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·Review·

Coordinated control of oligodendrocyte development by extrinsic and intrinsic signaling cues

Li He[1], Q. Richard Lu[2]

[1]*Department of Pediatrics and Obstetrics/Gynaecology, Institute of Stem Cell and Developmental Biology, West China Second Hospital, Sichuan University, Chengdu 610041, China*

[2]*Department of Developmental Biology and Kent Waldrep Foundation Center for Basic Neuroscience Research on Nerve Growth and Regeneration, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA*

Corresponding author: Q. Richard Lu. E-mail: qrichard.lu@utsouthwestern.edu

Oligodendrocytes, the myelin-forming cells for axon ensheathment in the central nervous system, are critical for maximizing and maintaining the conduction velocity of nerve impulses and proper brain function. Demyelination caused by injury or disease together with failure of myelin regeneration disrupts the rapid propagation of action potentials along nerve fibers, and is associated with acquired and inherited disorders, including devastating multiple sclerosis and leukodystrophies. The molecular mechanisms of oligodendrocyte myelination and remyelination remain poorly understood. Recently, a series of signaling pathways including Shh, Notch, BMP and Wnt signaling and their intracellular effectors such as Olig1/2, Hes1/5, Smads and TCFs, have been shown to play important roles in regulating oligodendrocyte development and myelination. In this review, we summarize our recent understanding of how these signaling pathways modulate the progression of oligodendrocyte specification and differentiation in a spatiotemporally-specific manner. A better understanding of the complex but coordinated function of extracellular signals and intracellular determinants during oligodendrocyte development will help to devise effective strategies to promote myelin repair for patients with demyelinating diseases.

Keywords: oligodendrocyte; specification; differentiation; myelination; Shh, BMP, Notch and Wnt signaling; transcription factors; chromatin remodeling factors; HDAC; miRNAs

Introduction

Oligodendrocytes, the myelinating cells in the central nervous system, are important for the structural integrity of white matter and proper neuronal functions. Failure of remyelination or demyelination caused by injury or disease impairs the rapid conduction of action potentials, and this leads to axonal degeneration in demyelinating diseases such as multiple sclerosis (MS), periventricular leukomalacia, cerebral palsy, Pelizaeus–Merzbacher disease, metachromatic leukodystrophy and Alexander's disease[1,2]. At present, very little is known about which and how signaling pathways are perturbed in demyelinating disorders such as MS. Recent evidence indicates that there are common features in normal myelination and remyelination during brain development and myelin repair process after brain injury. In rodents, oligodendrocyte development involves multiple well-defined stages including oligodendrocyte precursor cell (OPC) specification from neural progenitor cells, OPC differentiation into immature oligodendrocytes (non-myelinating cells) and maturation into myelinating oligodendrocytes[3]. The progression of oligodendrocyte development is tightly controlled by both extracellular signals and intrinsic determinants in a specific spatial and temporal manner. Oligodendrocytes do not become myelin-producing cells until perinatal stages. Thus, a balance of positive and negative

signals controls the timing of oligodendrocyte maturation, with the final myelination of axons being actively opposed until all neuronal components of the developing central nervous system (CNS) are in place. In this review, we discuss recent findings on the signaling mechanisms through which these pathways mediate oligodendrocyte differentiation and myelination.

Extracellular Signals that Regulate Oligodendrocyte Development

Opposing Functions of Shh and BMP Signaling in Controlling OPC Specification in Early Developing Spinal Cord

Sonic hedgehog (Shh) is a secreted factor from the notochord and floor plate that controls neural subtype patterning in the ventral spinal cord in the mammalian CNS. Spinal cord explant studies have shown that Shh induces the specification of ventral neural cell types including motor neurons and oligodendrocyte precursors in the pMN (motor neuron progenitor) domain and ventral interneurons in the V0–V3 domains[4-7]. In a search for factors that are critical for glial cell differentiation, the oligodendrocyte-lineage regulators Olig1 and Olig2 were identified in response to glial formation cues (Fig. 1A)[8-10]. Shh in the ventral neural tube induces OPC specification. On the contrary, bone morphogenetic protein (BMP) and Wnt signals from the dorsal neural tube inhibit OPC generation and differentiation by activating negative regulators of oligodendrocyte differentiation such as Id2/4 and β-catenin (Fig. 1B). The downstream effector Gli1/2 proteins in Shh signaling are also required for OPC specification[11-13]. Gli2-null mice exhibit a severe reduction of ventral neuroepithelium-derived oligodendrocyte formation in the spinal cord, as indicated by the delayed expression of myelin genes[14]. In the experimental autoimmune encephalomyelitis (EAE) model, Gli1 is upregulated during the early inflammation period and mediates Shh-induced neural progenitor differentiation[15]. In the

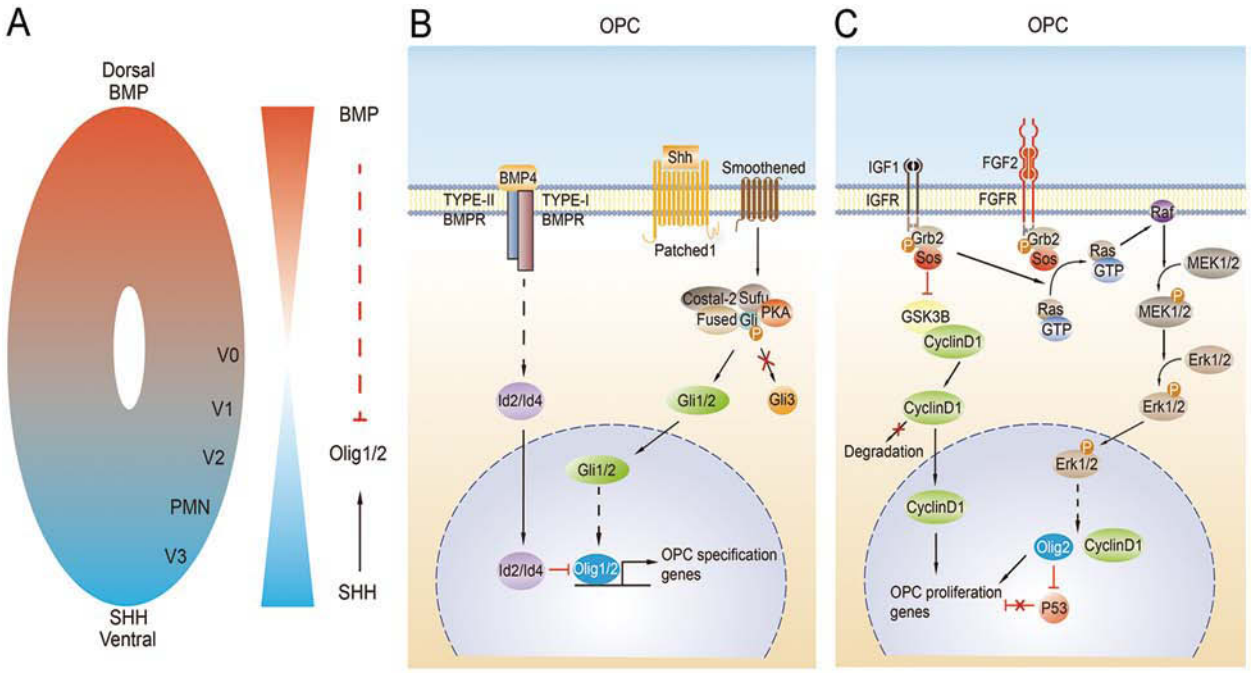

Fig. 1. Signaling regulation of OPC proliferation. A: The ventral SHH signal in the developing neural tube promotes oligodendrocyte precursor cell (OPC) generation in the pMN domain and V0–V3 domains by inducing Olig1/2 expression, and competes against the dorsal BMP signal. B: Ventral Shh-mediated activation of Gli1/2 and degradation of the Gli3 repressor contribute to the upregulation of Olig1/2. Dorsal BMPR signaling activates inhibitory Id2 and Id4 to block Olig1/2 activity. C: IGF and FGF stimulate OPC proliferation by promoting the expression of cyclin D1. IGF1 and FGF2 activate the Erk1/2 pathway, leading to the phosphorylation of Erk1/2 and their nuclear translocation, which activates Olig2 and Cyclin D1 to promote OPC proliferation. IGF1 represses GSK3β-mediated phosphorylation and degradation of Cyclin D1 to promote OPC proliferation.

presence of Shh, the full-length Gli proteins are resistant to proteolysis, and are processed into the active forms of Gli (Gli1/2) but not the repressive Gli (Gli3). Gli1/2 expression occurs in parallel with Shh during the induction of OPC genesis[16]; however, how and whether Gli1/2 regulate or interact with Olig1/2 have not been fully defined (Fig. 1B) .

Studies using pharmacological blocking of fibroblast growth factor 2 (FGF2) and Shh signaling suggest that Shh-mediated OPC specification mediates through the activation of FGF/FGFR signaling[17,18]. The Shh and BMP signaling pathways appear to control OPC specification by regulating Olig1/2 expression in the specialized domain of the neural tube during embryonic development, although the precise mechanisms of these two opposing signaling pathways in refining oligodendrocyte specification remain to be further defined.

Growth Factor Signaling in Oligodendrocyte Development

FGF and platelet-derived growth factor (PDGF) signaling FGF family members have distinct roles in regulating oligodendrocyte development by interacting with different FGF receptors. FGF2 appears to promote OPC proliferation from neural progenitor cells by upregulating Olig2 and PDGFRα[19]; however, it inhibits the subsequent OPC differentiation into mature oligodendrocytes[20,21]. FGF8 and FGF17 inhibit OPC differentiation *via* FGFR3[21], while FGF9 increases the process growth of differentiated oligodendrocytes *via* FGFR2[21]. FGF18 stimulates OPC proliferation but inhibits its further differentiation into mature oligodendrocyte *via* FGFR2 and FGFR3[21]. The induction of OPC specification by FGFs is thought to depend on activation of the MAPK kinase cascade (Fig. 1C)[17,22], although individual FGFs may function through different mechanisms.

PDGF-AA is an essential mitogen for OPC proliferation, as shown by both overexpression and loss-of-function studies[23,24]. Its receptor PDGFRα is restricted to OPCs in the developing and adult CNS[6,25,26]. Activation of PDGFRα kinase induces OPC proliferation by stimulating the MAP kinase, phosphatidylinositol 3-kinase (PI3K) and phospholipase C gamma (PLCγ) pathways[27]. In addition, PDGF promotes OPC proliferation by activation of alpha 6 beta 3 (α6β3) integrin signaling[28].

FGF signaling maintains the level of PDGFRα in OPCs[29]. The growth factors FGF and PDGF cooperate to promote rapid OPC division, but inhibit their differentiation and maturation[30]. FGF and PDGF act on OPC proliferation by activating multiple kinases such as p42/p44, p38 MAPK and p70 S6 kinases[31]. However, studies of oligodendrocyte myelination and remyelination indicate distinct roles for PDGF and FGF2 in the oligodendrocyte maturation process at different stages and in spontaneous remyelination[32,33]. The underlying mechanisms for the divergent functions of FGF and PDGF in the process of stage-specific myelination and remyelination remain to be defined.

IGF-1 signaling pathway positively regulates OPC proliferation and differentiation Insulin-like growth factor (IGF) was first reported to stimulate lipid metabolism in oligodendrocyte-enriched glial culture similar to insulin[34]. Mice with specific deletion of IGF1R in oligodendrocyte-lineage cells exhibit a reduced number of OPCs and mature oligodendrocytes, but current analysis cannot determine whether the reduction of mature oligodendrocytes is a consequence of progenitor deficiency or just OPC differentiation failure[35]. *In vivo* gain-of-function studies by overexpressing IGF-1 driven by metallothionein I promoter in the brain suggest that IGF-1 promotes OPC differentiation[36,37]. Moreover, IGF-1 is also reported to synergize with FGF2 to promote OPC proliferation, probably through the activation of cyclin D1[38,39]. A more recent study found that FGF2 activates the Erk1/2 (p44/p42 MAPK) pathway to enhance Cyclin D1 expression, while the presence of IGF-1 activates the PI3K/AKT pathway to phosphorylate GSK-3β, thus promoting the nuclear localization of Cyclin D1 (Fig. 1C)[40]. Furthermore, IGF-1 is reported to play an instructive role in promoting oligodendrocyte differentiation from neural progenitor cells, partially by negatively regulating BMP signaling[41].

Extracellular Matrix (ECM) and Integrin Signaling in OPC Survival and Migration

Migration of oligodendrocytes to the appropriate location ensures axonal contacts and ensheathment. This process is regulated by a variety of ECM components that provide correct migration instructions. For example, laminin-2, an ECM molecule, enhances myelin membrane formation in cultured oligodendrocytes[42]. Integrins, a group of receptors on the cell surface, recognize the ECM signals and generate secondary responses associated with cell motility, survival and growth[43]. The α6β1 integrin is expressed in

OPCs but not in differentiated oligodendrocytes, suggesting a potential role in OPC migration[44]. In addition, lack of α6β1 integrin leads to increased oligodendrocyte apoptosis[43,45]. α6β1 is associated with PDGFRα on the lipid raft of OPCs and activates PDGF signaling through PI3K to promote the proliferation and survival of oligodendrocytes[46]. On the other hand, α6 integrin forms a complex with proteolipid protein (PLP) and glutamate (AMPA or kainic acid) receptors through the N-terminal motif of the cytoplasmic domain and therefore reduces the interaction with the ECM and enhances OPC migration[47], suggesting an important role of α6β1 integrin in OPC proliferation and migration.

Wnt Signaling Inhibits OPC Maturation

Wnt signaling was first reported to prevent OPC differentiation *in vitro* since Wnt3A treatment inhibits OPC maturation[48]. Activation of β-catenin or ablation of adenomatous polyposis coli (APC), a negative regulator of Wnt signaling, results in severe defects in developmental myelination and remyelination, indicating that Wnt/β-catenin negatively regulate OPC differentiation[49,50]. Interestingly, the β-catenin effector TCF7L2/TCF4 is highly enriched in early-differentiating oligodendrocytes, but is downregulated in mature oligodendrocytes[49]. During remyelination after lysolecithin-mediated demyelination, TCF7L2 expression is also found in OPCs in the lesion penumbra[50,51]. However, the exact role of TCF7L2 in regulating the timing of the oligodendrocyte differentiation transition and remyelination remains to be further defined.

TCF7L2 partners with β-catenin in the nucleus to activate target genes. Disruption of this interaction or blocking the nuclear entry of β-catenin releases the inhibitory effect of Wnt signaling on OPC maturation. As expected, the competitive interaction of TCF7L2 with histone deacetylases (HDACs) and β-catenin enables HDAC1/2 to substitute for β-catenin in the binding of TCF7L2, thus switching TCF7L2 from a negative regulator to a positive regulator of OPC differentiation (Fig. 2)[49]. In addition, activation of Axin2, a key component in the APC disruption complex for β-catenin degradation, by inhibiting Tankyrase, accelerates OPC differentiation and remyelination after white matter injury[52]. Wnt3A treatment upregulates the differentiation inhibitor Id2 to block oligodendrocyte differentiation[49]. Since Id2 is a direct target of the β-catenin/TCF4 complex[53,54], Wnt/β-catenin/TCF7L2 signaling inhibits OPC differentiation probably by inducing differentiation inhibitors such as Id2 (Fig. 2). A recent study showed that β-catenin is expressed in both OPCs and oligodendrocytes in culture[51], and it remains to be determined whether β-catenin has a temporally-specific function in regulating oligodendrocyte differentiation.

Divergent Effects of Notch Signaling on OPC Development

Notch signaling has been shown to regulate different phases of oligodendrocyte development. Activation of Notch signaling in neural progenitor cells instructs glial fate specification, including OPC formation, while inhibiting neuronal differentiation[55,56], but continued activation of Notch signaling in OPCs prevents oligodendrocyte differentiation. Notch1/2/3 receptors are found in OPCs and oligodendrocytes[57]. When co-cultured with cells expressing Jagged1 or Delta1, ligands for Notch1, OPCs fail to differentiate into mature oligodendrocytes[58]. Consistently, the Notch signaling effectors Hes1 and Hes5 function as negative regulators of OPC differentiation[58-60]. Intriguingly, in the presence of the Notch ligand F3/contactin, Notch signaling activated by F3/contactin has a positive effect by promoting the expression of differentiation markers in an oligodendrocyte cell line (OLN93) and OPCs in culture by activating Deltex components[61]. These different effects mediated by distinct ligands on OPC differentiation need to be further clarified. Nonetheless, deletion of Notch1 enhances oligodendrocyte differentiation[59] and remyelination after LPC-induced injury[62], suggesting that Notch1 signaling plays an inhibitory role in oligodendrocyte maturation.

The Notch effectors Hes1 and Hes5 function in at least two ways: first, to act as transcriptional repressors to inhibit gene transcription; and second, to form heterodimers with other pro-myelinating basic helix-loop-helix (bHLH) factors to sequester their activity. Hes5 binds to the promoters of myelin genes in OPCs and inhibits their expression by recruiting the repressor complex containing HDACs. Hes5 inhibits the transcription of Sox10, a critical regulator of oligodendrocyte differentiation, and other myelin gene activators[60]. It is possible that Hes1/5 interact directly with Olig1/2 to prevent them from binding to specific myelin genes. Post-translational modification of bHLH factors such as phosphorylation of Olig2 or Hes1/5 appear to determine their cofactor-binding preference, and control the switching of the progenitor cell fate to oligodendrocytes instead of motor neurons[63].

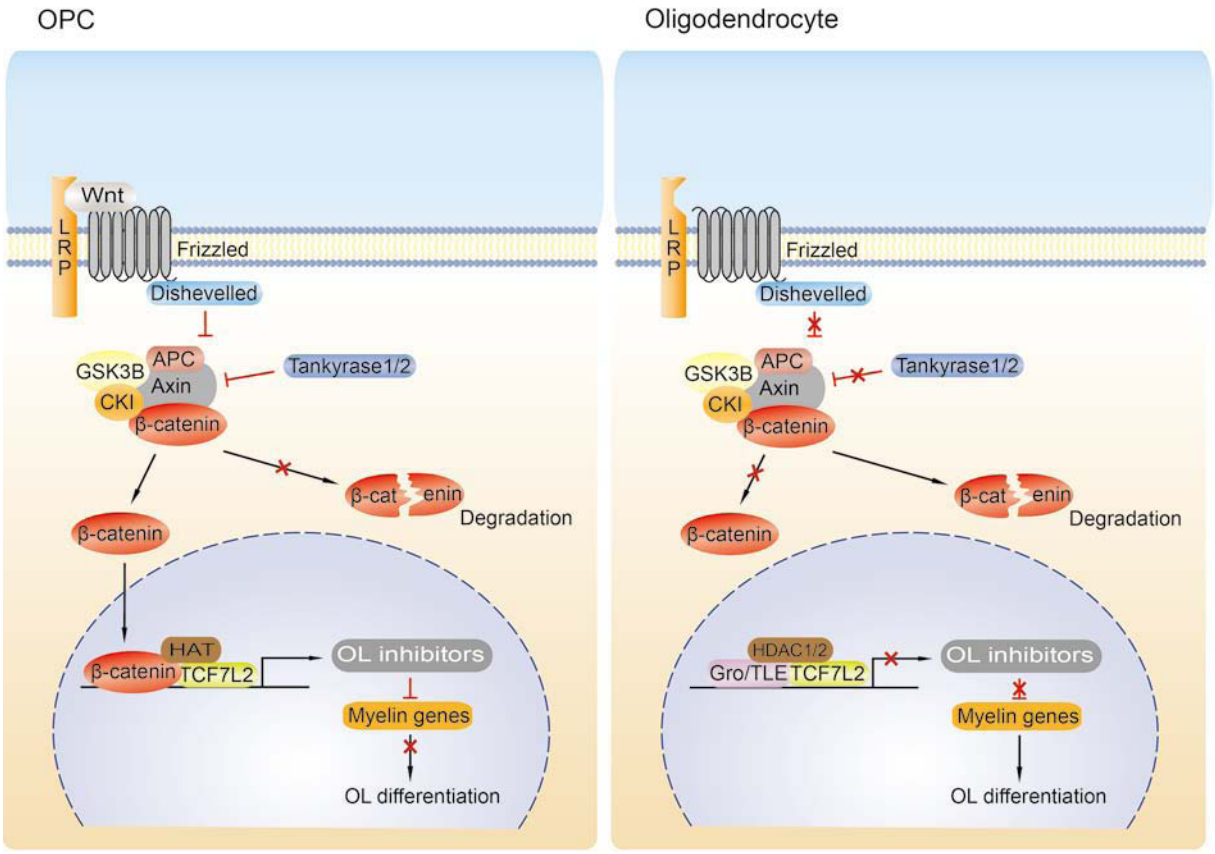

Fig. 2. Wnt signaling in oligodendrocyte development. When the extracellular Wnt binds to its receptor Frizzled, the receptor-associated protein Dishevelled is activated to inhibit the cytoplasmic protein complex of Axin, APC, and Gsk3β. Then the key component β-catenin is no longer phosphorylated and degraded, but enters the nucleus, where, in collaboration with TCF7L2/TCF4, it promotes the expression of differentiation inhibitors. On the contrary, when cells no longer receive Wnt signals, the β-catenin is degraded in the cytoplasm. In addition, TCF7L2 interacts with Gro/TLE, recruiting Hdac1 and Hdac2 to compete with β-catenin/TCF binding and therefore represses the expression of inhibitors to promote myelination.

BMP–Smad Signaling Negatively Regulates Oligodendrocyte Differentiation and Myelination

BMPs are a group of growth factors belonging to the TGF-β superfamily. Dorsally-derived BMPs such as BMP4 antagonize the ventral Shh signal to control the specification of oligodendrocyte progenitors in the spinal cord[64,65]. Blocking the activity of BMP signaling can facilitate OPC differentiation by elevating the expression of myelin genes[66], while overexpression of BMP4 under the neuron-specific enolase promoter in transgenic mice causes a remarkable increase in the density of astrocytes at the expense of OPCs[67]. BMP4 treatment of the progenitors of the embryonic lateral ganglionic eminence leads to upregulation of the HLH factor Id (inhibitor of differentiation protein)[68]. Id2 and Id4 directly interact with Olig1 and Olig2, leading to their nucleus-to-cytoplasm translocation. This interaction may prevent Olig1 and Olig2 from entering the nucleus and inhibit the expression of target genes such as myelination-related genes[68].

Activation of Id2 and Id4 by BMPs may mediate through Smad effectors[69-71] such as the BMP receptor-regulated Smads (R-Smad) including Smad1, Smad5, and Smad8. Smad4 is known as a co-Smad, which partners with R-Smads to regulate gene expression. Negative feedback regulation of BMP signaling is controlled by inhibitory Smad proteins such as Smad6 and Smad7, which interact with active phosphorylated R-Smads to block their nuclear translocation and recruit E3 ligase Smurf1/2 to provoke BMP receptor degradation (Fig. 3)[72]. Treatment with BMP2

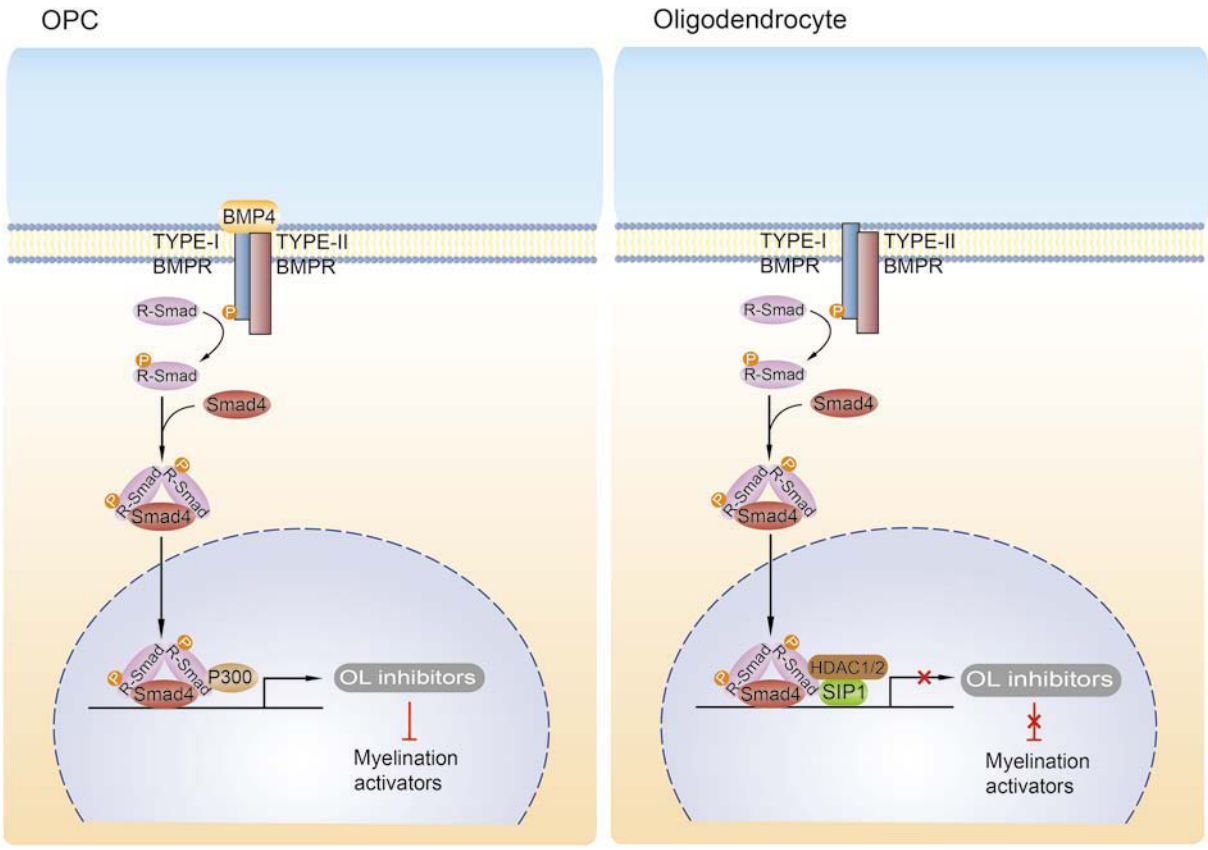

Fig. 3. BMP signaling in oligodendrocyte differentiation. In OPCs, BMP/BMPR–Smad signaling recruits histone acetyltransferases (HATs/p300) to activate their effectors, e.g. Id2 and Id4, which sequester Olig1/2 factors and block their functions, probably by translocating them to the cytoplasm. But during the transition of OPCs into oligodendrocytes, Sip1 is upregulated by Olig1 and Olig2. Sip1 might recruit the HDAC1/2-NuRD (nucleosome remodeling and histone deacetylation) complex to inhibit the activation of BMP–Smad signaling by disrupting p300 association with the activated R-Smad complex. In addition, Sip1 activates I-Smad Smad7 expression, which further inhibits BMP–Smad signaling, therefore promoting oligodendrocyte differentiation.

or BMP4 blocks OPC differentiation by upregulating phosphorylated Smad1/5/8 and Id4, suggesting that activation of the BMP/Smad/ID signaling axis represses oligodendrocyte differentiation[73]. A recent study demonstrated that the BMP/R-Smad/Smad4/p300 complex directly targets and activates the expression of differentiation inhibitors to repress the myelination program (Fig. 3)[74]. Antagonizing BMP signaling with chordin and noggin could be an effective treatment to promote myelin repair after demyelinating injury[75].

Lingo-1 Pathway Inhibits Oligodendrocyte Differentiation and Myelination

Lingo-1 (leucine-rich repeat and Ig domain-containing 1) is expressed in both neurons and oligodendrocytes. Oligodendroglial Lingo1 inhibits axonal growth by interacting with Nogo receptor NgR (Nogo66 receptor)/P75[76,77]. Attenuation of its function *in vitro* leads to increased oligodendrocyte differentiation and maturation *via* the activation of Fyn tyrosine kinase and downregulation of RhoA activity[78]. Lingo-1 knockout mice exhibit precocious axonal myelination in neonatal stages[78], and Lingo-1 antagonists appear to promote remyelination in the EAE model of MS[79-81]. However, whether the effects in EAE are due to the function of Lingo-1 in oligodendrocytes, neurons or immune cells remains to be elucidated.

Activation of GPR17 Signaling Inhibits Terminal Myelinogenesis

GPR17 (G protein-coupled receptor 17) is a newly-identified

GPR for oligodendrocyte myelination. The expression of GPR17 is mainly restricted to oligodendrocyte-lineage cells rather than other neural cell types such as neurons[82,83]. Both *in vivo* and *in vitro* expression studies indicate that GPR17 is present in the early stages of oligodendrocyte differentiation and is downregulated in mature oligodendrocytes[83,84]. GPR17 overexpression in CNP-positive differentiating oligodendrocytes in transgenic mice prevents terminal myelination and myelin assembly[83]. This negative effect is likely through promoting the nuclear translocation of the oligodendrocyte inhibitors Id2 and Id4, thus reducing the activity of the positive transcription factors Olig1 and Olig2. Conversely, GPR17 deficiency results in accelerated OPC differentiation and myelination *in vitro* and *in vivo*[83]. Thus, GPR17 may function as a signaling timer to control oligodendrocyte differentiation and myelin assembly. GPR17 expression is upregulated in the penumbra of demyelinating lesions in EAE[83], although its precise role in controlling oligodendrocyte remyelination remains to be further elucidated.

Intrinsic Regulators of Oligodendrocyte Development

bHLH Factors Olig1/2—Key Regulators of Oligodendrocyte Development

Olig genes were firstly discovered as oligodendrocyte-lineage genes in the developing neural tube[8,9]. Their restricted expression pattern in the ventral neural tube is regulated by SHH (Fig. 1A)[8,9]. Loss-of–function studies demonstrated that both Olig1 and Olig2 are required for oligodendrogenesis throughout the CNS[85,86]. Olig2 is necessary for the specification of oligodendrocyte progenitors and their differentiation[85,87,88]. While Olig1 is not required for OPC formation, Olig1-null mutants exhibit a defect in OPC differentiation and maturation[85,89]. Olig1 cooperates with Sox10 to promote myelin gene expression[90]. The two Olig1 single-knockout mice [Olig1Cre-neo (-/-) and Olig1Cre (-/-)] exhibit different extents of phenotypic severity in oligodendrocyte myelination[85,89]. Olig1Cre-neo (-/-) mice show a delayed myelination phenotype[85], while Olig1Cre (-/-) mice derived from the Olig1Cre-neo strain after removing the neomycin (neo)-targeting cassette develop severe myelination deficits[89]. At present, the exact reason for the phenotypic severity in these mice is not known. Perhaps it is due to the impact of the neo cassette on the expression of neighboring genes or noncoding RNAs, or the Olig1 promoter activity for Cre expression, or differences in the mouse background.

Nuclear translocation of Olig1 during the remyelination phase promotes myelin repair after demyelination induced by lysolecithin or cuprizone[91,92]. The molecular mechanism by which Olig1/2 regulate oligodendrocyte development is not yet fully understood. A genome-wide ChIP-sequencing study using purified OPCs and oligodendrocytes at different differentiation stages indicate that Olig2 targets specific enhancers that regulate oligodendrocyte-lineage progression[93]. These studies further revealed that Olig2 is a pre-patterning factor that directs the recruitment of chromatin remodelers such as the ATP-dependent chromatin remodeling BAF complex (Brg1/Brm-associated factors) to oligodendrocyte lineage-specific *cis*-regulatory enhancers during the critical transition from OPCs to immature oligodendrocytes (Fig. 4)[93]. These studies provide important insights into the molecular mechanism by which Olig2, a factor long known to be involved in the oligodendrocyte lineage, acts to regulate the development of this lineage. However, the mechanisms of how Olig1/Olig2 work with other stage-specific co-factors during oligodendrocyte-lineage progression remain elusive. Olig2 may interact with different lineage-specific transcriptional cofactors to control cell specification and differentiation, since Olig2 is reported to be a modulator of oligodendrogenesis, astrogliogenesis and neurogenesis[85,86,94-96]. Post-transcriptional modifications of Olig2, such as by phosphorylation at different conserved sites, have been shown to control the switch between motor neuron formation and oligodendrogenesis. The dephosphorylated state of Olig2 is required to promote OPC formation[63,97]. Thus, Olig2 exerts its functions by association with linage-specific transcription factors and/or through post-translational modifications to control cell-fate specification and lineage progression.

MRF—a Critical Factor for Oligodendrocyte Differentiation and Myelination

Myelin gene regulatory factor (MRF), also called gene model 98, is expressed in postmitotic oligodendrocytes, preceding and in parallel with the expression of major myelin genes (PLP and MBP). Ablation of MRF leads to the

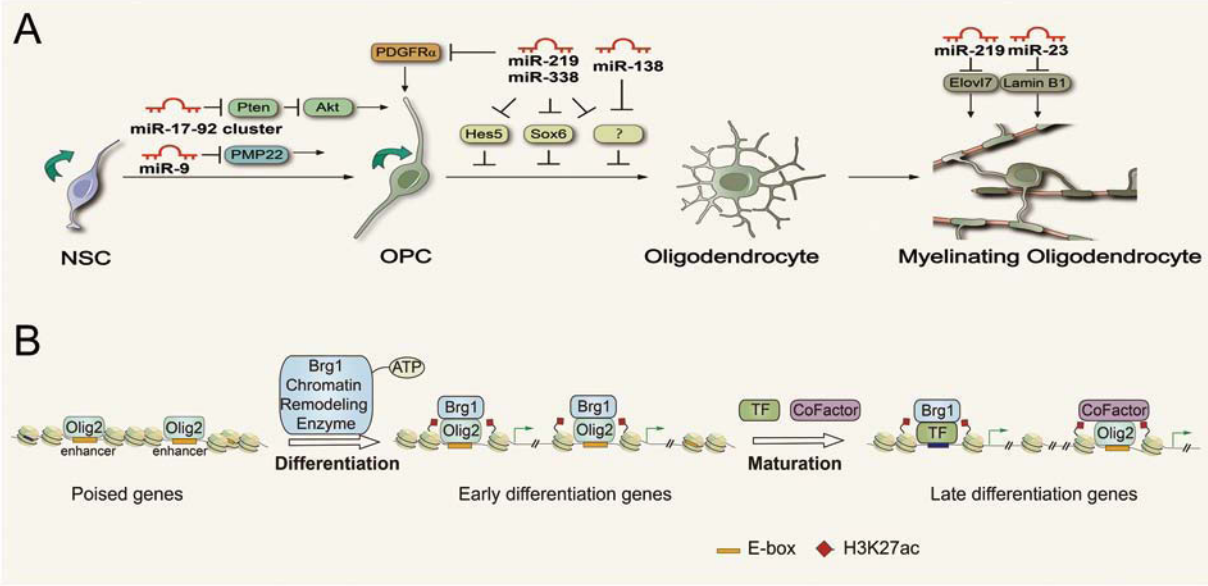

Fig. 4. Epigenetic miRNA and chromatin remodeling control of oligodendrocyte differentiation. A: During oligodendrocyte development, MiR-9 and MiR-17-92 regulate OPC identity and survival by targeting PMP22 and Pten, respectively. During the transition to OPC differentiation, MiR-219 and MiR-338 target differentiation inhibitors (e.g. Sox6 and Hes5), OPC proliferation signaling (PDGFRα) and pro-neural factors. At the terminal oligodendrocyte differentiation, MiR-219 and MiR-23 target Elovl7 and Lamin B1, respectively, to promote myelinogenesis. B: At the onset of oligodendrocyte differentiation, Olig2 recruits chromatin remodelers such as Brg1 to oligodendrocyte-lineage enhancers and activates differentiation-promoting genes (e.g. Sox10 and MRF). At later differentiation stages, Brg1- and Olig2-targeting redistributes to the distinct promoters and, in cooperation with other unidentified factors, regulates the genes required for the complex morphogenesis of oligodendrocytes.

decreased expression of many myelin genes (PLP, MAG, MBP, and MOG) in mice, while overexpression of MRF promotes myelin gene expression. Mice lacking MRF display a failure of myelin gene expression and subsequent myelination, and cannot survive due to severe neurological abnormalities[98,99]. However, premyelinating oligodendrocytes are spared in MRF-knockout mice, indicating that MRF is not essential for the early differentiation events but is crucial for terminal differentiation. However, the precise mechanisms by which MRF regulates myelin genes require further investigation.

Zfp488—an Oligodendrocyte-Specific Differentiation Regulator

Zfp488 is an oligodendrocyte-specific zinc finger transcription factor that was identified through gene profiling of downregulated genes in the CNS of an Olig1-null strain[100]. Its expression pattern parallels the well-known myelin genes and is restricted to differentiated oligodendrocytes. Enforced expression of Zfp488 in the chick neural tube promotes OPC formation in the presence of active Notch signaling, and induces ectopic and precocious oligodendrocyte differentiation in the presence of Olig2. RNAi-mediated Zfp488 knockdown decreases myelin gene expression, indicating that Zfp488 is crucial for normal oligodendrocyte differentiation[100]. A recent study showed that retrovirus-mediated Zfp488 overexpression promotes remyelination after cuprizone-induced demyelination in mice by enhancing the oligodendrocyte differentiation of neural stem/progenitor cells in the subventricular zone[101]. These studies suggest that Zfp488 plays a role in promoting myelination and remyelination.

Sip1 (Zfhx1b/Zeb2)—a Critical Factor for Oligodendrocyte Differentiation and Myelination

During a ChIP-sequencing and gene-profiling search for the downstream effector(s) regulated by both Olig1 and Olig2 that may coordinate the inhibitory pathways to promote myelination, a common target gene has been identified as Smad-interacting protein-1 (Sip1) [also named zinc finger

homeobox protein 1b (Zfhx1b) or Zeb2][74]. Sip1 inhibits the BMP–Smad negative regulatory pathway while activating the expression of crucial myelination-promoting factors[74].

Sip1 is enriched in differentiated oligodendrocytes but weakly expressed in OPCs in the white matter of brain and spinal cord, while its expression is significantly downregulated in Olig1- and Olig2-null mice. Oligodendrocyte lineage-specific Sip1-knockout mice exhibit a severe failure of myelin sheath formation without affecting OPC proliferation, indicating that Sip1 is required for the transition of OPCs to myelinating oligodendrocytes.

Sip1 can form a co-repressor complex with NuRD including HDAC1/2[102]. Sip1 blocks the transcriptional activation by BMP/Smad signaling of differentiation inhibitors such as Id2, Id4, Hes1, Hes5 and BMPR1a at both the BMP receptor and its downstream effectors (Fig. 3). This effect of Sip1 might be through the HDAC1/2–NuRD complex to inhibit the activation of BMP–Smad signaling by disrupting the association of p300 with the activated R-Smad complex, thus antagonizing the inhibitory action of BMP signaling on OPC differentiation[74]. Gene profiling analysis of down-regulated genes in Sip1 mutants further identified Smad7, a member of the inhibitory Smads (I-Smads) in the Smad pathway, as a key target induced by Sip1. Smad7 is highly enriched in oligodendrocytes both *in vivo* and *in vitro*, in contrast to the second I-Smad gene, Smad6, whose mRNA is hardly detectable in oligodendrocytes. Forced expression of Smad7 not only inhibits BMP signaling in OPCs, but also leads to the downregulation of β-catenin levels through a mechanism involving Smad7 and its cognate E3 ubiquitin ligase Smurf1, suggesting that Smad7 can block both the BMP and β-catenin negative regulatory pathways for oligodendrocyte differentiation. Furthermore, overexpression of Smad7 partially rescues the oligodendrocyte differentiation defects caused by Sip1 loss. Thus, by antagonizing the activation of BMP receptor–Smad signaling while inducing negative feedback by Smad7, Sip1 exerts dual-mode regulation of the Smad signaling pathway to control oligodendrocyte maturation (Fig. 3). It is worth noting that single-gene mutations in *SIP1/ZFHX1B* in humans cause Mowat-Wilson syndrome (MWS), displaying delayed myelination and motor development, seizures and epilepsy. The critical role of Sip1 in CNS myelination through oligodendrocyte lineage-specific mutagenesis suggests that mutations in *SIP1/ZFHX1B* contribute to the delayed myelination and white matter defects seen in patients with MWS[74].

Epigenetic and Chromatin Remodeling Control of Oligodendrocyte Development

Recently, epigenetic and chromatin remodeling events have been shown to be critical for oligodendrocyte differentiation. The several types of epigenetic mechanisms include DNA methylation, histone modification by HDACs and HATs, chromatin remodeling mediated by ATP-dependent SWI/SNF complex subunits, and post-translational silencing by noncoding RNAs such as small-noncoding RNAs.

HDACs Nucleus-expressing class I HDACs such as HDAC1 and HDAC2 are essential for OPC differentiation as well as myelination both *in vitro* and *in vivo*[103,104]. They are also required for the remyelination after demyelination induced by cuprizone, and this effect is age-dependent. A failure of recruitment of HDAC1 and HDAC2 to myelin gene promoters in old animals decreases the myelination potential[105]. Further genetic investigation showed that HDAC1 and HDAC2, but not individual HDACs, are required for myelination in mice[49]. Activation of the canonical Wnt/β-catenin pathway in HDAC1/2 double mutant mice contributes to the inhibition of oligodendrocyte differentiation. The Wnt/β-catenin effector TCF7L2 has been identified as an oligodendrocyte lineage-specific transcription factor and is critical for oligodendrocyte differentiation and perhaps remyelination[49,50]. This study further indicates that binding of HDAC proteins and β-catenin to TCF7L2 switches it from a repressor to an activator of oligodendrocyte differentiation (Fig. 2). Therefore, HDAC1/2 regulate oligodendrocyte differentiation, at least in part, by inhibiting Wnt signaling through disrupting β-catenin–TCF interactions [49]. At present, the roles of other HDACs in oligodendrocyte myelination remain to be defined. HDAC11 is reported to regulate oligodendrocyte-specific gene expression in an oligodendroglial cell line[106]. In Schwann cells, a member of the Sirtuin family of NAD^+-dependent deacetylases, Sirt2, regulates myelin formation by deacetylating Par-3, a key regulator of cell polarity[107]. In the CNS, Sirt2 is expressed throughout the oligodendrocyte lineage, and is associated with myelin[108,109], although its function in myelination is unknown. Loss of *Sirt2* in *Plp*-null mice suggests that PLP/DM20 is required for the transport of Sirt2 into the myelin compartment[110]. Currently, whether and how HATs regulate

oligodendrocyte development are not fully understood.

MicroRNAs in oligodendrocyte differentiation miRNAs function mainly to inhibit gene expression by forming an RNA-induced silencing complex at the perfectly or imperfectly corresponding bases in the 3' untranslated regions of target genes. In this way, they reduce the final output of target genes at the post-transcriptional level. MiR-23 is a negative regulator of lamin B1, overexpression of which causes severe myelin loss[111]. MiR-219 and MiR-338 are crucial for oligodendrocyte differentiation, and target oligodendrocyte differentiation inhibitors (e.g. Sox6 and Hes5) and OPC proliferation factors (PDGFRα) or neurogenesis-promoting factors (e.g. FoxJ3 and Zfp238) (Fig. 4)[112-114]. Recently, miR-7a was shown to induce OPC specification but not neuronal specification by directly targeting proneural genes (Pax6 and NeuroD4), but also prevent further OPC differentiation by repressing differentiation regulators[115]. However, the role of miRNAs in oligodendrocyte development *in vivo* remains to be further defined by gene-targeting in animals. Recently, small non-coding RNA 715 (snc715) was reported to regulate myelin basic protein synthesis[116]. How miRNA expression is regulated in a temporal-spatial manner and the upstream regulators remain to be discovered.

ATP-dependent chromatin remodeling Smarca4/Brg1 complex in myelination In an effort to map the global gene transcripts that are activated at different stages, the Smarca4/Brg1 gene, encoding the central catalytic ATPase subunit of the SWI/SNF chromatin-remodeling complex, has been identified as the most significantly-targeted gene by RNA polymerase II (RNAPII) at the onset of oligodendrocyte differentiation[93]. The Brg1 chromatin remodeler, which is upregulated in differentiated oligodendrocytes, is both necessary and sufficient to activate the expression of myelination-associated genes and oligodendrocyte-lineage progression. The ATP-dependent SWI/SNF chromatin remodeling complex BAF acts as a positive regulator of oligodendrocyte differentiation. Remarkably, Brg1 targeting specificity and activity on the enhancers is transcriptionally pre-patterned by Olig2 to precisely initiate and establish the transcriptional program that promotes oligodendrocyte differentiation and myelination[93] (Fig. 4).

In the peripheral nervous system, Brg1 is recruited by Sox10 to the promoters of Oct6 and Krox20, the key transcription factors in Schwann cell differentiation, and stimulates myelin gene expression[117]. In addition, NF-kB forms a complex with Brg1 to regulate Schwann cell differentiation, suggesting a critical role of Brg1 in regulating central and peripheral myelination[118]. Other ATP-dependent chromatin remodeling complexes such as CHD4 are also reported to control myelination in the periphery[119].

Genome-wide targeting at multiple developmental stages has uncovered a temporally-regulated mechanism of Olig2-directed Brg1 targeting in controlling stage-specific transcriptional programs for oligodendrocyte-lineage initiation and maturation[93]. These data suggest a stage-specific switch of Brg1 targeting in the regulation of distinct sets of genes from initiating the differentiation process to maintaining the differentiation state during lineage progression (Fig. 4). At the onset of oligodendrocyte differentiation, Brg1 targets the enhancers of differentiation-promoting genes such as Sox10 and MRF, while at late stages of differentiation, Brg1 appears to redistribute to distinct target-enhancers critical for cytoskeletal reorganization and curvature-dependent actin polymerization, which are required for complex morphogenesis during myelination (Fig. 4). These studies suggest that the dynamic distribution of chromatin-remodeler targeting controls stage-specific oligodendrocyte lineage progression[93]. The identification of stage-specific enhancers at the genome-wide level has unveiled sets of regulatory factors that control oligodendrocyte development. These genome-wide multiple-stage studies indicate that activation of ATP-dependent chromatin-remodeling complexes and the regulation of Brg1 functional specificity by Olig2 coupled with transcriptionally-linked chromatin modifications are critical steps to precisely initiate and establish the transcriptional program for promoting oligodendrocyte differentiation[93].

Summary

Understanding the molecular mechanisms that control oligodendrocyte myelination will provide effective treatment strategies and options to promote myelin repair for neurological disorders ranging from MS, cerebral palsy and spinal cord injury, to later-onset diseases including Parkinson's and Alzheimer's. The proliferation, differentiation, and process extension of oligodendrocytes to form myelin that ensheaths axons require the coordinated control of extracellular signals and intracellular responsive elements. In this review, we discuss the spatiotemporal coordination of distinct signaling pathways and their intracellular effectors

in controlling oligodendrocyte differentiation. Although many identified signals appear to inhibit oligodendrocyte maturation, such as the BMP, Wnt and Notch signaling pathways, myelination-promoting signaling pathways remain poorly defined. Although the functions of intracellular regulators such as ATP-dependent SWI/SNF chromatin-remodeling complexes and miRNAs in oligodendrocyte differentiation are beginning to be elucidated, our current understanding of the mechanisms of oligodendrocyte myelination is still in its infancy, and knowledge about the functional links between extracellular signals and chromatin/transcriptional regulators remains scant. Although curative treatments for demyelinating diseases currently elude our grasp, understanding the signaling pathways and their effectors during oligodendrocyte myelination will facilitate dissection of the disease etiology and eventually provide the framework and strategy for the treatment of neurological disorders associated with demyelination.

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