated axons present in the adult optic nerve. (*D*) Distributions of internode lengths of OLs born after P30 (red) or P120 (black). (Panels *C* and *D* from Young et al. 2013; reprinted, with permission, from Elsevier Limited © 2013.)

steered into a range of neural lineages to replace neurons, which are lost during neurodegenerative diseases. Nevertheless, there has been a recent report that OPCs can produce new neurons in the adult hypothalamus (Robins et al. 2013), potentially contributing to the function of circuits that control body homeostasis (e.g., appetite and satiety). Previous reports that OPCs might generate small numbers of new projection neurons in the adult piriform cortex (olfactory cortex) (Rivers et al. 2008; Guo et al. 2010) were not substantiated subsequently (Kang et al. 2010; Clarke et al. 2012).

Despite the perpetual loss and addition of OPCs in the adult CNS through cell death and differentiation, their numbers remain re-

markably constant. How is this homeostasis achieved? Although new OPCs can be generated from SVZ progenitors (Jablonska et al. 2010), particularly following demyelination, maintenance of the OPC population in the normal brain appears to rely primarily on local interactions: in vivo imaging indicates that loss of one cell through differentiation, apoptosis, or laser-ablation is accompanied by rapid division of an immediately adjacent OPC (Fig. 4A–D) (Hughes et al. 2013). These observations suggest that all OPCs have the capacity to enter the cell cycle, and replacement is achieved, not by mobilizing SVZ progenitors or by the actions of a subset of

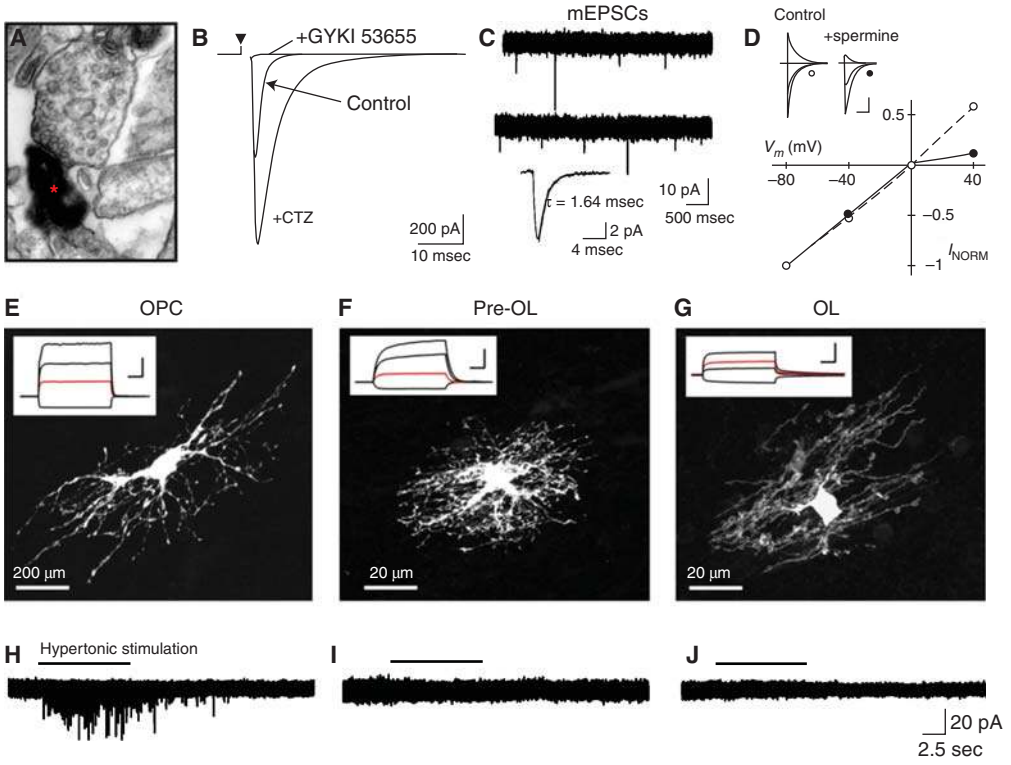

Figure 4. Synaptic signaling between neurons and oligodendrocyte precursor cells (OPCs). (*A*) Electron micrograph from a rat hippocampal brain slice in which one physiologically defined OPC was loaded with biocytin during a whole-cell recording and processed for peroxidase. A process of this cell (red asterisk) is visible as a postsynaptic partner to an axon terminal. (*B*) Whole-cell voltage-clamp recording from an OPC in the molecular layer of the cerebellum, showing the response to stimulation of a climbing fiber in control conditions, when cyclothiazide (CTZ) was used to block AMPA-receptor desensitization, and AMPA receptors were blocked with GYKI 53655. (*C*) Miniature excitatory postsynaptic currents (mEPSCs) recorded in the presence of tetrodotoxin (to block action-potential-dependent release of glutamate) from an OPC in the molecular layer of the cerebellum. *Inset* at *bottom left* shows the average mEPSC waveform and a single exponential fit (tau) to the rapid decay of the mEPSC. (*D*) Current-to-voltage relationship of EPSCs elicited in cerebellar OPCs by climbing fiber stimulation (open circles). Inclusion of the polyamine spermine increased inward rectification (filled circles), a hallmark of Ca^{2+}-permeable AMPA receptors. *Inset* at *top left* shows selected responses from each configuration. (*E–G*) Fluorescent images of OL lineage cells at different stages of maturation. Cells were filled with neurobiotin through the whole-cell electrode. The membrane properties of the cells are shown in the *inset* in the *upper left*. (*H–J*) Recordings of mEPSCs elicited in OPCs, premyelinating OLs (pre-OL) and mature OLs, by focal application of hypertonic solution during the indicated time periods (black bars). Note that mEPSCs are only observed in cells in the OPC stage. (Panel *A* adapted from Bergles et al. 2000; panels *B–D* from Lin et al. 2005; reproduced, with permission, from Elsevier Limited © 2005; panel *E* based on data from De Biase et al. 2010.)

highly proliferative OPCs, but rather through the homeostatic behavior of all members of the population. This is consistent with the fact that 100% of OPCs can incorporate the thymidine analogs BrdU or EdU if provided for a sufficient length of time (Kang et al. 2010; Young et al. 2013). It is not known what determines which of the many surrounding OPCs will divide after ablation of one of their number; however, OPC division is typically preceded by enhanced growth of a neighboring OPC into the territory of the lost OPC (Fig. 4D), raising the possibility that cell size, polarization, or enhanced access to mitogens, such as Pdgf (van Heyningen et al. 2001), could be the trigger for cell division (see section OL Population Dynamics and Homeostasis In Vivo).

The maintenance of OPCs in the adult CNS, and their near-complete coverage of the neuropil through tiling, might enable OPCs to monitor the local state of myelination and respond rapidly to demyelination or if there were a physiological demand for new myelin (see section Adaptive Myelination in Adulthood). Given this powerful homeostasis, it is surprising that the density of OPCs is substantially reduced in many demyelinated lesions from postmortem MS patients (Lucchinetti et al. 1999; Chang et al. 2000; Boyd et al. 2013), indicating that their homeostatic control is disrupted. If local interactions are required to detect demyelination, this loss of cells could influence the timing and extent of OL regeneration. Recent studies suggest that changes in the expression of Sema3A and Sema3F might contribute to this impaired recruitment (Boyd et al. 2013). Changes in the composition of the ECM within lesions and local exposure to cytokines might also alter their capacity to maintain their population density within lesions. Understanding the hierarchy of these signaling pathways and their spatial and temporal control will be required to comprehend their combined influences on myelin repair.

OPCs retain some of their progenitor characteristics in the adult CNS, including the ability to proliferate and migrate, features that might be crucial for detecting injury and mounting a rapid reparative response. However, preserving cells with these characteristics throughout life also carries significant risk, as OPCs appear to be particularly prone to transform to a state of uncontrolled growth. The expression of OL lineage genes by cells in some human gliomas (Robinson et al. 1998; Dougherty et al. 2012) has led to the suggestion that OPCs are a cell of origin for some CNS tumors. Indeed, deletion of the tumor suppressor genes P53 and the neurofibromatosis-related protein NF-1, or expression of an activated allele of the EGF receptor (*v-erbB*) within OPCs, triggers hyperproliferation and tumor formation (Persson et al. 2010; Liu et al. 2011). Moreover, direct injection or transgenic overproduction of Pdgf also leads to gliomas that contain cells with features of OPCs (Assanah et al. 2006; Lindberg et al. 2009; Persson et al. 2010; Nazarenko et al. 2011), suggesting that even genetically normal OPCs can be transformed when presented with surplus mitogens (also see Fig. 1H,I). A key step in their transformation might be down-regulation of pathways responsible for self-repulsion or the ability of growth factors to override self-repulsion. From an evolutionary perspective, it appears that the benefits provided by these cells in the adult CNS outweigh the risks associated with their propensity to transform into cancer cells.

AXOGLIAL SYNAPTIC SIGNALING AND DEVELOPMENT

The initial characterization of OPCs (then known as O-2A progenitors) in vitro revealed that they express a variety of receptors for neurotransmitters, including glutamate (both AMPA and *N*-methyl-D-aspartate [NMDA] receptors), GABA, and acetylcholine (Barres et al. 1990; Wyllie et al. 1991), observations that were confirmed by recording from OPCs in acute brain slices (Jabs et al. 1994; Steinhäuser et al. 1994) and gene expression profiling (Patneau et al. 1994; Seifert et al. 1997; Cahoy et al. 2008). These discoveries indicated that neurotransmitters might be used to alter the behavior of OPCs in response to the demands of surrounding neurons. OPCs also express a diverse complement of voltage-gated ion channels, including Na^+, K^+,

and Ca^{2+} channels (reviewed by Bergles 2012) and, early in development when their membrane resistance is high, they can generate small Na^{+}-dependent spikes when depolarized (Chittajallu et al. 2004; Káradóttir et al. 2008; De Biase et al. 2011). Moreover, OPCs appear to be the only glial cells that form direct synapses with neurons. OPCs form synapses with glutamatergic neurons in all gray and white matter regions that have been examined, including the hippocampus (Bergles et al. 2000; Jabs et al. 2005), cerebellum (Lin et al. 2005), cortex (Chittajallu et al. 2004), brainstem (Muller et al. 2009), and white matter tracts (Káradóttir et al. 2005; Kukley et al. 2007; Ziskin et al. 2007). In gray matter, they also form synapses with GABAergic neurons (Lin and Bergles 2004; Jabs et al. 2005; Mangin et al. 2008; Tanaka et al. 2009; Velez-Fort et al. 2010), suggesting that synaptic signaling is an important and highly conserved property of OPCs. Glutamatergic axon–OPC synapses are formed early in development and become more robust (larger currents, more abundant inputs) with age, paralleling the normal development of synapses that occurs in surrounding neurons, whereas GABAergic signaling in the cortex changes from synaptic to extrasynaptic with age (Velez-Fort et al. 2010). Unlike neurons, which participate in circuits as both presynaptic and postsynaptic partners, OPCs appear to be exclusively postsynaptic and receive input from neurons, rather than the reverse.

What is the evidence that OPCs engage in direct synaptic communication with neurons? There is both morphological and physiological evidence. In electron micrographs, discrete physical contacts between axons and OPC processes have been observed; at these sites, the axon and OPC membranes are rigidly aligned and separated by electron dense material and clusters of synaptic vesicles are found near the presynaptic membrane (Fig. 5A) (Bergles et al. 2000; Kukley et al. 2007; Ziskin et al. 2007; Haberlandt et al. 2011). Electrical stimulation of axons induces inward currents in nearby voltage-clamped OPCs that begin with minimal delay and show rapid increase and decay kinetics, comparable to excitatory postsynaptic currents recorded in neurons (Fig. 5B). These events are blocked by AMPA receptor-specific antagonists and are sensitive to compounds that modulate AMPA receptor kinetics (e.g., cyclothiazide); in appropriate conditions, GABAergic synaptic events can also be induced. Interestingly, activation of GABA-A receptors induces depolarization rather than hyperpolarization as a result of their high intracellular Cl^{-} concentration, as seen in immature neurons (Lin and Bergles 2004; Tanaka et al. 2009). Moreover, spontaneous, quantal miniature excitatory postsynaptic currents (mEPSCs) are visible in these cells when axonal action potentials are blocked, indicating that the amount of glutamate in a single synaptic vesicle is sufficient to induce rapid, synchronous activation of AMPA receptors, showing that glutamate is released in close proximity to these receptors (Fig. 5C).

Remarkably, OPCs retain synapses even during cell division (Kukley et al. 2008; Ge et al. 2009), which occurs through a fission-like process that allows each of the two daughter cells to inherit half of the original processes (Hughes et al. 2013). Nevertheless, because OPCs continually reorient their processes as they move through the parenchyma, whereas axons are stable and immobile (De Paola et al. 2006), it appears that these axon–OPC synapses must be transient structures. They are also transient within the lineage. AMPA and NMDA receptor expression is rapidly down-regulated and synapses are removed when OPCs begin to differentiate, indicating that the precursor stage is uniquely specialized to engage in rapid communication with neurons (De Biase et al. 2010; Kukley et al. 2010). In neurons, excitatory synapses induce depolarization to allow Ca^{2+} influx through NMDA receptors and voltage-gated Ca^{2+} channels, and initiate action potentials to induce changes in synaptic strength, gene expression, and to enable rapid transfer of information. The function of these inputs to OPCs is less clear. The resting membrane potential of OPCs is close to the equilibrium potential for K^{+} (~ -90 to -100 mV), that is, $\sim$20 mV more negative than in neurons, and unitary synaptic events elicit only small depolarizations. Moreover, OPCs are not excitable, in general, and do not possess an axon; thus, they do not

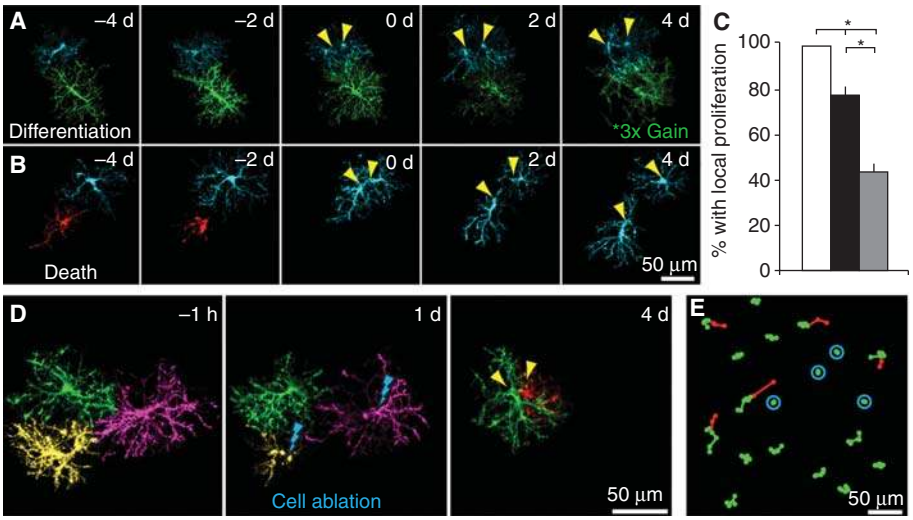

Figure 5. Homeostatic control of OPC density in the adult CNS. (*A*,*B*) Images of fluorescently labeled OPCs in the adult mouse somatosensory cortex (*NG2-mEGFP* mouse), collected using two-photon imaging through a cranial window. Individual cells have been digitally extracted from image stacks and pseudocolored. (*A*) Differentiation of the green cell is accompanied by division of the immediately adjacent blue cell to maintain a constant density of OPCs. (*B*) Death of the red cell is accompanied by division of the immediately adjacent blue cell; note that one of the blue sister cells migrates into the territory formerly occupied by the red cell. Time in days (d) is represented in the *upper right* corner. (*C*) Graph of the percentage of time that differentiation (white bar) or death (black bar) was associated with proliferation of an immediately adjacent OPC; the gray bar is the chance of observing proliferation of a neighbor. (*D*) Fluorescent image of three pseudocolored OPCs in vivo, as described above. Ablation of the yellow and magenta OPCs using the Ti:Sapphire laser–triggered division of the adjacent green OPC. h, hour. (*E*) Laser ablation of multiple OPCs triggers local proliferation and migration of nearby OPCs to fill the voids left by the ablated cells. Green dots represent the positions of the cell bodies of individual OPCs, red dots/lines represent the cell body positions after cell ablation. Cells targeted for ablation are circled in blue. (Adapted from data in Hughes et al. 2013.)

appear to play a conventional role in neuronal circuits. However, AMPA receptors expressed by OPCs in some brain regions (Lin et al. 2005) show high Ca^{2+} permeability (Fig. 5D), resulting from expression of the GluA2 (GluR2) AMPA receptor subunit, which might enable signal transduction without substantial depolarization, and NMDA receptors expressed by these cells show reduced Mg^{2+} sensitivity, allowing Ca^{2+} influx at more negative potentials (Káradóttir et al. 2005). Indeed, activation of these NMDA receptors on OPCs can induce changes in the composition and abundance of AMPA receptors (Ge et al. 2006). The latter are also modulated by the Cornichon and TARP accessory proteins (Zonouzi et al. 2011; Coombs et al. 2012), which control the trafficking and kinetics of AMPA receptors in neurons, so axon–OPC synapses appear to have considerable capacity for modification.

Studies in vitro in dissociated cells or brain slices indicate that stimulation of AMPA receptors with exogenous agonists reduces OPC proliferation, whereas blocking AMPA receptors inhibits differentiation (Gallo et al. 1996; Yuan et al. 1998; Gudz et al. 2006). However, these pharmacological manipulations are unable to distinguish between effects on OPCs and effects on neurons, as both cell types express similar receptors. Selective genetic knockout in OL lineage cells of the GluN1 (NR1) subunit, which is required to form functional NMDA receptors, did not alter the proliferation of OPCs or their morphology, density, or distribution, their ability to differentiate, or to generate myelinating OLs (De Biase et al. 2011; Guo et al. 2012).

However, OPCs deficient in NMDA-receptor signaling had slightly higher AMPA Ca^{2+} permeability (De Biase et al. 2011), suggesting that NMDA receptors might play a role in activity-dependent modification of neuron-OPC signaling. Note that the expression of functional NMDA receptors is substantially lower in OPCs than in neurons and NMDA receptor contributions to synaptic responses have not been reported, raising the possibility that these receptors are primarily extrasynaptic. Determining the role of AMPA receptor signaling through similar genetic manipulations is more challenging, as they are tetrameric receptors formed from combinations of subunits encoded by four distinct genes, all of which appear to be expressed by OPCs (Seifert et al. 1997; Cahoy et al. 2008), and, unlike NMDA receptors, functional homomeric receptors can be formed by combining individual subunits.

Why would OPCs use synapses for signaling, given the high energetic cost of expressing the many proteins required to form these connections and the need to continually dissolve and reform synapses because of the OPC's migratory behavior? The formation of transient synapses by OPCs allows them, periodically, to sample the patterns of activity of axons in their immediate vicinity. Unlike volume transmission, which is used by neuromodulatory transmitters (e.g., norepinephrine and serotonin) that are released at a distance to produce general changes in cellular activity, synapses enable highly specific, exclusive interactions between partners, allowing the postsynaptic cell to monitor and be influenced by continuously changing patterns of activity in the presynaptic cell. It has been known for a long time that blocking action potential propagation with the sodium channel blocker tetrodotoxin (TTX) can inhibit developmental myelination (Barres and Raff 1993; Demerens et al. 1996), and, conversely, artificial or physiological stimulation of neural circuits in adulthood can stimulate OPC proliferation and production of myelinating OLs along the active pathways (Li et al. 2010; Simon et al. 2011; Gibson et al. 2014; McKenzie et al. 2014). Electrical activity can also stimulate local myelin protein synthesis, leading to thickening of the myelin sheaths (decreased G ratios) in active fiber tracts (Wake et al. 2011; Gibson et al. 2014). However, it is not yet known whether axon–OPC synapses are involved in this regulation. Apart from their predominant role in electrical communication, synapses can also provide an entry-point for retrograde signals, such as growth factors (e.g., BDNF) or neuromodulators (e.g., endocannabinoids), as well as being foci for reciprocal cell–cell signaling (e.g., by integrins), potentially influencing the presynaptic cell to enhance or diminish axon excitability, speed of action potential transmission, axonal sprouting, or myelination. Future in vivo studies involving selective disruption of synaptic signaling in OPCs, for example, by selectively interfering with neurotransmitter receptors, will allow us to start teasing apart these complexities.

ADAPTIVE MYELINATION IN ADULTHOOD

A substantial proportion (~40%) of newly generated OLs in adult white matter go on to myelinate axons and survive long term. This occurs not only in the adult mouse corpus callosum, which contains many unmyelinated axons (~70% of the total), but also in the adult optic nerve, which contains almost exclusively (>98%) myelinated axons (Fig. 3C,D) (Young et al. 2013). New OLs might be required in the optic nerve (and elsewhere) to replace myelin that is lost through natural OL death or internode shedding. The lifetime of OLs in the normal healthy CNS is not known, but it is generally assumed that they survive for most of the animal's lifetime, in keeping with the observation that OLs continue to accumulate with age (McCarthy and Leblond 1988; Sandell and Peters 2002). It is also not known whether OLs can shed or add internodes over the long term, although there is evidence suggesting that differentiating OLs generate all their internodes within a rather narrow time window and do not alter much after that (Watkins et al. 2008; Czopka et al. 2013; Young et al. 2013). In the optic nerve, myelinating OLs that are formed during adulthood have a distinctive morphology with many more, shorter internodes than those born in the

early postnatal period (Fig. 3D) (Young et al. 2013). This is consistent with previous observations that average internode length decreases (Lasiene et al. 2009) and the number of nodes per unit volume increases (Peters and Kemper 2012) with the age of the animal, and suggests that late-forming OLs might intercalate new internodes among the earlier-formed internodes, perhaps initiating myelination from nodes of Ranvier to create two nodes from one. The functional or behavioral consequences of remodeling myelin in this way are unknown and difficult to predict. It might be that the conduction velocity of action potentials needs to be continually and minutely adjusted, particularly in pathways like the visual and auditory systems, which depend on rapid and synchronous information transfer and processing (reviewed by Kimura and Itami 2009). In the auditory system, for example, there is evidence that microsecond timing is achieved by dynamic adjustment of myelin internode length and thickness (Seidl et al. 2014).

Although most of their internodes are short, many adult-born OLs in the optic nerve produce one or two much longer internodes (>200 μm), which might ensheath the very small number of previously unmyelinated axons that are present in the adult nerve (Young et al. 2013). This would be expected to accelerate action potential propagation along those newly myelinated axons. If de novo myelination were a common function of adult-born OLs elsewhere in the CNS, in which there is a much larger proportion of unmyelinated axons, it would greatly alter the properties of the circuits involved and could contribute significantly to neural plasticity. There is a growing body of evidence from magnetic resonance imaging (MRI) in human subjects that structural changes in white matter, possibly including myelin production or remodeling, are associated with some types of learning, particularly learning motor skills, such as playing a musical instrument or juggling (Bengtsson et al. 2005; Scholz et al. 2009; reviewed by Zatorre et al. 2012). Practicing a motor task presumably involves repetitive firing of nascent or preformed neural circuits, which elicit the required sequence of movements. The new pattern of firing, at some threshold, might trigger new myelin synthesis by preexisting OLs within the circuit, or production of new myelinating OLs, or both. This could be mediated by activity-dependent synaptic or extrasynaptic communication mechanisms, reviewed in the previous section (Axoglial Synaptic Signaling and Development).

A recent study showed that rats trained in a unilateral reaching/grasping task developed MRI changes in the subcortical white matter on the contralateral side, as well as changes in the overlying gray matter (Sampaio-Baptista et al. 2013). Increased MBP immunolabeling was detected in the area of the altered MRI signal, suggesting that the learning task triggered new myelin synthesis. It has now been shown that motor-skills learning is dependent on new myelination (McKenzie et al. 2014). OL production and myelination was blocked in adult mice by conditional deletion of the transcription factor myelin regulatory factor (Myrf) in OPCs, by combining an *Myrf(flox)* allele with a tamoxifen-inducible *Pdgfra-CreER* transgene. After tamoxifen treatment, OPCs were effectively prevented from differentiating into new myelinating OLs, whereas preexisting OLs and myelin were unaffected. This prevented the mice from learning a new motor skill (learning to run at speed on a wheel with unevenly spaced rungs) without affecting their ability to recall and perform the same skill if it was acquired before tamoxifen treatment. Wheel running alters the dynamics of OPC proliferation and OL production (Ehninger et al. 2011; Simon et al. 2011; McKenzie et al. 2014), although it remains unclear whether this is primarily a response to exercise, novel experience, or both. Sleep is known also to be important in motor learning and memory consolidation; possibly related to this, OPC proliferation and differentiation have been reported to follow the circadian cycle (Matsumoto et al. 2011; Bellesi et al. 2013).

It is becoming clear that OL genesis, maturation, and myelination during adulthood is a dynamic, regulated process that continually adapts and refines CNS circuitry in response to diverse physiological demands and influences. Central myelination is sensitive to social

experience (Liu et al. 2012; Makinodan et al. 2012), enriched environment (Zhao et al. 2012), exercise (Ehninger et al. 2011; Simon et al. 2011), pregnancy (Gregg et al. 2007), and other influences (reviewed by Fields 2008; Richardson et al. 2011; Wang and Young 2014). The realization that OL development continues lifelong and is crucial for healthy brain function and plasticity, as well as for myelin repair in MS and other demyelinating conditions, adds further excitement and urgency to the task of exploring which of many complex pathways regulate OPC behavior in vivo under different physiological and pathological conditions. Compelling questions to be addressed include: What are the biological consequences of axon–OPC synaptic and extrasynaptic signaling? To what extent do the MRI changes observed during motor learning and other physiological processes reflect changes to OLs and myelin? Is adult myelination required for, for example, spatial and episodic (hippocampus-dependent) learning? How might we stimulate adult myelination to assist motor skills learning and prevent age-related motor and cognitive decline? What prevents remyelination of chronic MS demyelinated lesions and how can we overcome remyelination block? The development of new genetic tools and a greater understanding of the molecular characteristics of OPCs in the adult CNS will begin to yield answers to these important questions.

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