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The bright and the dark side of myelin plasticity: neuron-glial interactions in health and disease

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Abstract

Neuron-glial interactions shape neural circuit establishment, refinement and function. One of the key neuron-glial interactions takes place between axons and oligodendroglial precursor cells. Interactions between neurons and oligodendrocyte precursor cells (OPCs) promote OPC proliferation, generation of new oligodendrocytes and myelination, shaping myelin development and ongoing adaptive myelin plasticity in the brain. Communication between neurons and OPCs can be broadly divided into paracrine and synaptic mechanisms. Following the Nobel mini-symposium “The Dark Side of the Brain” in late 2019 at the Karolinska Institutet, this mini-review will focus on the bright and dark sides of neuron-glial interactions and discuss paracrine and synaptic interactions between neurons and OPCs and their malignant counterparts.

The bright side of myelin plasticity: **neuron-glial interactions and myelination**

The discovery twenty years ago that OPCs form functional synapses with neurons in the hippocampus[1] (Figure 1A) led to a paradigm shift in our understanding of the brain, refuting the idea that only neurons can form synapses with each other. The axon-OPC synapse has since been found during development and throughout the mature central nervous system (CNS), in both gray[1–3] and white matter[4–7]. It appears that OPCs receive synaptic inputs predominantly from unmyelinated axons in both white and gray matter[4,5,8]. The axon-OPC synapse enables OPCs to sense and decode neuronal activity, thus providing a possible mechanism for neuronal activity to regulate OPC proliferation and differentiation. OPCs have been shown to receive both glutamatergic and GABAergic synaptic inputs, in both grey matter (e.g., hippocampus, cortex, and cerebellum[4–7]) and white matter (e.g., corpus callosum and cerebellar white matter[8,9]), but the relative contributions of each may differ

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depending on the brain region. Similar to neuron – neuron synapses, rabies-virus tracing of presynaptic neuronal input to OPCs has shown that OPCs receive brain-wide input from multiple neurons and neuronal subtypes within a given circuit, and form both glutamate and GABAergic inputs[13], demonstrating that OPCs are positioned to integrate circuit activity with a complexity similar to that of neurons. Thus, axon-OPC synapses may provide a cellular mechanism through which OPCs can lead to myelin changes, by differentiating into myelinating oligodendrocytes in response to neuronal activity. The synaptic inputs, in particular the miniature inputs, detected in OPCs are similar in kinetics to those detected in some postsynaptic neurons, and OPCs express many of the molecules needed for postsynaptic development and function. Importantly they express both inotropic and metabotropic neurotransmitter receptors for the two main neurotransmitters in the CNS, glutamate and GABA, in addition to having receptors to neuromodulators. OPCs express all the ionotropic glutamate receptors e.g. α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), kainate receptors (KAR) and N-methyl-D-aspartate receptors (NMDARs), as well as metabotropic (G protein-coupled) glutamate receptors such as mGluR5, which has been found to regulate the expression of AMPAR[10]. Similarly, OPCs express ionotropic GABA receptors, $GABA_A$ receptors, and the metabotropic $GABA_B$ receptors[6,15–17], and as it is in early developing neurons, GABA is excitatory, like glutamate, in OPCs[3,16]. Therefore, OPCs and neurons are similarly equipped to monitor neuronal activity via synaptic inputs. However, unlike neurons, OPCs may potentially respond to these inputs by proliferating, or differentiating.

Emerging evidence clearly shows that neuronal activity promotes myelination. Increasing neuronal firing rate *in vivo* using optogenetics, chemogenetics, receptor agonists/antagonists, or physiological manipulations promotes OPC proliferation, differentiation[18,19], and enhances myelination[19–22]. Conversely, decreasing neuronal activity using pharmacological manipulations[23], physiological manipulations (whisker removal or raising mice in social isolation or with reduced sensory inputs[24–27]) or reducing activity directly with chemogenetics[28], impedes OPC differentiation and myelination in mice. However, the role that neuron-OPC synapses and neurotransmitter signaling may play in regulating OPC proliferation, differentiation, and subsequent myelination is not fully clear. Conceivably, the neuron-OPC synapse could mediate much of the effects of neuronal activity on OPCs. Rodent *in vitro* data indicate that neurotransmitters can modulate OPC proliferation, differentiation, or myelination[29–32] and in vivo data in the developing zebrafish indicate that vesicular release modulates myelination[21]. Hence, neuronal activity, via the release of neurotransmitters, is likely an important mechanism for regulating myelination.

It is important to note that myelination can also occur in the absence of neuronal activity[33–35]. Studies using similar approaches, including sensory deprivation or physiological manipulations, to alter neuronal activity have failed to show an effect on developmental myelination[36–38]. Likewise, it has become clear that oligodendrocytes can ensheath and make myelin like wraps, around inert nanofibers[33–35]. Studies aimed at elucidating the role of neurotransmitter signaling by knocking out neurotransmitter receptors in OPCs or vesicular release of neurotransmitter from axons have similarly failed to find support for neurotransmitter-dependent myelination during developmental myelination in the regions studied. These studies have shown that when vesicular release of glutamate from

axons is reduced (by knocking out VGlut2 in retinal ganglion cell axons) or when the AMPAR subunits GluR2, 3, and 4 (GluR1 is not expressed) or the NMDAR subunits GluN1 or GluN3 are knocked out in OPCs, there is little to no effect on OPC proliferation or myelination[39–42].

A potential explanation for these apparently conflicting findings, whether neuronal activity regulates myelination[43,30,44–49,21] or not[33–35,50–53], is that perhaps there are two distinct modes of myelination, one that is independent of neuronal activity and another that depends on activity-regulated signaling to OPCs[30]. In fact, different neuronal subtypes in the same brain regions, are either myelinated independent of activity or must be active to become myelinated[43,54]. For instance neuronal activity modulates myelination in cortico-callosal projection neurons, but not cortico-fugal projection neurons[43], and myelination of the reticulospinal, but not the commissural primary ascending neurons of the developing spinal cord depends on vesicular release, presumably of neurotransmitter[54]. When levels of the growth factors neuregulin 1 (NRG1) or brain derived neurotrophic factor (BDNF) are elevated, presumably by release from active neurons[55,56], the density of NMDARs in OPCs increases, and OPCs switch from an activity-independent mechanism of myelination to a faster activity-dependent mechanism[30]. Intriguingly, deleting ErbB3[57], a receptor for NRG1, in oligodendrocyte lineage cells has no effect on developmental myelination, but disrupts experience-dependent myelination[57], and blocking activity-dependent BDNF release or deleting the BDNF receptor TrkB in OPCs blocks activity-dependent myelination[58] in young adult animals. Similarly, neuronal regulation of myelination is perhaps a bit more nuanced; an orchestra of paracrine and synaptic (temporal) communications that need to co-exist in order to initiate activity-dependent myelination. Indeed, when AMPAR subunits are genetically modified postnatally at the peak of the myelination period, as opposed to being knocked out embryonically, OPC proliferation and differentiation are affected[59], suggesting that modifying receptor properties at specific timepoints can alter OPC dynamics and potentially activity-dependent myelination. This temporal dependence on receptors may be explained by the fact that OPCs differ between ages and brain regions[60–64]. One significant difference between OPCs with both age and region is their ion channel and neurotransmitter densities, and therefore the difference in their capacity to monitor and respond to neuronal activity[63]. Potentially, the paracrine signals in the environment around the OPCs may alter the ‘state’ of the OPCs and therefore their response to neuronal activity[65,66]. Conceivably, the activity-dependent myelination may have evolved in order to speed up and target myelination to ‘correctly’ firing axons during specific periods of circuit refinement or learning, and thus it may be important to fine-tune neuronal circuits.

The bright side of myelin plasticity: **neuron-glial interactions and remyelination**

Myelin regeneration is an exceptional regenerative process within the CNS. Several lines of evidence suggest that remyelination and myelin plasticity are two sides of the same process. OPCs that enter demyelinating lesions that are undergoing regeneration recapitulate postnatal OPCs, as identified by both electrophysiological and transcriptional studies[67–69]. In lesions, as at the peak of myelination, OPCs are equipped to monitor the firing pattern of neurons, as they express voltage-gated ion channels and glutamate receptors, and receive synaptic inputs from demyelinated neurons[29,70]. Blocking vesicular release, AMPARs or

NMDARs prevents remyelination in ethidium bromide-induced white matter lesions[29,71]. Similarly, as during myelination, blocking neuronal activity during remyelination prevents myelin regeneration[29], while enhancing activity[72] and stimulating BDNF signaling[58] improves remyelination. This suggests that adult *de novo* myelination (or myelin plasticity) and remyelination share a similar mechanism. Therefore, the neuron-OPC synapse might be an important signal through which neuronal activity regulates both myelin plasticity and remyelination. Understanding this common mechanism is important to identify therapeutic strategies to promote myelin regeneration after demyelinating injury.

The dark side of myelin plasticity: **neuron-glial interactions and brain cancer**

Neuron-glioma interactions mirror neuron-OPC interactions and regulate brain cancer growth

Malignant gliomas are a family of primary brain cancers that include adult glioblastoma, anaplastic astrocytoma, anaplastic oligodendroglioma, pediatric glioblastoma, diffuse intrinsic pontine glioma (DIPG) and other H3K27M+ diffuse midline gliomas. Collectively, these high-grade glial malignancies represent the leading cause of primary brain cancer-related death in both children and adults[73]. Precursor cells in the oligodendroglial lineage are thought to represent the cellular origins of many forms of malignant glioma[74–79], and prominent subpopulations of glioma cells in a given tumor molecularly resemble OPCs[80–82]. Given these similarities between OPCs and malignant glioma, it stands to reason that malignant gliomas may respond to the same environmental cues as healthy OPCs. Glutamatergic cortico-callosal projection neuronal activity robustly promotes the proliferation of healthy OPCs[43,58]. Activity-regulated secretion of BDNF is a required component of the mechanism regulating neuron-OPC interactions[58,71], and may prime OPCs to respond to additional activity-regulated cues[30]. Similarly, glutamatergic neuronal activity promotes the proliferation and growth of malignant glioma[83]. Activity-regulated, secreted factors contribute to the effect of cortical neuronal activity on glioma proliferation, an effect that is conserved across the various clinically and molecularly distinct subtypes of malignant glioma described above[83].

Paracrine mechanisms mediating neuron-glioma interactions: BDNF and Neuroligin-3

How do glutamatergic neurons influence glioma growth? Like the role BDNF plays in normal neuron-OPC interactions[30,58], BDNF is one mediator of neuronal activity-regulated glioma proliferation[83]. Unexpectedly, another key activity-regulated mechanism that mediates glioma proliferation involves activity-dependent shedding of neuroligin-3 (NLGN3)[83], a synaptic adhesion molecule[84]. Shedding NLGN3 robustly promotes the proliferation of each major subtype of high-grade glioma[83]. Not only is NLGN3 a powerful mitogen in glioma, but expression of NLGN3 in the brain microenvironment is required for tumor growth in preclinical models[85]. High-grade glioma xenografts fail to progress in the environment of the NLGN3 knock out mouse brain, while other cancer types, such as breast cancer brain metastases, can grow without impediment in the absence of NLGN3[85].

The surprisingly important role that NLGN3 appears to play in glioma pathophysiology demands a detailed understanding of NLGN3 release into the tumor microenvironment and subsequent actions in glioma cells. NLGN3 is present on the post-synaptic cell chiefly at excitatory synapses and contributes to synaptic maturation and function[86,87]. Neuroligins contain a large n-terminal ectodomain, with a transmembrane domain and a smaller c-terminal endodomain anchoring it to the post-synaptic membrane. The N-terminal ectodomain of NLGN3 is shed in an activity-dependent manner through the enzymatic activity of the metalloprotease ADAM-10[85]. While neurons are one source of shed NLGN3, OPCs also express robust levels of NLGN3[15,88] and represent a major source of shed NLGN3 in the brain[85]. Conditional genetic mouse modeling illustrates that while OPCs are the major source of activity-regulated NLGN3 shedding in the cerebrum, neurons are the source of activity-regulated ADAM10 secretion[85]. Since ADAM10 can be released in synaptic vesicles[89], these findings suggest that secretion of ADAM10 by presynaptic neurons at the axon-glial synapse may result in NLGN3 shedding by post-synaptic OPCs, although a non-synaptic mechanism of activity-regulated NLGN3 shedding by OPCs may also occur. Inhibition of NLGN3 shedding with pharmacological ADAM10 inhibitors blocks glioma progression in preclinical models, and this therapeutic strategy is presently in clinical trial for children with high-grade gliomas (NCT04295759).

How does NLGN3 induce proliferation of glioma cells? While the binding partner of NLGN3 on glioma cells remains to be defined, it is clear that upon binding, NLGN3 causes early upstream activation of focal adhesion kinase (FAK) and downstream activation of PI3K-mTOR, RAS and SRC signaling pathways[83,85]. While this helps to explain the role of NLGN3 in promoting glioma growth, it does not explain the unexpected dependency. The failure of glioma progression observed in the absence of microenvironmental NLGN3, as discussed above, suggests that NLGN3 contributes to a process fundamental to glioma pathophysiology. NLGN3 induces prominent changes in gene expression, including upregulation of numerous synapse-related genes[85], which raises the possibility of axon-glioma synapses, a malignant version of the axon-glial synapses observed between neurons and OPCs in the healthy brain.

Axon-glioma synapses mediate activity-dependent brain cancer growth

Examination of single cell transcriptomic data from each major subtype of malignant glioma revealed prominent expression of synapse-related genes, especially AMPAR subunit genes and synapse-related structural proteins[90,91]. Synapse-related gene expression is particularly enriched in the OPC-like tumor cells within a given patient tumor[92]. Electron microscopy shows structural evidence of synapses between presynaptic neurons and postsynaptic glioma cells in primary patient tumor tissue and patient-derived glioma xenografts[90,91]. Co-culture of patient-derived glioma cells with neurons isolated from NLGN3 knockout mice or wildtype mice supports a role for NLGN3 in glioma synaptogenes[90]. Whole cell patch clamp electrophysiology demonstrates calcium-permeable AMPAR-mediated synapses in a subset of glioma cells within each patient-derived xenograft model examined[90,91], as well as in acutely resected primary tumor tissue[91]. The calcium-permeable AMPAR-mediated axon-glioma synapses, which exhibit multiple electrophysiological synaptic characteristics such as miniature EPSCS and paired pulse facilitation, are reminiscent of similar calcium-permeable

AMPAR-mediated axon-glial synapses on OPCs[1] (Figure 1B). Genetic or pharmacological blockade of AMPAR signaling in glioma xenograft models robustly decreases tumor growth, indicating an important functional role for glutamatergic neurotransmission in glioma[90]. Membrane depolarization appears to be a key aspect of neuron-glioma synaptic signaling for glioma growth, as optogenetically inducing glioma cell membrane depolarization alone promotes glioma proliferation in vivo[90]. While the voltage-dependent mechanisms through which membrane depolarization promotes proliferation of malignant glioma cells remains to be determined, this observation parallels the roles played by electrical signaling in neural precursor cell populations during brain development[92].

Other neurotransmitter-mediated effects in glioma

While it remains to be determined if other synapses that use different neurotransmitters or neuromodulators exist in gliomas, signaling roles for a range of neurotransmitters are coming to light. Non-synaptic, autocrine/paracrine glutamate signaling can promote the proliferation and migration of adult glioblastoma cells[93,94]. Underscoring the heterogeneity between among various forms of gliomas, non-synaptic glutamate signaling promotes migration but not proliferation in pediatric glioma[90]. Roles are also emerging for other neurotransmitters. Like the effects of glutamate signaling, dopaminergic signaling may be growth-promoting in adult glioblastoma[95]. Conversely, GABAergic signaling appears to inhibit tumor progression in both patient-derived xenograft and murine models of adult glioblastoma[96,97]. However, the role of GABA signaling in pediatric gliomas remains to be fully determined. It is presently unknown whether other neurotransmitters such as acetylcholine and serotonin influence glioma progression.

Conclusions

The parallel paracrine and synaptic mechanisms that mediate normal plasticity, regeneration and malignant neuron-glial interactions underscores the extent to which effective regeneration depends on and glial malignancies subvert normal mechanisms of neurodevelopment and neural plasticity. This heightens the importance to fully understand the mechanisms of myelin plasticity for regeneration and calls for a neuroscience-based approach to understanding brain cancers. These shared mechanisms at play in normal circuit plasticity in health, circuit functional recovery after injury or malignant circuit establishment in brain cancer underscores the need for future work to leverage these mechanistic similarities for improved therapies. Myelin biology thus elucidates both “the bright and dark sides of the brain” in brain regeneration and glial malignancies, respectively.

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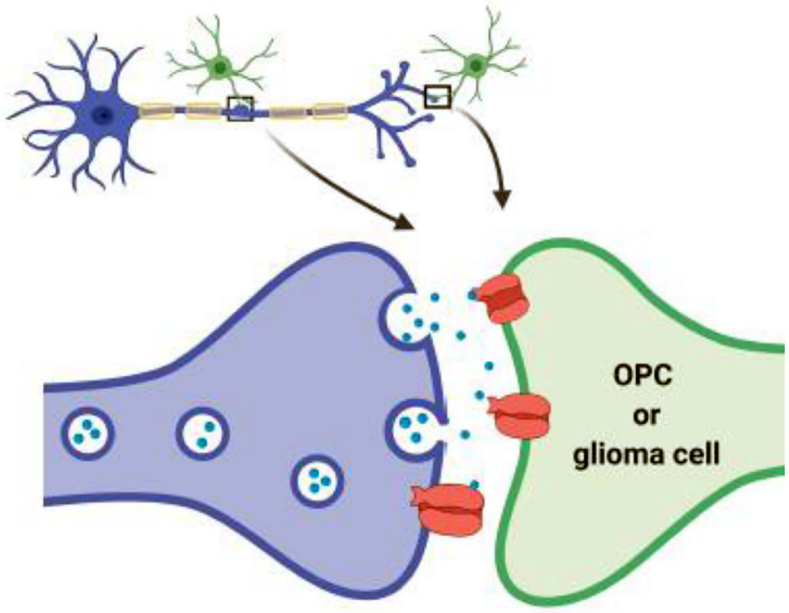

Figure 1.

Axon-glial and axon-glioma synapses. A) In the healthy brain, synapses form between presynaptic neurons (blue) and post-synaptic oligodendrocyte precursor cells (green), in both white matter (via 'en passage' synapse[8]), and grey matter (where OPCs often share synapses with neurons[1]). B) Similar synapses form between presynaptic neurons and post-synaptic malignant glioma cells (green) in brain cancer, as between neurons and OPCs in gray matter.