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Neuron–oligodendroglial interactions in health and malignant disease

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Abstract

Experience sculpts brain structure and function. Activity-dependent modulation of the myelinated infrastructure of the nervous system has emerged as a dimension of adaptive change during childhood development and in adulthood. Myelination is a richly dynamic process, with neuronal activity regulating oligodendrocyte precursor cell proliferation, oligodendrogenesis and myelin structural changes in some axonal subtypes and in some regions of the nervous system. This myelin plasticity and consequent changes to conduction velocity and circuit dynamics can powerfully influence neurological functions, including learning and memory. Conversely, disruption of the mechanisms mediating adaptive myelination can contribute to cognitive impairment. The robust effects of neuronal activity on normal oligodendroglial precursor cells, a putative cellular origin for many forms of glioma, indicates that dysregulated or 'hijacked' mechanisms of myelin plasticity could similarly promote growth in this devastating group of brain cancers. Indeed, neuronal activity promotes the pathogenesis of many forms of glioma in preclinical models through activity-regulated paracrine factors and direct neuron-to-glioma synapses. This synaptic integration of glioma into neural circuits is central to tumour growth and invasion. Thus, not only do neuron–oligodendroglial interactions modulate neural circuit structure and function in the healthy brain, but neuron–glioma interactions also have important roles in the pathogenesis of glial malignancies.

Introduction

Neuron–glial interactions are central to neural circuit form and function. Astrocytes promote synapse formation during developmental circuit establishment[1–3], microglia prune synapses in an activity-dependent manner to refine circuits[4,5] and oligodendrocytes form myelin that both provides metabolic support for axons[6] and regulates the speed of action potential conduction,[7] and thus tunes neural circuit dynamics. Such crosstalk between neurons and glial cells is also central to healthy circuit development, function and adaptive change (see ref. 8 for a review on neuron–glial interactions shaping neural circuit development and function). Thus, disruption or dysregulation of these neuron–glial interactions may

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contribute importantly to neurological and psychiatric dysfunction in a range of disease states[9,10]. Similarly, increasing evidence supports the principle that subversion of neuron–glial interactions in glial malignancies are central to brain cancer progression[11,12].

In this Review, we discuss neuron–glial interactions that contribute to adaptive brain function, that are disrupted in cognitive disease and that are hijacked in brain cancer. We focus on neuron–oligodendroglial interactions, with consideration of microglia and astrocytes in that context (see refs. 13–16 for dedicated reviews on the rich and complex biology of microglia and astrocytes). Here, we first discuss healthy neuron–oligodendroglial interactions underpinning myelin plasticity, followed by a discussion of how glial malignancies subvert and repurpose these powerful neuron–glial interactions to drive glioma pathophysiology.

Myelin plasticity and adaptive brain function

Myelin structure and opportunities for adaptive tuning

Myelin, concentric wraps of glial membrane that form compact lipid-rich lamellae around axons, is formed by oligodendrocytes in the CNS and by Schwann cells in the peripheral nervous system (for an excellent review on the history of discoveries in myelin biology, see ref. 17). Segments of myelin, called internodes, form between nodes of Ranvier, where voltage-gated sodium channels are concentrated to facilitate action potential propagation[7]. Ensheathment of axons by myelin internodes serves two major functions. First, myelin provides crucial metabolic support to axons[6,18,19]. Second, myelin robustly influences the action potential conduction velocity by decreasing transverse capacitance and increasing transverse resistance of the axonal membrane. This insulates the myelinated segments to enable saltatory conduction of action potentials from node to node[7]. Myelinated axon conduction velocity is 50-fold to 100-fold faster than that of unmyelinated axons[20]. Parameters of myelin structure that influence conduction velocity include the thickness of the myelin sheath relative to the axon diameter, internode length and internode spacing[7,21,22].

In the CNS, myelin development is a remarkably protracted postnatal process, with human CNS myelination extending into the fourth decade of life[23–25]. Myelination follows a predictable chronological and topographical developmental pattern. In some regions of the nervous system, such as the optic nerves and the spinal cord, myelin development completes relatively early in postnatal development[23,24] and myelination is fairly complete after development[26,27], with myelination of nearly all axons in the optic nerve and myelinated spinal cord tracts, which have myelin profiles that achieve more ‘optimal’ parameters for maximal conduction velocity[7,21,22]. In other regions of the nervous system, such as neocortex and intercortical association fibres, myelin development extends over a longer developmental period (into the late 20s to early 30s for humans)[23–25]. In neocortex and intercortical projections, myelination remains incomplete and axons exhibit heterogeneous myelin profiles after this protracted developmental period. For example, in the corpus callosum, a major white matter tract containing interhemispheric projections, as many as 30% of axons are unmyelinated and many myelinated axons exhibit thinner myelin sheaths than the ‘ideal’ sheath thickness to axon calibre ratio that facilitates maximal conduction

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velocity[28]. In the neocortex of both primates and rodents, myelin profiles are variable and frequently do not exhibit geometric parameters predicted to enable maximal conduction velocity[29,30]. Furthermore, a study applying cutting-edge techniques in electron microscopy in the somatosensory cortex of a young adult mouse revealed that individual axons of neocortical neurons exhibit variable myelination, with regions of intermittent myelination along the axon length[30]. These observations may reflect delayed myelin development in that neocortical brain region or could underscore the potential to adaptively tune the function of cortical and intercortical circuits through new myelination or myelin remodelling.

Oligodendroglial lineage dynamics over the life span

Oligodendrocytes are generated by oligodendrocyte precursor cells (OPCs) that emerge and expand in the late prenatal and postnatal periods[31,32] (see refs. 33,34 for excellent reviews discussing OPC developmental origins in detail). In the adult nervous system, OPCs persist in a regularly arranged, tiled pattern, maintaining a consistent cellular population density[35] that accounts for 5–10% of all cells in the CNS[36]. OPCs are progenitors that can divide asymmetrically to self-renew while producing a daughter oligodendrocyte, divide symmetrically to produce two daughter oligodendrocytes or directly differentiate without proliferation[35]. In addition to generating myelinating oligodendrocytes, OPCs also have functions unrelated to myelin, including pruning axons[37] and synapses[38]; thus, OPCs join microglia[4,5] and astrocytes[39] in contributing to synaptic pruning and neural circuit refinement.

OPCs continue to generate new oligodendrocytes throughout the life span of healthy rodents[40]. Genetic fate-mapping and intravital imaging studies have demonstrated that oligodendrocytes are long-lived, so the ongoing production of new cells cannot be explained by a homeostatic requirement to replace dying oligodendrocytes[41–43]. In the rodent neocortex and corpus callosum, but not the spinal cord or optic nerve, new oligodendrocytes and new myelin continue to accumulate throughout adulthood[41–43]. Similarly in non-human primates, oligodendrocytes accumulate in the cortex with age[44,45].

In the human brain, OPCs represent the major population of proliferating cells in healthy adult cortex and white matter[46]. A carbon-dating study that leveraged the carbon-14 by-product of mid-twentieth-century nuclear testing to date human brain cells at autopsy found evidence of substantial myelin turnover in the corpus callosum, but minimal new cell production after childhood[47]. One interpretation of these carbon-dating findings could be that myelin remodelling by existing oligodendrocytes may occur in the adult human corpus callosum more than new oligodendrocyte production, although this interpretation requires further evidence. This cellular carbon-dating study also demonstrated substantially (10-fold) higher ongoing rates of new oligodendrocyte generation in the adult human prefrontal cortex than in the corpus callosum[47]. These intriguing human carbon-dating findings have yet to be confirmed using alternative methodologies, but the finding of ongoing human cortical oligodendrogenesis is consistent with histological studies of human neocortex that reveal accumulation of cortical myelin over the life span[23].

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Activity-regulated myelination

Neuronal activity has a central role in shaping the form and function of neural circuitry throughout the life span (see ref. 8 for a review). Thus, it is not surprising that activity-regulated development and plasticity extend to myelin-forming cells as well. Indeed, a newly appreciated dimension along which neuronal activity modulates structure, and thus function, has emerged in the myelinated infrastructure of the brain. In 1993 Ben Barres first introduced the idea that neuronal activity may influence myelin-forming cell behaviour[48], and the well-described but still functionally enigmatic discovery that OPCs receive both glutamatergic and GABAergic synaptic inputs from neurons[49–51] stoked interest in the role neurons may have in myelin development and plasticity. Several elegant in vitro studies[52,53] and fascinating studies associating experience with changes in myelination in rodents[54,55] and white matter structure in non-human primates[56] and humans[57–59] subsequently supported this concept. However, the extent to which neuronal activity influences myelin-forming cells and modulates myelin structure in the healthy brain during development or adulthood remained a point of controversy, in part because activity-independent modes of myelination clearly also exist[60–62].

Robust evidence resulting from the application of newer tools in neuroscience, such as optogenetics and chemogenetics, to this pressing question in glial biology has provided direct evidence that neuronal activity can regulate and modulate myelination, at least in some contexts (Fig. 1). Optogenetic stimulation of premotor cortical projection neuron activity in awake behaving mice resulted in robust proliferation and subsequent differentiation of OPCs and less differentiated pre-OPCs in both juvenile and adult mice, with activity-regulated increase in myelination within the stimulated circuit[63]. The premotor cortex, a higher-order associative cortical region involved in motor planning, projects down the corticospinal tract (corticofugal projections) and across the corpus callosum (cortico-callosal projections); activity-regulated OPC proliferation was specifically observed in premotor cortico-callosal projections[63]. This suggests a difference in the oligodendroglial response to activity of intercortical association neurons and neurons projecting to the spinal cord, and underscores potential heterogeneity of neuron–glial interactions in different neuronal subtypes and different regions of the nervous system. Furthermore, activity-regulated, circuit-specific myelination of cortico-callosal projection neurons resulted in positive alterations to motor function that depend on the generation of new oligodendrocytes and the associated activity-regulated changes in myelin structure suited for tuning conduction velocity[63]. Similar motor circuit OPC proliferation and oligodendrogenesis resulted following a complex wheel motor learning task in mice[64], and histological markers of myelination increased following a single-pellet reaching task in rats[65]. Chemogenetic or whisker stimulation-mediated activation of the somatosensory cortex similarly demonstrated activity-regulated oligodendrogenesis and myelination of the stimulated axons[42,66]. Activity-regulated myelin changes in the adult rodent brain include both de novo formation of new internodes on previously unmyelinated axons or axon segments[30,42,66,67] and remodelling of myelin internodes by existing oligodendrocytes[68,69] (Fig. 1).

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Mechanisms mediating myelin plasticity

Numerous activity-regulated molecular mechanisms have been hypothesized to mediate the influence of neuronal activity on myelin-forming cells. Moreover, each mechanism may have a role in different contexts defined by neuronal subtype heterogeneity[63], OPC heterogeneity[70,71], the OPC state[72] and the frequency or pattern of neuronal firing[52].

One recent study illustrated that activity-regulated brain-derived neurotrophic factor (BDNF) signalling via the tyrosine receptor kinase B (TrkB) receptor on OPCs is a required mechanistic component of myelin plasticity in cortical projection neurons[9]. Loss of the TrkB receptor specifically in OPCs in the juvenile period or in adulthood completely abrogated OPC proliferation, oligodendrogenesis and myelin changes in response to cortical projection neuronal activity. However, this represents only part of what is likely to be a more complex mechanism that remains to be fully elucidated. Whether BDNF has a central role in myelin plasticity in other circuits and other neuronal types remains to be evaluated; it may be that just as neurons are heterogeneous and oligodendroglial cells are heterogeneous[70,71,73], the mechanisms that underlie myelin plasticity are similarly varied.

During development in the zebrafish, axonal activity and vesicular release can influence axon selection for successful myelination[74,75]; it remains to be determined which molecules packaged in vesicles mediate axon selection. In the juvenile superficial medial prefrontal cortex of mice, social isolation regulates the number of internodes generated by an oligodendrocyte through activity-regulated secretion of endothelin from cerebral vasculature that signals through oligodendrocyte endothelin B receptors[68]. Elucidating additional aspects of the molecular mechanisms mediating neuron–oligodendroglial interactions — and potential circuit or region-specific expression of such mechanisms — represents an area of intense investigation in the field.

Adaptive myelination and circuit function

Activity-regulated myelin changes and consequent alterations in conduction velocity modulate circuit dynamics to promote coordinated circuit activity[67]. Increasing evidence suggests that these adaptive myelin changes support healthy cognition. Conditional, inducible genetic mouse models showed that disruption of activity-dependent oligodendrogenesis and/or myelination impairs attention and short-term memory function[9], spatial memory consolidation[67], fear memory consolidation[76] and motor learning[64] (Fig. 1). It should be noted that several of these studies probing the functional role of experience and activity-regulated oligodendrogenesis utilized conditional genetic deletion of the transcription factor Myrf, which has roles in cell types other than the oligodendroglial lineage[77], and which also could influence myelin-independent functions of OPCs as discussed above.

Computational and experimental evidence supports the principle that myelin plasticity tunes circuit dynamics to promote coordinated circuit function, such as promoting synchronous oscillations between nodes in a neural network[67,78,79]. For adaptive myelin changes to confer the relatively subtle alterations in conduction velocity that promote coordinated circuit function such as oscillatory synchrony or to enable spike timing-dependent synaptic

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plasticity, circuit-wide information must be integrated by the oligodendroglial lineage cells. How this occurs with the required precision remains a fascinating mystery. Synapses between neurons and OPCs[49,50] have been well characterized, but their function remains incompletely understood. One hypothesis is that these enigmatic neuron–OPC synapses may have an important role for integrating circuit-level information. Mapping of OPC connectivity using monosynaptic rabies-based tracing illustrated brain-wide inputs from the circuits in which the mapped OPCs reside, including both cortical and thalamic projections[80]. How these inputs to neuron–OPC synapses are integrated and may contribute to adaptive changes in myelin remains to be determined.

Collectively, these insights support the emerging concept that myelin plasticity can contribute to structural changes sculpting adaptive development and ongoing neural plasticity in the adult brain. Given the importance of myelin plasticity to cognitive functions such as attention and learning and memory, it makes sense that loss of myelin plasticity may contribute to disorders of cognition (Box 1). Conversely, activity-regulated myelination may become maladaptive in diseases characterized by abnormally increased circuit activity or abnormal patterns of activity[10] (see ref. 81 for a review on maladaptive myelination).

Malignant myelin plasticity: neuron–glioma interactions drive brain tumour progression

Oligodendroglial origins for many gliomas

Malignant gliomas are a leading cause of brain tumour-related death in both children and adults[82]. Over the past decade, advances in understanding the molecular biology of these brain tumours refined the classification of glioma types[83]. Gliomas comprise a group of clinically and molecularly distinct entities, and within each tumour exist heterogeneous populations of malignant cells that exhibit transcriptional resemblances to OPCs, oligodendrocytes, astrocytes and — in some tumour types — neural stem or precursor cells[84–87] (Table 1). It is thought that the glioma stem-like cell population is responsible for driving tumour initiation, evolution and resistance to therapy[87–89]. The identity of these stem-like cells can differ between glioma types, with some tumours harbouring stem-like cell populations that resemble neural stem cells and others featuring a more OPC-like population of stem-like cells[84–87] (Table 1).

Gliomas are classified based on their clinical grading and location within the brain. Low-grade gliomas comprise a spectrum of histologic entities, which in adults (but not in children) often progress to higher grade malignancy[90,91]. High-grade gliomas may arise in the cerebral hemispheres, such as glioblastoma, or in the midline of the CNS, such as diffuse midline gliomas (DMGs) occurring in the thalamus, brainstem — often referred to as diffuse intrinsic pontine glioma (DIPG) — and spinal cord. Although histologically similar, adult and paediatric gliomas have distinct biological profiles and childhood tumours arise with a striking spatiotemporal pattern of incidence and region-specific molecular signatures[92]. Gliomas arising during childhood tend to occur within midline structures, such as in the brainstem and thalamus, whereas in young and older adults, gliomas chiefly arise in cerebral cortical and subcortical locations.

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This striking spatiotemporal pattern of glioma incidence maps well onto the chronological and topographical patterns of developmental myelination. For instance, a discrete wave of pontine myelination in mid-childhood coincides with the peak incidence of pontine DMG at age 6–8 years, and a discrete period of neocortical myelination in adolescence and young adulthood coincides with the timing of young adult hemispheric glioblastomas[23,93,94]. Concordantly, numerous studies have implicated precursor cells of the oligodendroglial lineage as the cell of origin for many forms of glioma[86,95–100]. Moreover, the regions in which these tumours typically arise within the adult brain exhibit ongoing oligodendroglial and myelin plasticity (see ref. 101 for an in-depth review).

Neuronal activity promotes glioma initiation, growth and progression

The observation that stem-like cell populations of many forms of glioma transcriptionally resemble OPCs inspired the hypothesis that malignant cells may possess a similar proliferative response to actively firing neurons within the tumour microenvironment. A foundational study applying techniques of modern neuroscience to cancer biology demonstrated that optogenetic stimulation of premotor cortical projection neurons in mice induced a circuit-specific proliferative response of patient-derived paediatric cortical high-grade glioma xenografted to their premotor cortex[11]. Optogenetically elevating neuronal activity over the course of a week resulted in increased glioma growth and increased tumour burden compared with identically manipulated littermate control mice lacking the light-sensitive opsin[11]. Further illustrating the effects of neuronal activity on high-grade glioma proliferation, co-culture of glioma cells with neurons exerted a robust, several-fold increase in the glioma proliferation rate[12]. Concordantly, reducing neuronal activity using a general anaesthetic inhibited patient-derived glioblastoma growth and invasion in mice[102].

The effects of neuronal activity on glioma are not restricted to high-grade gliomas such as glioblastoma. A recent study highlighted the effects of optic nerve activity on the initiation, growth and maintenance of optic pathway low-grade glioma[103], which frequently arises in young children with neurofibromatosis type 1 (NF1) tumour predisposition syndrome. Genetically engineered mouse models of NF1-associated optic pathway glioma predictably exhibit development of optic nerve tumours at 9 weeks of age[104]. Optogenetic stimulation of retinal ganglion cell axonal activity in the optic nerve induced an increase in the growth of optic nerve pathway gliomas in NF1-associated optic pathway glioma mice compared with identically manipulated, but not stimulated, littermate controls[103]. Furthermore, decreasing visual experience and consequent optic nerve activity by rearing these mice in complete darkness prior to tumour development (beginning at 6 weeks of age) abrogated the development of optic pathway gliomas in comparison with littermate control mice, which all developed an optic glioma when raised in normal light cycles[103]. Reducing optic nerve activity by rearing mice in complete darkness at later ages — at the time of initiation (beginning at 9 weeks of age) or after optic glioma development (beginning at 12 weeks of age) — resulted in fewer and smaller tumours at 16 weeks, demonstrating that optic nerve activity is important for not only initiation and growth but also tumour maintenance[103]. The reduction in tumour incidence and size when optic nerve activity is reduced after the time of tumour initiation in this model (9 weeks) most likely reflects a role for neuronal activity in glioma cell survival that should be further studied in future work. Subsequent

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studies also identified a role for peripheral nerve activity in peripheral nerve neurofibroma tumours in the NF1 tumour predisposition syndrome, and identified hyperexcitability in *NF1* heterozygous neurons due to NF1-regulated hyperpolarization-activated cyclic nucleotide-gated (HCN) channel function as a mechanism driving both optic nerve glioma and peripheral nerve neurofibromas[105]. This illustrates that *NF1* mutation or loss not only affects the cells that form tumours but also alters the behaviour of other cell types in the tumour microenvironment, such as neurons that contribute to the predisposition for tumour formation[105]. The role of neuronal activity in the initiation, growth and maintenance of molecularly and clinically distinct subtypes of low-grade gliomas remains to be determined.

Similarly to the findings in the NF1-associated optic pathway low-grade glioma mouse model, olfactory sensory experience and olfactory neuronal activity regulated tumour incidence and growth in a genetically engineered mouse model of olfactory bulb high-grade glioma[106]. In that mouse model, occluding the nares mechanically or reducing olfactory neuronal activity chemogenetically reduced the growth of high-grade gliomas of the olfactory bulb[106].

Paracrine neuron–glioma interactions

Activity-regulated factors secreted from murine cortical slices induce a proliferative effect across multiple distinct subgroups of patient-derived high-grade glioma cultures (including DIPG, adult and paediatric glioblastoma and anaplastic oligodendroglioma)[11]. Similarly, NF1-associated low-grade glioma proliferate in response to activity-regulated factors secreted from retina–optic nerve explants[103]. The effects of cortical or retina–optic nerve explants on glioma cell proliferation required explant neuronal activity, as it was lost when blocked using the voltage-gated sodium channel blocker tetrodotoxin[11,103]. Furthermore, proteomic analyses of the activity-regulated secretome, followed by necessity and sufficiency testing, revealed the presence of activity-regulated glioma mitogens. BDNF was among these mitogens[11], concordant with the role that BDNF has in activity-regulated proliferation of healthy OPCs[9]. In addition, insulin-like growth factor (IGF) mediated activity-regulated neuron–glioma paracrine signalling important for olfactory bulb gliomagenesis in the olfactory bulb glioma study discussed above[106]. Activity-regulated secreted factors also promote glioma cell migration and invasion, including a cortico-callosal projection neuronal activity-regulated invasion mechanism in adult glioblastoma that requires glioma expression of the axon guidance molecule semaphorin 4F (ref. 107). Together, these studies indicate that different activity-regulated paracrine factors may have distinctively important roles in different brain regions or neural circuits, and future work should seek to identify the region, circuit and neuronal subtype-specific mechanisms regulating brain cancer pathophysiology.

A shed form of the synaptic adhesion protein, neuroligin 3 (NLGN3) was unexpectedly identified in the cortical and retinal explant studies described above as an important activity-regulated paracrine growth factor, with 10 out of 11 diverse glioma models exhibiting a proliferative response to NLGN3 (refs. 11,103). In the healthy brain, the neuroligin protein family has a critical role in synapse form and function as the postsynaptic binding partner for neurexins (see ref. 108 for a review) and NLGN3 contributes to the function of both

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excitatory and inhibitory synapses[109,110]. As a synaptic adhesion molecule, it was not previously known that NLGN3 had a pro-proliferative role in any context and even more unexpected was a requirement of NLGN3 for glioma growth, as discussed below.

To test the relative contribution of NLGN3 to glioma progression, patient-derived gliomas were xenografted into the brains of wild-type or *Nlgn3* knockout mice. Surprisingly, glioma xenografts failed to grow in brains with an NLGN3-deficient microenvironment[111]. This unexpected dependency on microenvironmental NLGN3 was identified in patient-derived xenograft models of DIPG, paediatric glioblastoma and adult glioblastoma, but did not extend to a patient-derived model of breast cancer brain metastasis, suggesting specificity for gliomas[111]. However, over time, a subset of xenografted mice within each experimental cohort began to exhibit tumour growth in the NLGN3-deficient brain[111]. The mechanisms mediating circumvention of this apparent dependency on microenvironmental NLGN3 in the brain remain to be determined and represent an area of active research.

NLGN3 is also key to optic nerve activity-regulated optic glioma pathophysiology, and deletion of *Nlgn3* prevented optic glioma development in NF1-associated optic pathway glioma mice with normal visual experience[103]. Supporting an important role for NLGN3 in glioblastoma pathobiology, a retrospective analysis of bulk RNA sequencing data in The Cancer Genome Atlas database revealed that tumour *Nlgn3* expression levels inversely correlate with patient overall survival[11]. Stratifying tumours by molecular subtype (proneural, neural, classical and mesenchymal) revealed the lowest *Nlgn3* expression levels in tumours whose transcriptional profile is dominated by mesenchymal tumour cell states[11]. This point frames the question about which glioma cellular states are enriched for particular neuron–glioma interaction mechanisms (Box 2).

The receptor or interaction partner(s) of NLGN3 in glioma are presently unknown, so targeting NLGN3 for glioma therapy has to date focused on mechanisms of NLGN3 shedding. NLGN3 is proteolytically cleaved at the membrane in an activity-regulated manner by a disintegrin and metalloproteinase domain-containing protein 10 (ADAM10) enzyme, releasing the large amino-terminal ectodomain (shed NLGN3) into the tumour microenvironment[111]. Pharmacological inhibition of ADAM10 demonstrates significant preclinical efficacy in a range of glioma types, from adult glioblastoma to DIPG[111] and NF1-associated optic pathway glioma[103]. A phase I clinical trial using an ADAM10 inhibitor to block NLGN3-mediated neuron–glioma interactions is presently ongoing[112].

Mechanistically, shed NLGN3 binding to glioma cells stimulates several oncogenic signalling cascades, with the early activation of focal adhesion kinase and the initiation of its downstream PI3K–mTOR, Ras and Src effector pathways[111]. NLGN3 induces its own feedforward expression in glioma cells and increases *GJA1* and *TTYH1* expression[111] (Fig. 2). Connexin 43 (CX43) and tweety homologue 1 have roles in the formation of tumour microtubes, long processes connected to each other by CX43-mediated gap junctions that establish a tumour to tumour cell network[113,114]. These microtubes connecting glioma cancer cells contribute to glioma therapeutic resistance and progression[12,113,114]. In addition, NLGN3 exposure increased expression of *NTRK2* (encoding the BDNF receptor TrkB), several synapse-related genes (including those encoding glutamate receptor subunits),

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THBS1 (encoding the synaptogenic factor thrombospondin 1 (TSP1)), axon guidance genes and numerous genes involved in ion transport (encoding several potassium (K^+) channels, calcium (Ca^{2+}) channels and excitatory amino acid transporter 1)[111]. Thus, NLGN3 promotes transcriptomic enrichment for multiple aspects of glioma network integration (Fig. 2). As discussed below, such network integration is central to glioma pathophysiology, and these transcriptomic effects of NLGN3 may help explain the unexpected dependency of glioma on microenvironmental NLGN3 (ref. 111). An open question is whether redundant mechanisms regulate the expression of these processes that might explain the evolution of glioma resistance to NLGN3 loss[111] described above.

Underscoring the importance of these transcriptional programmes, pathway enrichment analysis of a large cohort of DIPG and other paediatric high-grade glioma tumours (>1,000) identified an enrichment for dysregulation of gene sets involved in neuronal communication across the diversity of the tumours[92]. More granular analysis of high-grade glioma single-cell transcriptomes identified robust expression of synapse-related genes enriched in the OPC-like population of these tumours[12]. These transcriptomic profiles highlighted the potential that, similar to the formation of neuron-to-OPC synapses in the normal brain[49], gliomas may retain postsynaptic capabilities, and that activity-regulated paracrine factors such as NLGN3 may promote neuron-to-glioma synaptogenesis.

Neuron-to-glioma synapses

Back to back publications in 2019 using electrophysiological and ultra-structural approaches in primary tumour tissue and patient-derived xenograft models demonstrated the presence of bona fide synapses between presynaptic neuronal axons and postsynaptic glioma cells[12,102]. Co-culture of glioma cells with *Nlgn3* knockout or wild-type mouse neurons supported the hypothesis that NLGN3 promotes synapse formation between neurons and glioma cells[12]. Whole-cell patch clamp electrophysiological recordings in both paediatric and adult glioblastomas revealed subpopulations of tumour cells that exhibit excitatory postsynaptic currents (ranging from 10 pA to 100 pA in magnitude) in response to evoked neuronal activity[12,102]. These functional neuron-to-glioma synapses are mediated by α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type ionotropic glutamate receptors on the glioma cells. In normal neuronal cells, the vast majority of AMPA receptors (AMPARs) are impermeable to calcium, either not containing a GluA2 subunit or containing GluA2 subunits that have undergone RNA editing at the glutamine or arginine (Q or R) site to alter ion permeability. Gliomas harboured under-edited GluA2 mRNA[12,102], which rendered the AMPARs Ca^{2+} permeable[115,116]. Calcium permeability of AMPARs can contribute to synaptic plasticity in neurons (for review, please see ref. 117); however, the functional consequences of AMPAR-mediated calcium influx in glioma remains to be fully elucidated.

The properties and function of AMPARs in OPCs, the putative cell of origin for many forms of high-grade glioma, remain somewhat enigmatic. However, OPCs exhibit neuron-to-OPC synapses also mediated by Ca^{2+}-permeable AMPARs[49], which may influence OPC proliferation and survival[118,119]. In both paediatric and adult high-grade glioma models, blocking signalling through AMPAR-mediated neuron-to-glioma synapses

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either pharmacologically using AMPAR-targeting anti-seizure medication (perampanel) or genetically by expressing a dominant-negative form of the GluA2 AMPAR subunit starkly reduced glioma proliferation, growth and progression[12,102].

Subsequent work has found that malignant neuron-to-glioma synapses hijack mechanisms of adaptive plasticity normally operant in synapses between neurons. For instance, activity-regulated secretion of BDNF promoted increased numbers of neuron-to-glioma synapses, as well as increased synaptic strength through increased trafficking of AMPARs to the postsynaptic membrane[120]. It is presently unknown whether other types of synapses, mediated by different neurotransmitter receptors, exist between additional neuronal subtypes and glioma cells. However, there is early evidence for GABAergic currents that are depolarizing (owing to high intracellular chloride concentration) and tumour growth-promoting in some types of gliomas[121,122].

A recent study in adult glioblastoma illustrates an important role for AMPAR-mediated neuron-to-glioma synapses in glioma invasion and expansion of the tumour throughout the brain[123]. Neuron-to-glioma synapses involving cells at the invasive edge of the tumour that resemble NPC-like cells and OPC-like cells promoted the extension of invasive tumour microtubes and increased the speed of tumour cell invasion[123]. Over time, these dynamic, invasive cells become stationary and transition from an NPC-like or OPC-like phenotype to a more astrocyte-like and mesenchymal-like cellular phenotype (Box 2), and interconnect with other glioma cells and with astrocytes via gap junctional coupling. Meanwhile, the NPC-like or OPC-like glioma cells at the tumour margins form new synapses within neural circuits as they invade and propagate the tumour radially to colonize increasing areas of the brain[123]. Concordantly, single-cell genomic studies of gliomas at initial diagnosis and at recurrence illustrate increased synaptic gene expression at later stages of the disease course[124]. Taken together, the studies discussed above elucidate an emerging picture of dynamic, evolving neural–glioma networks regulated, in part, by the activity within tumour-infiltrated neural circuits.

Other electrochemical neuron–glioma interactions

In addition to an excitatory postsynaptic current, neuronal activity can trigger a non-synaptic inward current that exhibits long duration kinetics (timescale of seconds) in a subset of glioma cells. These prolonged currents are evoked by extracellular K^+ released by actively firing neurons[12,102], with extracellular K^+ levels further increased owing to impaired K^+ clearance in the glioma microenvironment[125]. Such K^+-evoked currents are amplified across a network of glioma cells via glioma-to-glioma gap junction connections[12] and are reminiscent of the activity-dependent currents observed in normal astrocytes[126]. Seminal work by Frank Winkler's group established that a glioma-to-glioma network is formed through tumour microtubes that promote tumour resistance to therapy[114]. Such cellular coupling between glioma cells propagated synchronous Ca^{2+} wave formation via CX43 gap junction-mediated communication[114]. Pharmacological gap junction blockade not only de-synchronized the neuronal activity-dependent Ca^{2+} transients throughout the glioma network but also decreased the amplitude of neuronal activity-dependent, K^+-evoked currents[12,102].

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Blocking gap junctions, for example with the pain medication meclofenamate, decreased glioma proliferation in patient-derived orthotopic xenograft mouse models of glioma[12].

Voltage-dependent mechanisms of glioma progression

Membrane depolarization can trigger the opening of voltage-gated ion channels and downstream intracellular signalling cascades (Fig. 3) that regulate numerous cellular functions and gene expression (see refs. 127,128 for reviews). The importance of membrane depolarization in the developing brain to NPC proliferation, migration, differentiation and survival[129–134] raises the possibility that gliomas may be hijacking similar voltage-dependent mechanisms. In the prenatal brain, depolarization-induced Ca^{2+} waves occur in neural stem cells[135,136] and changes in membrane potential instruct precursor cell fate decisions during corticogenesis[137].

Whereas many details about the voltage-sensitive mechanisms regulating normal neurodevelopment remain to be fully elucidated, the importance of the precise control of ionic flux during prenatal development has been highlighted by the identification of mutations in ion channels and neurotransmitter receptor genes in individuals exhibiting prominent cortical malformations[138,139]. To test the functional consequences of membrane depolarization in glioma, patient-derived glioma cells were engineered to express the light-sensitive cation channel channelrhodopsin 2, xenografted to the mouse cortex and then optogenetically depolarized[12]. This demonstrated that glioma membrane depolarization alone is sufficient to promote malignant cell proliferation[12]. The intracellular events triggered by changes to membrane potential that regulate glioma cell proliferation remain an open question, as does the possibility that membrane depolarization influences additional cancer cellular functions beyond proliferation. Elucidating the voltage-sensitive signalling pathway(s) that mediate the functional effects of glioma membrane depolarization represents an area of intense ongoing investigation.

Thus, glioma is an electrically active tissue in which neuron-to-glioma synapses and glioma-to-glioma gap junctional coupling promote synchronous membrane depolarizations and consequent Ca^{2+} transients throughout networks of cancer cells. Glioma cells form a network that integrates structurally and electrically into the neural circuitry of the brain. In adult patients with hemispheric glioblastoma, intraoperative electrophysiology demonstrates that the degree of functional connectivity of the tumour with the rest of the brain is strongly inversely correlated with survival[140].

Autonomous currents in the glioma network

Underscoring the importance of activity-evoked Ca^{2+} transients in glioma, a small population of tumour cells exhibit autonomous oscillatory Ca^{2+} transients in both paediatric[12] and adult[141] high-grade gliomas. These cells with oscillatory Ca^{2+} transients (representing ~4% of total glioma cells in glioblastoma) are highly connected to other glioma cells within the gap junction-connected glioma-to-glioma network, forming a ‘hub’ within the network[141]. Autonomous, rhythmic oscillations of Ca^{2+} transients in these ‘hub cells’ are regulated by the Ca^{2+}-activated K^+ channel KCa3.1 — also expressed by pacemaker sinoatrial node cardiac myocytes[142] — and propagated to the connected network

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of gap junction-coupled tumour cells[141]. Analyses of signalling pathways regulated by these periodic Ca^{2+} transients highlighted tumour cell mitogen-activated protein kinase 2 and nuclear factor-κB pathways, both known to contribute to cancer cell behaviours[141]. Genetically or pharmacologically targeting KCa3.1, which abrogates these autonomous Ca^{2+} transients, reduced glioma cell viability, mitigated glioma growth and prolonged mouse survival in preclinical models of adult glioblastoma[141].

Glioma-induced neuronal excitability

Gliomas are an electrically active tissue, responding to neuronal input in both a synaptic manner and a non-synaptic manner[12,102]. These malignant cells are, in turn, able to promote excitability of neurons in both adult and paediatric glioma types[12,143–145] (Fig. 4). Glioma-associated seizures are a common symptom for patients with both low-grade and high-grade glioma[59,146,147]. Intraoperative electrocorticography in awake patients with hemispheric high-grade gliomas has demonstrated glioma-induced hyperexcitability in tumour-infiltrated cortex at rest[12] and during cognitive language tasks such as visual and auditory naming[140].

Several mechanisms of glioma-induced neuronal hyperexcitability have been identified, including tumour cell release of glutamate via cysteine–glutamate transport systems[143] and alterations in the neuronal network owing to loss of perineuronal nets[148]. Glioma-associated loss of inhibitory interneurons and glioma-associated switch from a hyperpolarizing to a depolarizing effect of GABA in excitatory neurons[148,149], elevated extracellular K^+ levels owing to impaired K^+ clearance in the glioma microenvironment[125] and promotion of neuronal synaptogenesis through glioma secretion of synaptogenic factors (such as glypican 3 (refs. 145,150) and TSP1 (ref. 140)) can also promote neuronal hyperexcitability. The glioma-associated loss of inhibitory interneurons and perineuronal nets occurred early in the course of disease in an adult glioblastoma mouse model[148] and seizure severity increased with tumour progression, correlated to an increasing proportion of tumour cells secreting synaptogenic factors[145].

The full consequences of glioma-induced neural circuit integration and remodelling on neural circuit function are beginning to come into sharp relief. Recent evidence from a landmark intraoperative electrophysiology study illustrates that high-grade gliomas functionally remodel neural circuitry: in patients with glioblastoma in the left hemisphere, involving but not limited to language areas, expressive language tasks recruited activity not only in the expected frontotemporal language areas but also in all cortical areas infiltrated by the tumour[140]. Tumour cell secretion of the synaptogenic factor TSP1 correlated with the degree of functional connectivity in patients and TSP1 was shown experimentally to promote neuron–glioma interactions and contribute to glioma pathophysiology[140], including both synaptogenesis[140] and tumour microtube formation[140,151]. The tumour-infiltrated language cortex remains functional, albeit at reduced efficiency[140], explaining some of the cognitive effects of glioma and also underscoring the well-established clinical observation that — unlike more other neurological disease processes — brain areas affected by gliomas retain a surprising degree of functionality. It is now increasingly clear how that preservation of activity drives brain cancer progression (Fig. 4).

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Therapeutic targeting of neuron–glioma interactions

Identifying the mechanisms involved in neuron–glioma interactions will enable clinically approved brain-penetrant drugs to be repurposed for modulation of tumour cell dependency on the active microenvironment. Neuronal activity-evoked tumour excitatory postsynaptic currents are targetable using the AMPAR-blocking anti-epileptic drug perampanel and such treatment has demonstrated preclinical efficacy in glioma patient-derived xenografts[12,102]. Glioma growth and invasion is decreased through targeting the gap junction-mediated Ca^{2+} transients using the anti-inflammatory drug meclofenamate in preclinical models[12,102]. Targeting glioma-induced synaptogenesis by blocking TSP1 signalling with the anti-epileptic drug gabapentin reduced glioma growth in glioma patient-derived xenografts[140]. As variable responses of NPCs to neuronal activity are observed depending on the neurodevelopmental context[129–134], it is difficult to predict the clinical relevance of targeting these neuron–glioma interactions in tumours that arise from different progenitor populations within the brain, such as those that arise from neuronal precursor cells[152–154]. The mechanistic effects of electrophysiological responses in other primary brain cancers will likely vary from those of gliomas, for example in those tumours which arise from neuronal-lineage precursor cells, such as medulloblastoma. The neuroscience of each individual brain tumour type must be studied to elucidate tumour-specific neural mechanisms regulating pathogenesis.

Whereas the role of neuronal activity in other primary brain tumours is yet to be fully appreciated, new insights into secondary brain cancers have confirmed an interaction with neurons that drives malignant progression. Brain metastatic breast cancer cells acquire an increased expression of a NMDA receptor subtype within the brain microenvironment which enables them to successfully colonize the brain[155]. Tumour progression is facilitated by the integration of the metastatic cells amongst glutamatergic neurons and subsequent stimulation of glutamate-activated NMDA receptor signalling[155], along with the formation of astrocyte–tumour gap junction coupling[156]. Investigations into neuron–tumour communication across all brain cancer subtypes will uncover specific signalling interactions, either by synaptic, perisynaptic or paracrine mechanisms, that are susceptible to therapeutic targeting.

Conclusions and outlook

Although the importance of neuron–glial interactions in brain development, adaptive plasticity and disease has become increasingly evident, numerous pressing questions remain. Elucidating the molecular and cellular mechanisms mediating adaptive oligodendroglial cell responses — which likely exhibit developmental stage, brain region, neural circuit and neuron subtype-specific heterogeneity — will be important for fundamental understanding of nervous system development, plasticity and function. Oligodendroglial plasticity is implicated in a growing list of brain functions, and maladaptive or deficient oligodendroglial plasticity may have important pathophysiological roles in an expanding number of neurological and neuropsychiatric diseases. Developing appropriate therapeutic interventions to target dysfunction of neuron–oligodendroglial interactions will require such fundamental mechanistic understanding. A stark example of this are glial malignancies.

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The mechanistic parallels evident in the neuron–oligodendroglial interactions that contribute to myelin plasticity and the neuron–glioma interactions that drive the pathogenesis of glial malignancies highlight the extent to which brain cancers hijack mechanisms of normal neural development and plasticity and underscore the importance of understanding the neuroscience of brain cancers. Elucidating key interactions between neurons and brain cancer cells and neuronal mechanisms hijacked by malignant cells reveals an avenue of potential therapeutic interventions that may improve outcomes for these lethal cancers. Major challenges to achieving the potential of this therapeutic approach include the need to adapt therapies to malignant neuron–glioma networks that will likely change and evolve in complex ways over the course of the disease, and to develop therapeutic interventions that selectively disrupt mechanisms in the cancer cells rather than in healthy neural cells.

Beyond brain cancer, interactions between the nervous system and cancers throughout the body are emerging as crucially important pathogenic mechanisms and promising therapeutic targets (for reviews on the emerging field of cancer neuroscience, see refs. 157–159). In every example studied to date, cancer cells subvert normal mechanisms by which the nervous system maintains tissue and organ homeostasis or promotes development and regeneration (see ref. 160 for a review on the neural regulation of ontogeny and oncology). Thus, fundamental discoveries in normal development and physiology are robustly synergistic with the study of diseases such as cancers. In the case of seemingly intractable brain cancers such as high-grade gliomas, progress towards effective therapy must take a multidisciplinary approach, incorporating crucially important lessons from neuroscience. In turn, mechanisms discovered in brain cancer may help inform principles of healthy brain development and plasticity.

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Box 1

Loss of myelin plasticity and cognitive impairment

Just as myelin plasticity promotes healthy cognitive function, disruption of activity-regulated neuron–oligodendroglial interactions may contribute to cognitive diseases. One illustrative example of a neurocognitive disease in which disruption of myelin plasticity appears to have an important role is the syndrome of cognitive dysfunction that frequently follows cancer chemotherapy, characterized by impaired attention, memory, speed of information processing and multi-tasking. Individuals suffering from chemotherapy-related cognitive impairment, colloquially known as ‘chemobrain’, frequently do not exhibit overt structural damage. However, advanced neuroimaging techniques reveal subtle white matter abnormalities[164,165]. Histological examination of human post-mortem frontal lobe samples from subjects with previous chemotherapy exposure demonstrates depletion of oligodendroglial lineage cells in subcortical white matter, but not in cortical grey matter. Depletion of oligodendrocyte precursor cells (OPCs) was particularly severe following exposure to high-dose methotrexate, a drug that is especially associated with long-term cognitive impairment[166].

A mouse model of high-dose methotrexate exposure demonstrates a similar depletion of white matter OPCs and mature oligodendrocytes[166]. These changes in oligodendroglial lineage cells are attributable to a perturbation of the gliogenic microenvironment, as chemotherapy-naïve OPCs transplanted into the previously methotrexate-treated brain exhibit similar dysregulation of oligodendroglial lineage populations. This microenvironmental disruption is associated with prominent microglial reactivity, specifically in white matter. Further work demonstrated that methotrexate directly induces microglial reactivity, and that this reactivity persists long after drug exposure. Methotrexate-induced microglial reactivity, in turn, induces neurotoxic astrocyte reactivity, and together these reactive glia cause the observed dysregulation of the oligodendroglial lineage, impaired myelin homeostasis (decreased myelinated axons and thinner myelin sheaths) and myelin plasticity failure[9,166,167]. The failure of activity-regulated OPC proliferation, oligodendrogenesis and myelination observed in mice previously treated with methotrexate can be understood in the context of a known mechanism required for adaptive myelin change: neuronal brain-derived neurotrophic factor (BDNF) expression is starkly decreased after methotrexate[9]. Underscoring the central role of microglial reactivity in this multicellular dysregulation, microglial depletion after chemotherapy restores neuronal BDNF expression, normalizes the myelin phenotype and rescues cognitive function in this mouse model of high-dose methotrexate exposure[9,166]. To establish the relative contribution of the observed myelin plasticity failure to the chemotherapy-induced deficits in cognitive function, the effects of a specific small molecule tyrosine receptor kinase B (TrkB) agonist were tested after methotrexate exposure in a genetic mouse model with or without inducible, OPC-specific deletion of TrkB. The TrkB agonist rescued myelination and cognitive performance even without microglial depletion; importantly, cognitive performance was only rescued in mice with intact OPC expression of TrkB[9].

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Cognitive symptoms that frequently follow COVID-19 closely mirror those that occur after cancer therapies, and persistent ‘brain fog’ is an important and debilitating component of long COVID-19 (see ref. 168 for a review). Preclinical work has uncovered similar patterns of persistent white matter-selective microglial reactivity, decreased OPC and oligodendrocyte numbers and impaired myelin homeostasis (with decreased myelinated axons in subcortical white matter) after even mild respiratory-restricted COVID-19 (ref. 167). Whether myelin plasticity is similarly impaired after COVID-19 as it is after methotrexate chemotherapy[9] and whether similar therapeutic strategies may rescue cognitive function after COVID-19 remain to be determined in future work.

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Box 2

Heterogeneous cellular substates in glioma are enriched for neuron–glioma interaction mechanisms

The introduction of next-generation sequencing technology has elucidated important principles of intertumoural and intratumoural cellular heterogeneity in gliomas. A landmark paper in 2010 examined bulk RNA sequencing data from glioblastoma cases in The Cancer Genome Atlas and found that tumours generally fit into one of four transcriptional phenotypes — 'neural', 'proneural', 'classical' and 'mesenchymal' — each associated with specific oncogenic mutations[169]. Later, single-cell RNA sequencing studies elucidated that each glioblastoma is composed of cells in these four states, and the bulk sequencing results reflected the dominant signature of that tumour at the time it was sampled[87]. Each of these four transcriptional signatures — neural, proneural, classical and mesenchymal — represents a cellular state that can also be described by the normal cell type it most resembles: neural precursor cell (NPC)-like (neural), oligodendrocyte precursor cell (OPC)-like (proneural), astrocyte-like (classical) and mesenchymal cell (MES)-like (mesenchymal). Specific oncogene aberrations and microenvironmental factors favour expression of each cellular state[87]. Glioblastoma cells are protean, so can change cellular states from one of these transcriptional phenotypes to another in response to therapeutic pressure, microenvironmental influences and tumour evolution over the disease course. As the various glioma subtypes have been examined using single-cell techniques, characteristic cellular compositions and hierarchies have emerged. For example, diffuse intrinsic pontine glioma (DIPG) and other diffuse midline gliomas (DMGs) — tumours that typically occur in childhood and are characterized by mutations in genes encoding histone H3 — are chiefly composed of OPC-like/oligodendrocyte-like and astrocyte-like tumour cells (Table 1), with OPC-like cells representing the tumour-initiating cancer stem cell population[86]. Unlike in *IDH*-wild-type glioblastoma, NPC-like cells are not present[86,163] and MES-like cells are chiefly found in older patients[163].

Each of these glioma cellular states is enriched for particular types of interactions within malignant neuron–glioma networks. Neuron-to-glioma synapses are enriched in the OPC-like and NPC-like populations of glioma cells[12,123], whereas gap junction-coupled glioma-to-glioma tumour microtubes are enriched in astrocyte-like and MES-like tumour cells[123]. K^+-evoked currents are prominent in glioma cells exhibiting gap junction-coupled tumour microtubes[12], which implies that K^+-evoked currents are prominent in, but likely not limited to, astrocyte-like tumour cells. Glioma 'hub cells' expressing the calcium-activated potassium channel KCa3.1 largely fall into the MES-like category in adult *IDH*-wild-type glioblastoma but can also have the other cellular states[141]. Astrocyte-like tumour cells secrete synaptogenic paracrine factors such as glypican 3 (ref. 150) and thrombospondin 1 (TSP1) (ref. 140), contributing to neuronal hyperexcitability and network remodelling[140,145,150]. Cellular substates, associated malignant neuron–glioma network interactions and relevant therapeutic targets and drugs that hit those targets have been found in most forms of glioma studied to date (Table 1). Not all aspects of neuron–glioma interactions have been tested in all

glioma subtypes; for example, neuronal activity-regulated paracrine factors are known to contribute to optic glioma pathophysiology, but neuron-to-glioma synapses remain to be studied in this tumour subtype.

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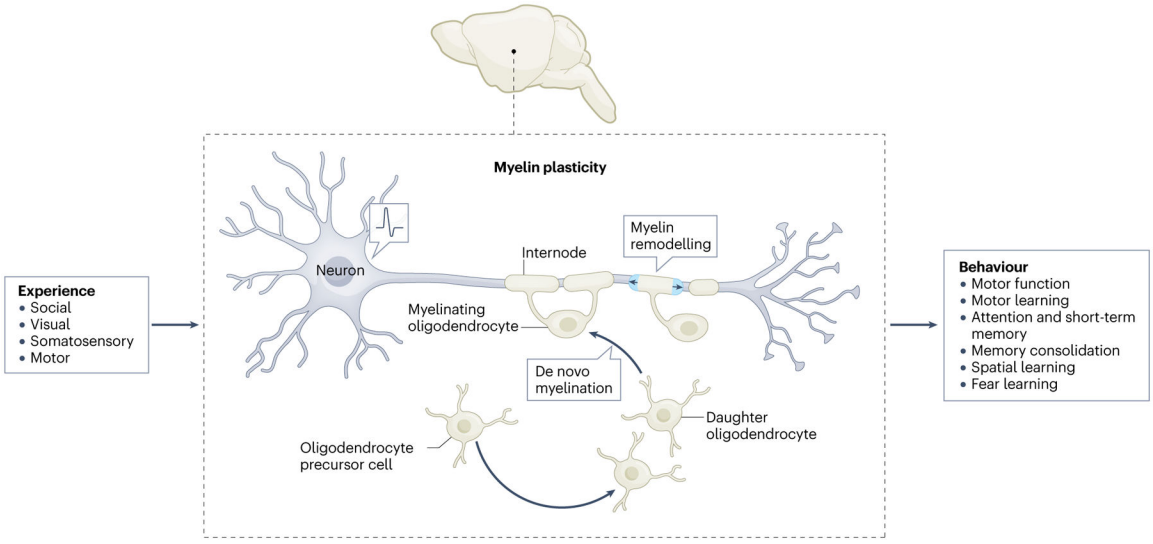

Fig. 1 |. Myelin plasticity: evidence and implications from rodent models.

Neuronal activity-regulated changes in myelin are evident in rodent models with direct manipulation of neuronal activity using optogenetics and chemogenetics, and evident with changes in sensory, motor and social experience. Myelin plasticity contributes to a range of neurological functions, including spatial, fear and motor learning.

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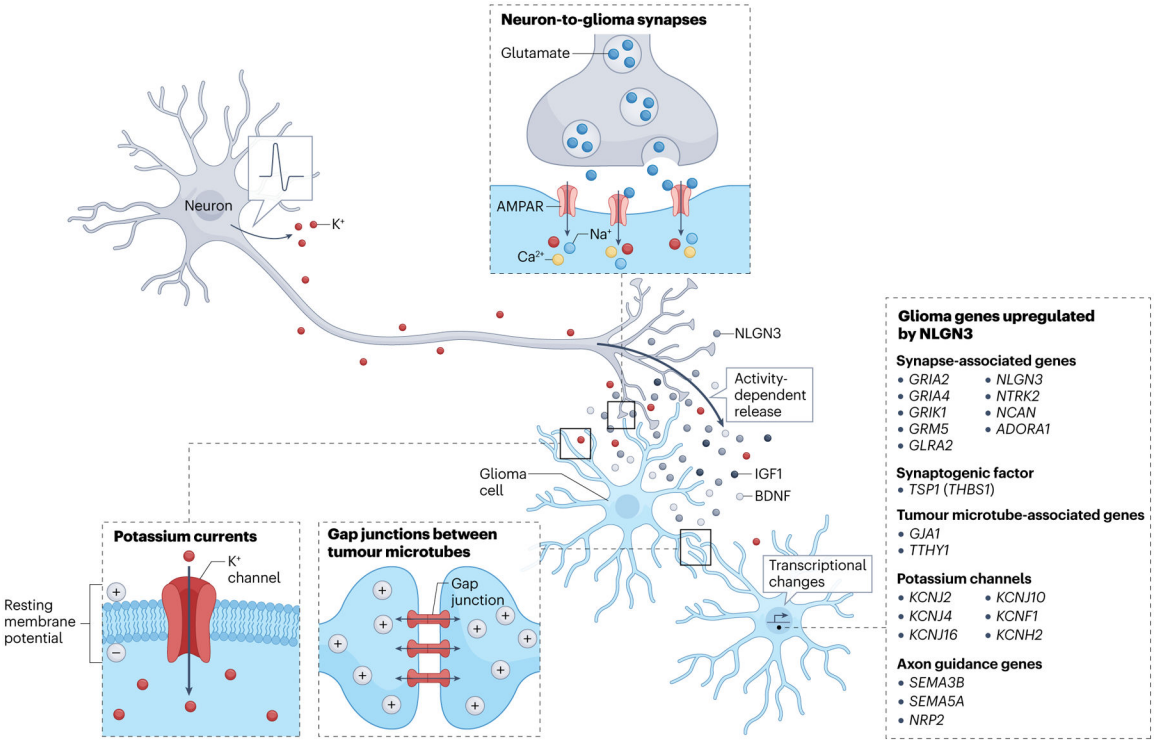

Fig. 2 |. Neuronal activity-regulated mechanisms of glioma growth.

Neuronal activity drives glioma proliferation, growth and progression through activity-regulated paracrine factors including neuroligin 3 (NLGN3)[11,103,111], brain-derived neurotrophic factor (BDNF)[11,120], insulin-like growth factor 1 (IGF1)[106], activity-regulated increases in potassium (K^+) that evoke K^+ currents in glioma cells[12,102] and bona fide neuron-to-glioma synapses[12,102,120,123]. K^+-evoked currents are amplified through gap junction coupling between glioma cells via tumour microtubes[12,102]. Activity-regulated interactions also induce gene expression changes in glioma cells relevant to multiple aspects of glioma network integration[11,111]. In particular, NLGN3 signalling induces glioma gene expression changes that underpin other neuron–glioma interactions, including upregulating synapse-associated genes, the BDNF receptor tyrosine receptor kinase B (TrkB) (*NTRK2*), the synaptogenic factor thrombospondin 1 (*TSP1*), genes encoding K^+ channels, tumour microtube-associated genes including connexin 43 (CX43) (*GJA1*) and axon guidance genes including semaphorins (implicated in glioma invasion[107])[111]. AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor.

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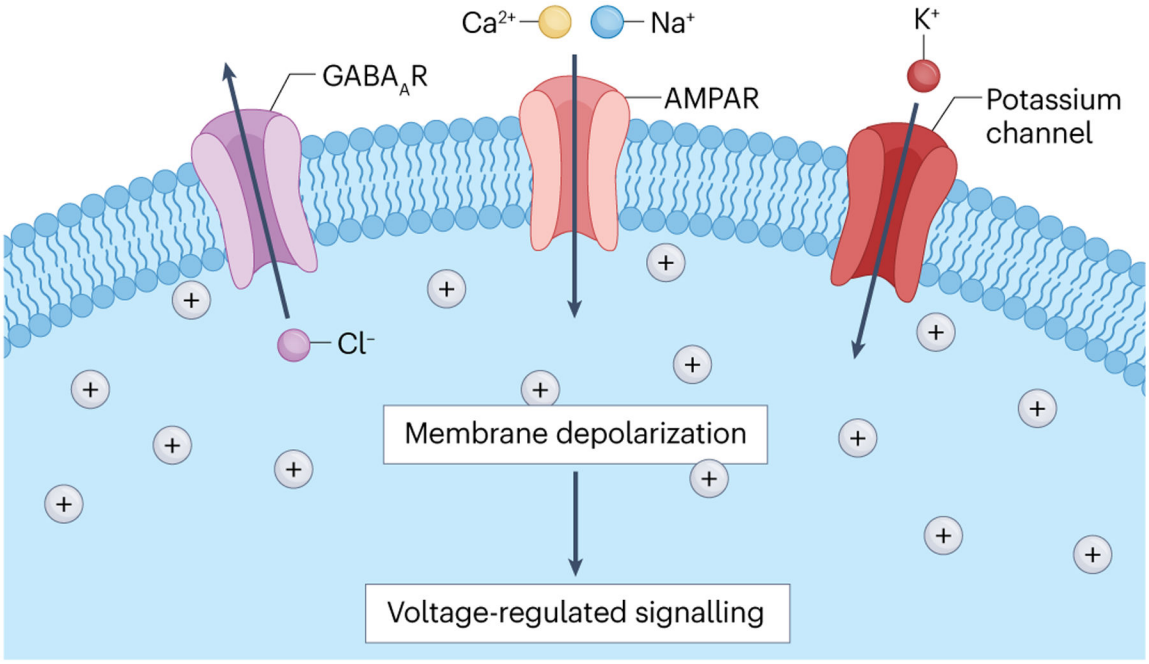

Fig. 3 |. Glioma membrane depolarization promotes tumour cell proliferation.
Gliomas exhibit multiple mechanisms of membrane depolarization, including calcium-permeable α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR)-mediated neuron-to-glioma synapses[12,102], activity-dependent potassium-evoked currents[12,102] and, in some glioma types, depolarizing GABAergic currents mediated by outward flux of chloride through $GABA_A$ receptors[122]. Membrane depolarization alone is sufficient to drive glioma proliferation[12]. Membrane depolarization can trigger opening of voltage-gated ion channels and consequent intracellular signalling events, but the details of voltage-sensitive mechanisms in glioma remain to be elucidated.

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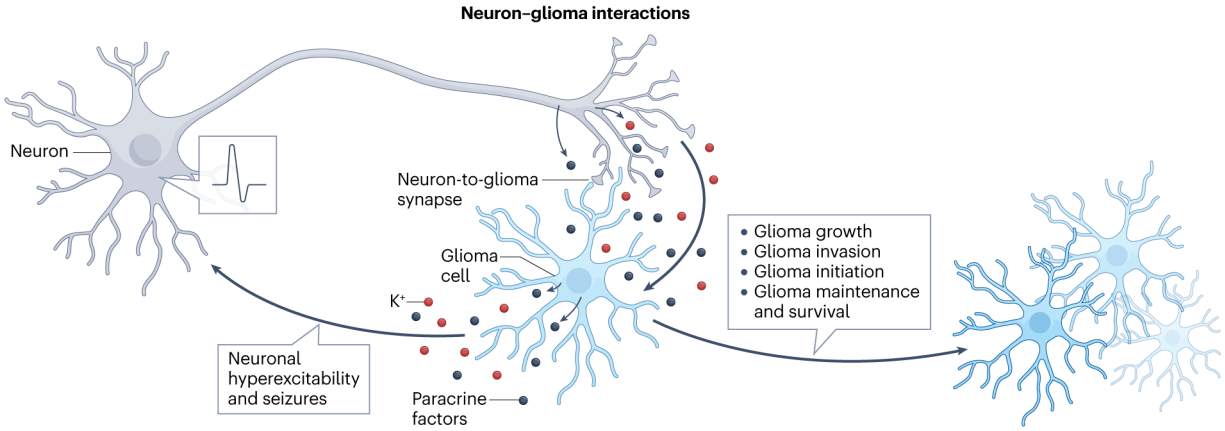

Fig. 4 |. Neuron–glioma interactions drive glioma pathobiology.

Paracrine and synaptic interactions between neurons and glioma cells promote cancer cell proliferation, invasion and survival, driving tumour initiation and growth. Reciprocally, glioma cells remodel neural circuits and promote neuronal hyperexcitability, resulting in glioma-associated seizures and increased neuronal input to the tumour.

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Table 1 |

Glioma cell state heterogeneity drives distinct mechanisms of network communication which informs potential therapeutic strategies

Glioma type	Cell state resemblance	Network interactions	Molecular mechanisms and therapeutic targets	Clinically available drugs that impact glioma preclinical models
Paediatric low-grade	OPC, astrocyte[161]	Paracrine[b], neuronal hyperexcitability[b]	NLGN3[b], HCN[b]	ADAM10 inhibitors[b], lamotrigine[b]
IDH and *H3* wild-type high-grade glioma	OPC, astrocyte, MES, NPC[87]	Neuron–glioma synapse, tumour microtube, neuronal hyperexcitability, paracrine, hub cells (also called pacemaker or oscillatory cells)	AMPAR, potassium channels, CX43, NLGN3, KCa, TSP1, IGF1	Perampanel, meclofenamate, senicapoc, gabapentin, ADAM10 inhibitors
IDH-mutant astrocytoma	NPC and OPC, astrocyte, oligodendrocyte[85]	Neuron–glioma synapse, tumour microtube, neuronal hyperexcitability	AMPAR, CX43	Perampanel[c], meclofenamate[c]
IDH-mutant oligodendroglioma	NPC and OPC, astrocyte, oligodendrocyte[85,162]	Paracrine, neuronal hyperexcitability	NLGN3	ADAM10 inhibitors[c]
H3 G34R/V-mutant DHG	INPC, NPC, astrocyte[152]	Unknown	Unknown	Unknown
H3 K27M-mutant DMG	OPC, astrocyte, oligodendrocyte, MES[a],86,163	Neuron–glioma synapse, tumour microtube, neuronal hyperexcitability, paracrine, hub cells	AMPAR, potassium channels, CX43, NLGN3	Perampanel, meclofenamate, ADAM10 inhibitors, senicapoc[c], gabapentin[c]

ADAM10, a disintegrin and metalloproteinase domain-containing protein 10; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CX43, connexin 43; DHG, diffuse hemispheric glioma; DMG, diffuse midline glioma; HCN, hyperpolarization-activated cyclic nucleotide-gated channel; IGF1, insulin-like growth factor 1; INPC, interneuron progenitor cell; MES, mesenchymal cell; NLGN3, neuroligin 3; KCa, calcium-activated potassium channel; NPC, neural precursor cell; OPC, oligodendrocyte precursor cell; TSP1, thrombospondin 1.

[a] Chiefly in older patients.

[b] Studied in neurofibromatosis type 1 (NF1)-associated low-grade optic gliomas.

[c] Drug mechanism has been identified but the drugs have not yet been tested in that specific glioma type.