Using the lineage determinants Olig2 and Sox10 to explore transcriptional regulation of oligodendrocyte development

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Funding information
Deutsche Forschungsgemeinschaft, Grant/Award Numbers: So251/5-1, We1326/15-1, RTG2162

Abstract
The transcription factors Olig2 and Sox10 jointly define oligodendroglial identity. Because of their continuous presence during development and in the differentiated state they shape the oligodendroglial regulatory network at all times. In this review, we exploit their eminent role and omnipresence to elaborate the central principles that organize the gene regulatory network in oligodendrocytes in such a way that it preserves its identity, but at the same time allows defined and stimulus-dependent changes that result in an ordered lineage progression, differentiation, and myelination. For this purpose, we outline the multiple functional and physical interactions and intricate cross-regulatory relationships with other transcription factors, such as Hes5, Id, and SoxD proteins, in oligodendrocyte precursors and Tcf7l2, Sip1, Nkx2.2, Zfp24, and Myrf during differentiation and myelination, and interpret them in the context of the regulatory network.

KEYWORDS
olig, oligodendrocyte, regulatory network, Sox, transcriptional regulation

1 | INTRODUCTION

Oligodendrocytes are the myelin-forming cells of the vertebrate central nervous system (CNS) and are indispensable for rapid saltatory conduction. They also provide metabolic support to axons, with which they form strongly interconnected functional units. Like CNS neurons, oligodendrocytes develop from neuroepithelial precursor cells in the ventricular zone of the CNS via fate-restricted precursors, the so-called oligodendrocyte progenitors (OPCs). Following the specification event, oligodendroglial cells, therefore, have to establish their own specific regulatory network that ensures the maintenance of oligodendroglial identity as well as proper lineage progression and eventually terminal differentiation and myelination. In general, cell-type-specific regulatory networks are built around transcription factors. Some are present at all times and ensure lineage identity. In oligodendroglial cells, these are the bHLH domain protein Olig2 and the HMG-domain containing Sox10 (Figure 1). A second group is active only at decision points or during certain phases. These factors drive lineage progression. Other network components include chromatin-modifying enzymes and remodeling complexes as well as short and long noncoding RNAs (microRNAs and lncRNAs).

Excellent recent reviews exist on various aspects of the oligodendroglial regulatory network and its components including transcription factors, chromatin-associated factors, or regulatory RNAs (Elbaz & Popko, 2019; Emery & Lu, 2015; C. Parras et al., 2020; Sock & Wegner, 2019; Tiane et al., 2019). For this review, we decided to focus on transcription factors and explain the regulatory network from the perspective of Olig2 and Sox10 as lineage determinants and major players. We are fully aware that such a focus is arbitrary and introduces a bias toward certain factors and mechanistic
FIGURE 1  Interactions and cross-relationships between the lineage determinants Olig2 and Sox10 and other transcription factors of the oligodendroglial regulatory network. After induction of Sox10 (red ovals, lower half) by Olig2 (magenta ovals, upper half), both factors are expressed in OPCs, premyelinating (preOL), and myelinating oligodendrocytes (OL). They induce Sox6, Sip1, Tcf7l2, Nfat proteins, Myrf, and Zfp488 (pointed arrows) and are in turn inhibited by Hes5 and Id proteins (blunted arrows). For the activation of genes with relevance in OPCs (OPC genes) and simultaneous inhibition of differentiation and myelin genes (OL genes), Sox10 cooperates with Sox6. Myrf inhibits the Sox10-dependent activation of OPC genes. OL genes are regulated by joint action of Olig2 and Sox10 with Tcf7l2, Myrf, Zfp24, and Zfp488. Functional interactions between transcription factors are marked by converging cocolored arrows, entry points for external stimuli by bolts.

aspects. However, we believe that the chosen approach is exceptionally well suited to highlight the fundamental principles that govern the oligodendroglial regulatory network and make it work during lineage progression, differentiation, and maintenance of the differentiated state.

2 OLIG2 AND SOX10 AS MAJOR OLIGODENDROGLIAL DETERMINANTS

In ventral CNS regions, the bHLH transcription factor Olig2 is already expressed in neuroepithelial cells before their specification to oligodendroglial cells (Rowitch et al., 2002; Takebayashi et al., 2000; Takebayashi et al., 2002; Vallstedt et al., 2005). Interestingly, Olig2 expression in neural progenitor cells is oscillatory and switches to a sustained mode after specification (Imayoshi et al., 2013). During these early phases, Olig2 appears to cooperate downstream of the Chd8 chromatin remodeler with the Brg1-containing BAF complex to induce chromatin remodeling events that are essential for oligodendroglial development (Marie et al., 2018; Yu et al., 2013; Zhao et al., 2018). Once present, Olig2 remains expressed throughout oligodendroglial development and is still expressed in the mature state. It, therefore, represents one of the central determinants of the oligodendroglial regulatory network (Q. R. Lu et al., 2002; Q. R. Lu et al., 2000; Takebayashi et al., 2002; Q. Zhou & Anderson, 2002; Q. Zhou et al., 2000).

The other major determinant is the HMG-domain containing transcription factor Sox10. At least in oligodendroglial cells of the ventral spinal cord Sox10 is a direct target gene of Olig2 and the Olig2-recruited Brg1-containing BAF complex (Figure 1) (Bischof et al., 2015; Kuhlbrodt et al., 1998; Küspert et al., 2011; C. C. Stolt et al., 2002; Yu et al., 2013). It appears immediately after the specification event and, thus, slightly later than Olig2. The occurrence of Olig2 and Sox10 defines the pre-OPC stage that progresses into the OPC stage with the appearance of Pdgfra and the NG2/Cspg4 proteoglycan. Both represent direct target genes of Sox10 (Baroti et al., 2016; Gotoh et al., 2018). Once induced, Sox10 remains present in the oligodendroglial lineage and exerts its effect as a main component of the regulatory network throughout development and in the mature state (Finzsch et al., 2008; C. C. Stolt et al., 2002). Essential properties of its role in the regulatory network are its ability to recruit Chd7- and Ep400-containing chromatin remodelers and the RNA polymerase II activating mediator complex through interaction with the Med12 subunit (Elsesser et al., 2019; D. He et al., 2016;
Vogl et al., 2013). Once present, Sox10 has a strong stimulatory effect on Olig2 expression so that both transcription factors reinforce each other’s expression (Z. Liu et al., 2007; Weider et al., 2015).

Neither Sox10 nor Olig2 is restricted to oligodendroglial cells. Olig2 is for instance also expressed during development in motoneurons, Purkinje cell precursors, and subgroups of astrocyte precursors, where it counteracts astrocytic maturation (Cai et al., 2007; Fukuda et al., 2004; Ju et al., 2016; Q. R. Lu et al., 2000; Q. Zhou et al., 2000). Sox10, on the other hand, additionally occurs in migratory neural crest cells and many of its derivatives including Schwann cells, satellite glia and enteric glia of the PNS as well as melanocytes (Britsch et al., 2001; Kuhlbrodt et al., 1998). It is, thus, reasonable to assume that neither Olig2 nor Sox10 defines oligodendroglial identity on their own. It rather is the combination of both factors.

Another shared feature between the two factors is that both are coexpressed in oligodendroglial cells with paralogs (Figure 1). For Olig2, this is the closely related Olig1 (Q. R. Lu et al., 2000; Q. Zhou et al., 2000). In most oligodendrocytes, Olig1 appears to be of minor relevance for lineage progression (Q.R. Lu et al., 2002; Q. Zhou & Anderson, 2002). Defects in OPC commitment and differentiation that occur in the absence of Olig1 are partial or transient depending on the particular CNS region arguing that missing Olig1 can be largely compensated by Olig2 (Dai et al., 2015). In contrast, there is little compensation of an Olig2 loss by Olig1. The influence of Olig1 on oligodendroglial development increases during terminal differentiation (Meijer et al., 2012). This coincides with a reduction in Olig2 levels.

During oligodendroglial development, Sox10 is accompanied by the paralogous Sox8 and Sox9 proteins (C.C. Stolt et al., 2004). This contrasts sharply with the situation in Schwann cells where Sox10 occurs alone. In oligodendroglial cells, Sox8 and Sox10 are coexpressed at all times (C.C. Stolt et al., 2004). Sox9 is additionally present until terminal differentiation (C.C. Stolt et al., 2003). In OPCs, Sox10 and Sox9 exert largely equivalent functions so that both factors have to be deleted to affect oligodendroglial development at this stage (Finzsch et al., 2008). Sox8 on the other hand appears of minor importance during lineage progression. It cannot compensate the terminal differentiation defect observed after Sox10 loss (Kellerer et al., 2006). Following Sox8 deletion, there is only a mild transient delay of developmental myelination (C.C. Stolt et al., 2004). Sox8 is, however, highly relevant for myelin maintenance in adult oligodendrocytes and in this context is functionally on a par with Sox10 (Turnescu et al., 2018). Despite their obvious importance, coexpression of paralogs is often not taken into account when Olig2 and Sox10 are functionally analyzed in oligodendroglial cells.

For Olig2, a further complication exists. It belongs to the class II (class B) of bHLH proteins and as common to this class performs many of its functions as heterodimer with class I (class A) bHLH proteins (Gokhan et al., 2005; Samanta & Kessler, 2004). Recent data indicate that Tcf4 represents the main class I bHLH heterodimerization partner of Olig2 in oligodendroglial cells (Wedel et al., 2020). Supporting the role of Tcf4 in oligodendroglial development, Tcf4-deficient oligodendroglial cells exhibit a strong but transient delay in developmental myelination. Alterations in amounts or activity of Tcf4, therefore, have an additional impact on Olig2 function.

As determinants of oligodendroglial identity, Olig2 and Sox10 should be functional at all times. Considering the different properties of OPCs and myelinating oligodendrocytes, it is, however, unlikely that these factors perform the same functions during the different developmental stages. Instead, it appears reasonable to assume that the activity of Olig2 and Sox10 within the oligodendroglial regulatory network is modulated in a stage-specific manner. Supporting evidence for such stage-specific functions is provided by experiments, in which deletion or overexpression of Olig2 at different times during oligodendroglial development results in different phenotypic outcomes (Mei et al., 2013; Wegener et al., 2015).

One way of altering transcription factor activity is by modulating the amount of available protein, either through changes in expression levels or through altered degradation kinetics. Indeed, observations exist that Olig2 and Sox10 amounts vary between stages. Mature oligodendrocytes, for instance, express only relatively modest levels of Olig2 as compared to OPCs and actively myelinating oligodendrocytes (Meijer et al., 2012). For Sox10, levels increase substantially with the onset of terminal differentiation (Weider & Wegner, 2017). These increased levels are important for oligodendroglial differentiation as Hif1α-induced repression of Sox10 expression prevents oligodendrocyte formation and myelination under hypoxic conditions (Allan et al., 2021). Intriguingly, it is the interaction with Olig2 that allows Hif1α to recognize gene regulatory regions of Ascl2 and Dlx3 as noncanonical targets that then prevent an increase in Sox10 expression, providing another example of the complex interactions, by which Olig2 and Sox10 mutually influence their expression. Data from melanoma cells argue additionally for a regulated degradation of Sox10 and a dependence of Sox10 stability on E3 ligases such as Fbxw7a (Lv et al., 2015). However, it is unclear at present whether regulated degradation is relevant in the oligodendrocyte lineage for any of the two proteins.

Alternatively, transcription factor activity can be modulated by post-translational modifications. Both Olig2 and Sox10 have been shown to be phosphorylated at multiple sites, particularly, but not exclusively in their aminoterminal regions (Cronin et al., 2018; J. Zhou et al., 2017). In case of Olig2, serine phosphorylation in the bHLH domain appears to impact the choice of interaction partners and may help to alter Olig2 function from a neuronal to a glial one (H. Li et al., 2011). Aminoterminal Olig2 phosphorylation has been
reported to regulate intranuclear compartmentalization and to maintain replication competence and proliferative capacity in neural progenitor and glioma cells (Meijer et al., 2014; J. Zhou et al., 2017). It may have similar functions in OPCs. In case of Sox10, the role of its phosphorylation has only been studied in melanoma cells. Reported effects range from subtle alterations in protein stability to inhibition of transcriptional activity (Cronin et al., 2018; Han et al., 2018). For Sox10, phosphorylation has also been linked to sumoylation as a second post-translational modification with influence on its activity (Han et al., 2018; Taylor & LaBonne, 2005). Again, it is currently unclear to what extent these mechanisms are relevant for oligodendroglial development and myelination.

As a third option, the transcriptional activity of Olig2 and Sox10 may be influenced by other network components that have a transient, probably phase-specific expression or activity. As interaction partners, they may influence the choice of targeted regulatory regions, synergistically increase or inhibit transcriptional activity by mechanisms of sequestration or competition for binding sites or interaction partners. If these proteins are additionally downstream effectors of signaling pathways they may sensitize the oligodendroglial regulatory network to signals from their environment and surrounding cells.

3 | KEEPERS OF THE PROGENITOR STATE

Notch, BMP, and Wnt signaling are important to keep OPCs in an undifferentiated state. In line with these findings, the class VI bHLH transcription factor Hes5 as the main effector of Notch signaling in oligodendroglial cells is preferentially detected in OPCs and disappears as these cells mature into myelinating oligodendrocytes (A. Liu et al., 2006). The class V bHLH proteins Id2 and Id4 as main effectors of BMP signaling are likewise enriched in OPCs as compared to oligodendrocytes (Marin-Husstege et al., 2006; Samanta & Kessler, 2004; S. Wang et al., 2001). Both Hes5 and the Id proteins maintain OPCs in the precursor state and prevent differentiation in multiple ways. At least one also affects Sox10 or Olig2 activity. Hes5 for instance lowers Sox10 expression and interacts physically with the Sox10 protein present in OPCs (A. Liu et al., 2006). The resulting sequestration of Sox10 in a complex with Hes5 prevents it from activating the expression of differentiation and myelin genes (Figure 1). Interestingly, not all Sox10 targets are similarly affected and genes activated by Sox10 in OPCs appear exempt (Xiao et al., 2020).

In a similar manner, Id proteins efficiently heterodimerize with Olig2 and the resulting heterodimers are not functional as transcription factors because of the lack of a DNA-binding domain in the Id proteins (Marin-Husstege et al., 2006; Samanta & Kessler, 2004; S. Wang et al., 2001) (Figure 1). However, the inhibitory effect is not unidirectional. A rise in Sox10 levels at the onset of terminal differentiation will lead to a depletion of functional Hes5 by the same sequestration mechanism that limits Sox10 activity in OPCs. Olig2, on the other hand, is able to interfere with Smad signaling through its direct target, the zinc finger transcription factor Sip1/Zeb2, and can thereby repress Id gene expression as a precondition to terminal differentiation and myelin gene expression (Weng et al., 2012) (Figure 1).

In case of Wnt signaling, it is noteworthy that expression of Tcf7l2 as the main effector of canonical Wnt signaling in oligodendroglial cells is regulated by Sox10 (Cantone et al., 2019). In OPCs, Tcf7l2 exists in a complex with β-catenin and thereby helps to maintain the progenitor state (Ye et al., 2009). Upon oligodendroglial differentiation, Tcf7l2 blocks Wnt and autocrine BMP signaling and actively promotes oligodendrocyte differentiation and myelination (Ye et al., 2009; S. Zhang et al., 2021; Y. Zhang et al., 2016) (Figure 1). To achieve this, Tcf7l2 sequentially exchanges its interaction partners from β-catenin via Kaizo/Zbtb33 to Sox10 during the process (Y. Zhang et al., 2016).

While Hes5 and Id proteins functionally interact with Olig2 and Sox10 in a mutually antagonistic manner, the relationship with Tcf7l2 is on a more complex, modulatory level. Similar modulatory effects have been noted for the HMG-domain containing SoxD proteins (C.C. Stolt et al., 2006). The closely related SoxD proteins Sox5 and Sox6 are both expressed in OPCs and disappear as the cells undergo terminal differentiation. Expression of Sox6 as the SoxD protein with highest expression is under transcriptional control of Sox10 (Figure 1). In OPCs, SoxD proteins appear to influence Sox10 activity in two ways. It was first found that they prevent Sox10 from activating terminal differentiation and myelin genes by competing for the relevant binding sites in the corresponding regulatory regions (C.C. Stolt et al., 2006). Later, it was reported that SoxD proteins also cooperate with Sox10 in stimulating the expression of Pdgfra as a central regulator of OPC survival, proliferation, and migration (Baroti et al., 2016). These data, therefore, imply that SoxD proteins modulate Sox10 activity in OPCs by directing it away from the regulatory regions of myelin genes toward regulatory regions of genes relevant in OPCs. Such cross-regulatory relationships within the regulatory network are crucial to allow for the flexibility required for lineage progression.

4 | DRIVERS OF THE DIFFERENTIATED STATE

Several transcription factors are involved in orchestrating the switch from the OPC state to the oligodendrocyte and initiating the differentiation and myelination processes. Some of them have limited documented functional interrelationships
with Olig2 or Sox10 such as Yy1 and Coup-Tf1 (Y. He et al., 2007; Yamaguchi et al., 2004). Many others interact in one way or another with the lineage determinants. This has, for instance, already been mentioned above for Sp1 as a BMP inhibitor under control of Olig2 or for Tcf7l2 as a Sox10 target and stage-specific modulator of Sox10 activity (Weng et al., 2012; Zhao et al., 2016).

Among other triggers of the oligodendroglial differentiation process, the homeodomain transcription factor Nkx2.2 figures prominently (Qi et al., 2001). There is little Nkx2.2 expression in OPCs and levels rise substantially in premyelinating oligodendrocytes, shortly before the onset of differentiation. Mouse studies furthermore confirm that oligodendrocyte differentiation and myelination are dramatically delayed in the absence of Nkx2.2 (Qi et al., 2001). How Nkx2.2 exerts its prodifferentiation effect on oligodendroglial development is not completely understood. However, the mechanism is probably complex as available evidence suggests that Nkx2.2 predominantly acts as a repressor so that a simple joint activation of differentiation and myelin genes with Olig2 and Sox10 appears unlikely. The induction of Nkx2.2 expression has to occur in the presence of Olig2 despite the fact that the two transcription factors have a strong tendency to cross-repress each other’s expression as shown during ventral spinal cord patterning (Sun et al., 2003). To render joint expression of Nkx2.2 and Olig2 possible in premyelinating oligodendrocytes, it is important that both genes are direct transcriptional targets of Sox10 (Z. Liu et al., 2007), and that the same regulatory regions are targeted by Sox10 and by Nfat transcription factors, among them Nfatc2 as a direct target of Sox10 in oligodendroglial cells (Weider et al., 2018) (Figure 1). Although amounts of Nfat proteins rise at the onset of terminal differentiation, they are already present in OPCs where they are preferentially localized to the cytoplasm, likely because of their phosphorylated state. Triggered by an as yet unidentified stimulus and following increases in intracellular calcium, Nfat proteins Relocalize to the nucleus at the onset of differentiation and now support Sox10 in Nkx2.2 induction and maintenance of Olig2 expression by cooperatively increasing Sox10-dependent activation and preventing cross-inhibitory effects. A similar role in jointly maintaining Nkx2.2 and Olig2 expression has also been detected for Ascl1/Mash1 and is a main aspect of its differentiation promoting role in oligodendroglial cells after an earlier function in OPC specification (C. M. Parras et al., 2004; Sugimori et al., 2007, 2008) (Figure 1). Because of the involvement of Nfat proteins, Nkx2.2 induction becomes dependent on external stimuli. It, therefore, represents a nice example of how external stimuli impact and reset the gene regulatory network to initiate differentiation.

Similar to Nfat proteins, the SCAN domain zinc finger transcription factor Zfp24 (formerly known as Zfp191) occurs in OPCs as well as oligodendrocytes (Elbaz et al., 2018). In OPCs, it is hyperphosphorylated and predominantly localized to the cytoplasm. As observed for Nfat proteins, dephosphorylation and relocalization to the nucleus occur at the onset of terminal differentiation, arguing that Zfp24 represents a second stimulus-dependent transcription factor in oligodendroglial differentiation. Once nuclear, Zfp24 activates Olig2 and Sox10 expression—just as these two factors help to maintain Zfp24 expression (Figure 1). Intriguingly, Zfp24 has also been found on the same regulatory regions of terminal differentiation and myelin genes that have previously been reported to be bound and controlled by Olig2 and Sox10 (Elbaz et al., 2018). These intricate relationships make Zfp24 another crucial component of the late-stage differentiation promoting regulatory network in oligodendrocytes.

Expression of Myrf is also under control of Sox10, Olig2, and Zfp24 (Elbaz et al., 2018; Hornig et al., 2013; Yu et al., 2013) (Figure 1). At least for Sox10, it has been shown that transcriptional activation of Myrf expression is direct and mediated via an intronic gene enhancer (Hornig et al., 2013). Why Myrf induction occurs in premyelinating oligodendrocytes and not before, has not yet been experimentally addressed. Activation of the intronic Myrf enhancer in vivo may, however, depend on the stimulus-dependent relocation of Zfp24 or Nfat proteins to the nucleus and their contribution to Myrf expression.

The Myrf protein is an unusual transcription factor. Although restricted in its occurrence within the CNS to oligodendrocytes, the protein otherwise occurs in many other cell types throughout the body (Huang et al., 2021). Myrf is a homotrimeric transcription factor that is synthesized as a longer precursor protein, anchored in the ER membrane via a transmembrane domain in its carboxyterminal part (Emery et al., 2009). Within the ER membrane, it is specifically complexed with Tmem98 (Huang et al., 2018). To exert its function in the nucleus, Myrf has to undergo autoproteolysis (Bujalka et al., 2013; Z. Li et al., 2013), which is inhibited in complex with Tmem98 (Huang et al., 2018). Therefore, it is tempting to speculate that Tmem98 regulates autoproteolysis. Such a mechanism would provide a further option for external or metabolic signals to influence the regulatory network and impact differentiation and myelination processes. After autoproteolysis, a homotrimer is generated that consists of the three aminoterminal parts, moves to the nucleus and binds to DNA as a trimer (Kim et al., 2017; Muth et al., 2016). Because of the presence of one Ndt80-type DNA-binding domain per subunit, it is not surprising that a high-affinity Myrf binding site consists of at least two recognition motifs with a defined distance between them (Aprato et al., 2020; Bujalka et al., 2013). Myrf and its binding sites have been found on many of the same regulatory regions of differentiation and myelination genes that are bound by Sox10, Olig2, and Zfp24 (Bujalka et al., 2013; Elbaz et al., 2018). There is furthermore clear evidence that Myrf cooperatively supports Sox10 in the
activation of these genes (Figure 1), arguing that Myrf is a key component of the regulatory network that induces and maintains the myelinated phenotype (Hornig et al., 2013). Recent experiments revealed yet another twist to the functional relationship between Sox10 and Myrf. Surprisingly, Myrf is also capable of repressing Sox10 activity on some of its target genes, namely on those that are normally activated in OPCs (Aprato et al., 2020). These genes seem to lack Myrf binding sites in their Sox10-responsive regulatory regions. It is, therefore, proposed that the repressive activity of Myrf depends on its ability to bind to Sox10 and sequester it away from regulatory regions that lack Myrf binding sites. These findings suggest that Myrf may be functionally more versatile than previously appreciated and may help to redirect Sox10 activity between different sets of target genes.

Another important component of the gene regulatory network in differentiating oligodendrocytes is the zinc finger transcription factor Zfp488 (S. Z. Wang et al., 2006). Within the CNS, Zfp488 expression is restricted to the oligodendroglial lineage. It represents a target gene of Olig2 and after its appearance cooperates with Olig2 and its differentiation-relevant paralog Olig1 during oligodendroglial differentiation (Figure 1). Zfp488 primarily appears to act as a transcriptional repressor. Therefore, the mode of its cooperative action with the Olig proteins is likely not straightforward on a mechanistic level, as previously mentioned for Nkx2.2.

Most of the transcription factors that become induced during oligodendroglial differentiation and myelination continue to be expressed in mature oligodendrocytes. However, some differences exist. Olig2 levels are usually lower in mature than in actively myelinating oligodendrocytes, and the vast majority of the related Olig1 is relocalized from the nucleus to the cytoplasm (Meijer et al., 2012). Nkx2.2 is strongly decreased in amounts and may even disappear. At the same time, the related Nkx6.2 appears arguing that it may replace Nkx2.2 because it may better fit the requirements for the maintenance state (Southwood et al., 2004). The available data currently argue against a major reconstruction of the gene regulatory network between the active phase of myelination and myelin maintenance and rather favor a model in which network adaptations are achieved by relatively limited adjustments.

5 CONCLUSIONS AND PERSPECTIVES

By looking at transcriptional regulation of oligodendroglial development from the side of the omnipresent lineage determinants Olig2 and Sox10, central organizational principles of the oligodendroglial regulatory network become evident. One of them is the existence of activating circuits by which essential regulatory components reinforce each other’s expression as shown for Olig2, Sox10, and Zfp24. Such circuits help to safeguard and reinforce expression of the essential components of the regulatory network and to stabilize crucial properties of oligodendroglial cells such as their lineage identity. Another essential principle consists of feedforward loops, in which Olig2 or Sox10 induce other factors that then cooperate and modulate their activity. Examples for such loops include the induction of Sip1 and Zfp488 by Olig2 or of Sox6, Nfatc2, and Myrf by Sox10. They allow the implementation of stage-specific programs including differentiation and myelination by the regulatory network. However, these inductions have to be tightly controlled as they need to occur at specific times and in a defined temporal order. Therefore, they require stimuli that get them started and mechanisms by which these stimuli influence the regulatory network. These may involve stimulus-dependent activation of transcription factors such as observed for Zfp24 and Nfat proteins or post-transcriptional modifications of Olig2 and Sox10 themselves. Obviously, inclusion of microRNA-dependent fine-tuning mechanisms and chromatin alterations may also contribute.

This review provides ample evidence that we have learnt a lot in recent years about the complex interactions of transcription factors and their consequences on the overall activity of the gene regulatory network. However, there is still a long way to go to a full understanding. In particular, we urgently need to obtain more information on the exact molecular mechanisms by which external stimuli and signals exert their effect on the gene regulatory network. We need to explore how these stimuli influence the behavior of OPCs during development and after insult or demyelination, their decision to proliferate or differentiate, as well as their choice of axon type and the eventual number and thickness of the myelin sheaths.

All transcription factors are furthermore assumed to be similarly active in most, if not all oligodendrocytes and to employ identical mechanisms. However, given the recent discovery of oligodendroglial heterogeneity (Marques et al., 2016), it is clearly imaginable that regulatory network differences exist between subpopulations. This additional layer of complexity has not been studied at all. In fact, it is currently completely unclear if and how the detected oligodendroglial heterogeneity is reflected on the level of the gene regulatory network, whether it is conferred by variations in contributing transcription factors or more a consequence of quantitative changes, microRNA activities, or alterations in chromatin structures. Thus, much remains to be done.

ACKNOWLEDGMENTS

The authors declare that they have no conflicts of interest. This work was supported by Grants from the Deutsche Forschungsgemeinschaft to ES (So251/5-1) and MW (We1326/15-1 and RTG2162).

Open access funding enabled and organized by Projekt DEAL.
CONFLICT OF INTEREST
The authors declare that there is no conflict of interest and no finances to disclose.

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**How to cite this article:** Sock, E., & Wegner, M. (2021). Using the lineage determinants Olig2 and Sox10 to explore transcriptional regulation of oligodendrocyte development. *Developmental Neurobiology, 81*, 892–901. https://doi.org/10.1002/dneu.22849