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Emerging roles of oligodendrocyte precursor cells in neural circuit development and remodeling

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Abstract

Oligodendrocyte precursor cells (OPCs) are non-neuronal brain cells that give rise to oligodendrocytes, glia that myelinate the axons of neurons in the brain. Classically known for their contributions to myelination via oligodendrogenesis, OPCs are increasingly appreciated to play diverse roles in the nervous system, ranging from blood vessel formation to antigen presentation. Here, we review emerging literature suggesting that OPCs may be essential for the establishment and remodeling of neural circuits in the developing and adult brain via mechanisms that are distinct from the production of oligodendrocytes. We discuss the specialized features of OPCs that position these cells to integrate activity-dependent and molecular cues to shape brain wiring. Finally, we place OPCs within the context of a growing field focused on understanding the importance of communication between neurons and glia in the contexts of both health and disease.

Glia are essential players in neural circuit formation, refinement, and remodeling

Healthy brain function relies upon the precise connectivity of neurons in the brain, which assemble into circuits through the formation of synapses. Uncovering the mechanisms of circuit development is among the major goals of neuroscience and, over the past 125 years, the primary focus in this context has been on defining the intrinsic molecular, morphological, and physiological properties of neurons and their synapses. These research priorities were in line with the classical notion that non-neuronal brain cells (glia, from the Greek word for ‘glue’) such as microglia, astrocytes, and oligodendrocytes serve as a support system or structural scaffold for neurons but do not play a role as active mediators of circuit organization and function. Thanks to recent methodological breakthroughs, including viral targeting of distinct cell types and reporter lines in mice, zebrafish, and fruit flies (among other species), it has become increasingly possible to interrogate the complex mechanisms underlying synaptic connectivity within physiological frameworks that preserve the cellular heterogeneity of the brain. These technological developments, in combination

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Declaration of interests

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with the movement of biomedical research toward an increasingly multidisciplinary model, have allowed neuroscientists to uncover essential roles for glia in actively sculpting neural circuits during brain development [1,2]. These studies have additionally revealed the requirement of glia for remodeling circuits in the adult to facilitate sensory processing, memory, and homeostasis [3–5]. Thus, over the past decade the field of neuroscience has experienced and continues to undergo a renaissance defined by an expanding appreciation for the many roles that glia play in the developing and mature brain.

Glia are now recognized to play important roles in virtually all stages of neural circuit construction and maintenance. For example, during embryonic development, radial glia, the neural stem cells (NSCs) of the neocortex, act as a thoroughfare by which immature neurons migrate to their final positions within discrete cortical layers [6]. Once the cell bodies of neurons are in place, both microglia and astrocytes provide signals that induce the formation of nascent synapses onto nearby neurons [7–11]. During developmental stages that follow synapse formation, microglia and astrocytes refine developing circuits through the phagocytic engulfment of excess synapses, a process that ensures that the proper number and organization of synapses is established by adulthood [12–14]. After axons have begun to connect with their targets, oligodendrocytes myelinate them, increasing the speed and efficiency of neurotransmission [15]. As the brain reaches maturity, astrocytes engage in glutamate reuptake and signaling to support synaptic function [16], while microglia utilize their innate immune abilities to protect neural circuits from inflammation, injury, and disease [17]. Given the breadth of glial functions in the brain, which extend far beyond these few examples, building and maintaining the precise connectivity of neural circuits can be conceptualized as a team effort that involves intricate and precise communication between neurons and glia.

Emerging roles of OPCs in the brain

While the growth of the glial biology field has rapidly advanced our understanding of non-neuronal brain cell function, crucial pieces of the puzzle are still missing. For example, one type of glial cell that has been long overlooked is the OPC. Also called ‘NG2 glia’ based upon their expression of the proteoglycan neural-glial antigen 2 (NG2) [18], OPCs are a unique class of highly proliferative cells within the oligodendroglial lineage that derive from multiple niches in the developing brain. These niches include the ganglionic eminences, the anterior entopeduncular area, and the cerebral cortex [19]. OPCs are also found in the spinal cord, where they originate from the ventricular zone [20]. Although mature patterns of myelination are largely established within the first few months (mice) or years (human) after birth, OPCs continue to make up about 5% of brain cells in the adult, leading to the hypothesis that these cells possess functions that are independent of oligodendrogenesis [18]. Consistent with this idea, a growing number of studies have described various functions for OPCs in the brain. For example, OPCs have been shown to promote angiogenesis, glial scar formation, and antigen presentation [21–24]. These findings, extensively discussed elsewhere (e.g., [25]), underscore that OPCs perform unique functions in both the healthy and diseased brain that are independent from their ability to generate oligodendrocytes.

A crucial open question is whether OPCs share with other non-neuronal brain cells an ability to actively sculpt neural circuits during development and to remodel circuits in the adult. In this review, we discuss emerging evidence that OPCs regulate neural circuit connectivity via mechanisms that are distinct from OPCs' differentiation into mature oligodendrocytes. We further consider the unique properties of OPCs that contribute to their ability to influence neural circuits. Finally, we speculate on the biological relevance of OPC-mediated circuit wiring and on the possibility that OPCs may represent effective therapeutic targets for treating disorders associated with impairments in synaptic connectivity. Ultimately, we aim to position OPCs within the broader context of a growing field focused on the multifaceted roles of communication between neurons and glia in brain wiring and function and its impact on health and disease.

Neurons establish *bona fide* synapses with OPCs

A crucial facet of neural circuit refinement and remodeling is that these processes are heavily influenced by the amount and pattern of neural activity at individual synapses [26–29]. One of the most unique features of OPCs is that they are the only non-neuronal cells in the brain thus far shown to receive direct synaptic input from neurons at *bona fide* synapses (henceforth referred to as neuron:OPC synapses). Electrophysiological analyses over the past three decades have demonstrated that OPCs express functional neurotransmitter receptors for both glutamate and GABA and that OPCs respond physiologically to presynaptic release of either of these neuro-transmitters [30,31]. Although it is unlikely that most OPCs exhibit action potentials *per* se (but see [32]), their synapses share several properties with those of neurons, such as quantal neuro-transmitter release, fast activation, and multiple forms of plasticity [30,33–35]. Similarly, ultrastructural analyses have confirmed the presence of synaptic junctions between OPCs and neurons [30] and tracing approaches have begun to reveal the connectivity of neurons and OPCs across brain regions [36]. Thus, synaptic communication may allow OPCs to interact with neurons in a unique fashion compared to other non-neuronal cell types.

What is the function of neuron:OPC synapses? While synaptic innervation of OPCs is likely to promote cellular proliferation and differentiation [37,38] (extensively reviewed elsewhere [39]), these results have mostly been considered through the lens of myelination. Beyond myelination, synaptic communication between OPCs and neurons may also enable OPCs to remodel neural circuitry. For example, OPCs are likely to receive synaptic input from axons that also connect to nearby neurons in their microenvironment [36]. If these synapses become particularly active during development, increased synaptic innervation may signal OPCs to strengthen, support, and/or protect these synapses. Conversely, if synapses onto OPCs are comparatively weak, reduced neurotransmitter levels may induce OPCs to eliminate or remodel synapses within their vicinity. Consistent with developmentally regulated functions of neuron:OPC synapses, these synapses are more abundant during development (though still present in the adult) and the composition of neurotransmitter receptors within OPCs dramatically shifts as the brain matures [40,41]. Given these observations, one function of neuron:OPC synapses may be to allow OPCs to regulate neural circuit construction and plasticity in an activity-dependent manner.

OPCs remodel retinotectal axons in zebrafish

While much remains to be discovered about the functions of OPCs beyond oligodendrocyte generation, pioneering work suggests that OPCs can remodel axons in the visual system. Taking advantage of the developing retinotectal circuit of the zebrafish as a model, Xiao *et al.* showed that OPCs in the optic tectum, a brain region that is devoid of myelin, are necessary for establishing retinal ganglion cell axonal arbor size and morphology early in development [42]. Ablation of OPCs during later stages of development was sufficient to impair not only axonal remodeling but also visual circuit function. For example, laser ablation of OPCs led to a significant reduction in axon arbor length and an increase in the number of branch processes that were added to individual arbors. At the behavioral level, zebrafish in which tectal OPCs had been ablated displayed an impaired ability to capture prey, as well as an increased possibility of failure to swim in response to a drifting grating cue. Calcium imaging of tectal neurons in zebrafish with and without OPCs showed that neurons were less responsive to visual stimuli in the absence of OPCs. Overall, these data provide compelling evidence that OPCs exert substantial control over neural connectivity and function via mechanisms that are independent of oligodendrogenesis [42].

OPCs engulf neuronal axons and synapses in the mammalian brain

Consistent with a role for OPCs in neural circuit remodeling, two studies provided evidence that OPCs phagocytose synapses in the developing and mature mouse visual cortex. In one study, Buchanan *et al.* used volumetric electron microscopy to generate detailed reconstructions of neurons and glia in the visual cortex from transgenic mice at relatively mature ages [postnatal day (P)36 and P54] [43]. These datasets provided high-resolution views of glial cell types, including OPCs and microglia. As expected, fragments of synaptic inputs were identifiable within microglial branches, where they localized to phagolysosomes (PLs), acidic compartments that represent the final stage of phagocytosis [44]. Surprisingly, however, neuronal axon fragments and synaptic boutons were also identified within OPCs [43]. Evidence of synaptic ingestion by OPCs included the presence of phagosomes, which represent the first stage of phagocytosis, along with lysosomes and numerous PLs, where a significant proportion of axon and input fragments were evident (Figure 1). The ultrastructure of the inputs found within OPCs most closely resembled excitatory rather than inhibitory axons. Remarkably, a similar analysis of PLs in microglia within the same dataset showed that PLs were ten times more abundant in OPCs than in microglia, despite microglia being the principal phagocytes of the brain [43]. These results are in line with single-nucleus RNA sequencing analyses showing that OPCs express genes that encode proteins with crucial roles in phagocytosis [45]. Overall, these findings indicated that OPCs may support the refinement or plasticity of neuronal circuits by phagocytosing synapses in the mammalian cortex at multiple ages.

While Buchanan *et al.* revealed evidence of neuronal material within OPCs in relatively mature mice, Auguste, Ferro *et al.* (henceforth Auguste *et al.*) applied diverse imaging approaches to demonstrate the presence of thalamocortical synapses within OPCs of mouse visual cortex during postnatal development (at P10, P20, and P27) and in the adult (P90) [46]. Confocal microscopy, structured illumination microscopy, and stimulated

emission depletion microscopy all revealed presynaptic inputs from the dorsal lateral geniculate nucleus of the thalamus (identified by immunostaining for the excitatory vesicular transporter vGluT2) within cortical OPCs. This finding was consistent with the conclusion of Buchanan *et al.* that most synapses ingested by OPCs are likely to be excitatory [43]. Extending beyond the analysis of OPC-mediated engulfment in fixed tissue, two-photon imaging of eGFP-labeled thalamocortical axons in the brains of tdTomato+ OPC reporter mice [CSPG4-Cre(ERT2); lsl-tdTomato mice] further demonstrated that both axons and synaptic inputs reside within OPCs *in vivo*. Notably, while the authors observed that both microglia and OPCs contain synapses, mature oligodendrocytes contained virtually no synaptic material, consistent with the findings of Buchanan *et al.* This result highlighted synaptic ingestion as a unique function of OPCs among other cells of the oligodendroglial lineage. Together, the studies by Xiao *et al.*, Buchanan *et al.*, and Auguste *et al.* established a new role for OPCs in regulating synaptic connectivity in the brain, which appears to be independent of their contributions to oligodendrogenesis and myelination (Figure 2, Key figure).

These discoveries raised an important question: what is the fate of synapses and axons internalized by OPCs? The localization of remnants of internalized boutons containing synaptic vesicles within PLs suggests that these inputs were in the process of being degraded [43]. In line with this notion, Auguste *et al.* observed that a substantial proportion of engulfed synaptic material within OPCs colocalizes with molecular markers of phagosomes and PLs, including EEA1, RAB7, and LAMP2. The authors also utilized an *in vivo* viral probe for synaptic digestion, pSynDig (similar to the ExPre construct [3]), to show that a large number of OPC-engulfed inputs reside within highly acidic compartments where they are likely in the process of being degraded. Thus, OPCs ingest, and digest, synapses at least in part via phagocytic pathways, similar to astrocytes and microglia.

The phagocytic engulfment of neuronal material by OPCs in the healthy brain is consistent with evidence that OPCs can adopt immune-competent states in the context of inflammatory demyelination and neurodegenerative disease [22,47,48]. For example, OPCs have been shown to present antigen, a function that may involve the phagocytosis of extracellular material other than axons and synapses [22,47]. OPCs also contribute directly to neuroinflammation through the expression of the phagocytic receptor LRP1, suggesting a potential phagocytic mechanism of OPC function in this context [49]. Finally, OPCs express genes that encode mediators of phagocytosis, further supporting a role in synaptic engulfment [45,50]. Altogether, the ability of OPCs to engulf synapses in the mouse visual system [43,46], combined with the requirement of OPCs for visual circuit remodeling in zebrafish [42], point toward a crucial role for OPCs in neural circuit development.

OPCs are heterogeneous in their phagocytic activity and transcriptomic profiles

Single-cell transcriptomic studies have revealed that OPCs are a heterogeneous cell class that becomes even more diverse across the lifespan of an animal [40,41,51–53]. This pattern of increasing heterogeneity arguably contrasts with that of microglia, which, according to

some accounts, become less heterogeneous with age [54]. These observations raise the question of whether some OPCs are specialized to engulf synapses while others are not. To address this question, Auguste *et al.* developed a high-throughput flow cytometry-based approach to profile the amount of presynaptic material within over 25 000 OPCs at a time. This analysis revealed that about 20% of OPCs do not contain synaptic inputs, 75% of OPCs contain a moderate number of inputs, and 5% of OPCs are 'heavy engulfers' that engulf a particularly large number of synapses [46]. Although other potential differences between OPCs that make up each of these three groups are not yet known, uncovering the distinct properties of these subpopulations across both transcriptomic and functional levels is a key next step in understanding the biological relevance of synapse engulfment by OPCs.

Key figure

Oligodendrocyte precursor cell (OPC) interactions in the brain

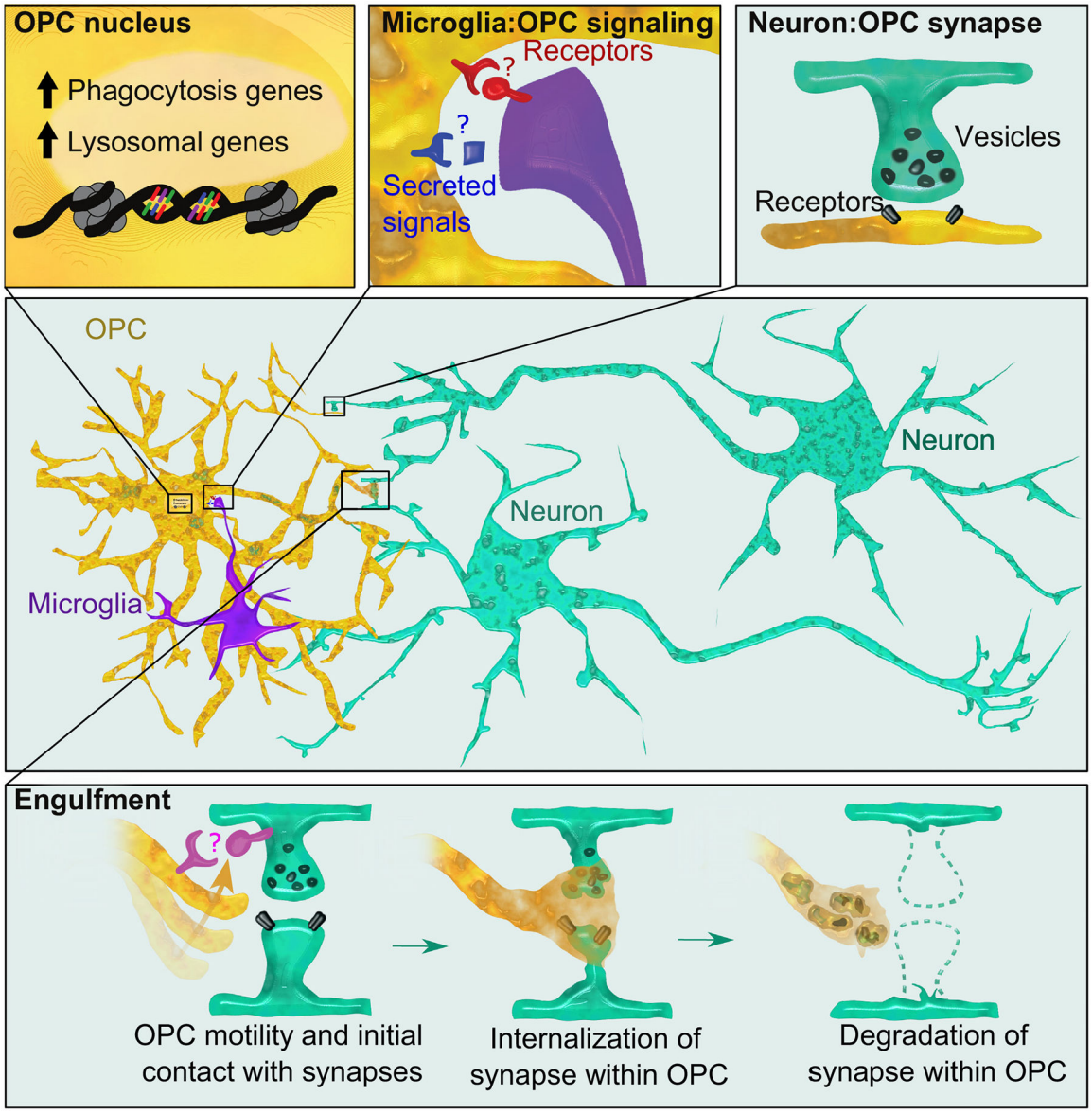

Figure 2.

OPCs (gold) extensively contact other cell types in the brain, including microglia (purple, top middle) and neurons (teal). OPCs express genes involved in phagocytosis and lysosomal processing (top left), receive direct synaptic input from neurons (top right), and phagocytose synapses (bottom). The molecular pathways engaged by OPCs to interact with microglia (top middle; cell-surface receptors, red; secreted signaling pathways, blue) and the mechanisms through which OPCs target and engulf synapses (bottom: putative ‘eat-me’ signals, pink) remain largely undefined.

OPC function is regulated by neural activity and interactions with other glia

Several lines of evidence suggest that OPC function can be shaped by neural activity. For example, the electrical activity of neurons in the mouse brain has a significant impact on the proliferation and differentiation of OPCs into oligodendrocytes [37] (reviewed elsewhere [39]). Likewise, in zebrafish, pharmacologically increasing activity induced OPC proliferation [51]. Consistent with these findings, acute visual stimulation of previously dark-reared mice significantly increased the amount of synapses engulfed by OPCs, indicating that activity influences both canonical and noncanonical functions of OPCs [46]. Interestingly, just like neurons provide activity-mediated signals that promote the proliferation and engulfment activity of OPCs, OPCs provide feedback to neurons to shape their electrophysiological properties via the shedding of the ectodomain of the proteoglycan NG2. Genetic deletion or pharmacological inhibition of NG2 dampened current amplitudes and reduced long-term potentiation in neurons of the somatosensory cortex [55]. In addition to NG2 shedding, OPCs have been shown to mediate the activity of neurons through the directed release of the inhibitory neurotransmitter GABA [56]. These results suggest a bidirectional relationship between neurons and OPCs that is tightly regulated by neural activity and may involve active communication at neuron:OPC synapses.

In addition to neural activity, OPC function is also shaped by OPCs' interactions with other types of glia, such as astrocytes and microglia. These multicellular interactions foster a cooperative environment that maintains tissue and circuit homeostasis [57–59]. For example, astrocytes secrete various growth factors, including platelet-derived growth factor (PDGF) and epidermal growth factor (EGF), which stimulate the growth and survival of OPCs [60]. PDGF is a particularly notable astrocyte- and neuron-derived molecule that binds the PDGFRα receptor on OPCs to influence OPC development and survival, while also promoting OPC differentiation and myelination by mature oligodendrocytes [61–65] (reviewed in [66]). Astrocytes also facilitate the maturation of OPCs via physical contact and by releasing soluble cues that promote myelination [58,67–71].

Similar to the roles of astrocytes in OPC differentiation, microglia express secreted factors such as tumor necrosis factor alpha (TNFα), interleukin family members, and vascular endothelial growth factor (VEGF) that have been shown to promote OPC differentiation and growth [72–75]. Microglia also associate with and phagocytose myelin sheaths to modify myelination during development [76]. While most of this work has focused on the ways in which microglia promote OPC survival and differentiation, depletion of microglia from the brain significantly decreased the synaptic phagocytic activity of OPCs, suggesting that microglia are important for multiple aspects of OPC function [46]. However, the specific mechanisms linking microglia and OPCs in this context are largely unknown.

While the molecular mechanisms through which OPCs engulf synapses remain mysterious, it is feasible that this process is influenced by some of the same factors that mediate OPC differentiation and proliferation. Indeed, both processes likely involve cytoskeletal restructuring of OPCs as, in order for OPCs to become functional oligodendrocytes, they must undergo dramatic morphological changes. These changes involve the reorganization of their branches, transformation of their nuclear morphology, production of myelin basic

protein (MBP), and extension of cytoplasmic processes that encase axons in spiral wraps [77–79] (reviewed in [80]). Furthermore, OPCs possess primary cilia, microtubule-based cell-surface projections that are non-motile, which can serve as loci of signaling interactions between OPCs and other cell types. For example, PDGF-PDGFRα crosstalk and Sonic Hedgehog (Shh) signals are transmitted through primary cilia that reside on the surface of OPCs [81]. In particular, Shh promotes OPC differentiation and increases the number of OPCs and premyelinating OLs expressing NG2. Once the transition from OPC to oligodendrocyte is completed, the primary cilium disassembles [81]. In summary, the constellation of interactions between OPCs and other glia, and the plethora of signaling molecules that affect OPCs, hint at the complexity of these enigmatic cells.

OPCs as potential therapeutic targets in neurological disease

As part of the oligodendroglial lineage, OPCs have long been known to contribute to diseases associated with white matter pathology and demyelination, such as multiple sclerosis [82]. Recent work suggesting a role for OPCs in neural circuit remodeling raises the question of whether OPC dysfunction may be a contributing factor to other neurological diseases as well, ranging from neurodevelopmental disorders like autism to neurodegenerative disorders including Alzheimer's disease. For example, single-nucleus RNA sequencing analyses of transcriptional perturbations in human patients at different stages of Alzheimer's disease progression revealed the widespread disruption of myelination- and inflammation-associated genes [48,83–85]. In particular, a subpopulation of OPCs in the brains of individuals with Alzheimer's disease was characterized by the upregulation of antigen presentation genes [48]. OPCs in Alzheimer's disease patients were also enriched for genes that negatively regulate cell death, possibly representing a compensatory response to protect damaged neurons [85]. If so, it is feasible that OPCs could be harnessed therapeutically to treat neurodegenerative disorders. Consistent with this possibility, work in animal models of Alzheimer's disease has revealed changes in OPC morphology, senescence, and differentiation during relatively early stages of disease progression [86–91]. These disruptions corresponded with significant alterations in gene expression in OPCs, suggesting that at least some OPCs can assume inflammatory profiles through which they contribute to neurodegenerative pathology. Given that Alzheimer's disease is associated with a pathological loss of healthy synapses, it will be important to determine whether synapse engulfment by OPCs may contribute to the neurobiological deficits underlying Alzheimer's disease and related conditions.

Another pathological context in which the involvement of OPCs has begun to be characterized is brain cancer, specifically glioma. OPCs represent the largest number of proliferative cells in the brain, a feature that can be advantageous or perilous. Normally, OPCs maintain a consistent homeostatic population of cells that tile the brain in part by actively repulsing branches to maintain territory [92]. The ability of OPCs to divide and differentiate across the lifespan establishes these cells as an endless pool of precursors ready to assist in remyelination following damage after injury or disease. However, the ability of OPCs to proliferate may also increase the likelihood of spurious mutations that can lead to cancer. In fact, OPCs have been identified as a major cell of origin in gliomas (although the contributions of astrocytes and NSCs have not been ruled out) [93,94]. Specifically,

the activation of OPCs by the loss of tumor suppressor genes *Neurofibromatosis 1 (NF1)* and *P53* caused glioma in a mouse model of disease [94]. Gliomas can be rapidly growing, making them difficult to treat, and are found in both children and adults [95]. The role of OPCs in glioma could point toward new treatment approaches to harness the robust proliferative abilities of these cells to treat cancer and other conditions, including neurodegenerative disorders.

OPCs are involved in the CNS response to brain and spinal cord injury as well. For example, Wnt signaling through the β-catenin receptor on OPCs is necessary for the injury-induced proliferation of OPCs and for the accumulation of activated microglia, macrophages, and astrocytes within the injured region [24]. Moreover, conditional removal of β-catenin selectively from OPCs dampened glial scarring and allowed axons to regenerate more readily following optic nerve crush [24]. In a separate study, OPCs were shown to engage the proteoglycan NG2 to entrap neurons and stabilize dystrophic axons for up to several weeks following spinal cord injury [96]. Interestingly, the physical association between injured axons and OPCs resembled synaptic-like connections, suggesting the possibility that synapses between injured axons and OPCs may help shape the long-term responses of OPCs to injury [96]. Further studies defining the direct contributions of OPCs to the CNS injury response may reveal new therapeutic directions for treating the injured brain.

Concluding remarks and future perspectives

Emerging evidence has revealed OPCs to be a dynamic and heterogeneous cell class with a diversity of functions in the developing and mature brain. In particular, work in mice and zebrafish has uncovered new roles for OPCs in circuit remodeling, a function that OPCs may facilitate at least in part through the phagocytic engulfment of synapses. In ongoing and future studies, it will be critical to determine the biological consequences of synapse engulfment by OPCs on brain wiring and function. For example, two key questions are: (i) is the elimination of synapses by OPCs necessary for establishing the proper number and organization of synapses between neurons in the brain? And (ii) how might synapse engulfment by OPCs affect the ability of neurons to respond to extrinsic stimuli at the physiological level?

To address these questions, methods for inhibiting OPC-mediated synapse engulfment without significantly impacting oligodendrogenesis would be highly instrumental. The roles of other cell types such as microglia have been characterized using cellular depletion methods in which a given cell class is removed entirely or mostly from the brain [97]. These approaches, however, have proven difficult to employ in studying OPCs because OPCs are highly resistant to modification given their ability to proliferate and replace cells that become unhealthy or undergo cell death [92,98]. A more precise approach will likely be to uncover molecular mechanisms governing synapse engulfment by OPCs, then conditionally remove these molecules from OPCs specifically and ask how this impacts brain wiring. Although the molecular pathways engaged by OPCs to engulf synapses remain unknown, it is conceivable that some of these pathways overlap with those used by astrocytes and/or microglia to phagocytose synapses. OPCs, for example, express MERTK, a receptor that mediates the astrocytic engulfment of synapses in the developing mouse brain.

However, OPCs do not express the microglial phagocytosis regulators Complement 1q or Fractalkine receptor, suggesting that the mechanisms through which OPCs and microglia engulf synapses are at least in part non-overlapping [45,50]. Another crucial goal of future work is to address the possible contributions of OPC-mediated synapse engulfment to neurological diseases, particularly conditions associated with pathological changes in synapse number such as autism and Alzheimer's disease (see Outstanding questions).

Outstanding questions

What are the biological consequences of OPC-mediated synapse engulfment? How does the phagocytosis of synapses by OPCs impact neural circuit connectivity and function?

Do OPCs engulf synapses outside of the mouse visual system?

Do synaptic connections between neurons and OPCs influence the ability of an OPC to engulf synapses?

Do OPCs exclusively engulf synapses between neurons or do they engulf neuron:OPC synapses as well?

Experimentally, how can the effects of OPCs on myelination be disentangled from their effects on circuit wiring?

Why do some OPCs engulf synapses but not others?

Does the dysregulation of OPC-mediated synapse engulfment contribute to neurological disorders characterized by deficits in synaptic connectivity? Can the unique proliferative properties of OPCs be harnessed to treat such disorders?

On a conceptual level, given that microglia and astrocytes are involved in circuit remodeling via the engulfment of synapses, it will also be important to determine why there is a biological need for three cell classes to perform a seemingly similar function. While answering this question will require substantially more experimental data, it is likely that one reason for this need is that the processes of synaptic pruning and remodeling are highly context-dependent. To this point, the effectiveness of each phagocytic cell class in regulating the remodeling of neural circuits is likely to vary depending upon a plethora of variables, such as age, sex, synapse type, and the brain region in question. Additional studies comparing the degree to which OPCs mediate synapse elimination across a variety of conditions will shed light on the specific features of OPCs that allow them to eliminate synapses in a context-dependent manner in both health and disease.

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Highlights

Oligodendrocyte precursor cells (OPCs) play diverse roles in the brain, extending beyond their classically recognized contributions to oligodendrogenesis and myelination.

In the developing and adult visual system, OPCs have been shown to remodel axons and to eliminate synapses through phagocytic engulfment.

The engulfment of synapses by OPCs is influenced by multiple factors, including neural activity and molecular signals from other brain cells.

Future work is needed to define the biological consequences and underlying molecular mechanisms of synapse engulfment by OPCs.

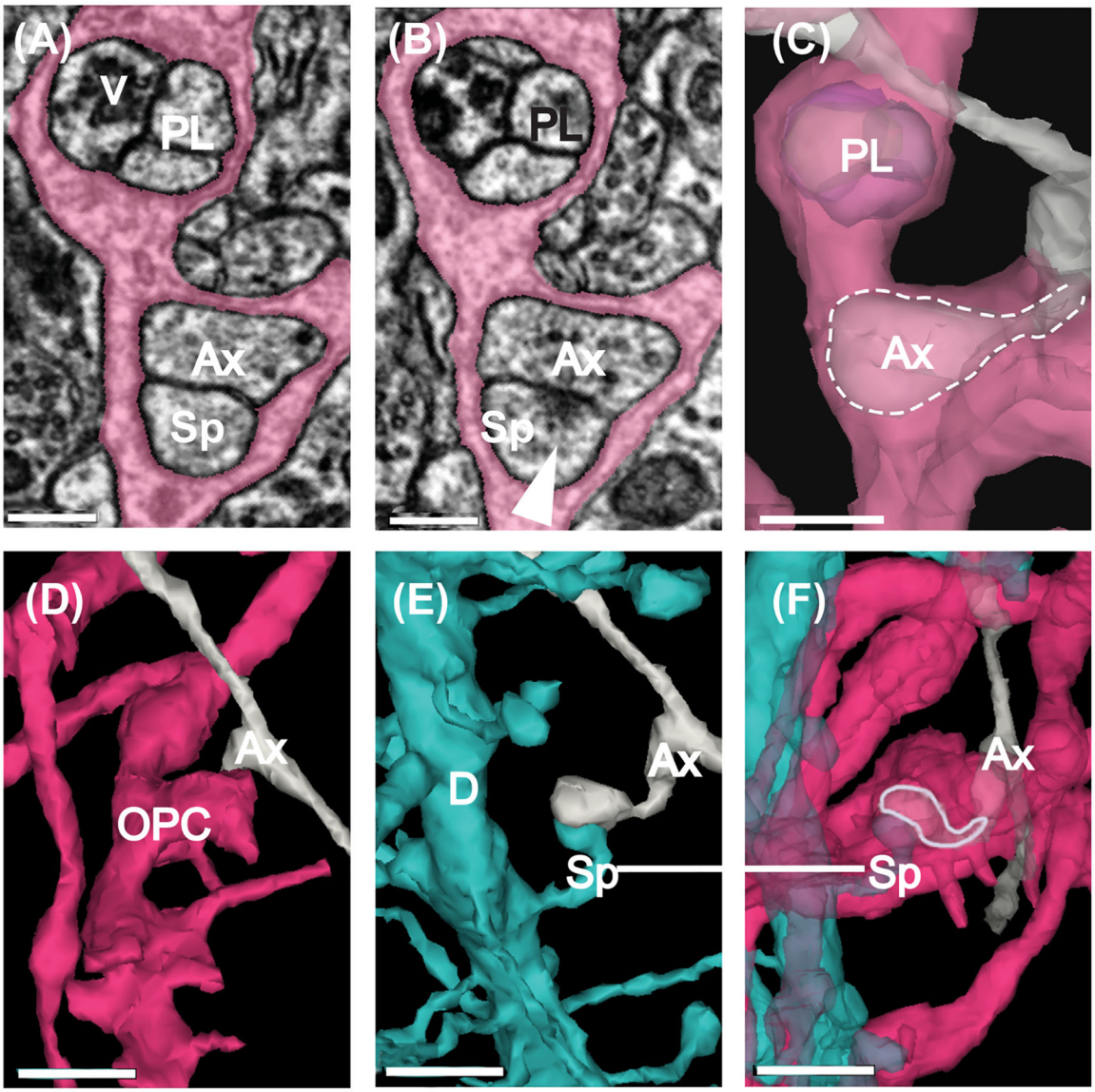

Figure 1. Oligodendrocyte precursor cells (OPCs) engulf synapses in the brain.

Serial electron microscopy images and 3D reconstructions of an interaction between an OPC and an intact neuronal synapse (i.e., an axon converging upon a dendritic spine) in mouse visual cortex at P36. (A) OPC process (pink) containing a phagolysosome (PL) with a vesicle cluster (V) adjacent to an engulfed synapse between an axon (Ax) and a dendritic spine (Sp). Scale bar, 300 nm. (B) A different view of the same OPC process, again showing the PL along with the postsynaptic density (arrow) of a synapse between the encapsulated axon and the dendritic spine. Synaptic vesicles are visible in the presynaptic axon. Scale bar, 300 nm. (C) A 3D rendering of the same OPC process showing the PL and the encapsulated axon collateral (broken outline) within the OPC cytoplasm. Scale bar, 500 nm. (D) A 3D rendering of the same OPC as in (A) with axon shown in gray. The synaptic bouton is encased within the OPC cytoplasm. (E) A 3D rendering of the dendrite (D) in blue indicating the spine synapsing with the axon shown in (D). The spine and collateral axon branch remain attached to their cells of origin but are fully surrounded by OPC cytoplasm

(not shown). (F) A 3D rendering of all structures together (axonal input outlined). Scale bars (D–F), 1 μm. Reproduced from [43].