Cellular and Molecular Neurobiology (2022) 42:2019–2029
https://doi.org/10.1007/s10571-021-01089-0

REVIEW PAPER

The Notch Signaling Pathway Regulates Differentiation of NG2 Cells into Oligodendrocytes in Demyelinating Diseases

Chengcai Li[1] · Zhiping Xie[1] · Zelong Xing[1] · Huaxin Zhu[1] · Wu Zhou[1] · Shenke Xie[1] · Zhixiong Zhang[1] · Mei-Hua Li[1]

Received: 30 October 2020 / Accepted: 29 March 2021 / Published online: 7 April 2021

Abstract

NG2 cells are highly proliferative glial cells that can self-renew or differentiate into oligodendrocytes, promoting remyelination. Following demyelination, the proliferative and differentiation potentials of NG2 cells increase rapidly, enhancing their differentiation into functional myelinating cells. Levels of the transcription factors Olig1 and Olig2 increase during the differentiation of NG2 cells and play important roles in the development and repair of oligodendrocytes. However, the ability to generate new oligodendrocytes is hampered by injury-related factors (*e.g.*, myelin fragments, Wnt and Notch signaling components), leading to failed differentiation and maturation of NG2 cells into oligodendrocytes. Here, we review Notch signaling as a negative regulator of oligodendrocyte differentiation and discuss the extracellular ligands, intracellular pathways, and key transcription factors involved.

Keywords NG2 cell · Notch signaling pathway · Oligodendrocyte · Demyelinating disease

Abbreviations

ALS	Amyotrophic lateral sclerosis
aTf	Apotransferrin
CNS	Central nervous system
CC	Corpus callosum
ET-1	Endothelin 1
FGF2	Fibroblast growth factor 2
MS	Multiple sclerosis
NICD	Notch intracellular domain
OLs	Oligodendrocytes
TGF-β1	Transforming growth factor β1
TR4	Testicular orphan receptor 4

✉ Mei-Hua Li
limeihua2000@sina.com

Chengcai Li
lichengcai123@sohu.com

Zhiping Xie
xiezhiping123@163.com

Zelong Xing
1021312184@qq.com

Huaxin Zhu
505914775@qq.com

Wu Zhou
1198293375@qq.com

Shenke Xie
447141961@qq.com

Zhixiong Zhang
571143092@qq.com

[1] Department of Neurosurgery, The First Affiliated Hospital of Nanchang University, No. 17 Yongwai Zheng Street, Nanchang 330006, Jiangxi, People's Republic of China

Introduction

NG2 cells are the source of oligodendrocytes (OLs) and thus termed oligodendrocyte precursor cells. NG2 cells are widely distributed in the gray and white matter of the central nervous system (CNS), comprising 4–8% of cells in the adult CNS (Dawson et al. 2003). NG2 cells are the fourth type of glial cell in the CNS, distinct from astrocytes, OLs, and microglia. Their morphology and functional properties differ among brain areas and environmental conditions (Chittajallu et al. 2004). NG2 cells can also differentiate into astrocytes and neurons in the presence of specific growth factors (Belachew et al. 2003). They divide, proliferate, and differentiate into mature OLs in various regions of the CNS throughout life (Li et al. 2020; Zhu et al. 2011) (Fig. 1).

Notch signaling can promote or suppress cell proliferation and differentiation, thus controlling cell fate during the development of organs, including the CNS (Givogri et al. 2002). Notch receptors, such as Notch1–4, are highly conserved transmembrane receptors. Notch ligands—including

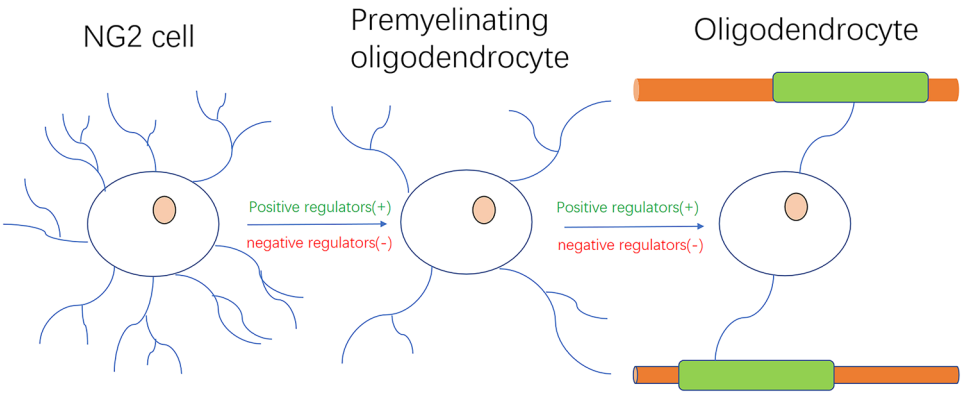

Fig. 1 Timing of the stages of NG2 cell differentiation

Jagged1, Jagged2, Delta-like1, Delta-like3, and Delta-like4—initiate Notch signaling via receptor binding (Gray et al. 1999). Multiple Notch receptors and ligands are expressed in the peripheral nervous system and CNS (Lindsell et al. 1996). Notch signal transduction relies on ligand–receptor binding, resulting in release of an active Notch fragment, which initiates intramembrane proteolysis. After release of the Notch intracellular domain (NICD) by proteolysis from a membrane tether, it travels to the nucleus, associates with a DNA-binding protein to assemble a transcription complex, and represses *Hes* target genes. This can be prevented by a gamma-secretase inhibitor (Jurynczyk et al. 2005).

NG2 cells proliferate and differentiate into mature OLs, which produce myelin basic protein (MBP) and proteolipid protein, which can wrap around axons. Hypomyelination may be caused by failed differentiation of NG2 cells, preventing the generation of new myelin. The Notch1 receptor is expressed in NG2 cells, the differentiation of which is controlled by the Notch pathway (Wang et al. 1998). Activation of Notch signaling suppresses differentiation of NG2 cells, leading to defective remyelination (Wang et al. 2017). Suppression of Notch1 expression in OLs results in an increased number of mature OLs in the gray matter of the developing CNS (Givogri et al. 2002).

As a kind of precursor cell, NG2 cells can not only differentiate into oligodendrocytes but also produce astrocytes and even neurons in special circumstances or pathological conditions (Diers-Fenger et al. 2001; Zhu et al. 2008). It has been found that activation of the Notch signaling pathway in the microenvironment after CNS injury leads to the differentiation of NG2 cells into more astrocytes (Khazaei et al. 2020), and astrocytes are the main cell types in glial scars (Hesp et al. 2018; Huang et al. 2018). Inhibition of the Notch signaling pathway inhibits the proliferation of reactive astrocytes and reduces inflammation-related secondary injury (Qian et al. 2019). After CNS injury, NG2 cells also have the potential to produce new neurons, which may be a potential strategy for neurofunctional repair (Boulanger and Messier 2017; Heinrich et al. 2014). However, the Notch signaling pathway has a negative effect on neuronal differentiation. Inhibition of the Notch signaling pathway promotes neuronal differentiation and maturation and the recovery of neural function (Chen et al. 2015).

Notch Signaling in the CNS

In the CNS, the ligand Jagged1 activates Notch1 receptors to inhibit the differentiation and maturation of NG2 cells. Notch1 receptors are expressed in NG2 cells, and Jagged1 is localized along the axons of retinal ganglion cells. In culture, NG2 cells do not express Notch ligands. Also, Notch and Jagged 1 expression decreased with age in the developing rat optic nerve (Wang et al. 1998).

Demyelinated axons are not a major source of Jagged1. However, Jagged1 is expressed at a high level in reactive astrocytes, whereas Notch1 receptors and Hes5 are expressed in NG2 cells in active multiple sclerosis (MS) lesions lacking remyelination. Jagged1 expression was increased in a broad zone from within the lesion center to the lesion border, and Jagged1 immunoreactivity decreased with distance from the area of demyelination. Astrocytes in remyelinated areas did not show Jagged1 immunoreactivity. Therefore, the expression of Jagged1 by astrocytes might be related to limited remyelination (John et al. 2002). Resting adult astrocytes do not express Notch1, but following demyelination, Notch1 is expressed by a small proportion of astrocytes at the lesion margins (Ge et al. 2002).

Jagged1 and Jagged2 are expressed constitutively in the trigeminal ganglion. Jagged1 is expressed in NG2 cells, OLs, and myelinating Schwann cells. Notch1 is present in post-mitotic neurons and OLs (Nonneman et al. 2018). In the SOD1-G93A model, Notch activation was universal in proliferating astrocytes, Jagged1 was upregulated only in proliferating microglia, and expression of the Notch ligand DLL4 was increased in activated astrocytes and degenerating OLs (Liu et al. 2020). The nigh-on ubiquitous expression

of Notch1 and Jagged1 suggests a role for Notch–Jagged signaling in the CNS.

The Notch pathway is activated upon ligand (DLL1, Jagged1, or Jagged2) binding to a receptor (Notch1 or Notch2) (Gray et al. 1999). This is followed by a series of cleavage events, releasing the NICD, which translocates to the nucleus and modulates the expression of Hes1 and Hes5, basic helix loop–helix-type transcriptional repressors. This results in the inhibition of NeuroD and Mash1 expression (Ohtsuka et al. 1999). Gamma-secretase is a critical component of the Notch signaling pathway, and its inhibition may interfere with Notch-related processes. The Notch signaling inhibitor, DAPT, suppressed the expression of Hes1 and Hes5 (Palagani et al. 2012).

Effect of Notch Signaling on the Proliferation and Differentiation of NG2 Cells

The Notch pathway plays a key role in cell fate determination in the CNS and is involved in several crucial events in glial cell development, such as maintaining NG2 cells in an undifferentiated state.

A regulatory role for the Notch pathway in the differentiation of NG2 cells was suggested by the finding that their differentiation was inhibited by Notch ligands. Other evidence supports a role for the Notch pathway in controlling the timing of NG2 cell differentiation (Wang et al. 1998). A study using the Cre/loxP system in transgenic mice to selectively inhibit Notch1 signaling in NG2 cells showed that the function of Notch1 is crucial for OL development and differentiation in the brain and spinal cord. Also, ablation of Notch1 in NG2 cells led to ectopic production of prematurely differentiated immature OLs in the mouse spinal cord. Most of the prematurely differentiated OLs were found in the gray matter at P0, where immature OLs were scarce in control animals (Genoud et al. 2002). To confirm involvement of Notch1 signaling in remyelination in vivo, Zhang and colleagues generated an Olig1Cre: Notch1$^{12f/12f}$ mouse model in which Notch1 was selectively inactivated throughout the oligodendrocyte lineage. In Notch-inactivated mice, the repair of demyelinated lesions in the corpus callosum (CC) was accelerated. In addition, experiments in vitro confirmed that Notch1 signaling promoted the expansion of NG2 cells but inhibited their differentiation and myelin formation (Zhang et al. 2009). To investigate whether Notch–Jagged signaling regulates the rate of remyelination, their expression was compared between young and older animals. However, no correlation between their expression and the remyelination rate was found, and the lesions underwent complete remyelination in older animals. Therefore, adult expression of Notch1 and Jagged1 neither prevented nor played a major rate-determining role in remyelination, in contrast to developmental myelination. Also, Notch1 ablation in NG2 cells of cuprizone-treated Plp-creER Notch1(lox/lox) transgenic mice did not significantly influence the remyelination parameters of knockout or control mice(Stidworthy et al. 2004).

Notch signaling also promotes differentiation of NG2 cells via other pathways. F3/contactin acts as a functional ligand of Notch, triggering gamma-secretase-dependent nuclear translocation of the NICD and recruitment of Deltex1 before or after releasing NICD into the cytoplasm. The NICD/RBP-J/Deltex1 complex may undergo specific but unknown modifications before moving to the nucleus, where it induces the expression of myelin-associated glycoprotein, promoting the differentiation of NG2 cells. This process can be blocked by dominant-negative expression of Notch1, Notch2, and two Deltex1 mutants lacking the RING-H2 finger motif, but not by dominant-negative expression of RBP-J or Hes1 antisense oligonucleotides. Therefore, F3/contactin initiates Notch/Deltex1 signaling, promoting oligodendrocyte maturation and myelination (Hu et al. 2003) (Fig. 2).

Delta–Notch signaling is required for spinal cord oligodendrocyte specification. In a transgenic, conditional expression system, constitutive Notch activity promoted the generation of excess NG2 cells. Additionally, dla$^{-/-}$, dld$^{-/-}$, and mib$^{-/-}$ embryos did not produce NG2 cells or

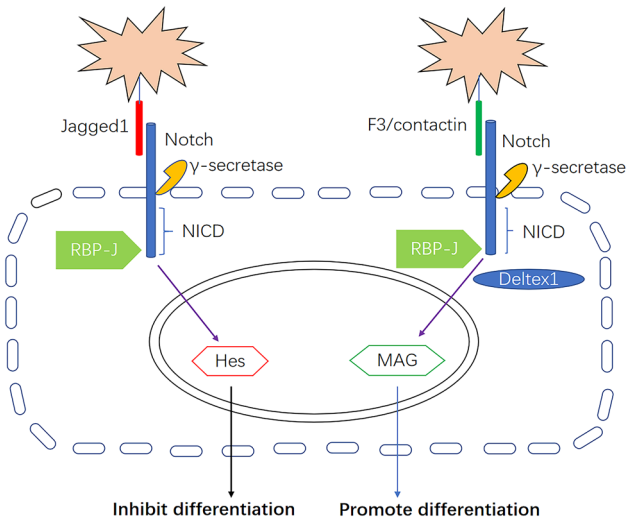

Fig. 2 Roles of Jagged1/Notch and F3/Notch in the differentiation of NG2 cells. Jagged1/Notch signaling activates Notch signaling, release of the Notch intracellular domain (NICD), and recruitment of RBP-J. Next, RBP-J forms a complex with NICD, translocates to the nucleus, and induces *Hes1*/*Hes5* expression to inhibit the differentiation of NG2 cells. In contrast, F3/contactin interacts with Notch receptors on the surface of NG2 cells, stimulating Notch signaling and recruiting Deltex1 before or after releasing NICD into the cytoplasm. The NICD/RBP-J/Deltex1 complex may undergo specific but unknown modifications before moving to the nucleus, where it induces the expression of myelin-associated glycoprotein (MAG) to promote the differentiation of NG2 cells

premyelinating OLs. Therefore, Delta–Notch signaling promotes the generation of NG2 cells. Notch signaling promotes the specification of neural precursors to an oligodendrocyte fate and subsequently regulates their differentiation, possibly matching the development of myelinating OLs to their target axons (Park and Appel 2003). In delta-like 1 mutant mice, neurospheres decreased the number of NG2 cells, and addition of a soluble Notch ligand to wild-type neurospheres enhanced their generation (Grandbarbe et al. 2003).

Hes1 and Hes5 are highly expressed in developing mammalian brain. Their activation by Notch signaling inhibits oligodendrocyte maturation and differentiation (Jarriault et al. 1998; Wang et al. 1998). The progressive decrease in Hes5 expression in vivo may also reflect a decrease in Notch signaling. Moreover, overexpression of Hes5 inhibits oligodendrocyte differentiation, which is induced by mitogen withdrawal or thyroid hormone addition. This suggests that Hes5 is important in Notch-mediated inhibition (Kondo and Raff 2000).

In zebrafish *notch3* mutants, analysis of *notch3*^{st51} and an insertional allele of *notch3* revealed that Notch3 is required for the development of, and MBP gene expression in, NG2 cells during larval development. Reduced MBP expression in embryos is associated with fewer NG2 cells in *notch3* mutants (Zaucker et al. 2013).

Effect of Other Signaling Pathways on the Proliferation and Differentiation of NG2 Cells

The timely proliferation and differentiation of NG2 cells depend on a highly coordinated series of events regulated by multiple intracellular and extracellular factors (Miller 2002). The Wnt/β-catenin signaling pathway is an obvious negative regulator of NG2 cell proliferation and differentiation, and the Notch signaling pathway also regulates these processes (Fancy et al. 2009). Other regulatory factors, including the GSK3 and PDGF signaling pathways, are also involved in the regulation of NG2 cell proliferation and differentiation, and they interact with each other. The Wnt/β-catenin signaling pathway is a typical negative regulator of NG2 cell differentiation, and abnormalities in this pathway can also lead to myelin regeneration disorder in multiple sclerosis (Galimberti et al. 2011; Fancy et al. 2009). In developing CNS, the Wnt/β-catenin signaling pathway mainly inhibits the differentiation and maturation of NG2 cells but does not affect the proliferation of NG2 cells (Langseth et al. 2010). Activation of β-catenin, a signaling molecule of the Wnt signaling pathway, can regulate the differentiation of NG2 cells but does not affect the proliferation of NG2 cells (Dai et al. 2014). However, the role of the Wnt/β-catenin signaling pathway as an inhibitor of myelin formation was challenged by a study that showed that inhibition of the Wnt/β-catenin signaling pathway prevented the formation of mature myelin. It was speculated that the Wnt/β-catenin signaling pathway might initially regulate the maturation of NG2 cells by inhibiting differentiation but later become a driving force in the later stage of myelin formation (Tawk et al. 2011). GSK3 is a key regulator of the Wnt/β-catenin signaling pathway that participates in the regulation of NG2 cell differentiation and myelin formation (Fancy et al. 2009). GSK3 is widely involved in a variety of cell biological processes, including division, proliferation, and differentiation, the regulation of which is of great significance in the treatment of diseases such as multiple sclerosis and white matter damage (Kockeritz et al. 2006). GSK3β is a negative regulator of cell fate and the target of many signaling pathways (Cohen and Goedert 2004). When GSK3β inhibitors are given, a large number of mature oligodendrocytes are formed (Azim and Butt 2011). This finding is helpful to promote the differentiation, maturation, and myelin regeneration of NG2 cells. The positive effect of GSK3β inhibitors is to counteract and overcome the negative effects of the Wnt/β-catenin signaling pathway on the differentiation and myelination of NG2 cells, and studies have also shown that inhibition of GSK3β reduces the activation of the Notch signaling pathway and promotes the differentiation of NG2 cells (Fancy et al. 2009). NG2 cells retain the expression of the PDGF-α receptor, which is also a specific index for the identification of NG2 cells (Sim et al. 2011). PDGF is an important neurotrophic factor that promotes the differentiation of NG2 cells (Mohapel et al. 2005). Activation of the PDGF signaling pathway can significantly increase the number of NG2 cells in an animal model of demyelination (Hill et al. 2013). There is also an interaction between the PDGF signaling pathway and the Notch signaling pathway that affects the transcriptional level of target genes in the Notch signaling pathway (Liang et al. 2017). In this chapter, we mainly discuss the effect of the Notch signaling pathway on the differentiation of NG2 cells in demyelinating diseases.

Crosstalk Between Other Molecular Events and Notch Signaling in the CNS

Diverse molecular events influence Notch signaling and the differentiation of NG2 cells, but the role of other molecular events in the CNS is unclear (Fig. 3).

F3/Contactin and NB-3

F3/contactin and NB-3 are members of the F3/contactin family of the immunoglobulin superfamily, and F3/contactin is expressed in various regions of the brain. F3/contactin and

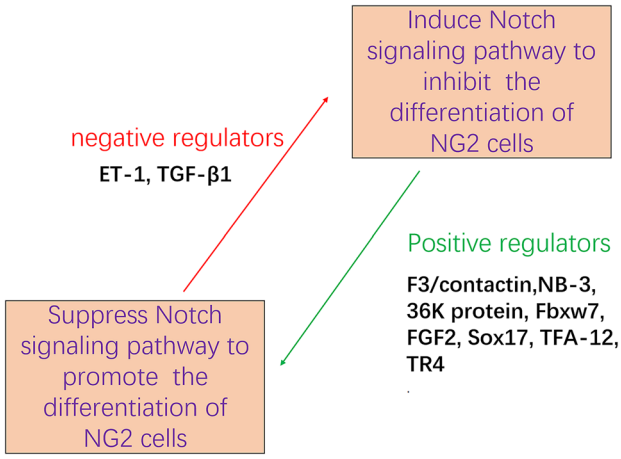

Fig. 3 Regulation of the differentiation of NG2 cells by the Notch signaling pathway. The differentiation and myelination status of NG2 cells can be determined by the balance between opposing signaling systems. Positive regulators of Notch signaling promote, and negative regulators inhibit, the differentiation of NG2 cells

NB-3, as functional ligands of Notch, enhance Notch1 and Notch2 expression, promoting oligodendrocyte maturation. All of these events require Deltex1 as an intermediate factor (Hu et al. 2006).

Myelin Protein 36 K

36 K is one of the most abundant proteins in the zebrafish brain. Identifying the function of 36 K in zebrafish myelin would enhance understanding of demyelinating diseases and remyelination in the human CNS. 36 K plays an important role in oligodendrocyte differentiation by inhibiting the Notch signaling pathway. 36 K also regulates the synthesis of transmembrane Notch ligands and promotes intramembrane gamma-secretase processing of Notch. A gamma-secretase inhibitor prevented activation of Notch, rescuing the number of NG2 cells in 36 K morphants (Nagarajan et al. 2020).

Astrocyte-Derived Endothelin 1 (ET-1)

ET-1 is a secreted signaling peptide that suppresses remyelination and is highly expressed in reactive astrocytes of demyelinated lesions. ET-1 promotes Notch activation in NG2 cells during remyelination by inducing Jagged1 expression in reactive astrocytes. Inhibiting ET signaling prevents Notch activation in demyelinated lesions and accelerates remyelination. Genetic ablation of ET-1 also modulates Jagged1/Notch1 signaling and the differentiation of NG2 cells. PD142,893, a potent inhibitor of ET-1 signaling, prevents Jagged1 induction and Notch activation (Hammond et al. 2014). However, although ET-1 inhibits differentiation of NG2 cells via an astrocyte-dependent pathway, it may also signal directly to NG2 cells, which also express ET receptors (Gadea et al. 2009). Endothelin-2 reportedly promotes remyelination in the rat cerebellum (Yuen et al. 2013).

Mutation of *fbxw7*

fbxw7 encodes the substrate recognition component of a ubiquitin ligase, which targets Notch and other proteins for degradation. Fbxw7 attenuates Notch signaling during zebrafish neural development, thereby suppressing generation of excess NG2 cells. Notch signaling is elevated in *fbxw7*-mutant embryos, indicating that Notch proteins are functionally relevant targets of Fbxw7-mediated ubiquitination during oligodendrocyte specification (Snyder et al. 2012).

Fibroblast Growth Factor 2 (FGF2)

FGF2 inhibits the differentiation of NG2 cells into myelinating OLs during development and remyelination by activating fibroblast growth factor receptor signaling, predominantly via fibroblast growth factor receptor 1, in oligodendrocyte-lineage cells (Zhou et al. 2006). FGF2 induces Notch1 expression in immature OLs (Faux et al. 2001). Notch1 signaling increases the responsiveness to FGF2 in telecephalic progenitors (Yoon et al. 2004). FGF2 signaling may interact with downstream components of the Notch signaling pathway, including Maml1 and Hes5. Therefore, the interaction of FGF2 with Notch signaling components may be critical for the regulation of differentiation and myelination of NG2 cells during CNS development (Zhou and Armstrong 2007).

Sox17

SRY-Box (Sox)-containing transcription factors are evolutionarily conserved proteins essential for the differentiation and maturation of the developing nervous system. Sox17 is the only member of the SoxF family involved in CNS glial development, and it is upregulated during postnatal oligodendrocyte development and promotes oligodendrocyte differentiation (Sohn et al. 2006). Sox17 also promotes the differentiation of cultured NG2 cells (Chew et al. 2011). The numbers of Olig2-expressing cells and mature OLs are decreased by Sox17 ablation, leading to hypomyelination and motor dysfunction. Following lysolecithin (LPC)-induced demyelination, Sox17 deficiency significantly inhibits oligodendrocyte regeneration. Sox17

promotes progenitor expansion and differentiation via Notch signaling and thus contributes to oligodendrocyte generation. TCF7L2 expression is also regulated by both Sox17 and Notch, and Sox17 regulates Notch1 receptor and Hes effectors (Chew et al. 2019).

Tocopherol Derivative TFA-12

The tocopherol long-chain fatty alcohol TFA-12 is a synthetic molecule that combines an α-tocopherol moiety and a neurotrophic ω-alkanol side chain with 12 carbon atoms. TFA-12 is a member of the vitamin E family and a modulator of MS because of its antioxidant and anti-inflammatory effects; it also ameliorates white matter damage in experimental models. TFA-12 is an inhibitor of microglial activation in vitro and decreases secretion of nitric oxide and tumor necrosis factor α (Muller et al. 2004). In two rodent models of MS (an experimental autoimmune encephalomyelitis model and LPC-induced demyelination model), TFA-12 promotes differentiation of NG2 cells into mature OLs and remyelination by inhibiting Notch/Jagged1 signaling (Blanchard et al. 2013). TFA-12 represses expression of the Notch downstream effectors Hes1 and Hes5 and concomitantly upregulates Mash1, a bHLH transcription factor involved in oligodendrocyte differentiation. TFA-12 also reverses the Jagged1-mediated inhibition of NG2 cell differentiation (Parras et al. 2007). TFA-12 directly binds to Notch receptors, inhibiting gamma-secretase activity and the nuclear translocation of NICD (Blanchard et al. 2013).

Transforming Growth Factor β (TGF-β1)

TGF-β1 has been detected in a range of CNS conditions with a traumatic or inflammatory etiology and induces Jagged1 expression in primary cultures of human astrocytes. In contrast, astrocytes do not show Jagged1 immunoreactivity in remyelinated areas. The effect of TGF-β1 on Jagged1 inhibits the maturation of NG2 cells but does not induce Delta1 ligand. Therefore, TGF-β1 is associated with activation of the Notch pathway, inhibiting oligodendrocyte maturation and myelination (John et al. 2002). However, other findings contradict the above notion that TGF-β promotes NG2 cell proliferation in 8-day adult brain SVZ neurosphere cultures and triggers their differentiation into mature OLs. The gamma-secretase inhibitor DAPT significantly decreased the population of PDGFRα$^+$ NG2 cells in TGF-β-treated neurospheres (Gomez et al. 2018).

Testicular Orphan Receptor 4 (TR4)

TR4 is an orphan nuclear receptor important in the development and maturation of the CNS, particularly in the differentiation and maturation of OLs in the forebrain (Young et al. 1997). Hypomyelination in TR4$^{-/-}$ forebrains was associated with a decreased number of mature OLs, possibly mediated by the Jagged1–Notch signaling pathway. Jagged1 expression is higher in axon fiber-enriched regions in the developing TR4$^{-/-}$ forebrain, indicating that Notch signaling is enhanced when NG2 cells contact these axons. This inhibits oligodendrocyte maturation and is correlated with decreased myelination but promotes astrocyte generation (Tanigaki et al. 2001). In addition, the timely downregulation of Jagged1 in axons is disrupted in the TR4$^{-/-}$ forebrain, implicating TR4 in the regulation of Jagged1. Notch signaling is more highly activated in TR4$^{-/-}$ brains in which Hes1 is not expressed, indicating that Hes1 is not a major effector. Regulation of Hes5 by TR4 via a non-Notch-related pathway is possible. Therefore, crosstalk between TR4 and Notch signaling is important for oligodendrocyte differentiation and maturation. The altered Jagged1–Notch signaling in the TR4$^{-/-}$ forebrain indicates that TR4 is necessary for proper myelination in the CNS (Zhang et al. 2007).

Notch and Demyelinating Diseases

MS

MS is an immune-mediated disorder characterized by inflammation and multifocal demyelination accompanied by progressive neurodegeneration, and it typically affects young people. MS is related to OL damage, failed remyelination, and axon degeneration, but these lost functions can be restored by generating OLs to place new myelin sheaths on demyelinated axons. NG2 cells give rise to OLs during CNS development, remain quiescent and undifferentiated during adulthood, and are recruited and undergo proliferation and differentiation during CNS injury. MS lesions contain numerous NG2 cells with myelination ability that do not differentiate into mature OLs, indicating no myelin synthesis. Activation of Notch signaling may hamper NG2 cell differentiation and remyelination, and inhibition of Notch could promote axon myelination, indicating therapeutic potential for MS (Zhang et al. 2009).

A model of focal demyelination induced by LPC injection in the CC has shown that a single intracranial injection of apotransferrin (aTf) induces an increase in F3/contactin levels and in myelin-associated glycoprotein gene

expression at 24 h. DAPT injection reverses aTf-induced remyelination, implicating Notch signaling in the promyelination activity of aTf (Aparicio et al. 2013). A mouse model of acute demyelination has enabled exploration of the effect of Notch1 on remyelination in MS. Inhibition of Notch1 suppressed the Hes and Jagged-1 protein levels and promoted the differentiation of NG2 cells and formation of myelin (Fan et al. 2018).

The toxic cuprizone-induced demyelination model, which mimics pattern III lesions of MS, shows an increased proportion of Jagged1^{+}/GFAP^{+} cells. This is associated with enhanced Jagged1-driven Notch signaling activation in NG2 cells during early demyelination, subsequently increasing the proportion of F3/contactin^{+}/NG2^{+} cells and promoting F3/contactin transcription during remyelination in the CC (Mathieu et al. 2019). Therefore, Notch signaling mediates degenerative disorders by regulating the proliferation, migration, and differentiation of NG2 cells and could be a therapeutic target in conditions related to demyelination.

Amyotrophic Lateral Sclerosis (ALS)

ALS is a late-onset degenerative disease affecting mainly motor neurons with an oligodendrocyte pathology and reactive astrocytes and microglia. The clinical features include muscle denervation, muscle weakness and atrophy, and ultimately paralysis and denervation of the respiratory muscles, leading to respiratory failure and death. In a model of ALS, the Notch signaling pathway is abnormally activated in the spinal cord of SOD1^{G93A} mice, as well as in that of patients with sporadic ALS. The Notch ligand Jagged1 is highly expressed in reactive astrocytes in the spinal cord of mice and patients with ALS (Nonneman et al. 2018). Therefore, abnormal Notch signaling activation contributes to the pathogenesis of ALS, participates in other pathogenetic processes, and influences the proliferation and differentiation of NG2 cells into mature OLs (Philips et al. 2013).

Exposure to Hyperoxia

Hyperoxia damages the immature brain by inducing an inflammatory response (Nasoohi et al. 2012). Death of NG2 cells has been reported in mice exposed to 80% oxygen for 48 h (Schmitz et al. 2011). Hyperoxia reduces the number of mature OLs (MBP^{+}) and increases that of NG2 cells after hyperoxia on postnatal day 12. DAPT pretreatment significantly ameliorates hyperoxia-induced disruption of oligodendrocyte maturation, increases the expression of MBP, and alleviates necrosis, cytoplast swelling, and karyoplast dissolution of immature brain cells in white matter. Mice pretreated with DAPT before hyperoxia showed significant decreases in the escape latency time and distance, dwell time, and frequency of crossing the platform, suggesting that the Notch pathway contributes to these cognitive changes in the immature brain. Therefore, Notch activation could hinder NG2 cell differentiation and induce dysregulation of oligodendrocyte maturation in the immature brain after hyperoxia and lead to behavioral abnormalities. Selective pharmacological inhibition of the Notch signaling pathway could ameliorate the adverse effects of hyperoxia. The Notch signaling pathway may be an important target for ameliorating hyperoxia-induced damage and behavioral changes in the neonatal brain (Du et al. 2017).

Schizophrenia

The key features of schizophrenia are white matter disturbances and myelin impairment. Electron microscopy of postmortem samples from patients with schizophrenia showed aberrant myelination of synaptic terminals, increased density of concentric lamellar bodies, and apoptosis/necrosis of OLs (Uranova et al. 2001). The Notch4 locus is a candidate susceptibility gene for schizophrenia (Stefansson et al. 2009), and the mRNA level of Notch1 is aberrant in parvalbumin-immunoreactive neurons in patients with schizophrenia (Pietersen et al. 2014). Quetiapine is a novel second-generation antipsychotic used to treat schizophrenia that promotes NG2 maturation, OL regeneration, and myelin repair (Zhang et al. 2012). Quetiapine exerted antipsychotic and myelin-protective effects in a Notch-dependent manner. Moreover, quetiapine ameliorated the cuprizone-induced inhibition of Notch signaling factors, such as Notch1, Hes1, and Hes5, in the forebrain, and MW167 suppressed these protective effects of quetiapine. Therefore, the antipsychotic and myelin-protective effects of quetiapine are mediated by Notch signaling, which thus has potential as a target for the development of antipsychotic drugs (Wang et al. 2015).

Stroke and Ischemia

Stroke is a neurological disease caused by many factors, such as cerebral artery stenosis, occlusion, or rupture, and its clinical manifestation is transient or permanent brain dysfunction. As one of the three most common diseases in the world, stroke has a high mortality and disability rate and is a serious threat to human life and health. Ischemic stroke is the most common form of stroke. White matter is particularly sensitive to stroke. Because the blood flow of white matter is lower than that of gray matter, deep white matter has a lower blood supply (Pantoni et al. 1996). Oligodendrocytes are the main cell types in white matter, and the differentiation and maturation of oligodendrocytes in the brain are very important for the maintenance and repair of white matter (Lo et al. 2003). NG2 cells are one of the cell types that respond quickly to ischemic injury and can differentiate into mature oligodendrocytes in the preparation for

the formation of a new myelin sheath (Zhang et al. 2013). It was shown that at 7 days after cerebral ischemia–reperfusion injury, the number of NG2 cells in the area around the ischemic focus had increased significantly, and there were morphological changes that included enlarged cell bodies and hypertrophic protuberances. However, the number of NG2 cells in the central area of the ischemic focus decreased significantly, and the number of NG2 cells in the contralateral brain area did not change. It has been suggested that after cerebral ischemia–reperfusion, the NG2 cells proliferating in the surrounding area may differentiate into mature oligodendrocytes, thus supplementing dead oligodendrocytes and participating in the myelination of axons, which is of great significance to the regeneration and repair of brain tissue after ischemic injury (Matsumoto et al. 2008; Tanaka et al. 2001). Another study found that the number of NG2 cells in the injured juvenile striatum increased significantly 7 days after transient middle cerebral artery occlusion, indicating that NG2 cells responded to ischemic injury and increased their proliferation rate. In adult mice, NG2 cells undergo morphological changes after ischemic injury. NG2 cells show high resistance to ischemic damage in the juvenile striatum (Ahrendsen et al. 2016; Levine 2016). In ischemic injury, NG2 cells also exhibit changes in ion channels and membrane receptors as well as cell death induced by excitotoxicity (Boda et al. 2011; Pivonkova et al. 2010). The Notch signaling pathway in glial cells is activated after ischemia–reperfusion. Treatment with DAPT maintains the proliferation of NG2 cells in the area around the ischemic focus but also reduces the proliferation of reactive astrocytes, enabling NG2 cells to retain the ability to promote myelin repair, which has a beneficial effect on the recovery of ischemic injury (Marumo et al. 2013). These findings suggest that NG2 cells will be a potential therapeutic target for the treatment of ischemic injury.

Reaction of Notch Signaling and NG2 Cells in Other CNS Diseases

NG2 cells respond not only to demyelinating diseases but also to a variety of CNS injuries, including brain injury, spinal cord injury, inflammation, and other neuropathological processes, by changing their own morphology, proliferation, differentiation, and migration, which plays an important role in functional recovery, myelin repair, and immune regulation (Dawson et al. 2003; Levine et al. 2001). NG2 cells can increase rapidly within 1–3 days after CNS injury at almost 100 times the basic proliferation rate. With increasing time after injury, NG2 cells gradually decrease and basically return to their original density within a few weeks (Simon et al. 2011). When brain injury occurred, the NG2 cells around the injury showed morphological changes including enlarged cell bodies and hypertrophic protuberances, and immunoreactivity was significantly enhanced (Tanaka et al. 2001). In a model of acupuncture injury of the cerebellar cortex, the number of NG2 cells increased at the site of injury, and the number of irregularly shaped NG2 cells increased at 48 h after injury (Levine 1994). Jones et al. found that NG2 cells increased significantly after spinal cord injury and reached a peak on the 7th day after injury (Jones et al. 2002). After spinal cord injury, NG2 cells proliferate and differentiate into oligodendrocytes, which directly and indirectly affect many aspects of spinal cord injury, including hemorrhage, angiogenesis, glial scar formation, laminin deposition, astrocyte reaction, and axonal growth (Hesp et al. 2018). In CNS injury, NG2 cells participate in myelin regeneration and axon protection, but NG2 cells also seem to participate in glial scar formation and hinder axon regeneration (Tran et al. 2018). Glial scars formed after CNS injury include a large number of NG2 cells (Tran et al. 2018). NG2 proteoglycan is a major obstacle to axonal growth (Gaudet and Fonken 2018). In vitro, when neurons were grown in an environment containing scattered NG2 proteoglycan, axon growth bypassed the area of NG2 proteoglycan distribution and extended to other regions (Dou and Levine 1994). Some studies related to axon regeneration have found that neutralizing NG2 proteoglycan with an anti-NG2 antibody after injury can promote sensory axon regeneration and functional recovery (Tan et al. 2006). However, other studies have found that NG2 proteoglycans have the opposite effect, suggesting that NG2 cells provide adhesion substrates for axonal growth (Yang et al. 2006). It has also been found that activation of the Notch signaling pathway in the microenvironment after CNS injury induces NG2 cells to differentiate into astrocytes, and astrocytes are the main cell types in glial scars (Huang et al. 2018; Khazaei et al. 2020). Reactive astrocytes lose their normal cellular function and have cytotoxic effects on local neurons and oligodendrocytes, and these effects are strongly associated with pathogenic progression (Xu et al. 2018). Inhibition of the Notch signaling pathway can inhibit the proliferation of reactive astrocytes and reduce inflammation-related secondary injury (Qian et al. 2019). In injured tissues, the immune response of NG2 cells often changes earlier than that of neurons and even earlier than that of other glial cells and macrophages, indicating that NG2 cells play an active role in neuropathology and may buffer the cytotoxins produced in the process of injury by releasing some biological factors and eliminating denatured tissue through inflammatory reactions (Wang and He 2009). However, the response of NG2 cells depends on the type of injury and the stage of development. Moreover, the significance of NG2 cell activation under injury conditions is uncertain. Therefore, in future research, it will be of great significance to explore the changes in and the role of NG2 cells in CNS diseases to fully utilize their protective functions and reduce their impairment, which will be

of great significance for the treatment and recovery of CNS diseases.

Conclusions

Notch signaling may represent a novel therapeutic target in demyelination disorders and enhances the understanding of demyelination/remyelination. However, caution is needed because interfering with Notch signaling could have harmful effects.

Acknowledgements This work was supported by the National Natural Science Foundation of China (NSFC; Grant No. 81860225).

Author Contributions LCC, XZP, XZL, ZHX, ZW, XSK, ZZX, and LMH reviewed the literature and drafted the manuscript. LCC and LMH critically revised the manuscript. All authors read and approved the final manuscript.

Declarations

Conflict of interest The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: All authors have no competing interest (e.g., Employment, consultancies honoraria, stock ownership or option, grants, contracts, patents received or royalties) to declare. We confirm that the manuscript has been read and approved by all named authors. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

Ethical Approval All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

References

Ahrendsen JT, Grewal HS, Hickey SP, Culp CM, Gould EA, Shimizu T et al (2016) Juvenile striatal white matter is resistant to ischemia-induced damage. Glia 64(11):1972–1986

Aparicio E, Mathieu P, Pereira LM, Almeira GM, Adamo AM (2013) The Notch signaling pathway: its role in focal CNS demyelination and apotransferrin-induced remyelination. J Neurochem 127(6):819–836

Azim K, Butt AM (2011) GSK3beta negatively regulates oligodendrocyte differentiation and myelination in vivo. Glia 59(4):540–553

Belachew S, Chittajallu R, Aguirre AA, Yuan X, Kirby M, Anderson S et al (2003) Postnatal NG2 proteoglycan-expressing progenitor cells are intrinsically multipotent and generate functional neurons. J Cell Biol 161(1):169–186

Blanchard B, Heurtaux T, Garcia C, Moll NM, Caillava C, Grandbarbe L et al (2013) Tocopherol derivative TFA-12 promotes myelin repair in experimental models of multiple sclerosis. J Neurosci 33(28):11633–11642

Boda E, Vigano F, Rosa P, Fumagalli M, Labat-Gest V, Tempia F et al (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

Boulanger JJ, Messier C (2017) Oligodendrocyte progenitor cells are paired with GABA neurons in the mouse dorsal cortex: unbiased stereological analysis. Neuroscience 362:127–140

Chen BY, Zheng MH, Chen Y, Du YL, Sun XL, Zhang X et al (2015) Myeloid-specific blockade of Notch signaling by RBP-J knockout attenuates spinal cord injury accompanied by compromised inflammation response in mice. Mol Neurobiol 52(3):1378–1390

Chew LJ, Shen W, Ming X, Senatorov VJ, Chen HL, Cheng Y et al (2011) SRY-box containing gene 17 regulates the Wnt/beta-catenin signaling pathway in oligodendrocyte progenitor cells. J Neurosci 31(39):13921–13935

Chew LJ, Ming X, McEllin B, Dupree J, Hong E, Catron M et al (2019) Sox17 regulates a program of oligodendrocyte progenitor cell expansion and differentiation during development and repair. Cell Rep 29(10):3173–3186

Chittajallu R, Aguirre A, Gallo V (2004) NG2-positive cells in the mouse white and grey matter display distinct physiological properties. J Physiol 561(Pt 1):109–122

Cohen P, Goedert M (2004) GSK3 inhibitors: development and therapeutic potential. Nat Rev Drug Discov 3(6):479–487

Dai ZM, Sun S, Wang C, Huang H, Hu X, Zhang Z et al (2014) Stage-specific regulation of oligodendrocyte development by Wnt/beta-catenin signaling. J Neurosci 34(25):8467–8473

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

Diers-Fenger M, Kirchhoff F, Kettenmann H, Levine JM, Trotter J (2001) AN2/NG2 protein-expressing glial progenitor cells in the murine CNS: isolation, differentiation, and association with radial glia. Glia 34(3):213–228

Dou CL, Levine JM (1994) Inhibition of neurite growth by the NG2 chondroitin sulfate proteoglycan. J Neurosci 14(12):7616–7628

Du M, Tan Y, Liu G, Liu L, Cao F, Liu J et al (2017) Effects of the Notch signalling pathway on hyperoxia-induced immature brain damage in newborn mice. Neurosci Lett 653:220–227

Fan H, Zhao JG, Yan JQ, Du GQ, Fu QZ, Shi J et al (2018) Effect of Notch1 gene on remyelination in multiple sclerosis in mouse models of acute demyelination. J Cell Biochem 119(11):9284–9294

Fancy SP, Baranzini SE, Zhao C, Yuk DI, Irvine KA, Kaing S et al (2009) Dysregulation of the Wnt pathway inhibits timely myelination and remyelination in the mammalian CNS. Genes Dev 23(13):1571–1585

Faux CH, Turnley AM, Epa R, Cappai R, Bartlett PF (2001) Interactions between fibroblast growth factors and Notch regulate neuronal differentiation. J Neurosci 21(15):5587–5596

Gadea A, Aguirre A, Haydar TF, Gallo V (2009) Endothelin-1 regulates oligodendrocyte development. J Neurosci 29(32):10047–10062

Galimberti D, Macmurray J, Scalabrini D, Fenoglio C, De Riz M, Comi C et al (2011) GSK3beta genetic variability in patients with multiple sclerosis. Neurosci Lett 497(1):46–48

Gaudet AD, Fonken LK (2018) Glial cells shape pathology and repair after spinal cord injury. Neurotherapeutics 15(3):554–577

Ge W, Martinowich K, Wu X, He F, Miyamoto A, Fan G et al (2002) Notch signaling promotes astrogliogenesis via direct CSL-mediated glial gene activation. J Neurosci Res 69(6):848–860

Genoud S, Lappe-Siefke C, Goebbels S, Radtke F, Aguet M, Scherer SS et al (2002) Notch1 control of oligodendrocyte differentiation in the spinal cord. J Cell Biol 158(4):709–718

Givogri MI, Costa RM, Schonmann V, Silva AJ, Campagnoni AT, Bongarzone ER (2002) Central nervous system myelination in mice with deficient expression of Notch1 receptor. J Neurosci Res 67(3):309–320

Gomez PL, Rodriguez D, Adamo AM, Mathieu PA (2018) TGF-beta pro-oligodendrogenic effects on adult SVZ progenitor cultures and its interaction with the Notch signaling pathway. Glia 66(2):396–412

Grandbarbe L, Bouissac J, Rand M, Hrabe DAM, Artavanis-Tsakonas S, Mohier E (2003) Delta-Notch signaling controls the generation of neurons/glia from neural stem cells in a stepwise process. Development 130(7):1391–1402

Gray GE, Mann RS, Mitsiadis E, Henrique D, Carcangiu ML, Banks A et al (1999) Human ligands of the Notch receptor. Am J Pathol 154(3):785–794

Hammond TR, Gadea A, Dupree J, Kerninon C, Nait-Oumesmar B, Aguirre A et al (2014) Astrocyte-derived endothelin-1 inhibits remyelination through notch activation. Neuron 81(3):588–602

Heinrich C, Bergami M, Gascon S, Lepier A, Vigano F, Dimou L et al (2014) Sox2-mediated conversion of NG2 glia into induced neurons in the injured adult cerebral cortex. Stem Cell Rep 3(6):1000–1014

Hesp ZC, Yoseph RY, Suzuki R, Jukkola P, Wilson C, Nishiyama A et al (2018) Proliferating NG2-cell-dependent angiogenesis and scar formation alter axon growth and functional recovery after spinal cord injury in mice. J Neurosci 38(6): 1366–1382

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

Hu QD, Ang BT, Karsak M, Hu WP, Cui XY, Duka T et al (2003) F3/contactin acts as a functional ligand for Notch during oligodendrocyte maturation. Cell 115(2):163–175

Hu QD, Ma QH, Gennarini G, Xiao ZC (2006) Cross-talk between F3/contactin and Notch at axoglial interface: a role in oligodendrocyte development. Dev Neurosci 28(1–2):25–33

Huang W, Bai X, Stopper L, Catalin B, Cartarozzi LP, & Scheller A et al (2018) During development NG2 glial cells of the spinal cord are restricted to the oligodendrocyte lineage, but generate astrocytes upon acute injury. Neuroscience 385:154–165

Jarriault S, Le Bail O, Hirsinger E, Pourquie O, Logeat F, Strong CF et al (1998) Delta-1 activation of notch-1 signaling results in HES-1 transactivation. Mol Cell Biol 18(12):7423–7431

John GR, Shankar SL, Shafit-Zagardo B, Massimi A, Lee SC, Raine CS et al (2002) Multiple sclerosis: re-expression of a developmental pathway that restricts oligodendrocyte maturation. Nat Med 8(10):1115–1121

Jones LL, Yamaguchi Y, Stallcup WB, Tuszynski MH (2002) NG2 is a major chondroitin sulfate proteoglycan produced after spinal cord injury and is expressed by macrophages and oligodendrocyte progenitors. J Neurosci 22(7):2792–2803

Jurynczyk M, Jurewicz A, Bielecki B, Raine CS, Selmaj K (2005) Inhibition of Notch signaling enhances tissue repair in an animal model of multiple sclerosis. J Neuroimmunol 170(1–2):3–10

Khazaei M, Ahuja CS, Nakashima H, Nagoshi N, Li L, Wang J et al (2020) GDNF rescues the fate of neural progenitor grafts by attenuating Notch signals in the injured spinal cord in rodents. Sci Transl Med. https://doi.org/10.1126/scitranslmed.aau3538

Kockeritz L, Doble B, Patel S, Woodgett JR (2006) Glycogen synthase kinase-3–an overview of an over-achieving protein kinase. Curr Drug Targets 7(11):1377–1388

Kondo T, Raff M (2000) Basic helix-loop-helix proteins and the timing of oligodendrocyte differentiation. Development 127(14):2989–2998

Langseth AJ, Munji RN, Choe Y, Huynh T, Pozniak CD, Pleasure SJ (2010) Wnts influence the timing and efficiency of oligodendrocyte precursor cell generation in the telencephalon. J Neurosci 30(40):13367–13372

Levine JM (1994) Increased expression of the NG2 chondroitin-sulfate proteoglycan after brain injury. J Neurosci 14(8):4716–4730

Levine J (2016) The reactions and role of NG2 glia in spinal cord injury. Brain Res 1638(Pt B):199–208

Levine JM, Reynolds R, Fawcett JW (2001) The oligodendrocyte precursor cell in health and disease. Trends Neurosci 24(1):39–47

Li R, Zhang P, Zhang M, Yao Z (2020) The roles of neuron-NG2 glia synapses in promoting oligodendrocyte development and remyelination. Cell Tissue Res 381(1):43–53

Liang T, Zhu L, Gao W, Gong M, Ren J, Yao H et al (2017) Coculture of endothelial progenitor cells and mesenchymal stem cells enhanced their proliferation and angiogenesis through PDGF and Notch signaling. FEBS Open Bio 7(11):1722–1736

Lindsell CE, Boulter J, DiSibio G, Gossler A, Weinmaster G (1996) Expression patterns of Jagged, Delta1, Notch1, Notch2, and Notch3 genes identify ligand-receptor pairs that may function in neural development. Mol Cell Neurosci 8(1):14–27

Liu C, Li D, Lv C, Gao Z, Qi Y, Wu H et al (2020) Activation of the Notch signaling pathway and cellular localization of notch signaling molecules in the spinal cord of SOD1-G93A ALS model mice. Neuroscience 432:84–93

Lo EH, Dalkara T, Moskowitz MA (2003) Mechanisms, challenges and opportunities in stroke. Nat Rev Neurosci 4(5):399–415

Marumo T, Takagi Y, Muraki K, Hashimoto N, Miyamoto S, Tanigaki K (2013) Notch signaling regulates nucleocytoplasmic Olig2 translocation in reactive astrocytes differentiation after ischemic stroke. Neurosci Res 75(3):204–209

Mathieu PA, Almeira GM, Rodriguez D, Gomez PL, Calcagno ML, Adamo AM (2019) Demyelination-remyelination in the central nervous system: ligand-dependent participation of the Notch signaling pathway. Toxicol Sci 171:172–192

Matsumoto H, Kumon Y, Watanabe H, Ohnishi T, Shudou M, Chuai M et al (2008) Accumulation of macrophage-like cells expressing NG2 proteoglycan and Iba1 in ischemic core of rat brain after transient middle cerebral artery occlusion. J Cereb Blood Flow Metab 28(1):149–163

Miller RH (2002) Regulation of oligodendrocyte development in the vertebrate CNS. Prog Neurobiol 67(6):451–467

Mohapel P, Frielingsdorf H, Haggblad J, Zachrisson O, Brundin P (2005) Platelet-derived growth factor (PDGF-BB) and brain-derived neurotrophic factor (BDNF) induce striatal neurogenesis in adult rats with 6-hydroxydopamine lesions. Neuroscience 132(3):767–776

Muller T, Grandbarbe L, Morga E, Heuschling P, Luu B (2004) Tocopherol long chain fatty alcohols decrease the production of TNF-alpha and NO radicals by activated microglial cells. Bioorg Med Chem Lett 14(24):6023–6026

Nagarajan B, Harder A, Japp A, Haberlein F, Mingardo E, Kleinert H et al (2020) CNS myelin protein 36K regulates oligodendrocyte differentiation through Notch. Glia 68(3):509–527

Nasoohi S, Hemmati AA, Moradi F, Ahmadiani A (2012) The gamma-secretase blocker DAPT impairs recovery from lipopolysaccharide-induced inflammation in rat brain. Neuroscience 210:99–109

Nonneman A, Criem N, Lewandowski SA, Nuyts R, Thal DR, Pfrieger FW et al (2018) Astrocyte-derived Jagged-1 mitigates deleterious Notch signaling in amyotrophic lateral sclerosis. Neurobiol Dis 119:26–40

Ohtsuka T, Ishibashi M, Gradwohl G, Nakanishi S, Guillemot F, Kageyama R (1999) Hes1 and Hes5 as notch effectors in mammalian neuronal differentiation. EMBO J 18(8):2196–2207

Palagani V, El KM, Kossatz U, Bozko P, Muller MR, Manns MP et al (2012) Epithelial mesenchymal transition and pancreatic tumor initiating CD44+/EpCAM+ cells are inhibited by gamma-secretase inhibitor IX. PLoS ONE 7(10):e46514

Pantoni L, Garcia JH, Gutierrez JA (1996) Cerebral white matter is highly vulnerable to ischemia. Stroke 27(9):1641–1646

Park HC, Appel B (2003) Delta-Notch signaling regulates oligodendrocyte specification. Development 130(16):3747–3755
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
Philips T, Bento-Abreu A, Nonneman A, Haeck W, Staats K, Geelen V et al (2013) Oligodendrocyte dysfunction in the pathogenesis of amyotrophic lateral sclerosis. Brain 136(Pt 2):471–482
Pietersen CY, Mauney SA, Kim SS, Passeri E, Lim MP, Rooney RJ et al (2014) Molecular profiles of parvalbumin-immunoreactive neurons in the superior temporal cortex in schizophrenia. J Neurogenet 28(1–2):70–85
Pivonkova H, Benesova J, Butenko O, Chvatal A, Anderova M (2010) Impact of global cerebral ischemia on K+ channel expression and membrane properties of glial cells in the rat hippocampus. Neurochem Int 57(7):783–794
Qian D, Li L, Rong Y, Liu W, Wang Q, Zhou Z et al (2019) Blocking Notch signal pathway suppresses the activation of neurotoxic A1 astrocytes after spinal cord injury. Cell Cycle 18(21):3010–3029
Schmitz T, Ritter J, Mueller S, Felderhoff-Mueser U, Chew LJ, Gallo V (2011) Cellular changes underlying hyperoxia-induced delay of white matter development. J Neurosci 31(11):4327–4344
Sim FJ, McClain CR, Schanz SJ, Protack TL, Windrem MS, Goldman SA (2011) CD140a identifies a population of highly myelinogenic, migration-competent and efficiently engrafting human oligodendrocyte progenitor cells. Nat Biotechnol 29(10):934–941
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
Snyder JL, Kearns CA, Appel B (2012) Fbxw7 regulates Notch to control specification of neural precursors for oligodendrocyte fate. Neural Dev 7:15
Sohn J, Natale J, Chew LJ, Belachew S, Cheng Y, Aguirre A et al (2006) Identification of Sox17 as a transcription factor that regulates oligodendrocyte development. J Neurosci 26(38):9722–9735
Stefansson H, Ophoff RA, Steinberg S, Andreassen OA, Cichon S, Rujescu D et al (2009) Common variants conferring risk of schizophrenia. Nature 460(7256):744–747
Stidworthy MF, Genoud S, Li WW, Leone DP, Mantei N, Suter U et al (2004) Notch1 and Jagged1 are expressed after CNS demyelination, but are not a major rate-determining factor during remyelination. Brain 127(Pt 9):1928–1941
Tan AM, Colletti M, Rorai AT, Skene JH, Levine JM (2006) Antibodies against the NG2 proteoglycan promote the regeneration of sensory axons within the dorsal columns of the spinal cord. J Neurosci 26(18):4729–4739
Tanaka K, Nogawa S, Ito D, Suzuki S, Dembo T, Kosakai A et al (2001) Activation of NG2-positive oligodendrocyte progenitor cells during post-ischemic reperfusion in the rat brain. NeuroReport 12(10):2169–2174
Tanigaki K, Nogaki F, Takahashi J, Tashiro K, Kurooka H, Honjo T (2001) Notch1 and Notch3 instructively restrict bFGF-responsive multipotent neural progenitor cells to an astroglial fate. Neuron 29(1):45–55
Tawk M, Makoukji J, Belle M, Fonte C, Trousson A, Hawkins T et al (2011) Wnt/beta-catenin signaling is an essential and direct driver of myelin gene expression and myelinogenesis. J Neurosci 31(10):3729–3742
Tran AP, Warren PM, Silver J (2018) The biology of regeneration failure and success after spinal cord injury. Physiol Rev 98(2):881–917
Uranova N, Orlovskaya D, Vikhreva O, Zimina I, Kolomeets N, Vostrikov V et al (2001) Electron microscopy of oligodendroglia in severe mental illness. Brain Res Bull 55(5):597–610
Wang A, He BP (2009) Characteristics and functions of NG2 cells in normal brain and neuropathology. Neurol Res 31(2):144–150
Wang S, Sdrulla AD, DiSibio G, Bush G, Nofziger D, Hicks C et al (1998) Notch receptor activation inhibits oligodendrocyte differentiation. Neuron 21(1):63–75
Wang HN, Liu GH, Zhang RG, Xue F, Wu D, Chen YC et al (2015) Quetiapine ameliorates schizophrenia-like behaviors and protects myelin integrity in cuprizone intoxicated mice: the involvement of Notch signaling pathway. Int J Neuropsychopharmacol. https://doi.org/10.1093/ijnp/pyv088
Wang C, Zhang CJ, Martin BN, Bulek K, Kang Z, Zhao J et al (2017) IL-17 induced NOTCH1 activation in oligodendrocyte progenitor cells enhances proliferation and inflammatory gene expression. Nat Commun 8:15508
Xu X, Zhang A, Zhu Y, He W, Di W, Fang Y et al (2018) MFG-E8 reverses microglial-induced neurotoxic astrocyte (A1) via NF-kappaB and PI3K-Akt pathways. J Cell Physiol 234(1):904–914
Yang Z, Suzuki R, Daniels SB, Brunquell CB, Sala CJ, Nishiyama A (2006) NG2 glial cells provide a favorable substrate for growing axons. J Neurosci 26(14):3829–3839
Yoon K, Nery S, Rutlin ML, Radtke F, Fishell G, Gaiano N (2004) Fibroblast growth factor receptor signaling promotes radial glial identity and interacts with Notch1 signaling in telencephalic progenitors. J Neurosci 24(43):9497–9506
Young WJ, Smith SM, Chang C (1997) Induction of the intronic enhancer of the human ciliary neurotrophic factor receptor (CNTFRalpha) gene by the TR4 orphan receptor. A member of steroid receptor superfamily. J Biol Chem 272(5):3109–3116
Yuen TJ, Johnson KR, Miron VE, Zhao C, Quandt J, Harrisingh MC et al (2013) Identification of endothelin 2 as an inflammatory factor that promotes central nervous system remyelination. Brain 136(Pt 4):1035–1047
Zaucker A, Mercurio S, Sternheim N, Talbot WS, Marlow FL (2013) notch3 is essential for oligodendrocyte development and vascular integrity in zebrafish. Dis Model Mech 6(5):1246–1259
Zhang Y, Chen YT, Xie S, Wang L, Lee YF, Chang SS et al (2007) Loss of testicular orphan receptor 4 impairs normal myelination in mouse forebrain. Mol Endocrinol 21(4):908–920
Zhang Y, Argaw AT, Gurfein BT, Zameer A, Snyder BJ, Ge C et al (2009) Notch1 signaling plays a role in regulating precursor differentiation during CNS remyelination. Proc Natl Acad Sci USA 106(45):19162–19167
Zhang Y, Zhang H, Wang L, Jiang W, Xu H, Xiao L et al (2012) Quetiapine enhances oligodendrocyte regeneration and myelin repair after cuprizone-induced demyelination. Schizophr Res 138(1):8–17
Zhang R, Chopp M, Zhang ZG (2013) Oligodendrogenesis after cerebral ischemia. Front Cell Neurosci 7:201
Zhou YX, Armstrong RC (2007) Interaction of fibroblast growth factor 2 (FGF2) and notch signaling components in inhibition of oligodendrocyte progenitor (OP) differentiation. Neurosci Lett 421(1):27–32
Zhou YX, Flint NC, Murtie JC, Le TQ, Armstrong RC (2006) Retroviral lineage analysis of fibroblast growth factor receptor signaling in FGF2 inhibition of oligodendrocyte progenitor differentiation. Glia 54(6):578–590
Zhu X, Bergles DE, Nishiyama A (2008) NG2 cells generate both oligodendrocytes and gray matter astrocytes. Development 135(1):145–157
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