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Two-tier transcriptional control of oligodendrocyte differentiation

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Abstract

Oligodendrocytes (OLs) are the myelin-forming cells of the central nervous system (CNS). They differentiate from proliferative OL precursor cells that migrate from the embryonic neuroepithelium throughout the developing CNS before associating with axons and elaborating myelin. Recent research into the regulation of OL differentiation has uncovered a two-stage mechanism of transcriptional control that combines epigenetic repression of transcriptional inhibitors with direct transcriptional activation of myelin genes. This ‘two-pronged’ approach creates a fail-safe system of genetic control to ensure orderly and unambiguous expression of the myelination program during development and during repair of demyelinated lesions.

Introduction

Oligodendrocytes (OLs), the myelinating cells of the central nervous system (CNS), are generated from migratory oligodendrocyte precursors (OLPs) that start life as pluripotent neuroepithelial precursors (NEPs) in the ventricular zone of the embryonic neural tube [1,2]. Regionally restricted signalling molecules (e.g. SHH and BMPs) act on NEPs to initiate OLP development. Mitogens and chemo-attractants (e.g. PDGF and FGF) act on OLPs, causing them to proliferate and migrate away from the ventricular zone throughout the developing CNS. At their final resting sites, signals in the local environment trigger OLPs to associate with axons and differentiate into myelinating OLs. At each stage, the transcriptional machinery and the chromatin state of OLPs become modified to activate or repress specific programs of gene expression. This review focuses on the transcriptional control of terminal OL differentiation and execution of the myelination program.

OL differentiation has been regarded as a default program, because OLPs cultured in defined medium without mitogens can exit the cell cycle, change shape and express myelin proteins in the absence of axons [3]. This simple observation suggests a model of OL differentiation that is based on de-repression of a constitutively repressed state. A ‘de-repression’ model is increasingly supported by the molecular evidence and also fits with more general ideas about how neural cell types are determined in the developing neural tube [4]. A picture is emerging of a two-step mechanism of transcriptional control. First, transcriptional repressors of myelin genes are inactivated by physical sequestration and/or by histone modification and chromatin condensation. Second, positive activators of myelin gene transcription are brought into play. This ‘de-repression/activation’ system of transcriptional regulation presumably ensures that

OL lineage progression takes place in an orderly sequence, preventing differentiated patterns of gene expression from being induced prematurely or in the wrong cells. Moreover, compacting and silencing early stage genes as an integral part of the differentiation program makes for an inherently robust and stable system, designed to maintain the differentiated OL phenotype over the lifetime of the organism. We have attempted to organise this article along parallel lines, first outlining transcriptional repression/de-repression, then activating the myelination program. We apologise to those whose work has been omitted because of space constraints.

Transcriptional repression of the myelination program

Notch/Hes pathway—In OLPs, Notch signalling can be activated by Jagged-1, a membrane-bound Notch ligand that is present on CNS axons [5]. Notch signalling is generally believed to repress OL differentiation. Conditional Notch-1 knockout in OL lineage cells led to premature OL differentiation in grey matter of the mouse spinal cord [6] and Notch-1 (+/−) mutant mice displayed increased myelin basic protein (MBP) and proteolipid protein (PLP) expression at postnatal day 15 (P15) and P35 [7]. A repressive role for Notch in Schwann cells has also been reported recently [8].

It is likely that Notch acts through transcriptional repression. Indeed HES5, a downstream target of Notch signalling, is a powerful repressor of myelin gene expression [9]. It represses Mbp transcription directly, by forming repressive complexes with histone deacetylases (HDACs) and indirectly, by inhibiting transcription of activators such as ASCL1 and by physical sequestration of SOX10 and ASCL1 [9]. In keeping with its repressive role, Hes5 knockout mice have increased postnatal expression of myelin genes including Mbp [9]. However, another study argues that Notch pathway activation mediated by Contactin/F3, an alternative axonal membrane-bound Notch ligand, can enhance OL differentiation [10]. Consistent with this, Contactin/F3 is highly expressed in demyelinated axons in patients with chronic multiple sclerosis and Notch-1 is activated in OLPs in these patients [11]. Moreover, following axotomy in zebrafish CNS, Contactin 1a is re-expressed both in OLs and the axotomised neurons [12]. Thus, the role of Notch-1 signalling in OL differentiation is currently controversial and remains to be clarified.

Wnt/TCF7L2/β-catenin pathway—WNT3A was originally reported to block differentiation of OLPs in explant cultures of rodent spinal cord [13]. Moreover, constitutively activating the canonical Wnt pathway by overexpressing an active form of β-catenin in OL lineage cells or by using APC^{min} mutant mice (which lack a critical Wnt signalling inhibitor), has recently been shown to inhibit OL differentiation [14••]. The transcription factor TCF7L2 (also known as TCF4) has been identified as a downstream effector of the canonical Wnt signalling pathway, through its ability to bind to β-catenin [15]. A role for TCF7L2 in OL development was originally proposed by He *et al.* [16••], who found that Tcf7l2 mRNA was overexpressed after birth in a mouse model of hypo-myelination (the Yy1 conditional knockout described below), compared to wild type. It was also reported that TCF7L2 can inhibit the expression of a luciferase reporter gene driven by the Mbp promoter in transfected cells [16••]. TCF7L2 has recently been identified by two other groups as a critical modulator of OL differentiation *in vivo* during developmental myelination [14••,17••] as well as during the remyelination of ethidium bromide-induced demyelinated lesions [14••]. Constitutive activation of β-catenin also impaired remyelination *in vivo* [14••]. TCF7L2 expression was observed in multiple sclerosis (MS) lesions of human patients, suggesting that Wnt-mediated repression of OL differentiation might underlie the chronic failure of remyelination that characterises late-stage MS [14••].

BMP/ID pathway—The Inhibitor of Differentiation (ID) gene products act downstream of BMP signalling. ID2 and ID4 are expressed in OL lineage cells and form heterodimers with OLIG1, OLIG2 or ASCL1, sequestering those factors and inhibiting OL differentiation until the appropriate time [18]. In keeping with this model, overexpressing Id2 or Id4 impairs myelin gene expression [19,20], while ablating Id4 results in premature OL differentiation [21,22]. ID-induced repression of myelin gene expression and OL differentiation is thought to be relieved eventually by the formation of an inhibitory complex between the transcription factor Yin Yang1 (YY1) and HDACs (see below).

De-repression of transcription and the role of histone deacetylation

Developmental programs of gene expression require long-range chromatin remodelling in addition to specific binding of transcription factors to regulatory elements in the vicinity of individual genes. Histone deacetylation is the first step of chromatin condensation (compaction), which represses gene expression in a global manner by sterically excluding the transcriptional machinery. A series of experiments has demonstrated that deacetylation of histone H3 by HDACs is necessary for OLs to differentiate into OLs both *in vitro* and *in vivo*. Treatment of OLs with trichostatin A (TSA), an HDAC inhibitor, prevented myelin gene expression without affecting cell cycle exit [23]. Similarly, myelination was inhibited *in vivo* when the HDAC inhibitor valproic acid (VPA) was administered systemically to neonatal rat pups during the first two postnatal weeks [24]. In zebrafish, inhibition of Hdac1 gene activity by the injection of specific antisense morpholinos or by the mutation of the Hdac gene prevented OL differentiation [25]. Isoform specificity was demonstrated by silencing experiments in cultured primary OLs that identified Hdac1 and Hdac2 but not other Hdac isoforms as critical for the differentiation [26••]. Recently, experiments with conditional Hdac knockouts, generated by crossing floxed Hdac1 and Hdac2 mice with Olig1-Cre transgenic mice, have emphasised the importance of histone deacetylation *in vivo* [17••]. Hdac1:Hdac2 double mutants (but not the single mutants) developed severe hypo-myelination leading to tremor and postnatal lethality [17••].

The role of HDACs in OL differentiation has been attributed to their ability to form repressive complexes that inhibit expression of transcriptional inhibitors of differentiation, effectively dis-inhibiting myelination by ‘repressing the repressors’ of the program [16••,26••]. For example, HDAC1 binds to YY1 to repress transcription of Id4 and Tcf7l2 [16••]. HDACs also repress Hes5, possibly by binding to distinct recruiters [9,26••].

Recent studies have further identified HDAC1 and HDAC2 as important inhibitors of the negative effect of Wnt signalling on OL differentiation [17••]; by competing with β -catenin for binding to TCF7L2, they prevent transcription of Id2/4. HDACs have also been implicated in the inhibition of Notch signalling by competing with NICD for binding to CBF1, thereby preventing transcription of Hes5 [27]. HDACs are therefore emerging as central points of convergence for multiple signal transduction pathways that control OL differentiation [28].

Transcriptional activators of the myelination program

Nuclear hormone receptors—*In vitro* experiments suggested that activation of retinoic acid receptors (RARs and RXRs) and thyroid hormone receptors (THR) is required for OLP differentiation [29,30]. In keeping with these experiments, an *in situ* hybridisation-based screen revealed a sharp increase of THR- β mRNA in remyelinating mouse spinal cord [14••]. Also, the zebrafish *neckless* mutant, which lacks the retinoic acid synthetic enzyme RALDH2 (ALDH1A2), was shown to be defective for MBP expression and myelin compaction during normal development [31]. Consistent with a role for TH signalling in regulating OL differentiation, hypo-thyroid and hyper-thyroid rats have delayed and accelerated myelination, respectively, although mice that lack both THR- α and THR- β have only slightly delayed optic

nerve myelination [32]. RAR/RXR and THR are ligand-dependent transcription factors that bind directly to DNA [33], but their downstream gene targets are currently unknown.

Basic helix–loop–helix transcription factors: OLIG1/2 and ASCL1—OLIG1 and OLIG2 are basic helix–loop–helix (bHLH) transcription factors that have been defined as important regulators of OL development [34]. These factors have been regarded as transcriptional repressors but they probably can be activators also, depending on their post-transcriptional modifications (they have many potential phosphorylation sites) and their choice of co-factors. In spinal cords of *OLIG1/2* double knockout mice, OL lineage cells are completely missing [35,36]. In *OLIG2* null spinal cord, OLs as well as motor neurons fail to develop, although in hindbrain and forebrain a small number of OLPs do exist, suggesting that *OLIG2* and *OLIG1* are partially redundant during OL development [35]. The first *OLIG1* knockout mouse to be described was developmentally normal but unable to remyelinate after experimental demyelination [35,37]. However, a subsequent study using a different *OLIG1* null mouse found a severe and ultimately lethal developmental defect in OL differentiation and myelination [38]. This discrepancy remains to be resolved.

ASCL1 (*MASH1*) is another bHLH transcription factor that is required for OL development [39–41]. *ASCL1* has a biphasic expression pattern — it is expressed highly in the VZ during ventral patterning, followed by a decrease during OLP specification and another peak during OL terminal differentiation [42•]. Consistent with this, fewer OLPs are initially generated in the spinal cords of *ASCL1* null embryos [43]. Then, although OLP numbers recover after birth, expression of myelin genes is significantly diminished [42•]. These results are consistent with *in vitro* evidence showing that co-expression of *ASCL1* with *OLIG2* or *NKX2.2* can activate myelin gene promoters [19] and induce OLP differentiation [42•]. *In vitro* data have demonstrated that *OLIG1* can activate expression of the myelin genes *Plp*, *Mbp* and *Mag* [38]; for *Mbp* this is because of a physical interaction between *OLIG1* and *SOX10* that stimulates *Mbp* transcription [44•]. An interaction between *OLIG2* and *SOX10* in mouse has also been reported [45] (note, however, that *OLIG2* and *SOX10* do not interact in zebrafish [44•]).

High mobility group (HMG) transcription factors: the SOX family—SOX proteins include more than 20 family members with an HMG domain. Of those, *SOX10* is one of the most critical determinants for OL terminal differentiation and myelin gene expression [46], while *SOX5* and *SOX6* are expressed in OLPs and downregulated during OL differentiation [47]. *Sox10* null mice have severely impaired OL differentiation [46] and *Sox10* expression is sufficient to induce ectopic OLP differentiation when electroporated into chick spinal cord [48•]. *SOX10* directly controls the expression of myelin genes *Mbp* and *Plp* [46]. *Sox10* can also interact with the thyroid hormone receptor-associated protein complex 230 (TRAP230, also known as MED12) [31,49], suggesting a link with TH signaling (see above and Figure 1). The expression patterns of *Sox8* and *Sox9* are partially overlapping with, though not identical to, that of *Sox10* [50] and their role in OL differentiation appears to be subsidiary to *Sox10* [51,52]. *Sox17* is also expressed in the OL lineage in mouse spinal cord and is involved in the induction of myelin gene expression *in vitro* [53].

Zinc-finger transcription factors: YY1, ZFP488 and MTY1—YY1 is a zinc-finger protein and a member of the GLI-Kruppel family of transcription factors. A role for YY1 in OL development was originally described by Berndt *et al.* [54], who found that ubiquitously expressed YY1 recognises the myelin *Plp* promoter *in vitro* and *in vivo* and directly enhances its transcription. Association of YY1 with other molecules is dependent on the acetylation status of the molecule itself and on the presence of specific extracellular signals favouring OL differentiation [16•,55]. YY1 binding to HDACs represses gene expression, while binding to histone acetyl transferases leads to transcriptional activation. In conditional knockouts

generated by crossing Yy1 (flox) and Cnp-cre mice, OLP development was arrested at an immature stage characterised by hypo-myelination and de-repression of transcriptional inhibitors such as ID4, SOX11 and TCF7L2. This suggested that in OLPs YY1 mainly formed repressive complexes with HDAC1 [16••] but did not rule out the possibility that, at later developmental stages, it might also act as an activator of gene expression [54].

Another zinc-finger transcription factor involved in OL differentiation is ZFP488, which starts to be expressed at the onset of OL differentiation. Specific knock-down of Zfp488 expression using siRNA downregulated myelin gene expression, while co-electroporating Zfp488 and Olig2 in the chick neural tube induced ectopic OL differentiation [56].

Myelin transcription factor 1 (MYT1) is a zinc-finger protein that can bind to the promoter region of the Plp gene [57]. Overexpression of dominant-negative MYT1 inhibits OL terminal differentiation [58]. In addition, it has been suggested that MYT1 might recruit HDACs through SIN3B, a transcriptional repressor that is also expressed in OLP [59].

NDT80 domain transcription factor: MRF—Myelin-gene Regulatory Factor (MRF), also called Gene Model 98 (GM98), is a homologue of the product of human gene C11Orf9 [60] and contains an NDT80 DNA binding domain. It was originally identified as a gene expressed in post-mitotic OLs but not in astrocytes, neurons or Schwann cells [61••]. Electroporation of Mrf in chick spinal cord induced ectopic expression of myelin genes and the effect was enhanced by co-electroporation with Sox10. Conditional ablation of this gene in using Olig2-cre or Cnp-cre mouse lines resulted in severe hypo-myelination as a result of impaired OL differentiation. It was noted that expression of MRF progressively increases in the white matter during the first two postnatal weeks and peaked at the third week, following a temporal pattern that resembles that of the master gene Krox20 in Schwann cells [61••]. On the basis of these data, it has been proposed that MRF might play an analogous role in the CNS to that played by KROX20 in the PNS [61••,62], although it remains to be determined whether the regulation of myelin genes is direct or indirect [61••]. Intriguingly, the presence of a highly conserved YY1 binding site in the first intron of the MRF gene suggests the possibility that YY1 might act as a regulator of MRF gene expression.

Homeodomain transcription factors: NKX2.2 and NKX6.2—Although the homeodomain protein NKX2.2 is expressed throughout the OL lineage including early migratory OLPs, it seems to function mainly or exclusively during OL differentiation. In Nkx2.2 null mice, Plp and Mbp expressions are delayed and reduced in white matter and absent in grey matter [63]. Whether NKX2.2 directly controls myelin gene expression is not known. *In vitro* studies suggest that NKX2.2 can drive the Plp promoter to express a reporter gene [63], while simultaneously repressing the activity of Mbp promoter-driven reporters [64]. Another homeodomain protein, NKX6.2, is also expressed during OL maturation and has been shown to regulate the axon–OL interaction at myelin paranodes [65].

Conclusions

This review summarises what has been learned about transcriptional regulation of OL differentiation, revealing the existence of a complex regulatory network (Figure 2). The crosstalk between extrinsic signals, transcription factors and chromatin modifiers modulates the balance between repressive signals that sustain progenitor status and prevent differentiation, and de-repressive signals that favour OL differentiation and myelination. These developmental pathways are frequently reactivated during remyelination, so lessons learned about developmental myelination might ultimately lead to new therapeutic approaches to Multiple Sclerosis and other demyelinating diseases.

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Figure 1.

A speculative model for transcriptional activation of myelin gene expression. SOX10, thyroid hormone receptor (THR), THR-associated protein 230 (TRAP230/MED12) and OLIG1/2 might conceivably form a transcriptional activating complex that could further synergise with ZFP488 and MRF/GM98. NKX2.2 might also bind to OLIG2, although its effect on myelin gene expression is not yet clear. YY1 can activate myelin promoters but its interactions with other transcription factors are still to be clarified.

Figure 2.

An intricate gene regulatory network controls OL differentiation. The crosstalk between extrinsic signals, transcription factors and chromatin modifiers determines the balance between repressive signals that inhibit OL differentiation and de-repressive signals that stimulate OL differentiation. Of all the factors described in this review, only those with two or more connections are illustrated in this figure. Red indicates repression and green represents activation. Dashed lines represent speculations; double-headed arrows indicate physical interactions. Reference numbers are marked on each pathway.