

NG2-glia, More Than Progenitor Cells

Jaime Eugenin-von Bernhardt and Leda Dimou

Abstract NG2-glia are a mysterious and ubiquitous glial population with a highly branched morphology. Initial studies suggested that their unique function is the generation and maintenance of oligodendrocytes in the central nervous system (CNS), important for proper myelination and therefore for axonal support and fast conduction velocity. Over the last years this simplistic notion has been dramatically changed: the wide and homogeneous distribution of NG2-glia within all areas of the developing CNS that is maintained during the whole lifespan, their potential to also differentiate into other cell types in a spatiotemporal manner, their active capability of maintaining their population and their dynamic behavior in altered conditions have raised the question: are NG2-glia simple progenitor cells or do they play further major roles in the normal function of the CNS? In this chapter, we will discuss some important features of NG2-glia like their homeostatic distribution in the CNS and their potential to differentiate into diverse cell types. Additionally, we will give some further insights into the properties that these cells have, like the ability to form synapses with neurons and their plastic behavior triggered by neuronal activity, suggesting that they may play a role specifically in myelin and more generally in brain plasticity. Finally, we will briefly review their behavior in disease models suggesting that their function is extended to repair the brain after insult.

Keywords NG2-glia · Myelination · Oligodendrocytes · Neuronal activity · NG2-glia neuronal synapse · Disease · Injury · Proliferation · Differentiation · Plasticity

J. Eugenin-von Bernhardt (✉) · L. Dimou (✉)
Physiological Genomics, Biomedical Center, Ludwig-Maximilians-University,
Großhaderner Str. 9, 82152 Planegg-Martinsried, Germany
e-mail: Jaime.Eugenin@med.uni-muenchen.de

L. Dimou
e-mail: Leda.Dimou@lrz.uni-muenchen.de

J. Eugenin-von Bernhardt
Graduate School of Systemic Neuroscience, Ludwig-Maximilians-University,
82152 Planegg-Martinsried, Germany

Abbreviations

A β	Amyloid protein β
AD	Alzheimer's disease
AMPA	<i>α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid</i>
AMPA R	AMPA receptor
Ascl1	Achaete-scute homolog 1
α ScTX	A-scorpion toxin
BrdU	<i>5-bromo-2'-deoxyuridine</i>
Ca _v s	Voltage-gated calcium channels
CC1	Adenomatous polyposis coli
CNS	Central nervous system
DNQX	<i>6,7-dinitroquinoxaline-2,3-dione</i>
EAE	Experimental autoimmune encephalomyelitis
EdU	<i>5-ethynyl-2'-deoxyuridine</i>
EPSC	Excitatory postsynaptic current
GABA _A R	<i>γ-aminobutyric acid</i> receptor
GPR17	G-protein coupled receptor 17
K _v s	Voltage-gated potassium channels
LPC	<i>α-lysophosphatidylcholine</i>
Mash1	Mammalian achaete-scute homolog 1
MBP	Myelin basic protein
MCAO	Middle cerebral artery occlusion
mEPSC	Miniature EPSC
MS	Multiple sclerosis
Na _v s	Voltage-gated sodium channels
NBQX	<i>2,3-dihydroxy-6-nitro-7-sulphamoyl-benzo(F)quinoxaline</i>
NG2	Neuron/glia antigen 2
NMDAR	<i>N-methyl-D-aspartate</i> receptor
OPCs	Oligodendrocyte progenitor cells
PDGF	Platelet-derived growth factor
PDGFR	PDGF receptor α
PFC	Prefrontal cortex
PLP	Proteolipid protein
PNS	Peripheral nervous system
PSD-95	Postsynaptic density protein 95
TeNT	Tetanus neurotoxin
TTX	Tetrodotoxin

NG2-glia in the Central Nervous System

In the mammalian central nervous system (CNS), oligodendrocytes that build the myelin, develop from a progenitor cell population during late gestational and early postnatal life (Miller 1996) (see Section “A Brief Introduction to Oligodendrocyte Structure and Function” in Chapter “Oligodendrocytes: Functioning in a Delicate Balance Between High Metabolic Requirements and Oxidative Damage,” for a description on oligodendrocyte genesis). These progenitors are known as oligodendrocyte progenitor cells (OPCs) during development and as NG2-glia at later stages, becoming the fourth major group of glial cells in the CNS. The name NG2-glia derives from the expression of the chondroitin sulfate proteoglycan neuron/glia antigen 2 (NG2) (Fig. 1a–c) on their cell surface. To distinguish these over the pericytes of the CNS that also express NG2 (Ozderdem et al. 2001), we use the term NG2-glia instead of simply NG2-positive cells. NG2-glia can also be found in the literature as polydendrocytes, because of their branched morphology revealed by the immunolabeling for NG2 and the platelet-derived growth factor receptor α (PDGFR α) (Fig. 1a, b and d) and as OPCs due to their association to the generation and maintenance of the oligodendrocyte population under physiological and pathological conditions. However, restricting NG2-glia to be simply

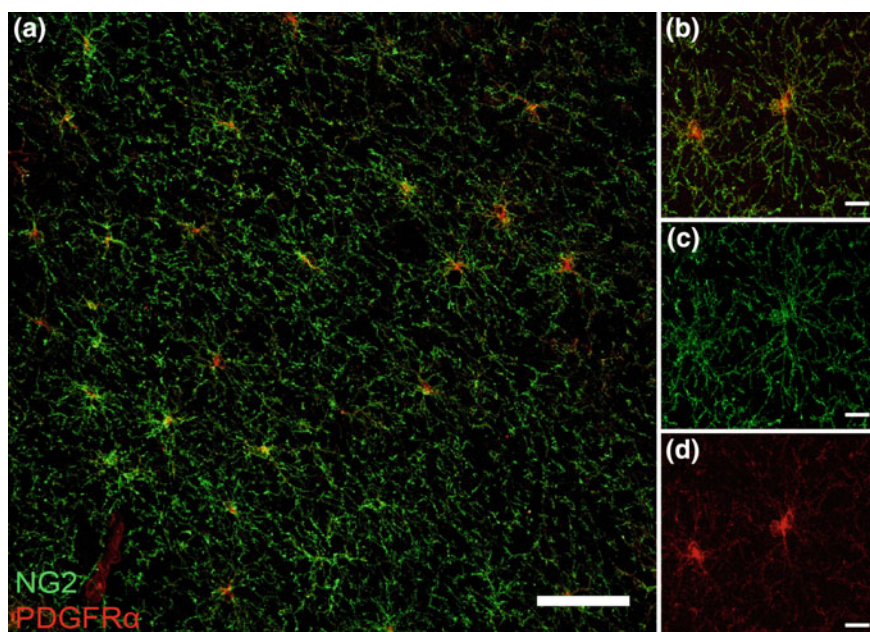


Fig. 1 **a** Confocal microscopy image showing the multiprocess morphology of NG2-glia co-expressing NG2 and PDGFR α . Scale bar represents 50 μ m. **b–d** Magnification of two NG2-glia; **b** co-expressing NG2 and PDGFR α , **c** expressing NG2 and **d** expressing PDGFR α . Scale bar represents 10 μ m

oligodendrocyte progenitors does not give them enough credit. In fact, it has not only been shown that NG2-glia represent the major proliferative cell population in the healthy adult brain (Psachoulia et al. 2009; Simon et al. 2011; Dimou and Götz 2014) outside the neurogenic niches but also that they can self-renew. In vitro and in vivo fate mapping experiments suggest that they can also give rise to a subpopulation of astrocytes in the ventrolateral forebrain during development (Raff et al. 1983; Zhu et al. 2008) and, strongly controversial, to neurons in the adult brain within restricted areas, like the piriform cortex and the hypothalamus (Guo et al. 2010; Robins et al. 2013) (Fig. 2). Nevertheless, the neuronal progeny of NG2-glia has been highly questioned in the field, as these results failed to replicate in several other mouse models genetically fate mapping NG2-glia (Dimou et al. 2008; Kang et al. 2010) leaving the question open if they are really capable to differentiate into neurons at least under physiological conditions.

NG2-glia represent around 5–10 % of the total cell population in the developing and adult brain and they are evenly distributed within the cerebral and cerebellar gray and white matter (Dawson et al. 2003) (Fig. 1a). Furthermore, NG2-glia can proliferate and differentiate into mature oligodendrocytes throughout life, although both their proliferation and differentiation rates depend on the area of the nervous system and decrease with age (Psachoulia et al. 2009; Kang et al. 2010; Zhu et al. 2011). Previous studies have supported the idea that NG2-glia can divide independently of extracellular signals to maintain their population and that they are

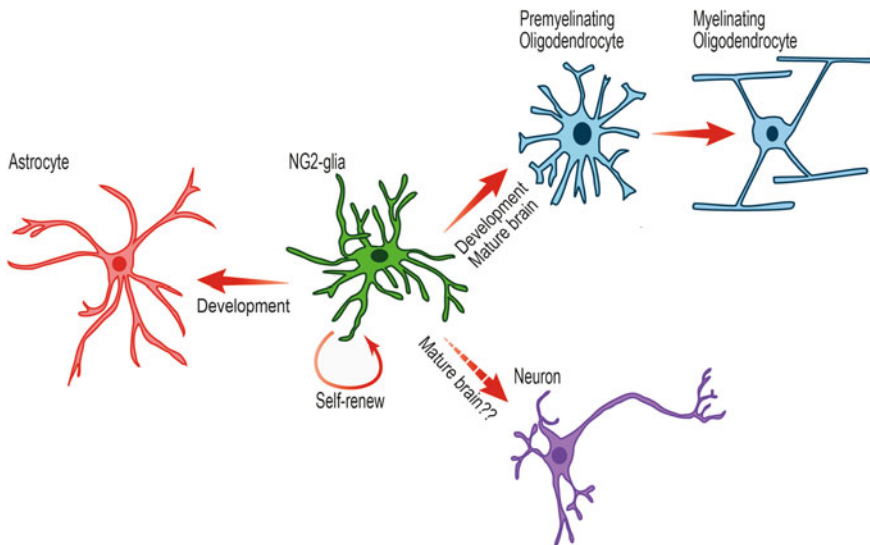


Fig. 2 Scheme representing the different cell fates of NG2-glia. Canonically, NG2-glia have the capability to proliferate and differentiate into oligodendrocytes in the immature and mature brain. However, NG2-glia can also differentiate into astrocytes in the ventrolateral forebrain during development. Additionally, some studies have suggested that, in the mature brain, NG2-glia could also differentiate into neurons, nevertheless, these claim is still under strong criticism

capable to proliferate and migrate short distances within the intact brain parenchyma, processes that are highly regulated by self-repulsion among NG2-glia (Hughes et al. 2013). Moreover, when a NG2-glia differentiates into an oligodendrocyte or after focal laser ablation of individual NG2-glia, neighboring NG2-glia proliferate and/or migrate in order to fill the “NG2-glia-free gap” in the mammalian and zebrafish CNS (Kirby et al. 2006; Hughes et al. 2013; Birey and Aguirre 2015). Furthermore, NG2-glia can divide asymmetrically giving origin to one NG2-glia and one oligodendrocyte (Hill et al. 2014), a common mechanism that progenitors have to differentiate without altering their total number. This feature, that is homeostatically controlled, opens several questions, e.g., why is a constant population of NG2-glia needed in the adult brain, even in areas where only few oligodendrocytes exist? The assumption that NG2-glia solely act as progenitors for oligodendrocytes has therefore been strongly questioned over the last years and the hypothesis for a further active and functional role of NG2-glia in the healthy and diseased brain has been supported.

Unexpectedly, other important features have been assigned to NG2-glia that until some years ago were thought to be exclusive for neurons. In vitro and in vivo studies could show that NG2-glia express voltage-gated sodium channels (Na_vs) (Karadottir et al. 2008; De Biase et al. 2010) sensitive to tetrodotoxin (TTX), voltage-gated potassium channels (K_vs), as well as low and high voltage-gated calcium channels (Ca_vs) on their processes that get downregulated during their maturation into oligodendrocytes (for review see Verkhratsky and Steinhauser 2000), revealing these channels to be required solely during their progenitor stage.

This wide expression of voltage-gated channels in NG2-glia suggests that these cells may have dynamic electrical properties, and theoretically they have all the components needed to generate and propagate action potentials. As a matter of fact, electrophysiological characterization of white matter NG2-glia in the rat has brought a thorough discussion regarding their possible ability to generate action potentials. The study of Karadottir et al. (2008) could show the existence of two subpopulations of NG2-glia within the white matter of the rat brain, proposing a classification of spiking and non-spiking populations and suggesting the existence of NG2-glia capable of generating action potentials (Karadottir et al. 2008). However, spiking NG2-glia have not been found in other species besides the rat white matter (Bergles et al. 2000; Karadottir et al. 2008; De Biase et al. 2010; Clarke et al. 2012), suggesting that this feature could be specific for NG2-glia in certain species or during certain developmental stages or both (Clarke et al. 2012). Therefore, generation and propagation of action potentials by NG2-glia appear to have no plausible role for the moment. Nevertheless, NG2-glia with different electrical properties rise an interesting point in the field, the NG2-glia heterogeneity.

NG2-glia Heterogeneity

Despite the even distribution of NG2-glia in the brain and their similar morphology, it is accepted in the last years that NG2-glia represent a highly heterogeneous population with diverse intrinsic properties and probably also distinct roles and functions. The heterogeneous nature of NG2-glia could be shown regarding different aspects of these cells, e.g., their morphology as well as their differentiation and proliferation properties. For instance, NG2-glia in the adult cerebral white matter can differentiate into oligodendrocytes faster and more efficiently than those located in the gray matter (Dimou et al. 2008). Subsequent homo- and heterotopic transplantation experiments revealed that these diverse differentiation properties between white and gray matter NG2-glia are the result of mainly intrinsic heterogeneity between these cells (Vigano et al. 2013). Interestingly, also their morphology and process distribution show differences between NG2-glia in these two areas (Vigano et al. 2013) (Fig. 3). NG2-glia in the white and gray matter have also been described to be different in regard to their cell cycle length. Although all NG2-glia can divide, gray matter cells have a longer cell cycle length than their white matter counterparts, further supporting the idea of the heterogeneity of NG2-glia (Psachoulia et al. 2009). Moreover, their response to extracellular signals is also variable. For example, NG2-glia in the white matter show a stronger proliferative response to platelet-derived growth factor (PDGF) than in the gray matter, despite that both populations express comparable levels of the receptor PDGFR α (Hill et al. 2013). Interestingly, in the last years NG2-glia heterogeneity has been suggested not only between different regions but also within the very same brain area. Indeed, some studies described the distinct expression of proteins only in subsets of NG2-glia located in the same region. For example, only 50 % of

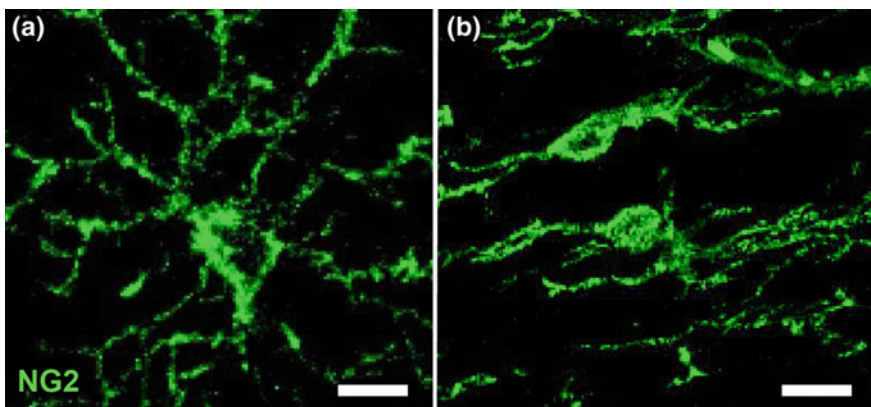


Fig. 3 NG2-glia are heterogeneous in regard to their morphology. Magnification of confocal images showing NG2-glia from **a** the gray matter and **b** white matter of the brain, highlighting clear morphological differences between both populations. Scale bar represents 10 μ m

NG2-glia in the cortical gray matter express the transcription factor achaete-scute homolog 1 or mammalian achaete-scute homolog 1 (Ascl1 or Mash1), an important factor for neuronal fate determination (Parras et al. 2007). However, by now no distinct roles could be assigned to these two populations. In the same line, also the G-protein coupled receptor 17 (GPR17), that is involved in the differentiation of NG2-glia (Boda et al. 2011; Chen et al. 2009), is only expressed in a subset of NG2-glia in different regions and at different ages. Interestingly, it could be shown that GPR17-positive cells represent a population of NG2-glia that differentiates very slowly in the intact brain. However, after a cerebral damage, they rapidly react and undergo maturation, suggesting a role as a “reserve pool” of adult progenitors that are maintained for repair processes (Vigano et al. 2016). Whether all these described differences between NG2-glia in distinct or even in the same area are the result solely of an intrinsic program or micro-environmental influences restricting or providing the cells special properties, is not clear; and the existence of evidences in favor and against both ideas keeps the question still unanswered (for review see Vigano and Dimou 2016).

Synapses Between NG2-glia and Neurons

In addition to the controversial possibility of generating action potentials, NG2-glia have shown other features, which are also shared with neurons. The formation of synapses between NG2-glia and neurons is a captivating observation. These synapses were first observed in the mouse, where stimulation of neurons located in the CA3 region of the hippocampus triggered an evoked excitatory postsynaptic current (EPSC) of a sodium current nature in NG2-glia located in the CA1 region (Bergles et al. 2000). Furthermore, the spontaneous fusion of transmitter-filled vesicles that occurs at individual excitatory synapses between NG2-glia and neurons resulting in miniature EPSCs (mEPSCs) has also been shown, a feature not exclusively present in the hippocampus, but also in several other brain areas (Bergles et al. 2000; De Biase et al. 2010). In the same line, the brief application of the neurotoxin pargyline, which enhances the frequency of vesicular release from nerve terminals, caused the appearance of high frequency bursts of mEPSCs in NG2-glia (Bergles et al. 2000), revealing a correlation between vesicular release and the electric properties of NG2-glia. In both studies, these currents were abolished by the application of the noncompetitive α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/Kainate receptor antagonist 2,3-dihydroxy-6-nitro-7-sulphamoyl-benzo(F)quinoxaline (NBQX) (Bergles et al. 2000; De Biase et al. 2010), demonstrating the glutamatergic nature of these signals. Finally, the existence of synapses between NG2-glia and neurons has also been confirmed by transmission electron microscopy that revealed presynaptic release sites in the axon membrane close to NG2-glia membrane (Bergles et al. 2000; Ziskin et al. 2007).

Notably, the complexity of these NG2-glia-neuron synapses is not limited to the expression of the AMPA receptor (AMPA), but extends to a wide variety of

typical postsynaptic receptors such as *N-methyl-D-aspartate* receptor (NMDAR) (for review see Dzamba et al. 2013), acetylcholine receptor (De Angelis et al. 2012), γ -aminobutyric acid receptor (GABA_AR) (Von Blankenfeld et al. 1991; Williamson et al. 1998) and others. Moreover, not only receptors can be found in NG2-glia, but as transcriptome data also suggest, they may also express proteins important for the establishment of a postsynapse like the postsynaptic density protein 95 (PSD-95) (Sakry et al. 2011), one of the major components of the postsynaptic density and important for synapse formation, maturation, and remodeling (El-Husseini et al. 2000; Marrs et al. 2001). Nowadays, many questions still remain unanswered regarding these synaptic glia-neuron structures. First, it is neither clear if these synapses are only sending information from neurons to NG2-glia in an unidirectional fashion or if they could also be part of a bidirectional communication mechanism, nor if these synapses are present in all or in just a subpopulation of NG2-glia. For example, it could also be that NG2-glia express different channels and form synapses with neurons only at a specific timepoint of their life when they need neuronal signals to perform specific functions like, e.g., differentiation or neuronal support. Moreover, neither the molecular composition of these synapses nor the main functions that these glia-neuron structures may have, have been elucidated (for review see Dimou and Gallo 2016).

Myelin Plasticity

Myelination of the nervous system enables fast electric conduction along the myelinated axon and reduces the metabolic cost of neuronal activity; features making myelination important for the proper function of the nervous system in gnathostomates vertebrates and some invertebrates (Davis et al. 1999). Myelin formation changes the electrical properties of axons by reducing the capacitance and increasing the peripheral resistance of the surrounded axon. Myelin sheaths do not cover the complete axon, but they are absent in short segments, structures known as nodes of Ranvier, that express high levels of Na_vs, important for the generation of action potentials in this area. This particular arrangement of myelin along axons provides neurons with the structural basis for the saltatory action potential propagation (Nave and Werner 2014).

In vertebrates, there are two cell types that have the unique ability to synthesize large amounts of membrane that wrap and compact around axons to form myelin: Schwann cells in the peripheral nervous system (PNS) and the oligodendrocytes in the CNS. Although both cell types have the capability to myelinate axons, they differ among other features enormously in regard to their developmental origin, their protein composition, the number of myelinated axonal segments each cell can establish, and the myelin periodicity. Therefore, this apparent structural and functional similarity of PNS and CNS myelin is a superb example of convergent cellular evolution of the nervous system (see Chapters “[Oligodendrocytes: Functioning in a Delicate Balance Between High Metabolic Requirements and Oxidative Damage](#)”

and “[Schwann Cell and Axon: An Interlaced Unit—From Action Potential to Phenotype Expression](#)” for further reading on oligodendrocytes and Schwann cells).

In the past, the two-dimensional nature of electron microscopy images had promoted the notion that myelin is a static structure in our nervous system. Nevertheless, lately it has been shown that myelin in the rodent brain is constantly remodeling during lifespan, giving us a new perspective of highly plastic processes. Different signals trigger changes in the compaction of myelin sheaths, in the internode length (the areas of the myelinated axons flanked by the nodes of Ranvier), in the number of sheaths surrounding one axon, and in the number of axons that one oligodendrocyte can myelinate (Nave and Werner 2014).

Neuronal activity has shown to be an important factor in the remodeling of the myelin along the axon. The inhibition of action potentials with TTX, which blocks Na_v s currents, leads for example to a decrease in myelination in vitro and in the mouse optic nerve in vivo (Demerens et al. 1996). Conversely, the stimulation of neuronal activity with α -scorpion toxin (αScTX), which delays the inactivation of Na_v s, or direct electric stimulation of neurons with an electrode, triggers the increase of myelination in mixed oligodendrocyte-neuronal cultures (Demerens et al. 1996; Gary et al. 2012). Furthermore, social deprived adult mice showed impaired myelination in the prefrontal cortex (PFC), an area which has been associated with complex emotional and cognitive behavior (Liu et al. 2012). Notably, neuronal activity dependent changes could also be observed in human white matter, a structure that primarily consists of myelinated axons, cells of the oligodendrocytic lineage, other glial cells, and no neuronal cell bodies. Diffusion tensor imaging (DTI) studies have shown that various complex visual-motor tasks, such as juggling or extensive piano playing, trigger changes in the white matter architecture, by significantly increasing its size (Bengtsson et al. 2005; Scholz et al. 2009). Amazingly, it appears that neuronal activity is not just limited in increasing the myelination of vertebrates' axons. Recent studies in the zebrafish larvae spinal cord have indeed shown that neuronal activity additionally provides a signal bias for which axons must be myelinated. By in vivo time lapse imaging of the zebrafish spinal cord, it was shown that while the initial axonal myelin wrapping is axon activity independent, the stabilization and extension of the prospective myelin sheaths depends on the activity-dependent secretion of axonal factors, like neurotransmitters and neurotrophic factors (Hines et al. 2015). Furthermore, blocking the synaptic vesicle release with tetanus neurotoxin (TeNT) decreases the number of myelinated axons and the total number of myelin sheaths per oligodendrocyte in the zebrafish spinal cord (Mensch et al. 2015). Interestingly, similar results could be obtained in rodents, where an activity independent myelination could be observed first, followed by an activity dependent myelination triggered by neuregulin (Lundgaard et al. 2013). Together, these studies show that neuronal activity has a direct effect on the oligodendrocytes population, defining which and how many axons must be myelinated.

Thus, one obvious potential role for NG2-glia-neuron synapses could be to regulate the proliferation and differentiation of NG2-glia. The outcome of these changes probably aims at improving or even modulating myelination of certain

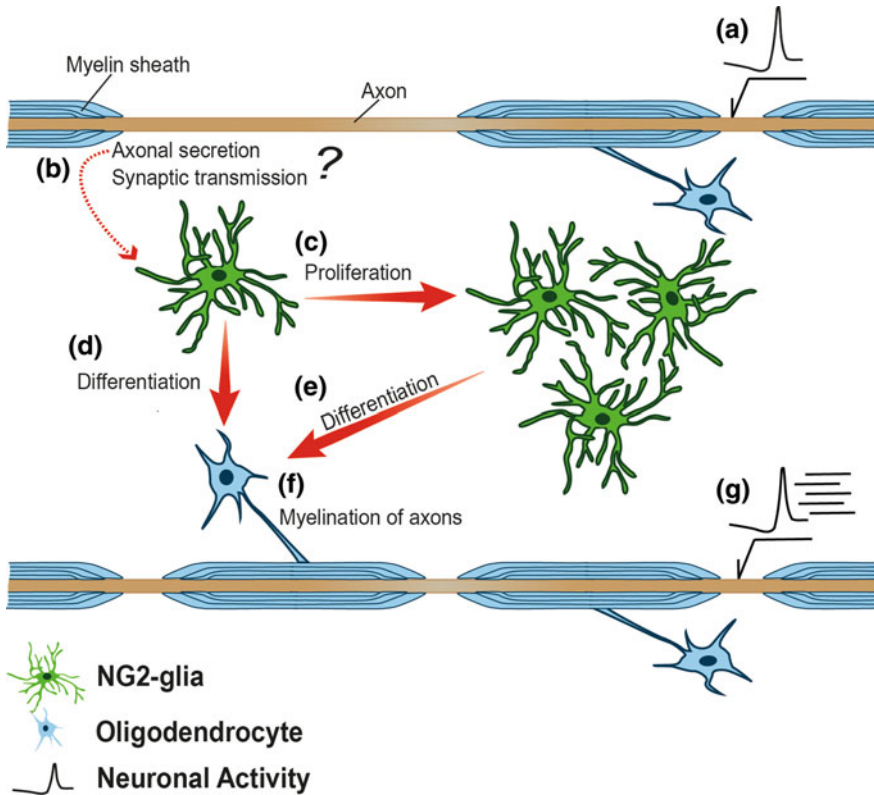


Fig. 4 Scheme of the effect of neuronal activity on NG2-glia behavior. In response to **a** neuronal activity, **b** neurons could release signals secreted from the axon or the soma; or secreted into the synaptic cleft formed between neurons and NG2-glia. These signals could manipulate NG2-glia **c** proliferation or **d** differentiation into oligodendrocytes. It is also possible that **e** after proliferation the newborn NG2-glia differentiate. If new oligodendrocytes are generated, they could potentially **f** myelinate surrounding axons and **g** change the electrical properties of neurons and therefore modify the properties of the neuronal network

circuits, therefore enhancing the computational properties of networks required to improve performance in certain specific tasks (Fig. 4).

NG2-glia Behavior and Dynamics Modulated by Neuronal Activity

Although many studies have been performed regarding the influence of neuronal activity on the cells of the oligodendrocyte lineage, it is still unclear whether this happens in a direct or indirect manner. Early work showed that intraocular injection

of TTX diminishes the proliferation of NG2-glia close to axons of the retinal ganglion cells by preventing the neuronal activity-dependent release of mitogens (Barres and Raff 1993). NG2-glia can express a wide variety of purinergic receptors and it has additionally been shown that neuronal activity induces adenosine release by neurons and decreases NG2-glia proliferation (Stevens et al. 2002). It is therefore possible that other extra-synaptic molecules, whose release is activity dependent, like growth factors, also play a significant role in the modulation of the proliferation and differentiation of NG2-glia.

Apparently NG2-glia that are proliferating and differentiating could be also modulated by signals provided directly by the neuro-glia synapses. It has been shown that neurotransmitter release may have an important role in the development of the oligodendrocyte lineage. Experiments in organotypic cultures of cerebellum slices obtained from P6 mice have shown that the exposition to glutamate receptor agonists like kainate and AMPA decrease the proportion of NG2-glia positive to the proliferation marker *5-bromo-2'-deoxyuridine* (BrdU), a thymidine analogue incorporated into the cell during the S-phase of the cell cycle. In contrast, administration of the kainate and AMPA receptor antagonist *6,7-dinitroquinoxaline-2,3-dione* (DNQX) lead to an increase in cell proliferation (Yuan et al. 1998).

Interestingly, this evidence indicates that neuronal activity promotes changes in the behavior of NG2-glia in both, a direct and indirect way. Unfortunately, the investigation of this idea in *in vivo* experimental models can be very challenging. It could be shown that high-frequency electrical stimulation applied in the medullary pyramids of rats increases the proliferation and differentiation of NG2-glia in the contralateral dorsal corticospinal tract (Li et al. 2010). However, the experimental approach in this last study required the implantation of electrodes to promote neuronal activity *in vivo* that inevitably resulted in injury and subsequently in inflammation. This brings serious complications in the interpretation of these results as NG2-glia show morphological and functional changes in response to damage, by, e.g., increasing their proliferation rate, becoming hypertroph, polarizing toward the injury, and migrating into the injury (Dimou et al. 2008; Simon et al. 2011; Hughes et al. 2013; for review see Dimou and Götz 2014). Therefore, most experiments in this field have been performed by promoting neuronal activity through indirect methods.

Physical stimuli, provided by keeping mice under enriched environment conditions, e.g., by adding running wheels or other toys into cages for two weeks, trigger an increase in the differentiation of NG2-glia into oligodendrocytes, in the motor and somatosensory cortex and in the amygdala (Simon et al. 2011; Ehninger et al. 2011). Another strategy implemented in this field has been stimuli deprivation, which also leads to changes in the behavior of NG2-glia. NG2-glia from the barrel cortex of layer IV are functionally innervated by thalamocortical fibers coming from the ventral basal thalamus, determining the distribution of these cells in the walls of the barrel cortex and not in its core (Mangin et al. 2012). After cauterizing mouse whiskers at birth, NG2-glia show an aberrant homogenous distribution in the whole barrel cortex. Additionally, an increased fraction of NG2-glia in the core of the barrel cortex is positive for Ki67, an active proliferation

marker. These results suggest the hypothesis that the thalamocortical fibers are inhibiting the proliferation of NG2-glia in the core of the barrel cortex (Mangin et al. 2012), resulting in the particular distribution of NG2-glia in the layer IV. Furthermore, in another experimental approach, clipping the whiskers of adult mice unilaterally induced a decrease in the total number of oligodendrocytes and an increased expression of activated caspase-3, a marker for apoptosis, in oligodendrocytes derived from proliferating NG2-glia in the somatosensory cortex ipsilateral to the clipped side (Hill et al. 2014). These results suggest that stimuli deprivation not only compromises the differentiation of NG2-glia into oligodendrocytes but also their survival (Hill et al. 2014).

New strategies to test how neuronal activity affects the dynamics of NG2-glia in vivo are emerging, promising to provide data while avoiding the collateral effects caused by CNS damage. The development of optogenetics, a technique in which light-sensitive ion channels can be selectively expressed in a specific subpopulation of neurons, which then can be activated through their exposure to a specific light wavelength, could result in great advances in this area. A recent study using a transgenic mouse line expressing the channel rhodopsin in neurons with an active Thy1 promoter, allowed the stimulation of neurons located in the cortical layer V and the analysis of the effects of this artificial stimulation in the dynamics of the oligodendrocyte lineage (Gibson et al. 2014). Indeed, stimulation of neurons lead to an increase in the number of cells positive for the thymidine analogue and proliferation marker, *5-ethynyl-2'-deoxyuridine* (EdU), in the neighborhood of the stimulated neurons. A fraction of these EdU-positive cells were positive for Olig2, a transcription factor used as a marker for the oligodendrocyte lineage (Gibson et al. 2014), for PDGFR α , a marker for NG2-glia (Dimou and Gotz 2014), and for the adenomatous polyposis coli (CC1), a marker for mature oligodendrocytes (Gibson et al. 2014). These results highlight the relation between the experimental increase of firing rate and the increase of the proliferation and differentiation dynamics of the oligodendrocyte lineage. Moreover, the study went even further and showed that increased stimulation of neurons lead to an increase in myelination, specifically of the axons from the stimulated neurons, leading to the improvement of behavioral-motor function of these animals (Gibson et al. 2014).

The above described data, and the additional growing evidence consistently show that neuronal activity, triggered by different physiological environmental or artificial stimuli, efficiently promotes proliferation and differentiation of NG2-glia in in vitro as well as in in vivo models. It has also been shown by correlation that the modulation of this behavior can result in an improvement in the myelination of axons belonging to neurons with increased activity and, therefore, improvement of the fine tuning of neuronal networks which subsequently ameliorates tasks performance depending on this specific network. However, although signals provided by neurons to induce proliferation and differentiation and the consequences related to the change in the NG2-glia behavior have been identified, the cellular and molecular mechanisms being triggered by neuronal activity in the NG2-glia still remain unclear.

NG2-glia reaction towards Central Nervous System Pathology

As we briefly mentioned before, NG2-glia change their dynamics and behavior when the CNS is damaged. Moreover, changes in NG2-glia in different models of injury and demyelination have suggested that NG2-glia may play an active role in repairing the brain under pathological conditions. Hypomyelinating mutant mouse lines like the *jimpy*, in which oligodendrocytes die as the result of a point mutation in the most abundant CNS myelin protein, the proteolipid protein (PLP), or the *shiverer*, in which oligodendrocytes are unable to form compact myelin sheaths due to the deletion of the myelin basic protein (MBP), have shown an increase in the proliferation and differentiation of NG2-glia in the spinal cord white matter in comparison to the control wild type groups (Wu et al. 2000; Bu et al. 2004). This shows an association between myelination defects and change of physiological NG2-glia behavior. Unfortunately, due to the mutation in important myelin proteins, both models are incapable to demonstrate if there is remyelination after NG2-glia reaction toward aberrant myelination. However, transplantation of healthy human NG2-glia into the *shiverer* mouse model resulted in improved remyelination of the brain, hinting into the capability of NG2-glia to repair demyelinated areas (Windrem et al. 2008) and therefore a probable strategy for the therapy of demyelinating diseases in the CNS (Franklin and Ffrench-Constant 2008) (see Chapter “[Peripheral Inflammation and Demyelinating Diseases](#)” for further reading on demyelinating diseases).

Other strategies have also been performed in this field to specifically injure brain white matter tracts and study the behavior and the remyelination properties of NG2-glia. Cultured cortical slices exposed to α -lysophosphatidylcholine (LPC), show damage in the corpus callosum, and subsequent demyelination of the affected area. After this acute lesion, an increase in proliferation of NG2-glia (Garay et al. 2011) and in their differentiation into myelinating oligodendrocytes (Gensert and Goldman 1997) could be observed. Two-photon in vivo imaging of postnatal cortical slices further confirmed these results and showed that this acute injury model changes the differentiation behavior of NG2-glia by increasing the asymmetric division of these cells, giving rise to one NG2-glia and one oligodendrocyte (Hill et al. 2014). Additionally, in the experimental autoimmune encephalomyelitis (EAE) mouse, a classic model for multiple sclerosis (MS; a disease that promotes demyelination and axonal loss in the CNS), or in antibody-induced demyelination, the number of NG2-glia also increased in those areas where extensive demyelination occurs, while the population of NG2-glia did not change in the tissue surrounding the lesions (Keirstead et al. 1998; Di Bello et al. 1999).

The role of NG2-glia during demyelination and the subsequent remyelination appears to be clear. The decrease in myelin triggers the proliferation and differentiation of NG2-glia in order to reestablish the loss of myelin in the CNS, making NG2-glia an excellent target for regenerative therapy. However, it is still unclear what the trigger for the reaction of NG2-glia after demyelination could be; it is e.g.

possible that NG2-glia possess the special capability to sense the lack of oligodendrocytes/myelin or that NG2-glia react to the aberrant neuronal activity promoted by the demyelination. It is known that the CNS of MS patients fails to remyelinate with disease progression. Interestingly, postmortem NG2 and PDGFR α immunolabeling of brains of these patients have revealed that NG2-glia are more frequently present in areas of the white matter undergoing active inflammatory demyelination, where commonly remyelination occurs, than in chronic lesions (Wilson et al. 2006), suggesting that NG2-glia are subjected to certain limitations for effective remyelination in long-term pathology, probably provided by an antagonistic environment or by an exhaustion of the NG2-glia limiting them to further proliferate and differentiate.

In contrast to de-/remyelination, the role of these cells in other brain insults like acute injury and neurodegeneration is not clear yet. After a stab wound injury in the cerebral cortex an increase in the proliferation and density of NG2-glia surrounding the lesion could be observed (Dimou et al. 2008; Simon et al. 2011). Moreover, in the APPS1 mice, a mouse model for Alzheimer's disease (AD), where also demyelination occurs, NG2-glia react with increased proliferation and differentiation (Behrendt et al. 2013) and become hypertrophe in the gray matter cerebral cortex (Sirko et al. 2013). Li et al. (2013) have also reported that NG2-glia cluster around the amyloid plaques and as already suggested for other glial cells that they are capable of engulfing the amyloid protein β (Abeta) and degrade it by an autophagy-lysosomal pathway playing a role in clearing it from the affected brain (Li et al. 2013). Although the specific function of NG2-glia remains unknown, it could be possible that they may serve as orchestra directors recruiting and modulating the function of other glial and immune cells in the CNS in order to reestablish the homeostasis of the brain.

Another important question addressed in the field is whether the whole population or only a subset of NG2-glia are actively participating in repairing the brain damage. As discussed above, an interesting subset of NG2-glia that expresses GPR17 seems to resemble NG2-glia specialized for repair. GPR17 is a orphanized receptor for both uracil nucleotides and cystein leukotrienes, cysLTs (e.g., UDP-glucose and LTD₄) (Lecca et al. 2008). Both ligands for GPR17 are secreted after brain injury and their extracellular concentration is increased suggesting a role of this receptor in "sensing" brain damage (Lecca et al. 2008). It has been shown that GPR17-positive NG2-glia in the adult brain increase their density after acute cortical stab wound injury in the gray matter surrounding the lesion and in the white matter underneath the lesion (Boda et al. 2011). Moreover, fate mapping studies of GPR17-positive cells have shown that although they have a limited differentiation capacity under physiological conditions, after stab wound injury or middle cerebral artery occlusion (MCAO), a model of ischemic stroke, these cells strongly differentiate into oligodendrocytes probably in order to repair the injured tissue. Interestingly, in the above described APP/PS1 mouse line, GPR17-positive NG2-glia were responsive specifically in the gray matter, but not in the white matter (Boda et al. 2011). This result highlights once again the potential heterogeneity of these cells and their functional differences in the brain.

Concluding Remarks

We have shown in this chapter that NG2-glia are a population of cells that are widely represented within the CNS during the late stage of development and in the whole adult lifespan. Their potential to possibly originate different cell types, their long cell cycle length and maintenance of their own population size resembles more the characteristics of neuronal stem cells rather than simple oligodendrocyte progenitors. Moreover, special features like the expression of channels and receptors, their response to neurotransmitters and growth factors and the synapse formation with neurons make them a unique group of glial cells. Additionally, the capability of NG2-glia to modulate their behavior and dynamics in response to neuronal activity and disease, suggest an important role not only for myelin maintenance and remodeling under physiological but also for repair under pathological conditions. There are still many mysteries around the specific NG2-glia functions in the healthy and diseased brain. The understanding of these cells may lead to significant improvement not only of our global knowledge of the complexity of the brain, but also of the treatment of traumatic and neurodegenerative diseases and the improvement of the quality of life during normal aging, which also has been related to an impairment of myelin (Sturrock 1976; Peters 2002; Lasiene et al. 2009; Lu et al. 2011; Lu et al. 2013).

References

- Barres BA, Raff MC (1993) Proliferation of oligodendrocyte precursor cells depends on electrical activity in axons. *Nature* 361(6409):258–260. doi:[10.1038/361258a0](https://doi.org/10.1038/361258a0)
- Behrendt G, Baer K, Buffo A, Curtis MA, Faull RL, Rees MI, Gotz M, Dimou L (2013) Dynamic changes in myelin aberrations and oligodendrocyte generation in chronic amyloidosis in mice and men. *Glia* 61(2):273–286. doi:[10.1002/glia.22432](https://doi.org/10.1002/glia.22432)
- Bengtsson SL, Nagy Z, Skare S, Forsman L, Forssberg H, Ullen F (2005) Extensive piano practicing has regionally specific effects on white matter development. *Nat Neurosci* 8(9):1148–1150. doi:[10.1038/nn1516](https://doi.org/10.1038/nn1516)
- Bergles DE, Roberts JD, Somogyi P, Jahr CE (2000) Glutamatergic synapses on oligodendrocyte precursor cells in the hippocampus. *Nature* 405(6783):187–191. doi:[10.1038/35012083](https://doi.org/10.1038/35012083)
- Birey F, Aguirre A (2015) Age-dependent Netrin-1 signaling regulates NG2+ glial cell spatial homeostasis in normal adult gray matter. *J Neurosci* 35(17):6946–6951. doi:[10.1523/JNEUROSCI.0356-15.2015](https://doi.org/10.1523/JNEUROSCI.0356-15.2015)
- Boda E, Vigano F, Rosa P, Fumagalli M, Labat-Gest V, Tempia F, Abbracchio MP, Dimou L, Buffo A (2011) The GPR17 receptor in NG2 expressing cells: focus on in vivo cell maturation and participation in acute trauma and chronic damage. *Glia* 59(12):1958–1973. doi:[10.1002/glia.21237](https://doi.org/10.1002/glia.21237)
- Bu J, Banki A, Wu Q, Nishiyama A (2004) Increased NG2(+) glial cell proliferation and oligodendrocyte generation in the hypomyelinating mutant shiverer. *Glia* 48(1):51–63. doi:[10.1002/glia.20055](https://doi.org/10.1002/glia.20055)
- Chen Y, Wu H, Wang S, Koito H, Li J, Ye F, Hoang J, Escobar SS, Gow A, Arnett HA, Trapp BD, Karandikar NJ, Hsieh J, Lu QR (2009) The oligodendrocyte-specific G

- protein-coupled receptor GPR17 is a cell-intrinsic timer of myelination. *Nat Neurosci* 12 (11):1398–1406. doi:[10.1038/nn.2410](https://doi.org/10.1038/nn.2410)
- Clarke LE, Young KM, Hamilton NB, Li H, Richardson WD, Attwell D (2012) Properties and fate of oligodendrocyte progenitor cells in the corpus callosum, motor cortex, and piriform cortex of the mouse. *J Neurosci* 32(24):8173–8185. doi:[10.1523/JNEUROSCI.0928-12.2012](https://doi.org/10.1523/JNEUROSCI.0928-12.2012)
- Davis AD, Weatherby TM, Hartline DK, Lenz PH (1999) Myelin-like sheaths in copepod axons. *Nature* 398(6728):571. doi:[10.1038/19212](https://doi.org/10.1038/19212)
- Dawson MR, Polito A, Levine JM, Reynolds R (2003) NG2-expressing glial progenitor cells: an abundant and widespread population of cycling cells in the adult rat CNS. *Mol Cell Neurosci* 24(2):476–488
- De Angelis F, Bernardo A, Magnaghi V, Minghetti L, Tata AM (2012) Muscarinic receptor subtypes as potential targets to modulate oligodendrocyte progenitor survival, proliferation, and differentiation. *Dev Neurobiol* 72(5):713–728. doi:[10.1002/dneu.20976](https://doi.org/10.1002/dneu.20976)
- De Biase LM, Nishiyama A, Bergles DE (2010) Excitability and synaptic communication within the oligodendrocyte lineage. *J Neurosci* 30(10):3600–3611. doi:[10.1523/JNEUROSCI.6000-09.2010](https://doi.org/10.1523/JNEUROSCI.6000-09.2010)
- Demerens C, Stankoff B, Logak M, Anglade P, Allinquant B, Couraud F, Zalc B, Lubetzki C (1996) Induction of myelination in the central nervous system by electrical activity. *Proc Natl Acad Sci USA* 93(18):9887–9892
- Di Bello IC, Dawson MR, Levine JM, Reynolds R (1999) Generation of oligodendroglial progenitors in acute inflammatory demyelinating lesions of the rat brain stem is associated with demyelination rather than inflammation. *J Neurocytol* 28(4–5):365–381
- Dimou L, Gallo V (2015) NG2-glia and their functions in the central nervous system. *Glia* 63 (8):1429–1451. doi:[10.1002/glia.22859](https://doi.org/10.1002/glia.22859)
- Dimou L, Götz M (2014) Glial cells as progenitors and stem cells: new roles in the healthy and diseased brain. *Physiol Rev* 94(3):709–737. doi:[10.1152/physrev.00036.2013](https://doi.org/10.1152/physrev.00036.2013)
- Dimou L, Simon C, Kirchhoff F, Takebayashi H, Gotz M (2008) Progeny of Olig2-expressing progenitors in the gray and white matter of the adult mouse cerebral cortex. *J Neurosci* 28 (41):10434–10442. doi:[10.1523/JNEUROSCI.2831-08.2008](https://doi.org/10.1523/JNEUROSCI.2831-08.2008)
- Dzamba D, Honsa P, Anderova M (2013) NMDA receptors in glial cells: pending questions. *Curr Neuropharmacol* 11(3):250–262. doi:[10.2174/1570159X11311030002](https://doi.org/10.2174/1570159X11311030002)
- Ehninger D, Wang LP, Klempin F, Romer B, Kettenmann H, Kempermann G (2011) Enriched environment and physical activity reduce microglia and influence the fate of NG2 cells in the amygdala of adult mice. *Cell Tissue Res* 345(1):69–86. doi:[10.1007/s00441-011-1200-z](https://doi.org/10.1007/s00441-011-1200-z)
- El-Husseini AE, Schnell E, Chetkovich DM, Nicoll RA, Brecht DS (2000) PSD-95 involvement in maturation of excitatory synapses. *Science* 290(5495):1364–1368
- Franklin RJ, Ffrench-Constant C (2008) Remyelination in the CNS: from biology to therapy. *Nat Rev Neurosci* 9(11):839–855. doi:[10.1038/nrn2480](https://doi.org/10.1038/nrn2480)
- Garay L, Tungler V, Deniselle MC, Lima A, Roig P, De Nicola AF (2011) Progesterone attenuates demyelination and microglial reaction in the lysolecithin-injured spinal cord. *Neuroscience* 192:588–597. doi:[10.1016/j.neuroscience.2011.06.065](https://doi.org/10.1016/j.neuroscience.2011.06.065)
- Gary DS, Malone M, Capestany P, Houdayer T, McDonald JW (2012) Electrical stimulation promotes the survival of oligodendrocytes in mixed cortical cultures. *J Neurosci Res* 90(1):72–83. doi:[10.1002/jnr.22717](https://doi.org/10.1002/jnr.22717)
- Gensert JM, Goldman JE (1997) Endogenous progenitors remyelinate demyelinated axons in the adult CNS. *Neuron* 19(1):197–203
- Gibson EM, Purger D, Mount CW, Goldstein AK, Lin GL, Wood LS, Inema I, Miller SE, Bieri G, Zuchero JB, Barres BA, Woo PJ, Vogel H, Monje M (2014) Neuronal activity promotes oligodendrogenesis and adaptive myelination in the mammalian brain. *Science* 344 (6183):1252304. doi:[10.1126/science.1252304](https://doi.org/10.1126/science.1252304)
- Guo F, Maeda Y, Ma J, Xu J, Horiuchi M, Miers L, Vaccarino F, Pleasure D (2010) Pyramidal neurons are generated from oligodendroglial progenitor cells in adult piriform cortex. *J Neurosci* 30(36):12036–12049. doi:[10.1523/JNEUROSCI.1360-10.2010](https://doi.org/10.1523/JNEUROSCI.1360-10.2010)

- Hill RA, Patel KD, Medved J, Reiss AM, Nishiyama A (2013) NG2 cells in white matter but not gray matter proliferate in response to PDGF. *J Neurosci* 33(36):14558–14566. doi:[10.1523/JNEUROSCI.2001-12.2013](https://doi.org/10.1523/JNEUROSCI.2001-12.2013)
- Hill RA, Patel KD, Goncalves CM, Grutzendler J, Nishiyama A (2014) Modulation of oligodendrocyte generation during a critical temporal window after NG2 cell division. *Nat Neurosci* 17(11):1518–1527. doi:[10.1038/nn.3815](https://doi.org/10.1038/nn.3815)
- Hines JH, Ravanelli AM, Schwandt R, Scott EK, Appel B (2015) Neuronal activity biases axon selection for myelination in vivo. *Nat Neurosci* 18(5):683–689. doi:[10.1038/nn.3992](https://doi.org/10.1038/nn.3992)
- Hughes EG, Kang SH, Fukaya M, Bergles DE (2013) Oligodendrocyte progenitors balance growth with self-repulsion to achieve homeostasis in the adult brain. *Nat Neurosci* 16(6):668–676. doi:[10.1038/nn.3390](https://doi.org/10.1038/nn.3390)
- Kang SH, Fukaya M, Yang JK, Rothstein JD, Bergles DE (2010) NG2+ CNS glial progenitors remain committed to the oligodendrocyte lineage in postnatal life and following neurodegeneration. *Neuron* 68(4):668–681. doi:[10.1016/j.neuron.2010.09.009](https://doi.org/10.1016/j.neuron.2010.09.009)
- Karadottir R, Hamilton NB, Bakiri Y, Attwell D (2008) Spiking and nonspiking classes of oligodendrocyte precursor glia in CNS white matter. *Nat Neurosci* 11(4):450–456. doi:[10.1038/nn2060](https://doi.org/10.1038/nn2060)
- Keirstead HS, Levine JM, Blakemore WF (1998) Response of the oligodendrocyte progenitor cell population (defined by NG2 labelling) to demyelination of the adult spinal cord. *Glia* 22(2):161–170
- Kirby BB, Takada N, Latimer AJ, Shin J, Carney TJ, Kelsh RN, Appel B (2006) In vivo time-lapse imaging shows dynamic oligodendrocyte progenitor behavior during zebrafish development. *Nat Neurosci* 9(12):1506–1511. doi:[10.1038/nn1803](https://doi.org/10.1038/nn1803)
- Lasiene J, Matsui A, Sawa Y, Wong F, Horner PJ (2009) Age-related myelin dynamics revealed by increased oligodendrogenesis and short internodes. *Aging Cell* 8(2):201–213. doi:[10.1111/j.1474-9726.2009.00462.x](https://doi.org/10.1111/j.1474-9726.2009.00462.x)
- Lecca D, Trincavelli ML, Gelosa P, Sironi L, Ciana P, Fumagalli M, Villa G, Verderio C, Grumelli C, Guerrini U, Tremoli E, Rosa P, Cuboni S, Martini C, Buffo A, Cimino M, Abbracchio MP (2008) The recently identified P2Y-like receptor GPR17 is a sensor of brain damage and a new target for brain repair. *PLoS ONE* 3(10):e3579. doi:[10.1371/journal.pone.0003579](https://doi.org/10.1371/journal.pone.0003579)
- Li Q, Brus-Ramer M, Martin JH, McDonald JW (2010) Electrical stimulation of the medullary pyramid promotes proliferation and differentiation of oligodendrocyte progenitor cells in the corticospinal tract of the adult rat. *Neurosci Lett* 479(2):128–133. doi:[10.1016/j.neulet.2010.05.043](https://doi.org/10.1016/j.neulet.2010.05.043)
- Li W, Tang Y, Fan Z, Meng Y, Yang G, Luo J, Ke ZJ (2013) Autophagy is involved in oligodendroglial precursor-mediated clearance of amyloid peptide. *Mol Neurodegener* 8:27. doi:[10.1186/1750-1326-8-27](https://doi.org/10.1186/1750-1326-8-27)
- Liu J, Dietz K, DeLoyht JM, Pedre X, Kelkar D, Kaur J, Vialou V, Lobo MK, Dietz DM, Nestler EJ, Dupree J, Casaccia P (2012) Impaired adult myelination in the prefrontal cortex of socially isolated mice. *Nat Neurosci* 15(12):1621–1623. doi:[10.1038/nn.3263](https://doi.org/10.1038/nn.3263)
- Lu PH, Lee GJ, Raven EP, Tingus K, Khoo T, Thompson PM, Bartzokis G (2011) Age-related slowing in cognitive processing speed is associated with myelin integrity in a very healthy elderly sample. *J Clin Exp Neuropsychol* 33(10):1059–1068. doi:[10.1080/13803395.2011.595397](https://doi.org/10.1080/13803395.2011.595397)
- Lu PH, Lee GJ, Tishler TA, Meghpara M, Thompson PM, Bartzokis G (2013) Myelin breakdown mediates age-related slowing in cognitive processing speed in healthy elderly men. *Brain Cogn* 81(1):131–138. doi:[10.1016/j.bandc.2012.09.006](https://doi.org/10.1016/j.bandc.2012.09.006)
- Lundgaard I, Luzhynskaya A, Stockley JH, Wang Z, Evans KA, Swire M, Volbracht K, Gautier HO, Franklin RJ, Charles F-C, Attwell D, Karadottir RT (2013) Neuregulin and BDNF induce a switch to NMDA receptor-dependent myelination by oligodendrocytes. *PLoS Biol* 11(12):e1001743. doi:[10.1371/journal.pbio.1001743](https://doi.org/10.1371/journal.pbio.1001743)
- Mangin JM, Li P, Scafidi J, Gallo V (2012) Experience-dependent regulation of NG2 progenitors in the developing barrel cortex. *Nat Neurosci* 15(9):1192–1194. doi:[10.1038/nn.3190](https://doi.org/10.1038/nn.3190)

- Marrs GS, Green SH, Dailey ME (2001) Rapid formation and remodeling of postsynaptic densities in developing dendrites. *Nat Neurosci* 4(10):1006–1013. doi:[10.1038/nn717](https://doi.org/10.1038/nn717)
- Mensch S, Baraban M, Almeida R, Czopka T, Ausborn J, El Manira A, Lyons DA (2015) Synaptic vesicle release regulates myelin sheath number of individual oligodendrocytes in vivo. *Nat Neurosci* 18(5):628–630. doi:[10.1038/nn.3991](https://doi.org/10.1038/nn.3991)
- Miller RH (1996) Oligodendrocyte origins. *Trends Neurosci* 19(3):92–96
- Nave KA, Werner HB (2014) Myelination of the nervous system: mechanisms and functions. *Annu Rev Cell Dev Biol* 30:503–533. doi:[10.1146/annurev-cellbio-100913-013101](https://doi.org/10.1146/annurev-cellbio-100913-013101)
- Ozderdem U, Grako KA, Dahlin-Huppe K, Monosov E, Stallcup WB (2001) NG2 proteoglycan is expressed exclusively by mural cells during vascular morphogenesis. *Dev Dyn* 222(2):218–227. doi:[10.1002/dvdy.1200](https://doi.org/10.1002/dvdy.1200)
- Parras CM, Hunt C, Sugimori M, Nakafuku M, Rowitch D, Guillemot F (2007) The proneural gene *Mash1* specifies an early population of telencephalic oligodendrocytes. *J Neurosci* 27(16):4233–4242. doi:[10.1523/JNEUROSCI.0126-07.2007](https://doi.org/10.1523/JNEUROSCI.0126-07.2007)
- Peters A (2002) The effects of normal aging on myelin and nerve fibers: a review. *J Neurocytol* 31(8–9):581–593
- Psachoulia K, Jamen F, Young KM, Richardson WD (2009) Cell cycle dynamics of NG2 cells in the postnatal and ageing brain. *Neuron Glia Biol* 5(3–4):57–67. doi:[10.1017/S1740925X09990354](https://doi.org/10.1017/S1740925X09990354)
- Raff MC, Miller RH, Noble M (1983) A glial progenitor cell that develops in vitro into an astrocyte or an oligodendrocyte depending on culture medium. *Nature* 303(5916):390–396
- Robins SC, Trudel E, Rotondi O, Liu X, Djogo T, Kryzskaya D, Bourque CW, Kokoeva MV (2013) Evidence for NG2-glia derived, adult-born functional neurons in the hypothalamus. *PLoS ONE* 8(10):e78236. doi:[10.1371/journal.pone.0078236](https://doi.org/10.1371/journal.pone.0078236)
- Sakry D, Karram K, Trotter J (2011) Synapses between NG2 glia and neurons. *J Anat* 219(1):2–7. doi:[10.1111/j.1469-7580.2011.01359.x](https://doi.org/10.1111/j.1469-7580.2011.01359.x)
- Scholz J, Klein MC, Behrens TE, Johansen-Berg H (2009) Training induces changes in white-matter architecture. *Nat Neurosci* 12(11):1370–1371. doi:[10.1038/nn.2412](https://doi.org/10.1038/nn.2412)
- Simon C, Gotz M, Dimou L (2011) Progenitors in the adult cerebral cortex: cell cycle properties and regulation by physiological stimuli and injury. *Glia* 59(6):869–881. doi:[10.1002/glia.21156](https://doi.org/10.1002/glia.21156)
- Sirko S, Behrendt G, Johansson PA, Tripathi P, Costa M, Bek S, Heinrich C, Tiedt S, Colak D, Dichgans M, Fischer IR, Plesnila N, Staufenbiel M, Haass C, Snaypan M, Saghatelian A, Tsai LH, Fischer A, Grobe K, Dimou L, Gotz M (2013) Reactive glia in the injured brain acquire stem cell properties in response to sonic hedgehog [corrected]. *Cell Stem Cell* 12(4):426–439. doi:[10.1016/j.stem.2013.01.019](https://doi.org/10.1016/j.stem.2013.01.019)
- Stevens B, Porta S, Haak LL, Gallo V, Fields RD (2002) Adenosine: a neuron-glial transmitter promoting myelination in the CNS in response to action potentials. *Neuron* 36(5):855–868
- Sturrock RR (1976) Changes in neurologia and myelination in the white matter of aging mice. *J Gerontol* 31(5):513–522
- Verkhratsky A, Steinhauser C (2000) Ion channels in glial cells. *Brain Res Brain Res Rev* 32(2–3):380–412
- Vigano F, Dimou L (2016) The heterogeneous nature of NG2-glia. *Brain Res.* doi:[10.1016/j.brainres.2015.09.012](https://doi.org/10.1016/j.brainres.2015.09.012)
- Vigano F, Mobius W, Gotz M, Dimou L (2013) Transplantation reveals regional differences in oligodendrocyte differentiation in the adult brain. *Nat Neurosci* 16(10):1370–1372. doi:[10.1038/nn.3503](https://doi.org/10.1038/nn.3503)
- Vigano F, Schneider S, Cimino M, Bonfanti E, Gelosa P, Sironi L, Abbracchio MP, Dimou L (2016) GPR17 expressing NG2-Glia: Oligodendrocyte progenitors serving as a reserve pool after injury. *Glia* 64(2):287–299. doi:[10.1002/glia.22929](https://doi.org/10.1002/glia.22929)
- Von Blankenfeld G, Trotter J, Kettenmann H (1991) Expression and developmental regulation of a GABAA receptor in cultured murine cells of the oligodendrocyte lineage. *Eur J Neurosci* 3(4):310–316

- Williamson AV, Mellor JR, Grant AL, Randall AD (1998) Properties of GABA(A) receptors in cultured rat oligodendrocyte progenitor cells. *Neuropharmacology* 37(7):859–873
- Wilson HC, Scolding NJ, Raine CS (2006) Co-expression of PDGF alpha receptor and NG2 by oligodendrocyte precursors in human CNS and multiple sclerosis lesions. *J Neuroimmunol* 176 (1–2):162–173. doi:[10.1016/j.jneuroim.2006.04.014](https://doi.org/10.1016/j.jneuroim.2006.04.014)
- Windrem MS, Schanz SJ, Guo M, Tian GF, Washco V, Stanwood N, Rasband M, Roy NS, Nedergaard M, Havton LA, Wang S, Goldman SA (2008) Neonatal chimerization with human glial progenitor cells can both remyelinate and rescue the otherwise lethally hypomyelinated shiverer mouse. *Cell Stem Cell* 2(6):553–565. doi:[10.1016/j.stem.2008.03.020](https://doi.org/10.1016/j.stem.2008.03.020)
- Wu Q, Miller RH, Ransohoff RM, Robinson S, Bu J, Nishiyama A (2000) Elevated levels of the chemokine GRO-1 correlate with elevated oligodendrocyte progenitor proliferation in the jimpy mutant. *J Neurosci* 20(7):2609–2617
- Yuan X, Eisen AM, McBain CJ, Gallo V (1998) A role for glutamate and its receptors in the regulation of oligodendrocyte development in cerebellar tissue slices. *Development* 125 (15):2901–2914
- Zhu X, Bergles DE, Nishiyama A (2008) NG2 cells generate both oligodendrocytes and gray matter astrocytes. *Development* 135(1):145–157. doi:[10.1242/dev.004895](https://doi.org/10.1242/dev.004895)
- Zhu X, Hill RA, Dietrich D, Komitova M, Suzuki R, Nishiyama A (2011) Age-dependent fate and lineage restriction of single NG2 cells. *Development* 138(4):745–753. doi:[10.1242/dev.047951](https://doi.org/10.1242/dev.047951)
- Ziskin JL, Nishiyama A, Rubio M, Fukaya M, Bergles DE (2007) Vesicular release of glutamate from unmyelinated axons in white matter. *Nat Neurosci* 10(3):321–330. doi:[10.1038/nn1854](https://doi.org/10.1038/nn1854)

Glial Cells in Health and Disease of the CNS

von Bernhardt, R. (Ed.)

2016, XI, 348 p. 46 illus., 35 illus. in color., Hardcover

ISBN: 978-3-319-40762-3