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Review

The role of the NG2 proteoglycan in OPC and CNS network function

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ABSTRACT

In the normal mammalian CNS, the NG2 proteoglycan is expressed by oligodendrocyte precursor cells (OPC) but not by any other neural cell-type. NG2 is a type-1 membrane protein, exerting multiple roles in the CNS including intracellular signaling within the OPC, with effects on migration, cytoskeleton interaction and target gene regulation. It has been recently shown that the extracellular region of NG2, in addition to an adhesive function, acts as a soluble ECM component with the capacity to alter defined neuronal network properties. This region of NG2 is thus endowed with neuromodulatory properties. In order to generate biologically active fragments yielding these properties, the sequential cleavage of the NG2 protein by α- and γ-secretases occurs. The basal level of constitutive cleavage is stimulated by neuronal network activity. This processing leads to 4 major NG2 fragments which all have been associated with distinct biological functions. Here we summarize these functions, focusing on recent discoveries and their implications for the CNS.

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1. Origin and structure of the NG2 proteoglycan

The NG2 proteoglycan is coded by the CSPG4 gene and belongs to the protein family of chondroitin sulfate proteoglycans (CSPGs). NG2 was first discovered in 1977 in a screen for neuronal and glial antigens in the rat (Stallcup, 1977). Homologs have been reported so far from mouse (Niehaus et al., 1999; Schneider et al., 2001; Stegmuller et al., 2002), human (Pluschke et al., 1996) and drosophila (Estrada et al., 2007; Schnorrer et al., 2007). Oligodendrocyte precursor cells (OPC) express the NG2 protein, while it is absent from other neural cells such as neurons (Clarke et al., 2012; Karram et al., 2008), astrocytes (Huang et al., 2014; Zhu et al., 2008) and resident microglia (Moransard et al., 2011). Within the oligodendrocyte lineage NG2 is down-regulated with ongoing differentiation of OPC into myelinating mature oligodendrocytes (De Biase et al., 2010; Kukley et al., 2010; Nishiyama et al., 2009). OPC are thus the exclusive source of NG2 amongst neural cells. OPC make up a stable cell population at all stages of development in gray and white matter, in the adult mammalian brain they make up around 5% of total neural cells (Dawson et al., 2003; Gallo et al., 2008). In addition to expression within the normal CNS, NG2 is expressed by populations of glioma cells, including the most aggressive glioblastoma (Al-Mayhani et al., 2011; Chekenya et al., 2008; Persson et al., 2010). Interestingly, OPC have been identified as constituting the cells of origin for gliomas (Liu et al., 2011) and NG2 seems to play an important role in likelihood for an OPC to became a tumor cell (Sugiarto et al., 2011). Subpopulations of pericytes, cells of the vascular system, also express NG2 (Ozerdem et al., 2002; You et al., 2014).

NG2 is a type-1 membrane protein with a protein core of 252 kD molecular weight (MW), the glycosylated form that is extractable from *in vivo* neural samples has a MW of 300 kD and exhibits a broad band pattern around this size on SDS gels, typical for a glycoprotein containing complex sugars. Glycosylation of the extracellular part yields one confirmed glycosaminoglycan (GAG-) chain (O-glycosylation) (Stallcup and Dahlin-Huppe, 2001), with several predicted N-glycosylation sites (Nishiyama et al., 1991). The extracellular part of 2200 amino acids (aa), makes up over 95% of the protein, while the transmembrane (TM) domain comprises 21 aa and the intracellular part 77 aa. Two N-terminal *Laminin Neurexin Sex-Hormone Binding Globulin* (LNS) domains represent conserved protein domains which recently have been shown to exhibit neuromodulatory properties (Sakry et al., 2014). These NG2 LNS domains are conserved throughout species from humans to drosophila (Rudenko et al., 2001). In the ensuing text we focus on summarizing functions of the intracellular part of NG2 including the binding partners, as well as novel functions of the extracellular part of NG2. We first provide an overview of the latest discoveries related to proteolytic processing of NG2, as this is essential to yield the biological functions of the protein.

2. Cleavage of NG2

Soluble forms of the NG2 ectodomain extractable from tissue with salt solutions (290 kD and 275 kD) were initially reported in 1995 (Nishiyama et al., 1995) and confirmed by others (Deepa et al., 2006; Morgenstern et al., 2003). We recently showed that the full-length (FL) NG2 protein (300 kD) is processed sequentially by the α-secretase ADAM10 and subsequently by the γ-secretase complex Fig. 1. Both these Q4 enzymes are expressed by OPC. α-secretase cleavage leads to an ectodomain of around 290 kD which can be released from the cell and a matching c-terminal fragment (CTF) of 12 kD. The membrane-bound CTF can be further processed by the γ-secretase complex releasing the intracellular part from the membrane stump: this released intracellular domain is termed the ICD (8.5 kD) (Sakry et al., 2014). Similar cleavage cascades are known for other type-1 membrane proteins such as Notch, N-Cadherin, Neuroligin, L1 or APP, involving the same or similar proteases. The NG2 FL, the ectodomain, the CTF and the ICD are the major forms of NG2 known to date.

A new focus was given to the biological relevance of these cleavage events when it was shown that α-secretase mediated cleavage of neuronal surface proteins such as neuroligin-1 and N-cadherin was stimulated by neuronal activity (Malinverno et al., 2010; Suzuki et al., 2012). We have recently shown that NG2 cleavage by α- and γ-secretases occurs constitutively and can be increased by neuronal activity acting on OPC (Sakry et al., 2014). This is especially interesting since OPC are unique glia entering into synaptic contact with the neuronal network in all major areas of the brain (Bergles et al., 2000; Jabs et al., 2005; Kukley et al., 2008; Mangin and Gallo, 2011). This implies that NG2 cleavage-dependent functions can be modulated by the neuronal network (Sakry et al., 2014). An important unresolved question for all such cleavage events is the mechanism of activation of the α-secretase (Sonderegger and Matsumoto-Miyai, 2014).

OPC are likely to play multiple complex roles in different types of CNS lesion, which are at present incompletely understood. It has been established that together with microglia OPC constitute the cellular response of resident CNS cells within the first few days after injury (Buffo et al., 2005; Dimou et al., 2008). The response of OPC to lesions involves increased proliferation, migration and differentiation (Simon et al., 2011) and has largely been interpreted as a response of the oligodendrocyte lineage to damage of myelin; little is known about their role in the glial scar (Buss et al., 2009; Honsa et al., 2012; Vadivelu et al., 2015). Furthermore OPC have been associated with injury-dependent increase of NG2 cleavage from the OPC (Jones et al., 2002; Levine, 1994; Morgenstern et al., 2003). Some studies report identified microglia with NG2 surface staining which is sometimes purported to be lesion-dependent expression of NG2 by microglia (Jones et al., 2002; Zhu et al., 2012), but may in fact be bound OPC-derived NG2 ectodomain. A detailed lineage-tracing study reported that CNS resident macrophages (microglia) do not express NG2 while invading macrophages from the blood can be NG2-positive (Moransard et al., 2011).

3. Intracellular functions of the NG2 proteoglycan

The intracellular part of NG2 (77 aa) can be cleaved by γ-secretase activity yielding the NG2 ICD (Sakry et al., 2014).

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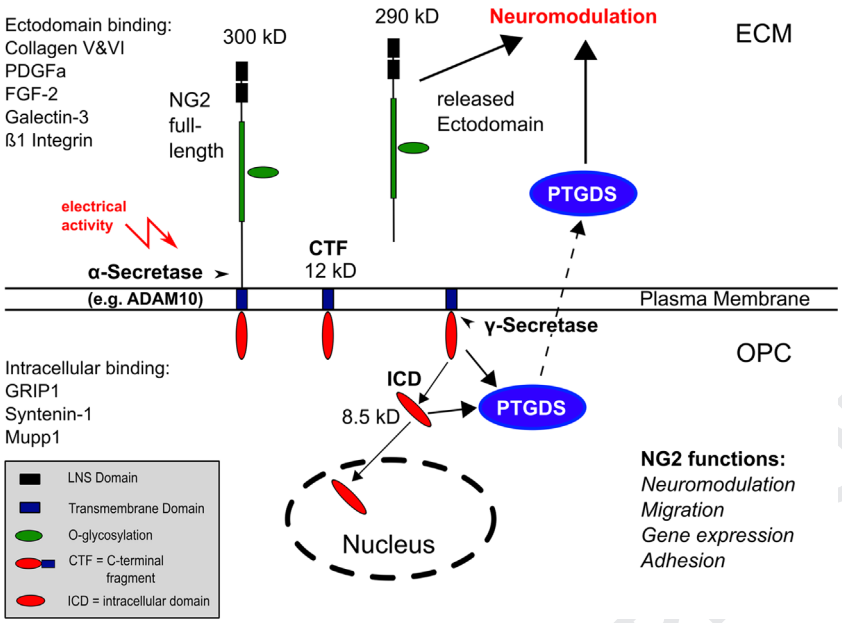

Fig. 1 – The role of the OPC-expressed NG2 protein in the CNS. The type-1 membrane protein NG2 (300 kD) is located at the OPC surface. Sequential cleavage of NG2 by α- and γ-secretases, leads to a released ectodomain (around 290 kD) and membrane bound c-terminal fragment (CTF, 12 kD). The CTF can then be further processed by the γ-secretase releasing the so called ICD (intracellular domain of 8.5 kD). Activity of the α-secretase ADAM10 on NG2 can be increased by electrical activity of the neuronal network via the neuron–glia synapse. The CTF and ICD modulate expression of the secreted enzyme PTGDS, which has reported neuromodulatory functions and has recently been shown to be expressed by OPC in an NG2-dependent manner. The LNS domains of the NG2 ectodomain alter defined glutamatergic synaptic properties of neuron–neuron synapses.

This region of the protein contains two phosphorylation sites, Thr-2256 and 2314, the first is a target for PKCα and the second for ERK (Makagiansar et al., 2007). The C-terminus contains a *PSD95/DiscsLarge/Zho1* (PDZ) binding motif (QYWV). Binding partners are to date the thirteen PDZ domain containing scaffolding protein Mupp1 (Barritt et al., 2000), Syntenin, a cytoplasmic adapter whose interaction with NG2 is important for migration of OPC (Chatterjee et al., 2008) and the synaptic protein GRIP1 which binds the AMPAR subunit GluR2 together with NG2 on OPC (Stegmuller et al., 2003). We have observed that NG2 also binds to the serine protease OMI/HtrA2, localized in the intermembrane space in mitochondria. This molecule plays a role in apoptosis induction and we suggest that sequestration of the protease may help protect OPC from apoptosis-inducing stress. (Maus et al., unpublished results).

Recently a complex signal pathway resulting in directed migration of OPC in response to gradients of FGF or PDGF-aa has been reported (Biname et al., 2013). In this study FGF-dependent polarization of OPC was altered in cortical lesions of mice lacking the NG2 protein (NG2-KO mice, (Karram et al., 2008)). The underlying cellular signal cascade within the OPC has been shown to involve Rac/Rho dependent phosphorylation of the intracellular region of NG2, reviewed by Biname (2014).

The NG2 CTF and ICD influence target gene expression in OPC. The enzyme PTGDS catalyzes the conversion of prostaglandin H2 to the neuromodulatory form prostaglandin D2. PTGDS has been shown to be expressed and released by mature oligodendrocytes and the meninges (Taniike et al., 2002) and recently shown to be additionally expressed by OPC (Sakry et al., 2015). In OPC, the level of PTGDS expression is modulated by the NG2 CTF and ICD, as well as by a complete lack of NG2 (Sakry et al., 2015). Interestingly expression of high levels of the NG2 ICD in OPC after transfection results in localization of the ICD into the nucleus, suggesting a potential regulatory function in gene expression (Sakry et al., 2015). CNS PTGDS levels have been shown to be increased in lesions of the human demyelinating disease Multiple Sclerosis (MS) (Chabas et al., 2001) and neurological disorders (Marin-Mendez et al., 2012), in MS lesions PTGDS can be additionally expressed by astrocytes (Kagitani-Shimono et al., 2006). Taken together, OPC can thus be seen as an additional cellular source of PTGDS expression in the CNS and OPC contribute to the neuromodulatory functions of PTGDS in an NG2-dependent manner. Interestingly in the PNS, PTGDS is reported to be expressed by DRG neurons where the neuregulin I ICD influences expression levels (Trimarco et al., 2014).

4. Extracellular functions of the NG2 proteoglycan

NG2 has been postulated as a cell adhesion molecule for quite some time. This has been strengthened by the observation that the extracellular region between the TM domain and the LNS domains binds to collagen V and VI and integrins (Fukushi et al., 2004; Tillet et al., 1997); thus NG2 functions as a cell-surface anchor within the extracellular matrix (ECM). Other family members of the chondroitin sulfate proteoglycan (CSPG) family such as brevican are secreted proteins with defined roles within the ECM (Deepa et al., 2006; Frischknecht

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et al., 2014). ECM integrity is important for AMPAR signaling at synapses influencing lateral diffusion of the receptor and consequently synaptic signal propagation (Frischknecht et al., 2009).

Interestingly, the two NG2 N-terminal LNS domains (which so far lack a binding partner) are similar to the LNS domains of the neuronal synaptic adhesion proteins the neurexins (NX), here they are responsible for binding to the interaction partners the neuroligins (NL) (Aoto et al., 2013; Ichtchenko et al., 1995; Ichtchenko et al., 1996; Krueger et al., 2012) as well as LRRTMs, Calsyntenins, Cerebellin, dystroglycan, and neurexophilins (Ko et al., 2009; Linhoff et al., 2009; Petrenko et al., 1996; Pettem et al., 2013; Sugita et al., 2001; Uemura et al., 2010). NL–NX interaction is an essential for forming and maintaining chemical synapses of the neuronal network (Krueger et al., 2012). Mutations within the NX LNS domains have been related to severe synaptic phenotypes found in human patients with neural diseases such as autism spectrum disorder (ASD) (Sudhof, 2008). The sequence conservation of LNS domains between laminins and neurexins is around 20–25% together with high functional similarities of the 3-dimensional structure (Rudenko et al., 1999; Rudenko et al., 2001). The NG2 LNS domains are no exception here: they show highest sequence similarities of up to 26% with the LNS domains of neurexins.

As discussed above, the NG2 extracellular region can be released by the activity of the α-secretase ADAM10 into the ECM, and is thus regarded as a soluble 290 kD NG2 ectodomain (Sakry et al., 2014). This cleavage from the OPC surface occurs constitutively, is increased in an activity-dependent fashion and elevated in response to lesion. The question thus posed is: what is the biological function of the NG2 ectodomain in its soluble form as it can be extracted from the ECM? We recently showed that the two LNS domains of the NG2 ectodomain modulate synaptic AMPAR currents and kinetics of pyramidal neurons within the rodent somatosensory cortex, suggesting an influence on subunit composition of the AMPAR (Sakry et al., 2014). The AMPAR-phenotype observed in this neuronal population in mice lacking NG2 (NG2-KO mice) can be rescued by incubation of brain slices with a recombinant protein containing solely the two NG2 LNS domains. Furthermore, in NG2-KO mice reduced NMDAR-dependent LTP is observed within the same neuronal population as a consequence of the altered AMPAR and NMDAR currents. NG2-KO mice exhibit a postsynaptic phenotype which is regulated by the NG2 LNS domains, while presynaptic characteristics such as the paired-pulse ratio remain unchanged (Sakry et al., 2014). Thus the NG2 LNS domains regulate postsynaptic signaling and modulate glutamergic signaling of the neuronal network. Interestingly in NG2-KO mice behavioral differences compared to wild-type littermates have been observed in tests related to integration of sensory input. In particular, a test based on the response of the auditory system (acoustic startle response, paired-pulse-ratio) showed abnormalities in NG2-KO mice (Sakry et al., 2014) similar to those observed in patients with schizophrenia.

Subpopulations of pericytes express NG2. A contribution of NG2-expressing pericytes of the vascular system to the described ectodomain effects cannot be completely excluded but is likely to play if at all, a minor role. Pericytes ensheathe the endothelial cells making up blood vessels. It is not known so far if and how efficient pericytes can release protein factors through the other layers of the blood-brain-barrier into the ECM of the CNS. Cleavage of OPC NG2 has been shown in acute slices, primary OPC (pOPC) and an OPC cell-line (Sakry et al., 2014), our pOPC culture lacks pericytes (Sakry et al., 2015). Furthermore in slices and pOPC NG2 cleavage is increased by neuronal activity and glutamate (Sakry et al., 2014), as far as is known pericytes do not respond to network activity nor receive synaptic input from neurons.

Recent analysis of the response of the NG2 KO mice to lesions also suggests that the loss of NG2 has effects beyond the neuronal network and that cytokine production by neural and immune cells may also be influenced by the lack of NG2.

Even though we know very little at present about the exact molecular mechanism underlying the modulation of neuronal signaling by the two NG2 LNS domains, these results show that the release of NG2 ectodomain (including the LNS domains) is under the control of the neuronal network via activity-dependent cleavage in OPC, initiated at their so called "neuron–glia" synapses (Bergles et al., 2010; Mangin and Gallo, 2011; Sakry et al., 2011). In response, the neuronal network is regulated by the released NG2 ectodomain. These novel results have introduced a new paradigm: a feedback mechanism (neuron–glia–neuron) integrating OPC as a glial cell population within the neuronal network (Sakry et al., 2014) as originally hypothesized in (Sakry et al., 2011).

5. Summary

Recent studies focused on the NG2 protein have revealed a defined role of NG2 in brain homeostasis. This includes intracellular functions within the OPC including modulation of migration, target gene expression and AMPAR clustering. The first two functions of NG2 seem to be of particular importance in lesioned brain tissue. Cleavage of the full-length NG2 protein by α- and subsequently γ-secretase activity turns out to be a core aspect, as the cleavage fragments (ectodomain, CTF, ICD) exhibit defined roles within the CNS. The fact that increased α-secretase mediated NG2 cleavage is modulated by neuronal activity is especially interesting as it integrates NG2-expressing OPC into the neuronal network. The story becomes even more exciting, since the released NG2 ectodomain, specifically the two LNS domains, are able to modulate excitatory neuronal synapses; thus, introducing a neuron–OPC–neuron feedback loop within the CNS.

6. Outlook

Future studies are aimed at defining the biological roles of the NG2 intracellular cleavage fragments CTF and ICD within the OPC. These are likely to include a nuclear function of the NG2 ICD and defined roles of the CTF and ICD in target-gene regulation.

NG2-dependent expression of PTGDS by OPC especially in CNS diseases like MS, needs further investigation as well.

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The neuromodulatory function of the two LNS domains of the NG2 ectodomain evoke questions as to the identity of possible neuronal binding partners and an explanation of the effects on AMPA receptor characteristics, as well as detailed further characterization of the involved neuronal networks. A role in excitatory/inhibitory homeostasis of the neuronal network has already become apparent as the LNS domains increase synaptic transmission at excitatory synapses on pyramidal neurons within the somatosensory system. Furthermore, since a lack of the NG2 LNS domains was linked to altered animal behavior similar to that found in human diseases with known excitatory/inhibitory misbalance such as schizophrenia, a link to other neurological disorders involving excitatory/inhibitory misbalance is very likely. It is also possible that NG2-expressing gliomas may influence the surrounding neuronal networks by the mechanisms described above.

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REFERENCES

Al-Mayhani, M.T., et al., 2011. NG2 expression in glioblastoma identifies an actively proliferating population with an aggressive molecular signature. Neuro-Oncol. 13, 830–845.

Aoto, J., et al., 2013. Presynaptic neurexin-3 alternative splicing trans-synaptically controls postsynaptic AMPA receptor trafficking. Cell 154, 75–88.

Barritt, D.S., et al., 2000. The multi-PDZ domain protein MUPP1 is a cytoplasmic ligand for the membrane-spanning proteoglycan NG2. J. Cell. Biochem. 79, 213–224.

Bergles, D.E., et al., 2000. Glutamatergic synapses on oligodendrocyte precursor cells in the hippocampus. Nature 405, 187–191.

Bergles, D.E., Jabs, R., Steinhauser, C., 2010. Neuron-glia synapses in the brain. Brain Res. Rev. 63, 130–137.

Biname, F., et al., 2013. NG2 regulates directional migration of oligodendrocyte precursor cells via rho GTPases and polarity complex proteins. J. Neurosci.: Off. J. Soc. Neurosci. 33, 10858–10874.

Biname, F., 2014. Transduction of extracellular cues into cell polarity: the role of the transmembrane proteoglycan NG2. Mol. Neurobiol. 50, 482–493.

Buffo, A., et al., 2005. Expression pattern of the transcription factor Olig2 in response to brain injuries: implications for neuronal repair. Proc. Natl. Acad. Sci. USA 102, 18183–18188.

Buss, A., et al., 2009. NG2 and phosphacan are present in the astroglial scar after human traumatic spinal cord injury. BMC Neurol. 9, 32.

Chabas, D., et al., 2001. The influence of the proinflammatory cytokine, osteopontin, on autoimmune demyelinating disease. Science 294, 1731–1735.

Chatterjee, N., et al., 2008. Interaction of syntenin-1 and the NG2 proteoglycan in migratory oligodendrocyte precursor cells. J. Biol. Chem. 283, 8310–8317.

Chekenya, M., et al., 2008. The progenitor cell marker NG2/MPG promotes chemoresistance by activation of integrin-dependent PI3K/Akt signaling. Oncogene 27, 5182–5194.

Clarke, L.E., et al., 2012. Properties and fate of oligodendrocyte progenitor cells in the corpus callosum, motor cortex, and piriform cortex of the mouse. J. Neurosci.: Off. J. Soc. Neurosci. 32, 8173–8185.

Dawson, M.R., et al., 2003. NG2-expressing glial progenitor cells: an abundant and widespread population of cycling cells in the adult rat CNS. Mol. Cell. Neurosci. 24, 476–488.

De Biase, L.M., Nishiyama, A., Bergles, D.E., 2010. Excitability and synaptic communication within the oligodendrocyte lineage. J. Neurosci.: Off. J. Soc. Neurosci. 30, 3600–3611.

Deepa, S.S., et al., 2006. Composition of perineuronal net extracellular matrix in rat brain: a different disaccharide composition for the net-associated proteoglycans. J. Biol. Chem. 281, 17789–17800.

Dimou, L., et al., 2008. Progeny of Olig2-expressing progenitors in the gray and white matter of the adult mouse cerebral cortex. J. Neurosci.: Off. J. Soc. Neurosci. 28, 10434–10442.

Estrada, B., Gisselbrecht, S.S., Michelson, A.M., 2007. The transmembrane protein Perdido interacts with Grip and integrins to mediate myotube projection and attachment in the Drosophila embryo. Development 134, 4469–4478.

Frischknecht, R., et al., 2009. Brain extracellular matrix affects AMPA receptor lateral mobility and short-term synaptic plasticity. Nat. Neurosci. 12, 897–904.

Frischknecht, R., et al., 2014. Neural ECM molecules in axonal and synaptic homeostatic plasticity. Prog. Brain Res. 214, 81–100.

Fukushi, J., Makagiansar, I.T., Stallcup, W.B., 2004. NG2 proteoglycan promotes endothelial cell motility and angiogenesis via engagement of galectin-3 and alpha3beta1 integrin. Mol. Biol. Cell 15, 3580–3590.

Gallo, V., et al., 2008. Synapses on NG2-expressing progenitors in the brain: multiple functions?. J. Physiol. 586, 3767–3781.

Honsa, P., et al., 2012. Polydendrocytes display large lineage plasticity following focal cerebral ischemia. PloS One 7, e36816.

Huang, W., et al., 2014. Novel NG2-CreERT2 knock-in mice demonstrate heterogeneous differentiation potential of NG2 glia during development. Glia 62, 896–913.

Ichtchenko, K., et al., 1995. Neuroligin 1: a splice site-specific ligand for beta-neurexins. Cell 81, 435–443.

Ichtchenko, K., Nguyen, T., Sudhof, T.C., 1996. Structures, alternative splicing, and neurexin binding of multiple neuroligins. J. Biol. Chem. 271, 2676–2682.

Jabs, R., et al., 2005. Synaptic transmission onto hippocampal glial cells with hGFAP promoter activity. J. Cell Sci. 118, 3791–3803.

Jones, L.L., et al., 2002. NG2 is a major chondroitin sulfate proteoglycan produced after spinal cord injury and is expressed by macrophages and oligodendrocyte progenitors. J. Neurosci.: Off. J. Soc. Neurosci. 22, 2792–2803.

Kagitani-Shimono, K., et al., 2006. Lipocalin-type prostaglandin D synthase (beta-trace) is upregulated in the alphaB-crystallin-positive oligodendrocytes and astrocytes in the chronic multiple sclerosis. Neuropathol. Appl. Neurobiol. 32, 64–73.

Karram, K., et al., 2008. NG2-expressing cells in the nervous system revealed by the NG2-EYFP-knockin mouse. Genesis 46, 743–757.

Ko, J., et al., 2009. LRRTM2 functions as a neurexin ligand in promoting excitatory synapse formation. Neuron 64, 791–798.

Krueger, D.D., et al., 2012. The role of neurexins and neuroligins in the formation, maturation, and function of vertebrate synapses. Curr. Opin. Neurobiol. 22, 412–422.

Kukley, M., et al., 2008. Glial cells are born with synapses. FASEB J.: Off. Publ. Fed. Am. Soc. Exp. Biol. 22, 2957–2969.

Kukley, M., Nishiyama, A., Dietrich, D., 2010. The fate of synaptic input to NG2 glial cells: neurons specifically downregulate transmitter release onto differentiating oligodendroglial cells. J. Neurosci.: Off. J. Soc. Neurosci. 30, 8320–8331.

Levine, J.M., 1994. Increased expression of the NG2 chondroitin-sulfate proteoglycan after brain injury. J. Neurosci.: Off. J. Soc. Neurosci. 14, 4716–4730.

Linhoff, M.W., et al., 2009. An unbiased expression screen for synaptogenic proteins identifies the LRRTM protein family as synaptic organizers. Neuron 61, 734–749.

Liu, C., et al., 2011. Mosaic analysis with double markers reveals tumor cell of origin in glioma. Cell 146, 209–221.

Makagiansar, I.T., et al., 2007. Differential phosphorylation of NG2 proteoglycan by ERK and PKCalpha helps balance cell proliferation and migration. J. Cell Biol. 178, 155–165.

Malinverno, M., et al., 2010. Synaptic localization and activity of ADAM10 regulate excitatory synapses through N-cadherin cleavage. J. Neurosci.: Off. J. Soc. Neurosci. 30, 16343–16355.

Mangin, J.M., Gallo, V., 2011. The curious case of NG2 cells: transient trend or game changer?. ASN Neuro 3, e00052.

Marin-Mendez, J.J., et al., 2012. Differential expression of prostaglandin D2 synthase (PTGDS) in patients with attention deficit-hyperactivity disorder and bipolar disorder. J. Affect. Disord. 138, 479–484.

Moransard, M., et al., 2011. NG2 expressed by macrophages and oligodendrocyte precursor cells is dispensable in experimental autoimmune encephalomyelitis. Brain: J. Neurol. 134, 1315–1330.

Morgenstern, D.A., et al., 2003. Expression and glycanation of the NG2 proteoglycan in developing, adult, and damaged peripheral nerve. Mol. Cell. Neurosci. 24, 787–802.

Niehaus, A., et al., 1999. Cell-surface glycoprotein of oligodendrocyte progenitors involved in migration. J. Neurosci.: Off. J. Soc. Neurosci. 19, 4948–4961.

Nishiyama, A., et al., 1991. The primary structure of NG2, a novel membrane-spanning proteoglycan. J. Cell Biol. 114, 359–371.

Nishiyama, A., Lin, X.H., Stallcup, W.B., 1995. Generation of truncated forms of the NG2 proteoglycan by cell surface proteolysis. Mol. Biol. Cell 6, 1819–1832.

Nishiyama, A., et al., 2009. Polydendrocytes (NG2 cells): multifunctional cells with lineage plasticity. Nat. Rev. Neurosci. 10, 9–22.

Ozerdem, U., Monosov, E., Stallcup, W.B., 2002. NG2 proteoglycan expression by pericytes in pathological microvasculature. Microvasc. Res. 63, 129–134.

Persson, A.I., et al., 2010. Non-stem cell origin for oligodendroglioma. Cancer Cell 18, 669–682.

Petrenko, A.G., et al., 1996. Structure and evolution of neurexophilin. J. Neurosci.: Off. J. Soc. Neurosci. 16, 4360–4369.

Pettem, K.L., et al., 2013. The specific alpha-neurexin interactor calsyntenin-3 promotes excitatory and inhibitory synapse development. Neuron 80, 113–128.

Pluschke, G., et al., 1996. Molecular cloning of a human melanoma-associated chondroitin sulfate proteoglycan. Proc. Natl. Acad. Sci. USA 93, 9710–9715.

Rudenko, G., et al., 1999. The structure of the ligand-binding domain of neurexin Ibeta: regulation of LNS domain function by alternative splicing. Cell 99, 93–101.

Rudenko, G., Hohenester, E., Muller, Y.A., 2001. LG/LNS domains: multiple functions—one business end?. Trends Biochem. Sci. 26, 363–368.

Sakry, D., Karram, K., Trotter, J., 2011. Synapses between NG2 glia and neurons. J. Anat. 219, 2–7.

Sakry, D., et al., 2014. Oligodendrocyte precursor cells modulate the neuronal network by activity-dependent ectodomain cleavage of glial NG2. PLoS Biol. 12, e1001993.

Sakry, D., et al., 2015. Oligodendrocyte precursor cells synthesize neuromodulatory factors. PloS One 10, e0127222.

Schneider, S., et al., 2001. The AN2 protein is a novel marker for the Schwann cell lineage expressed by immature and nonmyelinating Schwann cells. J. Neurosci.: Off. J. Soc. Neurosci. 21, 920–933.

Schnorrer, F., Kalchhauser, I., Dickson, B.J., 2007. The transmembrane protein Kon-tiki couples to Dgrip to mediate myotube targeting in Drosophila. Dev. Cell 12, 751–766.

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, 869–881.

Sonderegger, P., Matsumoto-Miyai, K., 2014. Activity-controlled proteolytic cleavage at the synapse. Trends Neurosci. 37, 413–423.

Stallcup, W.B., 1977. Nerve and glial-specific antigens on cloned neural cell lines. Progress Clin. Biol. Res. 15, 165–178.

Stallcup, W.B., Dahlin-Huppe, K., 2001. Chondroitin sulfate and cytoplasmic domain-dependent membrane targeting of the NG2 proteoglycan promotes retraction fiber formation and cell polarization. J. Cell Sci. 114, 2315–2325.

Stegmuller, J., et al., 2002. AN2, the mouse homologue of NG2, is a surface antigen on glial precursor cells implicated in control of cell migration. J. Neurocytol. 31, 497–505.

Stegmuller, J., et al., 2003. The proteoglycan NG2 is complexed with alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors by the PDZ glutamate receptor interaction protein (GRIP) in glial progenitor cells. Implications for glial-neuronal signaling. J. Biol. Chem. 278, 3590–3598.

Sudhof, T.C., 2008. Neuroligins and neurexins link synaptic function to cognitive disease. Nature 455, 903–911.

Sugiarto, S., et al., 2011. Asymmetry-defective oligodendrocyte progenitors are glioma precursors. Cancer Cell 20, 328–340.

Sugita, S., et al., 2001. A stoichiometric complex of neurexins and dystroglycan in brain. J. Cell Biol. 154, 435–445.

Suzuki, K., et al., 2012. Activity-dependent proteolytic cleavage of neuroligin-1. Neuron 76, 410–422.

Taniike, M., et al., 2002. Perineuronal oligodendrocytes protect against neuronal apoptosis through the production of lipocalin-type prostaglandin D synthase in a genetic demyelinating model. J. Neurosci.: Off. J. Soc. Neurosci. 22, 4885–4896.

Tillet, E., et al., 1997. The membrane-spanning proteoglycan NG2 binds to collagens V and VI through the central nonglobular domain of its core protein. J. Biol. Chem. 272, 10769–10776.

Trimarco, A., et al., 2014. Prostaglandin D2 synthase/GPR44: a signaling axis in PNS myelination. Nature Neurosci. 17, 1682–1692.

Uemura, T., et al., 2010. Trans-synaptic interaction of GluRdelta2 and Neurexin through Cbln1 mediates synapse formation in the cerebellum. Cell 141, 1068–1079.

Vadivelu, S., et al., 2015. NG2+ Progenitors derived from embryonic stem cells penetrate glial scar and promote axonal outgrowth into white matter after spinal cord injury. Stem Cells Transl. Med. 4, 401–411.

You, W.K., et al., 2014. NG2 proteoglycan promotes tumor vascularization via integrin-dependent effects on pericyte function. Angiogenesis 17, 61–76.

Zhu, L., et al., 2012. Microglia/monocytes with NG2 expression have no phagocytic function in the cortex after LPS focal injection into the rat brain. Glia 60, 1417–1426.

Zhu, X., Bergles, D.E., Nishiyama, A., 2008. NG2 cells generate both oligodendrocytes and gray matter astrocytes. Development 135, 145–157.

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