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REVIEW

From CNS stem cells to neurons and glia: Sox for everyone

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Abstract Neuroepithelial precursor cells of the vertebrate central nervous system either self-renew or differentiate into neurons, oligodendrocytes or astrocytes under the influence of a gene regulatory network that consists in transcription factors, epigenetic modifiers and microRNAs. Sox transcription factors are central to this regulatory network, especially members of the SoxB, SoxC, SoxD, SoxE and SoxF groups. These Sox proteins are widely expressed in neuroepithelial precursor cells and in newly specified, differentiating and mature neurons, oligodendrocytes and astrocytes and influence their identity, survival and development. They exert their effect predominantly at the transcriptional level but also have substantial impact on expression at the epigenetic and posttranscriptional levels with some Sox proteins acting as pioneer factors, recruiting chromatin-modifying and -remodelling complexes or influencing microRNA expression. They interact with a large variety of other transcription factors and influence the expression of regulatory molecules and effector genes in a cell-type-specific and temporally controlled manner. As versatile regulators with context-dependent functions, they are not only indispensable for central nervous system development but might also be instrumental for the development of reprogramming and cell conversion strategies for replacement therapies and for assisted regeneration after injury or degeneration-induced cell loss in the central nervous system.

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Introduction

The generation of the right cell type in the right place and at the right time is a major challenge during tissue development, turnover and repair. In the developing central nervous system (CNS), neurons and macroglia (i.e., oligodendrocytes and astrocytes) as the predominant cell types arise from multipotent neuroepithelial precursor (NEP) cells that line the ventricles and the spinal canal. Defined progenitor domains within the neuroepithelium usually first give rise to neurons of a certain subtype and subsequently to glia. The complex changes in transcription program and epigenetic status that initiate neurogenesis, the neuron-to-glia switch and gliogenesis in NEP are only partially understood.

Transcriptional regulation is one of the main mechanisms for guiding cells to a specific identity. Among essential transcription factors, members of the Sox protein family are prominently represented. They are named and characterized by their DNA-binding domain, a HMG (high-mobility group)-box with high similarity to the eponymous Sry-box, the HMG-box of the Sry protein. Classification of the 20 mammalian Sox proteins into groups SoxA-SoxH is based primarily on the degree of amino acid identity within the HMG-box (Fig. 1). Additionally, members of the same group exhibit a conserved domain organization. DNA binding by the three alpha helices of the HMG-box occurs sequence-specifically in the minor groove and introduces a strong bend, thereby changing the architecture of targeted regulatory DNA elements. These conformational changes contribute to the recruitment of further transcription factors, components of the basal transcription machinery or DNA-modifying complexes (for a review, see Wegner 2010). A typical feature of

Sox proteins is their gain in activity by interaction with other transcriptional regulators (for a review, see Kamachi et al. 2000). The variation of interaction partners in a wide range of cellular contexts is the reason for the diverse effects that one Sox protein can exert.

Members of groups SoxB, SoxC, SoxD, SoxE and SoxF are of importance in neural progenitors and CNS cell lineages and therefore the focus of this review (Fig. 1). The SoxB group is further sub-divided into SoxB1, with members Sox1, Sox2 and Sox3 and SoxB2 comprising Sox14 and Sox21. In addition to their highly similar HMG-box, SoxB1 and SoxB2 share a conserved group B homology domain directly behind the HMG-box. However, they are different with respect to the main function of their C-terminal domain, which is mostly transactivating in SoxB1 proteins but transrepressing in SoxB2 proteins (Sandberg et al. 2005; Fig. 1). The SoxC group consists of Sox4, Sox11 and Sox12. These three Sox proteins share a conserved C-terminal transactivation domain (Dy et al. 2008; Hoser et al. 2008). Sox5, Sox6 and Sox13 represent the SoxD group. They homo- or heterodimerize with other SoxD members via a coiled-coil domain and have no inherent transactivation or transrepression domain (Lefebvre 2010). The SoxE proteins Sox8, Sox9 and Sox10 contain a conserved C-terminal transactivation domain, a centrally located protein-protein interaction domain and, in addition, a dimerization domain that precedes the HMG-box and mediates cooperative binding to DNA (Wegner 1999). Monomeric and dimeric binding of SoxE proteins results in various effects and contributes to the complexity of Sox protein functions in diverse genetic contexts (Schlierf et al. 2002). Sox7, Sox17 and Sox18 are members of the SoxF group and are characterized by an N-terminal HMG-box and two conserved domains with transactivating activity (Francois et al. 2010; Fig. 1).

In many tissues, more than one Sox protein is expressed at a time. Co-expressed members of the same group often exert redundant functions, whereas Sox proteins from different groups counteract or cooperate with each other (for a review, see Wegner 2010). As the consensus heptameric DNA binding motif (A/T)(A/T)CAA(A/T)G is valid for all Sox proteins, co-expression of the different members can result in competition for binding at regulatory elements. However, because of the variation of single amino acids in the HMG-boxes, the different groups exhibit slightly different binding preferences (Jauch et al. 2011). Therefore, the exact nucleotide composition of a binding site might favour recruitment of a Sox protein from a certain group. Further target specificity results from the joint binding of Sox proteins and their interaction partners to so-called composite elements (for reviews, see Kamachi et al. 2000; Wegner 2010).

The objective of this article is to give an overview of the dazzling array of functions that Sox proteins fulfil during CNS development. Other transcriptional regulators with known functions during the same processes are only discussed when evidence is available for the functional interaction between these proteins and Sox factors in the context of the relevant regulatory network. We aim to provide as much mechanistic detail as possible. Peripheral nervous system (PNS) development in contrast will not be a major focus of this review, although Sox proteins are also important in this part of the nervous system. Likewise, discussion of the role of Sox proteins in the invertebrate nervous system is beyond the scope of this article. Most of the reviewed findings have been obtained in mammalian model systems and some in chicken. They are presented and organized by relevant cell type and Sox group, with Sox protein functions being first discussed with regard to NEP cells and then to the development of neurons, oligodendrocytes and astrocytes.

Sox proteins in NEP cells

SoxB1

The SoxB1 protein Sox2 is not only essential for maintaining pluripotency in stem cells of the inner cell mass and epiblast in the early embryo but is also later required to establish a neuroectodermal fate (Zhao et al. 2004). Hence, all neural cells in the CNS depend on Sox2. After contributing to neural fate induction, Sox2 is broadly expressed in NEP cells together with its relatives Sox1 and Sox3 (Bylund et al. 2003; Graham et al. 2003). During early development, Sox2 appears to act as a pioneer factor that prepatterns neural regulatory elements, already in embryonic stem cells, for subsequent binding by other SoxB1 proteins in NEP cells (Bergsland et al. 2011). All three SoxB1 members keep NEP cells in an undifferentiated state by counteracting proneural bHLH (basic helix-loop-helix) proteins, which force neuronal differentiation (Bylund et al. 2003). SoxB1 proteins interfere primarily with bHLH protein activity rather than expression. As a consequence, SoxB1 proteins suppress neurogenesis and maintain progenitor multipotency and renewal. An active role of SoxB1 proteins in cell cycle progression has not been observed. For neurogenesis to proceed, proneural bHLH proteins have to overcome SoxB1-dependent inhibition and then, in turn, repress SoxB1 gene expression (Bylund et al. 2003). Despite their suppressive effect on neurogenesis, Sox2 and Sox3 bind to regulatory regions of neuronal genes in NEP cells. This probably keeps these genes

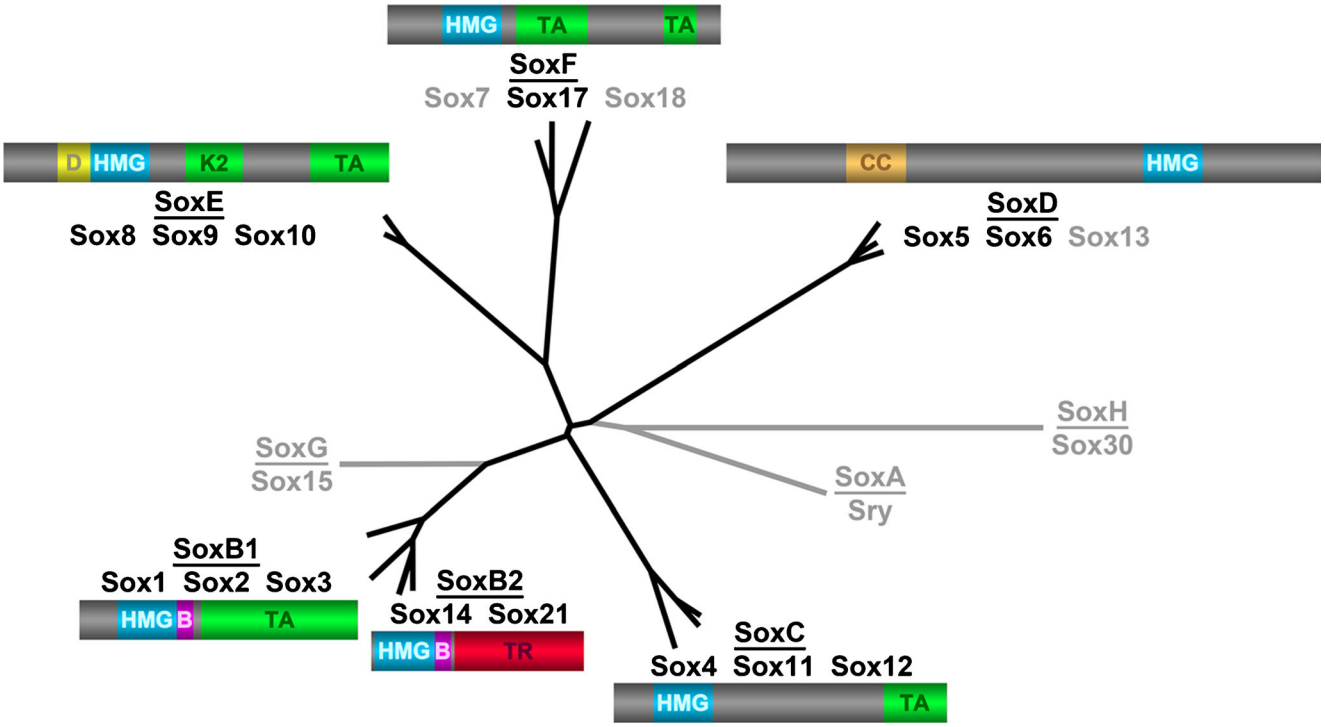

Fig. 1 Phylogenetic relationship and structure of Sox proteins. Unrooted phylogenetic tree showing the relationship of high-mobility group (*HMG*) domains from the 20 mouse Sox proteins (www.trex.uqam.ca). Closely related Sox proteins cluster and are combined in groups (*SoxA–SoxH*). Sox proteins with relevance in CNS development and the groups to which they belong are presented in *black*, whereas Sox proteins with no or unknown CNS functions are shown in *grey*. The arrangement of conserved domains is depicted for each Sox group. These include HMG domain (*blue*), coiled-coil domain (*CC*, *brown*), dimerization domain (*D*, *yellow*), group B homology domain (*B*, *purple*), transactivation domain (*TA*, *green*), transrepression domain (*TR*, *red*) and SoxE-specific protein interaction domain (*K2*, *green*)

in a poised state. Sox2 and Sox3 thereby predetermine cells for neuronal differentiation and, at the same time, hinder precocious maturation and ensure an undifferentiated state (Bergsland et al. 2011; Wegner 2011). Sox2 is also expressed in proliferating progenitors of adult neurogenic niches, i.e., in the subventricular zone of the lateral ventricles and the subgranular zone of the dentate gyrus of the hippocampus (Ferri et al. 2004). As in embryonic NEP cells, one of its functions is to maintain cells as proliferative precursors. Accordingly, neural progenitor pools are depleted in Sox2 mutant mice and adult neurogenesis is strongly decreased. Interestingly, the adult CNS seems to be even more sensitive to reduced levels of Sox2 than the embryonic CNS, probably because less overlap occurs between the expression of Sox2 and the other SoxB1 proteins (Ferri et al. 2004).

The essential role of Sox2 for neural fate determination and the generation and maintenance of pluripotent neural precursor cells is also supported by its role as a potent reprogramming factor for the induction of neural stem cells. Several combinations of transcription factors have been used to generate induced neural stem cells, all of which include Sox2 (for a review, see Maucksch et al. 2013). The induction of neuroectodermal fate and the suppression of mesodermal fate by Sox2 seem to be decisive steps towards a neural progenitor (Thomson et al. 2011).

SoxE

Whereas SoxB1 proteins are the only Sox proteins with strong expression in NEP cells from the start, Sox9 expression follows quickly. In the mouse spinal cord, it is initiated around 10.5 days post coitum (dpc) and broadly overlaps with SoxB1 protein expression after 11.5 dpc (Scott et al. 2010; Stolt et al. 2003). Sox9 expression appears to strengthen the capacity of NEP cells to self-renew and to give rise to glia in addition to neurons as indicated by the following observations. Sox2-positive but Sox9-negative early NEP cells are less potent in neurosphere formation than those from later stages that express both Sox2 and Sox9. The few neurospheres that develop from Sox2-positive-only NEP cells furthermore tend to primarily generate neurons rather than a mixture of neurons and glia. This suggests that the combination of Sox9 and Sox2 is essential for a neural stem cell phenotype (Scott et al. 2010; Fig. 2). Whereas the ability of Sox2 to preselect embryonic stem cells to become neural progenitor cells is independent of

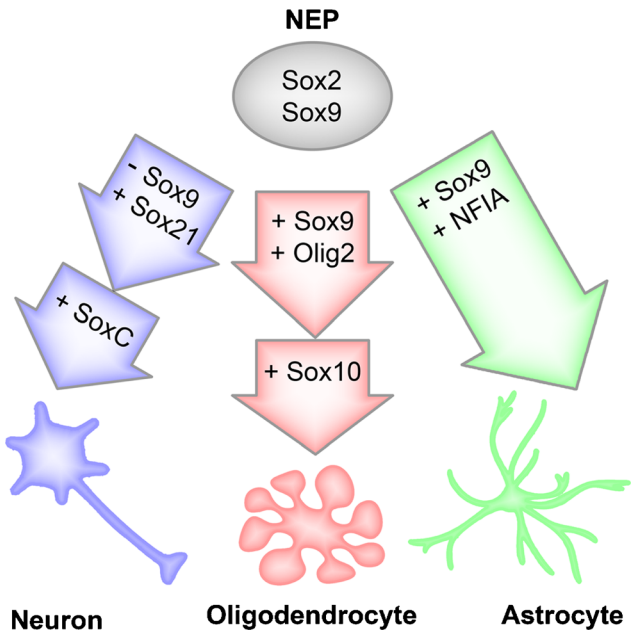

Fig. 2 Essential Sox proteins and interaction partners in CNS development. The most relevant Sox proteins are shown, plus other selected transcription factors whose upregulation (+) or downregulation (−) is required in neuroepithelial precursors (*NEP*) or for their development into neurons, oligodendrocytes and astrocytes

Sox9, its repressive effect on neurogenesis might rely on Sox9. In agreement with such an assumption, Sox9 on its own has been shown to be an inhibitor of neuronal differentiation in subventricular zone cells of the adult (Cheng et al. 2009) and the loss of Sox9 in embryonic mouse spinal cord results in a transient increase in moto- and interneuron generation (Stolt et al. 2003).

SoxD

Further Sox proteins with expression in the neuroepithelium are Sox5 and Sox6 from the SoxD group (Martinez-Morales et al. 2010; Stolt et al. 2006). In the spinal cord, many NEP cells co-express the two SoxD proteins (Stolt et al. 2006). In other regions of the CNS, expression can be mutually exclusive. Subpallial NEP cells, for instance, predominantly express Sox5, whereas pallial NEP cells are Sox6-positive (Azim et al. 2009; Lai et al. 2008). Their role in progenitor cells is largely uncharacterized in the mouse model but Sox5 has been studied in the chicken neural tube (Martinez-Morales et al. 2010). Its expression in NEP cells peaks during neurogenesis before the onset of gliogenesis and is eventually downregulated in most of the post-mitotic differentiating neurons and glia (Martinez-Morales et al. 2010; Stolt et al. 2006). Premature overexpression of Sox5 in the chicken neural tube forces NEP cells to exit the cell cycle and induces apoptosis so that the size of the spinal cord and its total cell number are reduced (Martinez-Morales et al. 2010). Sox5 strongly enhances the expression of Axin2, which itself is an inhibitor of active β-catenin. Hence, β-catenin can no longer induce cyclinD1 and cells are forced to exit the cell cycle. Sox5 thus acts as a modulator of canonical Wnt signaling in NEP cells (Martinez-Morales et al. 2010).

Sox proteins in neurogenesis

SoxB

During specification to a neuronal fate, the Sox protein expression pattern changes. Downregulation of Sox9 expression appears to be an essential prerequisite for neurogenesis (Fig. 2), at least in the adult subventricular zone and appears to be mediated, at least in part, by microRNA miR124 (Cheng et al. 2009). Another requirement for neurogenesis is the induction of Sox21, which depends on proneural bHLH proteins and commences in proliferating NEP cells that are still SoxB1-positive in the ventricular zone (Sandberg et al. 2005). Sox21 expression levels alternate substantially along the dorsoventral axis between areas of lower and higher expression. The different subtypes of neurons might thus vary in their dependence on Sox21. Sox21 belongs to the SoxB2 group and strongly resembles SoxB1 proteins, apart from the presence of a C-terminal transrepression domain instead of a transactivation domain (Uchikawa et al. 1999). The shift from SoxB1 to SoxB2 represents a shift from transactivators to transrepressors with highly similar binding preferences. Most likely, Sox21 interferes with the anti-neurogenic activity of SoxB1 proteins by competition for binding to common target genes and subsequent repression. Accordingly, the exchange of its repressor domain by a VP16 transactivation domain converts Sox21 to a SoxB1-like inhibitor of neurogenesis (Sandberg et al. 2005). Evidence suggests that the antagonism of SoxB1 and SoxB2 proteins arose late during evolution, as it is not observed in *Drosophila* in which both the SoxB1 protein SoxNeuro and the SoxB2 protein SoxB2.1/Dichaete perform similar and partially redundant functions during neural fate induction and neuroblast formation (for reviews, see Guth and Wegner 2008; Wegner and Stolt 2005).

Sox21 expression also forces cell cycle exit and extends into the early stages of neuronal differentiation before eventually fading with proceeding maturation. Post-mitotic expression has only been observed in a few V2 interneurons (Sandberg et al. 2005). In contrast to the embryo where Sox21 is not expressed in the hippocampus, it is found in this region in the adult (Matsuda et al. 2012). Its deletion interferes with adult neurogenesis and results in a reduced number of newly generated neurons because of the impaired differentiation of transient amplifying progenitors in the subgranular

zone. To promote adult neurogenesis, Sox21 directly interferes with the anti-neurogenic Hes5 (Matsuda et al. 2012).

So far, little is known about SoxB1 expression and function in neurons. Most neuroblasts downregulate SoxB1 expression upon their exit from the cell cycle (Bylund et al. 2003). Only some subtypes of neurons still depend on Sox1, Sox2 or Sox3 once they have entered the stage of differentiation. In addition to its expression in embryonic and adult proliferating neural precursors, Sox2 is maintained in differentiated areas of the thalamus, striatum and septum (Ferri et al. 2004). In adult hypomorphic Sox2 mutant mice, these areas exhibit neurodegeneration suggesting that Sox2 prevents the death or degeneration of these neurons (Ferri et al. 2004). An influence on differentiation has also been observed in cortical GABAergic neurons that are diminished and morphologically abnormal in Sox2 hypomorphic mutants (Cavallaro et al. 2008). A further requirement of Sox2 is seen in retinal ganglion cell development. In these cells, Sox2 is the only expressed SoxB1 member (Taranova et al. 2006). Sox2 determines progenitor cell fate in the retina and although downregulated post-mitotically, regulates differentiation to the appropriate retinal cell type by directly targeting the Notch pathway (Taranova et al. 2006). In hypomorphic Sox2 mouse mutants, retinal neural progenitors undergo aberrant differentiation. Deletion of Sox2, on the other hand, results in a loss of proliferation and differentiation competence (Taranova et al. 2006). Region-specific functions of Sox2 in maintenance and differentiation of neurons thus exhibit a certain dosage sensitivity (Ferri et al. 2004; Taranova et al. 2006). In vitro data indicate that the effects of Sox2 on differentiation also rely on its expression already in neural progenitors and not only in differentiating cells (Cavallaro et al. 2008). In support of such an assumption, the differentiation of newly generated neurons in adult neurogenic niches is strongly impaired upon the reduction of Sox2 levels (Ferri et al. 2004).

Functions in neurons have also been reported for Sox1 and Sox3. Sox1, for instance, is expressed in telencephalic neurons of the ventral striatum throughout development (Ekonomou et al. 2005). In the absence of Sox1, the early differentiation of these neurons appears normal but migration to the proper location is affected. The early expression of Sox1 is furthermore not sufficient to rescue ventral striatal neurons. Rather, additional expression into the mature stage is necessary (Ekonomou et al. 2005). For Sox3, a role in the development of hypothalamic neurons has been suggested in knockout mice, which furthermore exhibit morphological abnormalities of midline CNS structures (Rizzoti et al. 2004).

SoxC

Transition from a NEP cell to a neuroblast is characterized not only by loss of Sox9 expression and exchange of SoxB1 by SoxB2 proteins but is also defined by the induction of SoxC transcription factors (Fig. 2). Interestingly, the future binding sites for SoxC proteins appear to have been preselected at earlier cell stages by Sox2 and Sox3 (Bergsland et al. 2011). The nestin gene represents a prominent example (Tanaka et al. 2004). It contains an intronic neural enhancer that is bound by SoxB1 proteins and class III POU proteins in NEP cells and then by SoxC proteins and class III POU proteins in neuroblasts.

Among the SoxC proteins, Sox4 and Sox11 are the most extensively studied. Sox12 is co-expressed but appears to be a minor contributor to overall SoxC protein function in the CNS (Hoser et al. 2008). Expression analyses in chicken and mouse spinal cord show the highest amounts of Sox4 and Sox11 in newly specified neuroblasts right after their exit from the cell cycle (Bergsland et al. 2006; Hoser et al. 2008). Overexpression of Sox4, Sox11 or Sox12 in chicken and mouse has revealed an inductive effect on pan-neuronal gene expression and differentiation (Bergsland et al. 2006). Several components of the neuronal cytoskeleton have been identified as direct targets including tubulin beta 3, MAP2 and doublecortin (Bergsland et al. 2006; Hoser et al. 2008; Mu et al. 2012). This link to the cytoskeleton appears to be evolutionarily conserved as the *Drosophila* SoxC protein also influences the expression of cytoskeletal components during dendritic pruning in the nervous system of the fly upon metamorphosis (Kirilly et al. 2009).

Despite their important role, SoxC proteins are not the only activators of pan-neuronal differentiation, since residual neurons differentiate in the absence of Sox4 and Sox11. These neurons express the typical proteins including tubulin beta 3 with correct timing and location (Thein et al. 2010). SoxC proteins play a similar role in adult neurogenic niches. In the subgranular zone of the hippocampal dentate gyrus, Sox4 and Sox11 are expressed in cells committed to a neuronal fate as soon as they downregulate Sox2 (Haslinger et al. 2009; Mu et al. 2012). They remain expressed in neuroblasts and finally disappear in mature neurons (Haslinger et al. 2009; Mu et al. 2012). SoxC gain of function induces adult neurogenesis, whereas loss of function represses it. In the absence of Sox4 and Sox11, adult neural precursor cells do not differentiate but, instead, maintain Sox2 expression (Mu et al. 2012). A recent gene expression screening of cells microdissected from the hippocampal subgranular zone has confirmed the strong expression of Sox4 and Sox11 in neuroblasts in this adult neurogenic niche (Miller et al. 2013). Consistent with the reported role of these Sox proteins in subgranular zone cell differentiation, the hippocampus is completely missing in the combined absence of Sox4 and Sox11 (Miller et al. 2013). During embryonic and adult neurogenesis, Sox4 and Sox11 activate the pan-neuronal differentiation program independently of the proliferative status of the cell and do not force cell cycle exit on their own (Bergsland et al. 2006; Haslinger et al. 2009).

Furthermore, SoxC proteins act as survival factors. A massive increase in apoptosis occurs in the absence of one or more

SoxC proteins (Bhattaram et al. 2010; Thein et al. 2010) with neurons being one of the most affected cell types. This points to a particularly important role of SoxC proteins in neurons on top of the limited capacity of post-mitotic neurons to compensate apoptosis by increased proliferation (Thein et al. 2010). Low levels of SoxC are possibly sufficient to protect cells from apoptosis, because cell death is only increased upon loss of two (Sox4 and Sox11) or all three SoxC proteins. This might also explain the absence of increased apoptosis after knockdown of Sox4 and Sox11 in chicken in which residual SoxC protein might be sufficient to guarantee cell survival (Bergsland et al. 2006).

Recently, Shim et al. (2012) implicated Sox4 and Sox11 in the development of corticospinal projection neurons. In the absence of Sox4 and Sox11, the cortical expression of reelin is lost causing an inversion of the upper and deeper cortical layers. Whereas we do not know whether the regulation of reelin is direct, evidence is available that Sox4 and Sox11 bind and activate the E4 enhancer of the *Fezf2* (forebrain embryonic zinc finger-like protein2) gene, which is a critical regulator of corticospinal neuron specification and connectivity. Regulation of the E4 element is an example of competition and counteraction of Sox proteins from other groups. The SoxD protein Sox5 competes with SoxC proteins for binding to E4 but, in contrast to Sox4 and Sox11, represses the enhancer (Shim et al. 2012). In post-mitotic deep-layer (layer VI) cortical and subplate neurons, Sox5 downregulates the expression of Fezf2 thereby restricting it to layer V (Kwan et al. 2008).

SoxD

The role of SoxD proteins in neuronal development has been intensely studied in mouse embryonic development. As is obvious from the phenotype of knockout mice, Sox5 is important for the differentiation, migration and projection of deep-layer cortical and subplate neurons. In the absence of Sox5, the positioning of layer V and layer VI neurons is inverted. Neurons fail to differentiate and axons of some subcortical projection neurons are lost and others are misguided (Kwan et al. 2008; Lai et al. 2008). However, in contrast to Sox4 and Sox11 knockout mice, reelin expression and upper layer composition is normal. Since the time of birth of the various cortical neuron subtypes is a critical aspect of proper positioning and differentiation, one possible function of Sox5 might be to suppress the premature generation of usually later-born subcerebral projection neurons (Lai et al. 2008). Sox5 refines the gene-regulatory network in deep-layer and subplate neurons by repressing expression of the transcription factors Fezf2 and Ctip2 (COUP-TF-interacting protein2) in layer VI (Kwan et al. 2008). In support of this finding, additional deletion of Ctip2 can rescue the Sox5-deficient phenotype (Lai et al. 2008).

Although belonging to the same SoxD group, Sox6 differs from Sox5 in its expression pattern in the embryonic brain. In the pallium, Sox5 is expressed in post-mitotic cells but, in the subpallium, it is only present in NEP cells as previously mentioned. Vice versa, Sox6 is found in pallial NEP cells but subpallially in post-mitotic neurons (Azim et al. 2009). At the neuroblast stage, Sox6 controls the proper segregation of pallial and subpallial fates by repressing the subpallial differentiation program. Mechanistically, Mash1 (mammalian achaete-scute homolog 1) is one of the targets that Sox6 represses in cooperation with the pro-neural bHLH protein Ngn2 (neurogenin2) in this context. Later on, Sox6 expression in subpallial post-mitotic neurons serves to guarantee proper interneuron differentiation (Azim et al. 2009). In the absence of Sox6, interneurons are generated but adopt aberrant subtype characteristics (Azim et al. 2009; Batista-Brito et al. 2009). Intriguingly, the functions of Sox5 in subcortical projection neurons and of Sox6 in cortical interneurons exhibit some similarities, as the SoxD protein suppresses untimely subtype differentiation in each case.

Sox proteins in oligodendrogenesis

SoxE

Oligodendrocyte development is still most extensively analysed and best understood in the spinal cord, which therefore serves as a model region for studying oligodendrogenesis. During embryonic spinal cord development, the first oligodendrocyte precursor cells (OPC) appear ventrally in the neuroepithelium in a defined domain. This is the motoneuron precursor (pMN) domain in which motoneurons have previously been generated. Several of the Sox proteins that are present in NEP cells of all domains (including those of the pMN domain, see above) remain expressed in OPC. One example is Sox9. At least in the ventral part of the neuroepithelium where it has been primarily studied, the switch from a NEP cell that predominantly generates neurons to a NEP cell that produces glia and the glial specification itself relies on Sox9 (Stolt et al. 2003; Fig. 2). Only a few OPC become specified in the spinal cord of mice with conditional CNS-specific Sox9 deletion. Instead, supernumerous motoneurons are generated from the ventral pMN domain arguing for a defective neuro-glial switch. However, oligodendroglial specification is not completely inhibited. The incomplete penetrance is, at least in part, ascribed to functional redundancy with Sox8, which is induced slighty later than Sox9 and then co-expressed in the ventral neuroepithelium (Stolt et al. 2005). Accordingly, the deficiency of both Sox8 and Sox9 is needed to completely abolish the specification of oligodendroglia (Stolt et al. 2005).

Those few OPC that are generated in the absence of Sox9 exhibit higher proliferation rates and have the ability to replenish the OPC pool during embryonic development, so that OPC numbers are almost normal again in the Sox9-deficient spinal cord at the time of birth. This argues that Sox9 becomes dispensable once OPC are specified. However, it does not mean that Sox9 is without function in OPC. Rather, it functions in a largely redundant manner with Sox10, which is induced in OPC upon specification (Fig. 2) and is then co-expressed with Sox9 and Sox8 (Stolt et al. 2002, 2003, 2005). SoxE proteins activate the expression of Pdgfra (platelet-derived growth factor receptor alpha; Finzsch et al. 2008), which is required for the proliferation, survival and proper migration of OPC (Armstrong et al. 1990; Barres et al. 1992). Deficiency for either SoxE protein alone still allows the expression of Pdgfra in OPC, albeit at reduced levels per cell (Finzsch et al. 2008; Stolt et al. 2002). Combined deletion of Sox9 and Sox10 in previously specified OPC, however, results in a loss of Pdgfra expression and, as a consequence, leads to impaired migration and increased apoptosis (Finzsch et al. 2008).

Whereas Sox9 expression extinguishes as OPC start to differentiate, Sox10 and Sox8 continue to be expressed. Indeed, Sox10 is even strongly upregulated at the onset of terminal differentiation and represents a decisive regulator of this process (Stolt et al. 2002). The overlapping expression with Sox8 is one reason that, in the constitutive absence of Sox10, myelin gene expression as an indicator of myelination is severely impaired but not completely abolished. Inhibition is only complete upon the combined deletion of Sox8 and Sox10 (Hornig et al. 2013). The relationship between Sox8 and Sox10 and their relative importance during terminal differentiation thus resemble those between Sox8 and Sox9 during OPC specification (Hornig et al. 2013; Stolt et al. 2004).

The central role of Sox10 for the initiation of terminal differentiation includes direct and indirect mechanisms as is evident from overexpression studies in chicken and loss-of-function studies in mice. Sox10 is a central component of the transcriptional network for oligodendrogenesis, which in addition to Sox10 includes Nkx2.2, Myrf (myelin regulatory factor) and the Olig bHLH proteins Olig1 and Olig2 (Emery et al. 2009; Lu et al. 2002; Qi et al. 2001; Zhou and Anderson 2002). Olig2 is expressed already in NEP cells of the pMN domain and induces the expression of Sox10. Later, it continues to be expressed in OPC and oligodendrocytes in which it is involved in the maintenance of Sox10 expression (Liu et al. 2007; Fig.3a). Part of this regulation is mediated by the U2 enhancer 36 kb upstream of the *Sox10* gene, which exhibits Olig2-dependent activity in OPC (Küspert et al. 2011). In turn, Sox10 contributes to the maintenance of Olig2 expression once induced. It additionally activates the expression of other components of the oligodendroglial regulatory network such as Nkx2.2 (Liu et al. 2007) and Myrf (Hornig et al. 2013; Fig. 3a). In the case of the *Myrf* gene, Sox10 has been shown to mediate its effects by binding to an enhancer in intron 1. Sox10 also induces genes that are characteristically expressed in differentiating oligodendrocytes such as the connexins 32 and 47, the major myelin genes Mbp (myelin basic protein), Plp (proteolipid protein) or Mag (myelin-associated glycoprotein; Bondurand et al. 2001; Hornig et al. 2013; Schlierf et al. 2006; Stolt et al. 2002). This can happen alone or in combination with other transcription factors of the oligodendroglial network (Fig. 3a). Sox10 for instance interacts with Olig1 to induce Mbp expression (Li et al. 2007). In several cases, including the expression of connexin 32 and 47, Mbp and Mag, Sox10 cooperates with Myrf, which synergistically increases transactivation by Sox10 (Hornig et al. 2013). At least in some cases, synergy appears to be based on the joint binding of Sox10 and Myrf to the same regulatory regions. A comparison of ChIP-Seq data sets has revealed that more than 30 % of regions bound by Myrf are simultaneously enriched in Sox10 precipitates arguing for common regulatory functions of both transcription factors (Bujalka et al. 2013). Binding to neighbouring DNA motifs might be facilitated by protein-protein interaction between Sox10 and Myrf. Such interaction indeed occurs and has been mapped to the dimerization and HMG domains of Sox10 (Hornig et al. 2013). Hence, Sox10 first activates Myrf expression and then cooperates with Myrf to activate myelin gene expression (Fig.3a). A similar feed-forward mechanism has been described during peripheral myelination in Schwann cells in which Sox10 first induces Krox20 and then interacts with this zinc finger transcription factor to activate myelin genes (Ghislain and Charnay 2006; Jones et al. 2007; Reiprich et al. 2010).

In Schwann cells, Sox10 is a potent regulator of microRNA expression (Gokey et al. 2012). By analogy, we can assume that Sox10 function in oligodendroglial development also involves microRNAs (Fig. 4). Interestingly miR388, which is one of the microRNAs under control of Sox10 in Schwann cells, also occurs in oligodendrocytes in which it has pro-differentiation functions and is important for myelination (Dugas et al. 2010; Gokey et al. 2012; Zhao et al. 2010). In support of a role for Sox10 in the regulation of miR338 in oligodendrocytes, Sox10 is bound to a putative enhancer region of this microRNA not only in the PNS but also in the CNS (Gokey et al. 2012). miR338 might thus also mediate part of the pro-differentiation functions of Sox10 in oligodendrocytes.

In its role as a transcription factor, Sox10 interacts with the mediator complex via its Med12 subunit (Vogl et al. 2013). The mediator complex connects transcription factors at cell-type-specific enhancers to the general transcription machinery at the promoter and thereby secures enhancer function. Not only the dimerization and HMG domains of Sox10 but also the C-terminal transactivation domain are involved in protein-protein interaction with Med12. The relevance of this

interaction for myelination has been inferred from the finding that Med12-deficient OPC fail to terminally differentiate (Vogl et al. 2013).

Another aspect of the function of Sox10 might involve its ability to recruit chromatin-modifying and -remodelling activities. In Schwann cells, Sox10 has been shown to recruit histone deacetylases Hdac1 and Hdac2 and Brg1-containing chromatin remodelling BAF (Brg1-associated factor) complexes to its target genes and to rely on their activity during terminal differentiation (Jacob et al. 2011; Marathe et al. 2013; Weider et al. 2012). As histone deacetylases and chromatin-remodelling complexes are also involved in oligodendrogenesis (Marin-Husstege et al. 2002; Yu et al. 2013), a similar mode of action for Sox10 in differentiating oligodendrocytes appears likely. Whether Sox10 function in oligodendrocytes involves the same chromatin-modifying and -remodelling activities as in Schwann cells or different ones is currently unclear.

Sox8 is similar enough to Sox10 to share many of its biochemical properties: like Sox10, it can bind to the enhancer of the *Myrf* gene in vitro, induce myelin gene regulatory sequences in reporter gene assays and interact with the same protein complexes (Hornig et al. 2013; Stolt et al. 2004; Wissmüller et al. 2006). However, its transactivating potential is usually lower compared with that of Sox10 (Hornig et al. 2013). Therefore, the ability of Sox8 to rescue oligodendrocyte differentiation is limited, even when expressed in amounts like those of Sox10, as shown in a mouse model with genetic replacement of Sox10 by Sox8 (Kellerer et al. 2006). Compared with Sox9 and Sox10, Sox8 is thus of minor importance during oligodendrocyte development. Accordingly, when deleted alone, oligodendrocytes exhibit only a mild and transient delay of terminal differentiation (Stolt et al. 2004). In summary, SoxE proteins promote lineage progression at several points of oligodendroglial development, with Sox9 being primarily important for oligodendroglial specification both Sox9 and Sox10 jointly supporting OPC survival and lineage progression and Sox10 driving oligodendroglial differentiation.

The essential role of Sox10 in particular during oligodendrogenesis is also supported by two recent reports on the generation of induced OPC (iOPC) from mouse embryonic fibroblasts by lentiviral transduction of transcription factor cocktails (Najm et al. 2013; Yang et al. 2013). Sox10 has proved to be an indispensable component, if not the most decisive factor in this transcription factor mix, which additionally has to contain Olig2 and either Nkx6.2 (Najm et al. 2013) or Zfp536 (Yang et al. 2013) as the third component.

SoxD

Sox5 and Sox6 fulfil functions in oligodendroglial development that are contrary to those of SoxE proteins. They mainly act as inhibitors of lineage progression. The early neuroepithelial expression of Sox5 and Sox6 continues in OPC and ends during the terminal differentiation of these cells into oligodendrocytes (Stolt et al. 2006). Sox5 and Sox6 inhibit the untimely specification and differentiation of oligodendroglia. Accordingly, their absence results in the precocious generation of OPC from NEP cells at mid-embryogenesis and in premature myelination at the end of embryonic development.

Although the neuronal expression of Sox5 and Sox6 is often mutually exclusive, they are jointly expressed in OPC. However, compared with Sox6, the expression of Sox5 is lower in OPC. Correspondingly, Sox5 deficiency results in a weaker phenotype than that of Sox6. SoxD proteins are another example of redundantly acting Sox proteins in oligodendroglia because, compared with Sox6 deletion alone, the additional loss of Sox5 increases the number of precocious OPC and myelinating oligodendrocytes dramatically (Stolt et al. 2006). In analogy to their function in several types of neurons, SoxD proteins therefore regulate the proper timing of differentiation in oligodendrocytes.

Interestingly, SoxD proteins are active in the same events of oligodendroglial development that are regulated by SoxE proteins. This suggests that the functions of both groups of Sox proteins are interlinked. This assumption has indeed been supported by mechanistic studies (Fig. 4). Sox5 and Sox6 compete with SoxE proteins for binding to major myelin gene promoters and thereby inhibit myelin gene activation (Stolt et al. 2006; Fig. 4a). Their action might include the recruitment of co-repressors such as Ctbp2 (C-terminal binding protein2; Stolt et al. 2008). Linkage between SoxE and SoxD protein function has also been described in other cell lineages. Intriguingly, their relationship can be synergistic and antagonistic. In chondrocytes, for instance, many terminal differentiation genes are jointly activated by a combination of Sox9, Sox6 and Sox5 (Lefebvre et al. 2001).

The complex relationship between SoxE and SoxD proteins is also evident from findings that the expression of the SoxD protein Sox6 in OPC depends on Sox9 (Stolt et al. 2006; Fig. 4a). Whether Sox9 activates the transcription of the *Sox6* gene directly is currently unclear. Intriguingly, SoxE proteins might not only be responsible for the induction and maintenance of Sox6 expression in OPC but might also arrange its downregulation in differentiating cells by a microRNA-mediated mechanism. miR338 as a potential target of Sox10 (Gokey et al. 2012) and miR219 are upregulated concomitantly with rising Sox10 levels in terminally differentiating oligodendrocytes. Both microRNAs have been shown to decrease Sox6 levels (Dugas et al. 2010; Zhao et al. 2010; Fig.4b). As a consequence, SoxD protein levels are reduced at the same time as Sox10 levels increase, so that they are less efficient competitors of Sox10 function at the onset of terminal differentiation. This in turn should boost the ability of Sox10 to activate myelin gene expression and the myelination program (Fig. 4b).

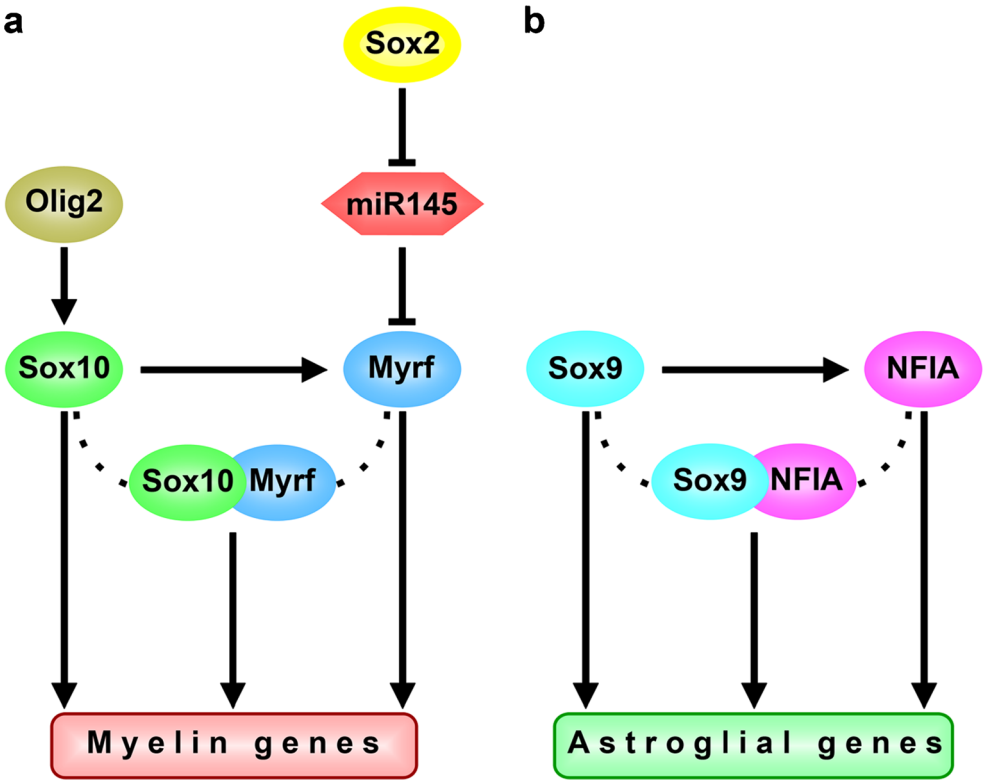

Fig. 3 Important regulatory circuits in glial development. **a** Essential regulatory steps for the induction of myelin gene expression are shown. Olig2 induces Sox10 in OPC. Myelin regulatory factor (*Myrf*) is upregulated directly by Sox10 and indirectly by Sox2, which represses microRNA miR145 and thereby releases Myrf from inhibition by miR145. Sox10 and Myrf then activate myelin gene expression, either alone or cooperatively. Complex formation between Sox10 and Myrf is indicated by *dotted lines*. **b** Essential regulatory steps for the induction of astroglial gene expression. Sox9 induces NFIA expression. Sox9 and NFIA then activate astroglial gene expression, either alone or jointly. Complex formation between Sox9 and NFIA is indicated by *dotted lines*

SoxC

Like SoxD proteins, SoxC proteins appear to act as inhibitors of terminal differentiation in the oligodendrocyte lineage (Potzner et al. 2007). Sox4 and the closely related Sox11 are expressed not only in specified and immature neurons but also transiently in emerging OPC (Kuhlbrodt et al. 1998). Evidence for their functional relevance in oligodendroglial differentiation comes from a transgenic mouse model in which the oligodendroglial expression of Sox4 is prolonged into the differentiated state. This results in hypomyelination (Potzner et al. 2007). Whether SoxC proteins function in a manner similar to or differently from SoxD proteins is currently unclear.

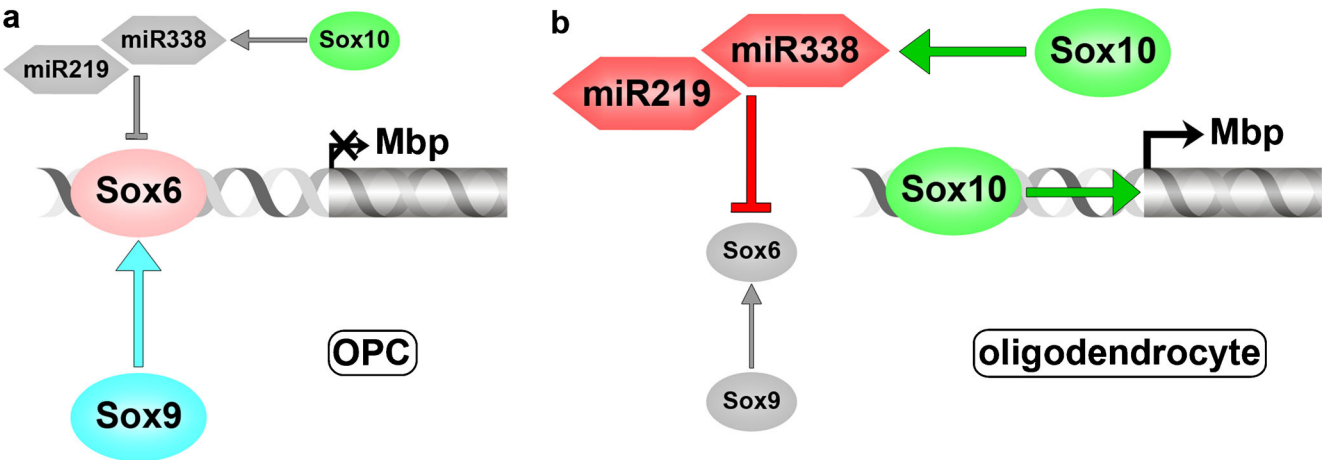

Fig. 4 Control of myelin gene expression in OPC and differentiating oligodendrocytes. **a** In OPC, Sox9 activates Sox6 expression. Sox6 competes with Sox10 for binding to regulatory regions of myelin genes (exemplified by the *Mbp* [*myelin basic protein*] promoter) and represses myelin gene expression. **b** In myelinating oligodendrocytes, increased Sox10 levels induce the expression of miR338. Together with miR219, miR338 represses Sox6. As a consequence, Sox10 obtains unrestricted access to regulatory regions and activates myelin genes (*grey* inactive elements of regulatory circuit)

SoxB1

An unexpected influence of Sox2 and Sox3 on the terminal differentiation of oligodendrocytes has recently been observed (Hoffmann et al. 2014). Among SoxB1 proteins, Sox2 and Sox3 but not Sox1, are expressed in OPC into the initial stages of terminal differentiation and myelin gene expression. The deletion of Sox2 or Sox3 in previously specified OPC leaves early development, proliferation and migration unaltered but impairs terminal differentiation and hence myelination. Again, closely related Sox proteins seem to act redundantly because myelination is much more severely affected in the absence of both Sox2 and Sox3 than after deletion of only one of them. With regard to the terminal differentiation of oligodendroglia, the phenotype resembles a weaker manifestation of the terminal differentiation defect observed in the absence of Sox10. However, mechanistic studies indicate a different underlying cause. In vitro, Sox2 is able to directly activate myelin gene expression but does so less efficiently than Sox10. As the expression of Sox10 is unaltered in the absence of Sox2 and Sox3, the terminal differentiation defect is unlikely to be caused by the weak direct influence of SoxB1 proteins on myelin gene transcription. Rather, SoxB1 proteins appear to exert their function, at least in part, by an indirect de-repression of pro-differentiation factors. Sox2 represses miR145 and thereby releases miR145 targets from inhibition (Fig.3a). Among the targets of miR145 in oligodendroglial cells are Myrf, Med12 and Sox9, all three having direct relevance for oligodendrocyte development and differentiation (Emery et al. 2009; Vogl et al. 2013). Intriguingly, Myrf as a central regulator of CNS myelination is thus not only under the positive transcriptional control of Sox10 but is also de-repressed by Sox2 (Hoffmann et al. 2014). Additionally, Sox2 might exert part of its function as a pioneer factor in OPC. Similar to its role in NEP and neuroblasts (Bergsland et al. 2011), Sox2 might preselect genes of pro-myelinating factors and myelin proteins for future binding of Sox10 during terminal differentiation.

SoxF

Among SoxF proteins, Sox17 expression has been reported during oligodendroglial development. Its expression is highest before or concomitant with cell cycle exit and the onset of terminal differentiation. In oligodendroglial cells, Sox17 interferes with the Wnt/β-catenin pathway, which has inhibitory effects on OPC differentiation (Chew et al. 2011). Additionally, Hedgehog signaling is under the influence of Sox17. In the prolonged and increased presence of Sox17, Gli2 as a mediator of Hedgehog signaling is upregulated. With Hedgehog signaling being a negative regulator of β-catenin (Schneider et al. 2010), Sox17 might partly exert its influence on the Wnt signaling pathway by inducing the Gli2-dependent repression of β-catenin expression (Ming et al. 2013). Additionally, Sox17 appears to recruit β-catenin and its binding partner Tcf4 into a complex, thereby initiating the proteasomal degradation of β-catenin. By interfering with Wnt signaling, Sox17 favours cell cycle exit in OPC and promotes the induction of terminal differentiation in cell culture and in a Sox17-overexpressing mouse model (Chew et al. 2011; Ming et al. 2013). The cell cycle effect appears to be attributable to the inhibition of cyclinD1, which is under Wnt control and is thus indirectly responsive to the presence of Sox17. Sox17 is, to date, the only Sox protein with a reported influence on the cell cycle in cells of the oligodendrocyte lineage (Chew et al. 2011; Sohn et al. 2006). Furthermore, direct effects on myelin gene expression might be of importance because Sox17 can transactivate the Mbp promoter in cell culture (Sohn et al. 2006).

Sox proteins in astrogenesis

SoxE

Just as oligodendrocytes, astrocytes are generated from distinct domains of the neuroepithelium after the neuro-glial switch. Many Sox proteins are expressed in developing astrocytes but knowledge about their functions is limited. For SoxB1 (Hoffmann et al. 2014) and SoxD proteins (Stolt et al. 2006), no more than their expression in astroglia has been described. From the SoxE group, only Sox9 is expressed in astrocytes, whereas Sox10 and Sox8 are exclusive to oligodendroglia.

Sox9 is important not only for the induction of the neuroglial switch in the pMN domain of the ventral spinal cord to initiate oligodendrogenesis but also in the surrounding domains in which astrogenesis occurs (Stolt et al. 2003; Fig. 2). Accordingly, astrogenesis is impaired in the absence of Sox9 resulting in severely reduced numbers of astrocytes (Stolt et al. 2003). One function of Sox9 is the induction of NFIA (nuclear factor-IA), itself a crucial regulator of gliogenesis (Deneen et al. 2006) (Fig. 3b). Sox9 is necessary and sufficient for the initiation of NFIA expression via binding to the e123 enhancer of the *NFIA* gene (Kang et al. 2012). After NFIA induction, Sox9 interacts physically with NFIA to induce genes with relevance for astrocyte migration and metabolism, such as Apcdd1 and Mmd2, leading to the formation of ectopic GLAST (glutamate aspartate transporter)-positive astrocytes (Kang et al. 2012). This is another example of a feed-forward loop in which a Sox protein induces a decisive transcription factor with which it teams up subsequently to activate cell-type-specific protein expression (Fig.3b). It thus resembles the mechanisms described for Sox10 and Myrf in oligodendrogenesis or for Sox10 and Krox20 in peripheral myelinogenesis.

Concluding remarks

As outlined above, Sox proteins influence many different processes in the CNS including cell determination events, lineage progression, differentiation, cell survival and phenotypic homeostasis, with important roles in all major CNS cell lineages. We thus conclude that they are extremely versatile transcriptional regulators that can be put to use under many different conditions. As a prerequisite for such multifunctionality, Sox proteins employ various strategies and mechanisms and undergo complex relationships not only with a multitude of interacting regulators but also among each other. The early activity of one Sox protein can pave the way for the later action of other Sox proteins, as described for SoxB1 and SoxC proteins during neurogenesis. However, Sox protein function can also be antagonistic and thus initiate or delay developmental decisions, as observed for SoxB1 and SoxB2 proteins during neural fate specification or SoxE and SoxD proteins during oligodendrocyte development. Additionally, ample evidence has been presented for the partitioning of function in cases in which Sox proteins are co-expressed. Alternatively, closely related Sox proteins often exhibit functional redundancy when co-expressed, as observed for SoxB1 proteins in NEP cells, SoxC proteins during neurogenesis or SoxE proteins during oligodendrogenesis. Redundancy might serve as a means to impart a certain degree of robustness to the regulated process.

Much of the function of Sox proteins can be attributed to their role as classic transcription factors that directly induce cell-type and stage-specific effector genes during a defined developmental process with the help of interacting transcription factors, the basal transcription machinery and accessory complexes such as the Mediator complex. However, recent evidence has also uncovered a whole array of alternative modes of action amongst which are epigenetic functions including pioneer factor functions as reported for Sox2 during neural induction and the ability to recruit chromatin-modifying or -remodelling complexes as best exemplified by Sox10. Their impact on microRNA expression furthermore allows them to influence and fine-tune cell development and identity not only at the epigenetic and transcriptional level but also at the posttranscriptional level. With these many functions, some Sox proteins represent essential nodes in their respective regulatory networks and exert functions that would have been described in previous times as “master regulators”.

Recently, Sox2 has been associated with the function of super-enhancers in ES cells (Hnisz et al. 2013; Whyte et al. 2013). Super-enhancers represent large clusters of enhancers in the vicinity of key cell identity genes that are occupied by master regulators and that govern the expression of these genes. Although few data exist concerning the role of super-enhancers in neural development, Sox proteins might be associated with them, either as master regulators that bind to these super-enhancers and contribute to their activity or as cell identity genes that are under super-enhancer control.

Whereas Sox protein function is fairly well understood in NEP, neurons and oligodendrocytes, comparatively little is known about their function in astrocytes. This is not too surprising as the transcriptional control of astrocytes and their development have been poorly studied in the past. However, this is about to change and, with astrocyte development becoming a major research focus, more information should become available soon. However, even from the little information currently available, a significant function of Sox proteins in astrogenesis is evident, as summarized in this review.

The essential role of Sox proteins is also evident from their indispensable contribution to reprogramming and cell conversion schemes. Existing and future mechanistic insights into Sox protein function during neurogenesis and gliogenesis therefore have the potential to further our understanding of these processes and might be instrumental in optimizing these strategies for use in cell replacement or assisted regeneration. Undoubtedly, Sox proteins will keep us busy for some time to come.

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