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The Yin and yang of Sox proteins: activation and repression in development and disease

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Abstract

The general view of development consists of the acquisition of committed/differentiated phenotypes following a period of self-renewal and progenitor expansion. Lineage specification and progression are phenomena of antagonistic events, silencing tissue-specific gene expression in precursors to allow self-renewal and multipotentiality, and subsequently suppressing proliferation and embryonic gene expression to promote the restricted expression of tissue-specific genes during maturation. The high mobility group-containing *Sox* family of transcription factors constitutes one of the earliest classes of genes to be expressed during embryonic development. These proteins are not only indispensable for progenitor cell specification, but are also critical for terminal differentiation of multiple cell types in a wide variety of lineages. *Sox* transcription factors are now known to induce or repress progenitor cell characteristics and cell proliferation, or activate the expression of tissue-specific genes. *Sox* proteins fulfill their diverse functions in developmental regulation by distinct molecular mechanisms. Not surprisingly, in addition to DNA binding and bending, *Sox* transcription factors also interact with different protein partners to function as co-activators or co-repressors of downstream target genes. In this article, we seek to provide an overview of the current knowledge of *Sox* gene functional mechanisms, in an effort to understand their roles in both development and pathology.

Keywords

HMG; SOX; Development; transcription; Wnt; interactions

Introduction

The *Sox* protein family of transcription factors has been identified as one of the most important groups of developmental regulators both in vertebrates and invertebrates (Bowles et al. 2000; Wegner 1999). The biological functions of these proteins during embryonic and postnatal development have been defined in a variety of tissues and cell types. Furthermore, the roles of *Sox* transcription factors are also being investigated in disease and in cell repair. The *Sox* family has no single biological function and, among their multiple roles, *Sox* transcription factors induce or suppress progenitor cell properties such as proliferation and multipotentiality, or initiate differentiation programs by activating the expression of tissue-specific genes. Despite overlapping functions within families, each *Sox* protein modulates a unique set of target genes in a specific cell type. There is already a large body of evidence supporting the generation of specific *Sox*-mediated cellular responses through mechanisms

of DNA bending, binding, and recruitment of different interacting protein partners to function as co-activators or co-repressors of downstream target genes.

As is required of developmental regulators with multiple functions, *Sox* transcription factors display very diverse tissue-specific expression patterns during embryonic and postnatal development. These expression patterns are not only modified during normal development, but also in a variety of pathological states, to the extent that some members of the *Sox* family are considered important diagnostic markers of childhood brain tumors (de Bont et al. 2008).

All these findings continue to raise a number of important issues that are crucial to understand the relationship between the molecular properties of *Sox* proteins, and the extreme diversity of their functional roles. The molecular mechanisms of gene activation or gene repression mediated by *Sox* proteins, and the functional redundancy of these transcription factors represent important questions for current and future research directions. In the present review article, we will highlight functional aspects of *Sox* proteins in the context of developmental events, with a particular focus on *Sox* proteins as transcriptional repressors, in an effort to understand their roles in both development and disease.

The *Sox* subfamily within the HMG superfamily, classification into *Sox* subgroups and some molecular properties

The *Sox* transcription factors bind to the minor groove in DNA, and were first identified based on molecular conservation of the 79 amino acid HMG (high mobility group) DNA binding domain found in the gene for the mammalian testis-determining factor SRY (Gubbay et al. 1990). Almost all *Sox* (SRY-BOX) genes display at least 50% amino acid similarity with the *Sry* HMG box. To date, the total number of *Sox* transcription factors identified is approximately 30 (20 in humans and mice, and 8 in *Drosophila*), subgrouped into 10 distinct families (A-J), not only based on homology within the HMG domain and other structural motifs, but also on functional properties (Schepers et al. 2002). These groups include: A, *Sry*; B, *Sox1*, -2, -3, -14 and -21; C, *Sox4*, -11 and -12; D, *Sox5*, -6 and -13; E, *Sox8*, -9 and -10; F, *Sox7*, -17 and -18; G, *Sox15* and -20; H, *Sox30*. The existence of two new subgroups - I and J - was postulated, including *Xenopus Sox31* and *C. elegans SoxJ*, respectively (Bowles et al. 2000). A thorough molecular analysis of the evolutionary history of the *SOX* family was based on the entire number of available HMG domain sequences and full-length protein sequences (Bowles et al. 2000; Wegner 1999). This study demonstrated that the majority of the *SOX* subfamilies defined in vertebrates were also represented in invertebrates by a single *Sox* gene.

All *Sox* factors recognize a similar DNA binding motif $A/T^A/TCAA^A/TG$, but their amino acid sequences outside the HMG domain are highly variable and display domains that favor binding with other regulatory protein partners. Molecular interactions with other transcriptional regulators are crucial for each *SOX* factor to recognize a specific target gene, as each protein of this family is expressed in many different cellular contexts and a specific cell type can co-express many *SOX* factors (Wegner 1999). *SOX* proteins can form stable transcription factor complexes with a variety of co-regulators to activate or repress gene transcription by modulating promoter activity. A typical example of this cooperative interaction is the demonstration that *SOX2* and *PAX6* activate transcription of the lens-specific δ -crystallin gene by acting on its *DC5* enhancer (Kamachi et al. 2001). There are also several examples of *SOX/OCT* complexes that regulate expression of different genes. *SOX2* and *SOX3* interact with *Oct3/4* to regulate *Fgf4*, *UTF1* and *osteopontin* gene expression in the embryo (Botquin et al. 1998; Kamachi et al. 2000; Nishimoto et al. 1999; Yuan et al. 1995). *SOX* and *Oct* binding sites are necessary for enhancer activity and cell

specificity of the *Hoxb1* gene, which encodes a protein involved in hindbrain patterning. A single *SOX* protein can also simultaneously recruit more than one transcription factor to regulate gene expression from a single promoter or enhancer (Ma et al. 2000), or can promote binding with transcriptional repressors to promoters, as demonstrated by the *SOX6/CtBP2* interaction (Murakami et al. 2001).

It is currently thought that the HMG domain itself not only plays a crucial role in the DNA-binding of *SOX* factors, but also in their interaction with other transcriptional co-regulators and in nuclear import (Wilson and Koopman 2002). However, as HMG domains are interchangeable between *SOX* factors (Bergstrom et al. 2000), other parts of the protein outside the HMG domain are likely to play a major role in selecting specific protein partners and generate cell- and developmental stage-specific functions for *SOX* transcription factors (Wilson and Koopman 2002). A recent study of *SoxE* binding partners revealed specific interactions with *Oct3/4*, *C/EBP*, *Olig2*, *Pax3* and *SP1*, but not the receptors for estrogen or thyroid hormone (Wibmuller et al. 2006), which supports the pleiotropic nature of *SOX* protein activity, although the manner in which cell-type or temporal specificity is determined is not understood.

Sox proteins in mechanisms involving functional antagonism during differentiation

SoxB1 members (Sox1–3)

Although it is well established that neural progenitors in the CNS are prevented from premature differentiation, the mechanism by which this occurs is poorly understood. The expression of *SoxB1* members in dividing CNS progenitor cells, and not in those expressing p27Kip1 or definitive neuronal markers such as NeuN, Tuj1 and Lim2 (Bylund et al. 2003), strongly suggests a role for these *SoxB1* transcription factors in the maintenance of the progenitor state. Indeed, inhibition of *Sox2* signaling resulted in enhanced neuronal differentiation (Graham et al. 2003). Consistent with this hypothesis, it was demonstrated that these *Sox* genes 1–3, with some measure of redundancy (Graham et al. 2003), prevented neurogenesis by antagonizing the function of proneural bHLH proteins, namely neurogenin (*Ngn*), and were downregulated once progenitor cells left the cell cycle (Bylund et al. 2003). *SoxB1* members bear transactivation domains, and the conclusion that they function as transcriptional activators was revealed by a hybrid HMG domain-containing with the Engrailed protein repressor module. HMG-VP16 activator suppressed neuronal differentiation similar to intact Sox1–3, whereas HMG-EnR generated post-mitotic neurons (Bylund et al. 2003). While these *Sox* genes collectively specify and maintain stem cells and progenitors, differential functions for each are being discovered in more recent studies. While *Sox1–3* are downregulated in mature neurons, the expression of *Sox1*, although not required for neurosphere generation, was shown to be necessary for the differentiation of neural progenitors from the ganglionic eminence and dorsal telencephalic wall into GAD65+ neuronal progenitors (Kan et al. 2007). *Sox1*-null mutant mice also lack telencephalic neurons that constitute the ventral striatum (Ekonomou et al. 2005). Indeed, only *Sox1*, not *Sox2* or *3*, was shown to be capable of inducing neuronal lineage commitment by repressing *Hes1* gene expression (Kan et al. 2004). In addition to upregulating the transcription of *Ngn1*, *Sox1* suppresses beta-catenin-mediated TCF/LEF signaling to attenuate the Wnt pathway and promotes cell cycle exit, leading to neuronal cell differentiation (Kan et al. 2004). Like *Sox1*, *Sox3* is transiently expressed by proliferating and differentiating neural progenitors in the olfactory bulb and dentate gyrus, while persisting in specific postmitotic neuronal populations (Wang et al. 2006), although the mechanism by which *Sox3* induces neurogenesis is unclear.

In contrast to *Sox1* or *Sox3*, *Sox2* has been more consistently associated with multipotentiality and progenitor cell proliferation (Rex et al. 1997). *Sox2* expression is itself subject to repression by histone deacetylase activity (Lyssiotis et al. 2007), which is important for oligodendrocyte maturation (Shen et al. 2005; Shen et al. 2008). *Sox2* expression was restricted to proliferating progenitor cells, and its overexpression was observed to inhibit neurogenesis (Bani-Yaghoub et al. 2006). *Sox2* is thought to maintain cellular proliferative potential through the upregulation of Notch1 (Bani-Yaghoub et al. 2006) for the purpose of generating sufficient numbers of progenitors (Ellis et al. 2004). *Sox2*-deficient neural stem cells, however, remain multi-potent, likely due to compensation by *Sox3*, but the capacity for generating sufficient neurons is greatly reduced (Miyagi et al. 2008). This notion of progenitor maintenance is in agreement with the finding of high levels of *Sox2* expression in glial tumors of astroglial, oligodendroglial and ependymal lineages (Phi et al. 2008), but not in neuronal tumors. Possible molecular mechanisms were offered by studies in non-neural systems and in embryonic stem cells, implicating the regulation of cyclin D1 expression as a primary function of *Sox2* activity. In breast cancer cells, modulation of *Sox2* activity by overexpression or knockdown had little effect on other cell cycle-regulated genes including cyclin D3, cyclin E, p21^{Cip} and p27^{Kip} (Chen et al. 2008). The authors also demonstrated that *Sox2* and beta-catenin interact directly to synergistically activate the cyclin D1 proximal promoter (Chen et al. 2008). In embryonic stem cells, *Sox2* and Oct4 bound to the promoter of miR-302 - a cluster of miRNAs specifically expressed in stem cells and pluripotent cells - to stimulate its expression. miR-302a repressed the translation of cyclin D1, and promoted a decrease in G1 cells and an increase in S phase-cells (Greer Card et al. 2008). These observations are consistent with the notion of *Sox2* as a promitotic regulator, and while cell cycle regulation alone is insufficient to alter cell-fate decisions through the modulation of cyclin D1 expression (Lobjois et al. 2008), *SoxB1* proteins function to maintain neural precursors by mechanisms that may involve the *Notch* pathway. *Sox2* and *Sox1* respectively activate (Bani-Yaghoub et al. 2006) or inhibit (Kan et al. 2004) *Notch* signaling, but there is also evidence that *SoxB1* and *Notch* inhibit neuronal maturation by distinct mechanisms (Holmberg et al. 2008).

SoxB2: (Sox14, Sox21)

The *SoxB2* group possesses repression domains, and *Sox21* and *Sox14* inhibit the activation of the *delta-crystallin DC5* enhancer to different extents (Uchikawa et al. 1999). *Sox21* promotes neurogenesis by counteracting the activities of *Sox1-3*, and the ability of proneural proteins to promote lineage progression relies on their ability to upregulate *Sox21* expression (Sandberg et al. 2005). *Ngn2* stimulates *Sox21* expression and the latter in turn is associated with increased cell cycle exit, although the detailed mechanism is presently unknown.

SoxC (Sox4, Sox11, Sox12)

As activators, *Sox4* and *Sox11* have been shown to induce a neuronal phenotype in immature neuronal precursors of the early chicken embryo (Bergsland et al. 2006) in a manner that is independent of cell cycle exit. In the oligodendrocyte lineage however, prolonged expression of *Sox4* in vivo under the control of the *MBP* promoter results in reduced and delayed myelin gene expression in the spinal cord (Pötzner et al. 2007). High levels of *Sox11* are also found in human gliomas, in accordance with the degree of cell dedifferentiation (Weigle et al. 2005). In further support of an inhibitory role of *SoxC* in oligodendrocyte development, the ablation of *YY1*, which resulted in hypomyelination, also increased the levels of oligodendroglial lineage repressors, including *Sox11* (He et al. 2007). These *SoxC* proteins thus appear to possess opposing effects on neuronal versus glial differentiation, promoting one and repressing the other. The mechanism of *SoxC* protein repression is not understood, but since *SoxC* proteins, unlike *SoxD*, do not interfere with

Sox10-dependent upregulation of myelin genes (Pötzner et al. 2007), it is believed that the *SoxC*-induced hypomyelination is an indirect effect on the *MBP* gene.

SoxD (Sox5, L-Sox5, Sox6, Sox13)

Members of this group possess an HMG domain, but are missing transactivation domains, suggesting roles in structural organization in gene expression. *Sox5* and *Sox6* are essential for neuronal and chondrocyte development, while *Sox6* is also an important enhancer of erythropoiesis (Dumitriu et al. 2008). *Sox5* was recently found to prevent the premature development of later-born neurons, and thus regulates the timing of neocortical neuronal subtypes (Lai et al. 2008). *Sox5* promotes cell proliferation by repressing the expression of SPARC (Huang et al. 2008), a protein believed to be a tumor suppressor. In chondroblast differentiation, *Sox5* and *Sox6* promote the development of a proliferating pool of chondroblasts, and act by downregulating Indian hedgehog signaling, and the expression of *FGFR3* and *Runx2* (Smits et al. 2004).

In neural crest development, *Sox5* is expressed in early neural crest cells and continues to be expressed in melanocytes, but its loss does not affect melanoblast generation. However, the loss of *Sox5* rescues melanoblast generation in *Sox10*-reduced mice. *Sox5* binds to, and represses melanocytic target genes of *Sox10*, such as *Mitf* and *Dct* (Stolt et al. 2008). *Sox5* alone did not modulate these genes directly, but did so only in the presence of *Sox10* (see below, *SoxE* proteins). While competition for the same DNA binding site is possible, it appears more likely that in situations with multiple *Sox* recognition sites, the recruitment of co-repressors, C-terminal binding protein 2 (*CtBP2*) and *HDAC1* to the promoters of *Mitf* and *Dct* genes could be more effective. *Sox5* does not function exclusively as a co-repressor, but also recruits co-activators to *Sox9* target genes in chondrocytes (Hattori et al. 2008).

Sox6 promotes cardiomyocyte differentiation, an event associated with the downregulation of an L-type Ca^{2+} $\alpha 1\text{c}$ gene. There are eight consensus *Sox* recognition sites in 1.6kb of the Ca^{2+} $\alpha 1\text{c}$ promoter, and overexpression of *Sox6* suppresses reporter expression in constructs bearing this promoter region (Cohen-Barak et al. 2003). *Prtb* (proline-rich transcript of the brain), which interacts with *Sox6*, represses the activity of the $\alpha 1\text{c}$ gene promoter alone, as does *Sox6* alone, but interestingly, repression of reporter expression is abolished by co-expression of *Prtb* with *Sox6* (Cohen-Barak et al. 2003). This suggests that *Prtb* and *Sox6* antagonize each other as repressors. Skeletal muscle development consists of two successive waves of myogenesis, embryonic and fetal, generating slow and fast fibers respectively. *Sox6* mutant mice show increased slow fiber type-specific gene expression and reduced fast fiber gene expression (Hagiwara et al. 2005). *Sox6* has been demonstrated to repress the transcription of slow fiber type-specific genes typified by the Myosin heavy chain-beta ($\text{MyHC}\beta$), slow isoform (Hagiwara et al. 2007).

During erythropoiesis, definite erythroid cells in the fetal liver express adult beta globins while the epsilon gene is silenced. *Sox6* represses embryonic epsilon gene expression by directly binding its promoter (Yi et al. 2006). *Sox6* has been shown to silence other targets in various systems: i) the *Fgf-3* promoter through the recruitment of a corepressor, *CtBP2* (Murakami et al. 2001), ii) the *insulin II* gene by serving as an interacting co-repressor of the homeobox factor *PDX1* (Iguchi et al. 2005), and iii) the cyclin D1 promoter by interacting with beta-catenin and histone deacetylase (Iguchi et al. 2007).

Sox13 is expressed at high levels in a subset of neural progenitor cells as they exit from the cell cycle and migrate away from the ventricular zone (Wang et al. 2005). In T lymphocyte differentiation, *Sox13* promotes the development of gammaDelta lineage from progenitors while suppressing differentiation to the alphaBeta lineage (Melichar et al. 2007). This fate determination was mediated through inhibition of *Wnt* signaling, not by interacting with

beta-catenin per se, but instead by antagonizing its coactivator T-cell factor 1 (*TCF1*). *Sox13* also downregulated a known *TCF1* target gene, *Ly49a* in EL4 T cells. Finally, *Sox13*-null mice showed enhanced rates of thymocyte proliferation, indicating that *Sox13* antagonism of Wnt/TCF signaling mediated both lineage commitment and proliferative arrest (Melichar et al. 2007).

SoxE (Sox 8, 9, 10)

SoxE proteins promote neural crest progenitor formation, as well as differentiation of neural crest derived melanoblasts and glia (Bondurand et al. 2000; Britsch et al. 2001; Hong and Saint-Jeannet 2005; Kim et al. 2003; Taylor and LaBonne 2005), oligodendrocyte differentiation (Stolt et al. 2004; Stolt et al. 2003; Stolt et al. 2002) and cartilage development (Akiyama et al. 2002; Lefebvre et al. 1998; Sekiya et al. 2000).

SoxE, in particular *Sox9*, acts in two phases of neural crest development: promotion of neural crest properties, and of glial and melanocyte fate, while suppressing neuronal fates (Cheung and Briscoe 2003; Kim et al. 2003). *Sox9* suppresses the expression of neuronal markers *Pax6*, *Pax7*, *Nkx6*, *Irx3*, and its mode of action appears to be independent of *BMP* or *Wnt* signaling (Cheung and Briscoe 2003). In the neural crest, *Sox10* acts to maintain characteristics of multipotentiality in neural crest stem cells (Kim et al. 2003), and modulates neural crest progenitor properties by promoting glial development (Britsch et al. 2001) and by overcoming the antigliogenic and antineurogenic activities of *BMP2* and *TGFbeta*, respectively (Kim et al. 2003). The loss of *Sox10* from Schwannoma cells promotes differentiation into myofibroblasts with carbachol-stimulated contraction and calcium transients, indicating the role and bias of this *SoxE* protein in repressing myofibroblast-specific genes in a cell system known to transdifferentiate into several derivatives (Roh et al. 2006).

SoxE proteins are responsible for oligodendrocyte specification and maturation, with *Sox9* and *Sox10* playing critical roles in determining progenitor fate commitment and terminal differentiation. Initially, both proteins appear to function redundantly in oligodendrocyte precursors, but *Sox9*, whose expression precedes that of *Sox10* and *Sox8*, has been shown to be essential for the neuron-glia fate switch, suppressing the formation of spinal cord motoneurons, V2 interneurons and gray matter astrocytes. On the other hand, *Sox10*, which continues to be expressed in developing oligodendrocytes and astrocytes, is essential for myelination (Stolt et al. 2004; Stolt et al. 2003; Stolt et al. 2002). More recently, simultaneous deletion of *Sox9* and *Sox10* revealed a joint function in the maintenance of PDGFR α ⁺ oligodendrocyte progenitor cells (Finzsch et al. 2008), which underscores the importance of multiplicity of progenitor function of *Sox9*. *SoxD* family members *Sox5* and *Sox6* are now known to modulate *SoxE* protein function in oligodendrocyte development by preventing precocious oligodendrocyte specification (Stolt et al. 2006).

During skeletogenesis, cartilage and bone progenitors arise from a common precursor, which is specified by *Sox9* (Akiyama et al. 2005; Akiyama et al. 2004). Osteoblast and chondrocyte development are mutually exclusive events: *Wnt*/beta-catenin signaling determines fate decisions between osteoblast and chondrocyte lineages (Day et al. 2005; de Crombrughe et al. 2001; Hill et al. 2005). *Sox8* expression is downregulated upon differentiation of osteoblasts; it specifically prevents untimely osteoblast maturation (Schmidt et al. 2005) and premature expression of the run-related transcription factor 2 (*Runx2*), a master regulator of osteoblast differentiation and bone formation. *Sox9* inhibits osteoblast development and osteoblast developmental regulators such as beta-catenin (Day et al. 2005), and overexpression of *Sox9* drives cartilage formation, a process that is mimicked by beta-catenin deletion. The reverse is also observed (Akiyama et al. 2004). Furthermore, the commitment of progenitors to produce cartilage by the process of

chondrogenesis is also effected through *Sox9* by activating extracellular matrix genes *aggrecan*, *Col11a2* and *Col2a1* (Bridgewater et al. 1998; Kawakami et al. 2005; Sekiya et al. 2000). Interestingly, the recruitment of *Sox9* to the *aggrecan* gene enhancer element is itself facilitated by *SoxD* members, *L-Sox5* and *Sox6* (Han and Lefebvre 2008a).

In promoting chondrogenesis, *Sox9* induces cell cycle arrest or exit, and reduces the levels of the mitogen-activated protein kinase, ERK1 (Panda et al. 2001), whose inhibition had previously been found to promote chondrogenesis (Chang et al. 1998). Mechanistically, LEF/TCF transcription factors, which are beta-catenin coactivators, bind the same domain of beta-catenin as does *Sox9*. The binding of beta-catenin by *Sox9* prevents LEF/TCF binding, inhibiting the expression of *Wnt* target genes. Interaction with beta-catenin could also inhibit the transactivating functions of *Sox9*, leading to the eventual degradation of the *Sox9*/beta-catenin complex. In addition to beta-catenin, *Sox9* also represses *Runx2* function in osteoblasts (Zhou et al. 2006). The loss of *Sox9* derepresses the expression of *Runx1*, *Runx2* and *Runx3*, as well as target genes of *Runx2* such as *Col10a1*, indicating that *Sox9*-*Runx2* antagonism regulates skeletal fate determination.

In the intestinal epithelium, *Sox9* ablation results in increased cell proliferation and hyperplasia (Bastide et al. 2007). The hyperplastic crypts of the *Sox9*-deficient intestine were found to overexpress *Wnt* pathway-related genes, such as c-Myc and cyclin D1, as well as an increase in the number of cells expressing these genes. Direct interaction between *Sox9* and beta-catenin could not be demonstrated by coimmunoprecipitation in this study, however, a mutated DNA binding domain of *Sox9* ablated the ability of *Sox9* to modify beta-catenin-TCF activity. Interestingly, when the transactivating and beta-catenin interacting domains of *Sox9* were replaced with a VP16 transactivating domain, inhibition of beta-catenin-TCF activity surpassed that of the native *Sox9*. This observation indicated that the action of *Sox9* on beta-catenin function was likely to be mediated by the induced expression of an inhibitor of beta-catenin-TCF (Bastide et al. 2007), which would agree well with the findings that many *Sox* proteins of different classes, which lack homology outside of their HMG domains, possess the conserved property of inhibiting beta-catenin activity.

In myogenesis, *Sox8* and *Sox9* inhibit the MyoD-induced conversion of C3H 10T1/2 cells into myoblasts, and repress the expression of myogenin by MyoD. This supports the notion that *Sox8* and *Sox9* are responsible for maintaining myoblasts in an undifferentiated state to prevent precocious differentiation into myotubes (Schmidt et al. 2003).

In all three systems of melanocyte, oligodendrocyte and chondrocyte development, *SoxD* and *SoxE* proteins are coexpressed. Whereas *Sox5* and *Sox6* co-stimulate *Sox9* target genes in chondrocytes (Han and Lefebvre 2008b), *Sox5* was recently shown to repress the transcriptional activity of *Sox10* during melanocyte development from the neural crest (Stolt et al. 2008) by binding to *Sox10* response elements in melanocytic target genes, *Mitf* and *Dct*, in which multiple binding sites for *Sox10* have been mapped.

In the oligodendrocyte lineage, *Sox5* and *Sox6* are co-expressed with *Sox10* in progenitor cells that have not yet begun to express *MBP*, and ablation of *Sox5* and *Sox6* results in precocious specification of ventricular zone cells to oligodendrocyte progenitor cells (Stolt et al. 2006). Both *SoxD* proteins repress terminal differentiation of oligodendrocytes by interfering with *SoxE*-dependent stimulation of myelin gene expression (Stolt et al. 2006), so that binding of either class of protein to known *Sox10*-responsive elements in vitro was found in gel-shift assays to be mutually exclusive. Using chromatin immunoprecipitation however, both *Sox6* and *Sox10* were found at the *Sox10*-responsive *MBP* promoter at E16.5, but only *Sox10* was present on these sites in postnatal spinal cord (Stolt et al. 2006). It would appear that in myelin regulation, the nature of repression by *SoxD* includes competition for

interacting proteins, as both *Sox5* and *Sox6* interacted with *Olig2* and *Neurogenin 2* in GST-pulldown assays. These observations attest to the mode of *SoxD* protein activity - repression by competition for DNA or co-activator binding, or selective recruitment of co-repressors at specific promoters. The last possibility is believed to be the likely mechanism for *Sox5* in the neural crest (Stolt et al. 2008). Indeed, *Sox9* promotes *Sox10* expression in Neuro2A cells, and co-expression of either *Sox5* or *Sox6* with *Sox9* ablated *Sox9*-dependent *Sox10* expression (Stolt et al. 2003), indicating that *Sox5* and *Sox6* could interfere with the ability of *Sox9* to regulate the *Sox10* promoter. The precise mechanisms regarding *Sox9*-dependent *Sox10* expression still await elucidation.

SoxF (*Sox7*, *Sox17* and *Sox18*)

This group has been shown to be critical for endoderm and hair development (Irrthum et al. 2003; Kanai-Azuma et al. 2002), cardiogenesis (Liu et al. 2007), and angiogenesis (Matsui et al. 2006; Young et al. 2006). The gene targets of *SoxF* proteins identified to date, such as *FoxA* and *HNF1beta* (Sinner et al. 2004), *laminin alpha1* (Niimi et al. 2004), *VCAM1* (Matsui et al. 2006) and *FGF-3* (Sinner et al. 2004) are dependent on their transactivation functions, and few specific repressed targets have been described. In respiratory epithelial cells, *Sox17* promotes transdifferentiation of alveolar type II cells into epithelial cells, and stimulates promoter activities of *mFoxj1* while repressing that of *mSftpc*, an alveolus-specific gene (Park et al. 2006). However, repression of gene expression by *Sox17* may also be indirect. In the endoderm, *Sox17* induces the expression of a zinc-finger protein, *Zfp202*, which represses the expression of the transcription factor *HNF4a* (Patterson et al. 2008); thus gene targets of *Sox17* transactivation have turned out to be transcriptional repressors themselves. Currently, the best established mechanism of repression by *SoxF* proteins is the interference of *Wnt* signaling, as is frequently observed with *Sox* proteins of other subfamilies. In the endoderm, *Sox17* cooperates with beta-catenin to induce endodermal genes, and there is a shared sequence motif between *Sox17* and *Sox7* that mediates the physical interaction between beta-catenin and *Sox17* (Sinner et al. 2004). Deletion of this motif abolished binding to beta-catenin, and partially reduced beta-catenin-mediated transcriptional activity in lung cancer cells (Guo et al. 2008). The *Sox7* promoter was found to be hypermethylated in prostate cancer cell lines and colorectal cancers, and demethylation of the *Sox7* promoter resulted in a dramatic increase in *Sox7* expression. Ectopic expression of *Sox7* in *Sox7*-null cells inhibited the proliferation of colon cancer cells, indicating that *Sox7* inactivation is involved in cell proliferation and tumor progression (Guo et al. 2008). *Sox17* interacts with both TCF and beta-catenin (Sinner et al. 2007), and both domains on *Sox17* are required to antagonize *Wnt* signaling by promoting their proteasomal degradation.

Dual roles for *Sox17* in promoting cell cycle exit and progenitor maturation were also revealed in the oligodendrocyte lineage, where reduced progenitor cell proliferation and increased morphological differentiation were simultaneously induced by the overexpression of *Sox17* (Sohn et al. 2006). Understanding *Wnt* pathway modulation by *Sox* proteins could help to demystify the complex relationship between cell cycle control and lineage progression. The ability of *SoxF* members to regulate *Wnt* pathway signaling was further highlighted in a recent study comparing the repression of beta-catenin/TCF activity by various *Sox* family members (Sinner et al. 2007). Both *Sox10* and *Sox17* are potent inhibitors of beta-catenin-mediated transcription (Sinner et al. 2007) and are activators of myelin gene expression in the oligodendrocyte lineage (Sohn et al. 2006; Stolt et al. 2002), whereas members of *SoxC* (*Sox4* and *11*) were potent activators of *Wnt* signaling (Sinner et al. 2007), with *Sox4* recently shown to be an inhibitor of oligodendrocyte maturation (Pötzner et al. 2007). The activities of *Sox* proteins as activators and repressors have been summarized in Tables 1 and 2.

Sox transcription factors and disease

Sox factors expression and function is modified in a variety of tumors and neurological disorders. Here we discuss recent findings that suggest a role for these proteins in the formation and maintenance of some brain tumors. *Sox2* expression was analyzed in different types of brain tumors, based on the hypothesis that cancer stem cells are responsible for their propagation (Phi et al. 2008). *Sox2* was expressed in a variety of glial tumors of astroglial, oligodendroglial and ependymal lineages. *Sox2* was also found in tumors of embryonal origin (supratentorial primitive neuroectodermal tumors), but not in medulloblastomas and pineoblastomas. As most of the *Sox2*-expressing cells in the tumors co-expressed GFAP, and *Sox2*-negative cells in medulloblastomas and pineoblastomas expressed neuronal markers, it was concluded that *Sox2* might be a marker of tumors of glial lineages (Phi et al. 2008). Conversely, heterozygous loss-of-function mutations in *SOX2* causes anophthalmia, microphthalmia and coloboma. These patients often present with extraocular abnormalities, such as learning disability, seizures, motor dysfunction, and postnatal growth failure (Ragge et al. 2005). Additionally, a number of patients with *SOX2* mutations show hypogonadotropic hypogonadism, with anterior pituitary hypoplasia and gonadotropin deficiency (Tziaferi et al. 2008), lending support to a multi-system function of *SOX2* in human development. Surveys of gene expression in medulloblastomas have found an overexpression of *SOX4* and *SOX11* (Lee et al. 2002; Yokota et al. 2004), with strong nuclear staining in a majority of these tumors (de Bont et al. 2008). As *SOX11* is expressed in fetal progenitors (Weigle et al. 2005) and absent from normal mature cerebellum (de Bont et al. 2008), the expression of this marker suggests an embryonic origin of the tumor. *SOX6* is expressed at higher levels in human gliomas and fetal brain than in normal adult tissue, and it is considered a potential diagnostic marker for these tumors (Ueda et al. 2004). In an independent study, *SOX6* was found to be upregulated together with *SOX8* and *SOX13* in oligodendrogliomas (Schlierf et al. 2007). *SOX10* is also ubiquitously expressed in gliomas (Bannykh et al. 2006). Altogether, these findings are consistent with the hypothesis that glioma cells are less differentiated than normal adult glia. Interestingly, *Sox* genes were found to be upregulated in tumors of both oligodendroglial and astrocytic lineages, consistent with the notion that gliomas might share a common origin from stem cells or glial progenitors. This hypothesis has also been confirmed in pheochromocytomas, in which both *Sox9* and *Hey1* - genes that are involved in the maintenance of a progenitor state - are highly expressed (Powers et al. 2007).

Different mutations in the *SOX10* gene are associated with two distinct groups of neurocristopathies: a milder form comprising Waardenburg syndrome (WS) and Hirschsprung disease (HSCR), and a more severe trait, peripheral demyelinating neuropathy, central dysmyelinating leukodystrophy, Waardenburg syndrome and Hirschsprung disease (PCWH). PCWH is characterized by deficiencies in Schwann cells, oligodendrocytes, melanocytes and enteric ganglia neurons (Inoue et al. 2002; Inoue et al. 1999). WS and HSCR are autosomal dominant disorders caused by cellular defects in the embryonic neural crest. WS and HSCR occur simultaneously in patients with Waardenburg-Shah syndrome (WS4). *Sox10* mutations were identified in families with WS4, but not in patients with HSCR alone (Pingault et al. 1998). Importantly, these mutations are likely to cause haploinsufficiency of the *SOX10* protein. Analysis of these disease-causing *SOX10* mutations have revealed premature terminating codons, and a relationship between the position of the mutation and the severity of disease (Inoue 2004). Efforts to characterize the various mutant *Sox10* proteins have demonstrated some dominant negative properties (Inoue 2004), but are however unable to fully explain the toxic effects of extending translation into the 3' untranslated region (Inoue 2007).

Recent studies point to a role of *SOX10* and oligodendrocytes in the pathophysiology of schizophrenia. In patients with schizophrenia, the *Sox10* gene is highly methylated in the CpG island of the sex-determining region Y-box and its expression is significantly decreased (Iwamoto et al. 2005). Importantly, the methylation status of *Sox10* correlated with its reduced expression and with modified expression of other oligodendrocyte genes. The CpG island of the oligodendrocyte transcription factor *Olig2* was rarely methylated, and the methylation status of myelin basic protein was not associated with changes in other oligodendrocyte gene expression (Iwamoto et al. 2005). The authors of the study concluded that in schizophrenia *Sox10* methylation is likely to be an epigenetic indicator of oligodendrocyte dysfunction.

Closing remarks

It is apparent that oligodendrocyte dysfunction found in schizophrenia could be attributed to the activating functions of *Sox10*, but in many tumors, the silencing function of Sox proteins on the proliferative effects of Wnt signaling has been attenuated (Guo et al. 2008). Given the structural features of the known *Sox* groups and the diversity of protein interactions documented to date, the mechanism of target gene selection by *Sox* proteins in specific cell types has become a subject of intense study. Current models indicate that the dynamic pattern of tissue-specific *Sox* gene expression, coupled with partner protein availability and selectivity, are mechanisms likely to underlie the specific changes in gene expression associated with fate decisions and important transitional phases in development (Kamachi et al. 2000). Selective DNA binding of promoters that are activated by *Sox* proteins and their co-factors is enhancer context-dependent (Kamachi et al. 1999), and it would be reasonable to expect that transcriptional repression by *Sox* proteins would be no less complex and more difficult to predict, since neither activation domains nor DNA binding would be required. Elucidating mechanisms of target specificity in developmental regulation by Sox proteins will be enhanced by continued efforts in the identification and characterization of Sox protein function.

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References

- Akiyama H, Chaboissier MC, Martin JF, Schedl A, de Crombrughe B. The transcription factor Sox9 has essential roles in successive steps of the chondrocyte differentiation pathway and is required for expression of Sox5 and Sox6. *Genes Dev.* 2002; 16:2813–2828. [PubMed: 12414734]
- Akiyama H, Kim JE, Nakashima K, Balmes G, Iwai N, Deng JM, Zhang Z, Martin JF, Behringer RR, Nakamura T, de Crombrughe B. Osteo-chondroprogenitor cells are derived from Sox9 expressing precursors. *Proc Natl Acad Sci.* 2005; 102:14665–14670. [PubMed: 16203988]
- Akiyama H, Lyons JP, Mori-Akiyama Y, Yang X, Zhang R, Zhang Z, Deng JM, Taketo MM, Nakamura T, Behringer RR, McCrea PD, de Crombrughe B. Interactions between Sox9 and beta-catenin control chondrocyte differentiation. *Genes Dev.* 2004; 18:1072–1087. [PubMed: 15132997]
- Bani-Yaghoob M, Tremblay RG, Lei JX, Zhang D, Zurakowski B, Sandhu JK, Smith B, Ribocco-Lutkiewicz M, Kennedy J, Wallker PR, Sikorska M. Role of Sox2 in the development of the mouse neocortex. *Dev Biol.* 2006; 295(1):52–66. [PubMed: 16631155]
- Bannykh SI, Stolt CC, Kim J, Perry A, Wegner M. Oligodendroglial-specific transcription factor SOX10 is ubiquitously expressed in human gliomas. *J Neurooncol.* 2006; 76(2):115–127. [PubMed: 16205963]

- Bastide P, Darido C, Pannequin J, Kist R, Robine S, Marty-Double C, Bibeau F, Scherer G, Joubert D, Hollande F, Jay P. Sox9 regulates cell proliferation and is required for Paneth cell differentiation in the intestinal epithelium. *Journal of Cell Biology*. 2007; 178(4):635–648. [PubMed: 17698607]
- Bergsland M, Werme M, Malewicz M, Perlmann T, Muhr J. The establishment of neuronal properties is controlled by Sox4 and Sox11. *Genes Dev*. 2006; 20:3475–3486. [PubMed: 17182872]
- Bergstrom DE, Young M, Albrecht KH, Eicher EM. Related function of mouse SOX3, SOX9 and SRY HMG domains assayed by male sex determination. *Genesis*. 2000; 28(3-4):111–124. [PubMed: 11105052]
- Bondurand N, Pingault V, Goerich DE, Lemort N, Sock E, Le Caignec C, Wegner M, Goossens M. Interaction among SOX10, PAX3 and MITF, three genes altered in Waardenburg syndrome. *Human Molecular Genetics*. 2000; 9:1907–1917. [PubMed: 10942418]
- Botquin V, Hess H, Fuhrmann G, Anastassiadis C, Gross MK, Vriend G, Scholer HR. New POU dimer configuration mediates antagonistic control of an osteopontin preimplantation enhancer by Oct-4 and Sox-2. *Genes Dev*. 1998; 12:2073–2090. [PubMed: 9649510]
- Bowles J, Schepers G, Koopman P. Phylogeny of the SOX family of developmental transcription factors based on sequence and structural indicators. *Developmental Biology*. 2000; 227:239–255. [PubMed: 11071752]
- Bridgewater LC, Lefebvre V, de Crombrughe B. Chondrocyte-specific enhancer elements in the Col11a2 gene resemble the Col2a1 tissue-specific enhancer. *J Biol Chem*. 1998; 273:14998–15006. [PubMed: 9614107]
- Britsch S, Goerich DE, Riethmacher M, Peirano RI, Rossner M, Nave KA, Birchmeier C, Wegner M. The transcription factor Sox10 is a key regulator of peripheral glial development. *Genes Dev*. 2001; 15:66–78. [PubMed: 11156606]
- Bylund M, Andersson E, Novitch B, Muhr J. Vertebrate neurogenesis is counteracted by Sox1–3 activity. *Nat Neurosci*. 2003; 6(11):1162–1168. [PubMed: 14517545]
- Chang S-H, Oh C-D, Yang M-S, Kang S-S, Lee Y-S, Sonn J-K, Chun J-S. Protein kinase C regulates chondrogenesis of mesenchymes via mitogen-activated protein kinase signaling. *Journal of Biological Chemistry*. 1998; 273(30):19213–19219. [PubMed: 9668109]
- Chen Y, Shi L, Zhang L, Li R, Liang J, Yu W, Sun L, Yang X, Wang Y, Zhang Y, Shang Y. The molecular mechanism governing the oncogenic potential of SOX2 in breast cancer. *Journal of Biological Chemistry*. 2008; 283(26):17969–17978. [PubMed: 18456656]
- Cheung M, Briscoe J. Neural crest development is regulated by the transcription factor Sox9. *Development*. 2003; 130:5681–5693. [PubMed: 14522876]
- Cohen-Barak O, Yi Z, Hagiwara N, Monzen K, Komuro I, Brilliant MH. Sox6 regulation of cardiac myocyte development. *Nucleic Acids Research*. 2003; 31(20):5941–5948. [PubMed: 14530442]
- Day TF, Guo X, Garrett-Beal L, Yang Y. Wnt/beta-catenin signaling in mesenchymal progenitors controls osteoblast and chondrocyte differentiation during vertebrate skeletogenesis. *Dev Cell*. 2005; 8:739–750. [PubMed: 15866164]
- de Bont JM, Kros JM, Passier MMCJ, Reddingius RE, Sillevs Smitt PAE, Luider TM, den Boer ML, Pieters R. Differential expression and prognostic significance of SOX genes in pediatric medulloblastoma and ependymoma identified by microarray analysis. *NeuroOncology*. 2008; 10
- de Crombrughe B, Lefebvre V, Nakashima K. Regulatory mechanisms in the pathways of cartilage and bone formation. *Current Opinion in Cell Biology*. 2001; 13:721–727. [PubMed: 11698188]
- Dumitriu B, Patrick MR, Petschek JP, Cherukuri S, Klingmuller U, Fox PL, Lefebvre V. Sox6 cell-autonomously stimulates erythroid cell survival, proliferation, and terminal maturation and is thereby an important enhancer of definitive erythropoiesis during mouse development. *Blood*. 2008; 108(4):1198–1207. [PubMed: 16627753]
- Ekonomou A, Kazanis I, Malas S, Wood H, Alifragis P, Denaxa M, Karagogeos D, Constanti A, Lovell-Badge R, Episkopou V. Neuronal migration and ventral subtype identity in the telencephalon depend on Sox1. *PLoS Biol*. 2005; 3(6):e186. [PubMed: 15882093]
- Ellis P, Fagan BM, Magness ST, Hutton S, Taranova O, Hayashi S, McMahon A, Rao M, Pevny L. SOX2, a persistent marker for multipotential neural stem cells derived from embryonic stem cells, the embryo or the adult. *Dev Neurosci*. 2004; 26:148–165. [PubMed: 15711057]

- Finzsch M, Stolt CC, Lommes P, Wegner M. Sox9 and Sox10 influence survival and migration of oligodendrocyte precursors in the spinal cord by regulating PDGF receptor alpha expression. *Development*. 2008; 135:637–646. [PubMed: 18184726]
- Graham V, Khudyakov J, Ellis P, Pevny L. SOX2 functions to maintain neural progenitor identity. *Neuron*. 2003; 39(5):749–765. [PubMed: 12948443]
- Greer Card DA, Hebbar PB, Li L, Trotter KW, Komatsu Y, Mishina Y, Archer TK. Oct4/Sox2-regulated miR-302 targets cyclinD1 in human ESC. *Molecular and Cellular Biology*. 2008
- Gubbay J, Collignon J, Koopman P, Capel B, Economou A, Munsterberg A, Vivian N, Goodfellow P, Lovell-Badge R. A gene mapping to the sex-determining region of the mouse Y chromosome is a member of a novel family of embryonically expressed genes. *Nature*. 1990; 346:245–250. [PubMed: 2374589]
- Guo L, Zhong D, Lau S, Liu X, Dong X-Y, Sun X, Yang VW, Vertino PM, Moreno CS, Varma V, Dong J-T, Zhou W. Sox7 is an independent checkpoint for beta-catenin function in prostate and colon epithelial cells. *Mol Cancer Res*. 2008; 6(9):1421–1430. [PubMed: 18819930]
- Hagiwara N, Ma B, Ly A. Slow and fast fiber isoform gene expression is systematically altered in skeletal muscle of the Sox6 mutant, p100H. *Dev Dyn*. 2005; 234:301–311. [PubMed: 16124007]
- Hagiwara N, Yeh M, Liu A. Sox6 is required for normal fiber type differentiation of fetal skeletal muscle in mice. *Developmental Dynamics*. 2007; 236
- Han Y, Lefebvre V. L-Sox5 and Sox6 drive expression of the aggrecan gene in cartilage by securing binding of Sox9 to a far-upstream enhancer. *Mol Cell Biol*. 2008a; 28(16):4999–5013. [PubMed: 18559420]
- Han Y, Lefebvre V. L-Sox5 and Sox6 drive expression of the aggrecan gene in cartilage by securing binding of Sox9 to a far-upstream enhancer. *Molecular and Cellular Biology*. 2008b; 28(16):4999–5013. [PubMed: 18559420]
- Hattori T, Coustry F, Stephens S, Eberspaecher H, Takigawa M, Yasuda H, de Crombrugge B. Transcriptional regulation of chondrogenesis by coactivator Tip60 via chromatin association with Sox9 and Sox5. *Nucleic Acids Research*. 2008; 36:3011–3024. [PubMed: 18390577]
- He Y, Dupree J, Wang J, Sandoval J, Li J, Liu H, Shi Y, Nave KA, Casaccia-Bonnel P. The transcription factor Yin Yang 1 is essential for oligodendrocyte progenitor differentiation. *Neuron*. 2007; 55(2):217–230. [PubMed: 17640524]
- Hill TP, Spater D, Taketo MM, Birchmeier W, Hartmann C. Canonical Wnt/beta-catenin signaling prevents osteoblasts from differentiating into chondrocytes. *Dev Cell*. 2005; 8:727–738. [PubMed: 15866163]
- Holmberg J, Hansson E, Malewicz M, Sandberg M, Perlmann T, Lendahl U, Muhr J. SoxB1 transcription factors and Notch signaling use distinct mechanisms to regulate proneural gene function and neural progenitor differentiation. *Development*. 2008; 135(10):1843–1851. [PubMed: 18417619]
- Hong CS, Saint-Jeannet JP. Sox proteins and neural crest development. *Semin Cell Dev Biol*. 2005; 16:694–703. [PubMed: 16039883]
- Huang D-Y, Lin Y-T, Jan P-S, Hwang Y-C, Liang S-T, Peng Y, Huang C-Y, Wu H-C, Lin C-T. Transcription factor SOX-5 enhances nasopharyngeal carcinoma progression by down-regulating SPARC gene expression. *Journal of Pathology*. 2008; 214:445–455. [PubMed: 18085523]
- Iguchi H, Ikeda Y, Oka u M, Tanaka T, Urashima Y, Ohguchi H, Takayasu S, Kojima N, Iwasaki S, Ohashi R, Jiang S, Hasegawa G, Ioka RX, Magoori K, Sumi K, Maejima T, Uchida A, Naito M, Osborne TF, Yanagisawa M, Yamamoto TT, Kodama T, Sakai J. SOX6 attenuates glucose-stimulated insulin secretion by repressing PDX1 transcriptional activity and is down-regulated in hyperinsulinemic obese mice. *J Biol Chem*. 2005; 280:37669–37680. [PubMed: 16148004]
- Iguchi H, Urashima Y, Inagaki Y, Ikeda Y, Okamura M, Tanaka T, Uchida A, Yamamoto TT, Kodama T, Sakai J. SOX6 suppresses cyclin D1 promoter activity by interacting with beta-catenin and histone deacetylase 1, and its down-regulation induces pancreatic beta-cell proliferation. *Journal of Biological Chemistry*. 2007; 282:19052–19061. [PubMed: 17412698]
- Inoue K. Molecular mechanism for distinct neurological phenotypes conveyed by allelic truncating mutations. *Nature Genetics*. 2004; 36(4):361–369. [PubMed: 15004559]

- Inoue K. Translation of Sox10 3' untranslated region causes a complex severe neurocristopathy by generation of a deleterious functional domain. *Human Molecular Genetics*. 2007; 16(24):3037–3046. [PubMed: 17855451]
- Inoue K, Shilo K, Boerkoel CF, Crowe C, Sawady J, Lupski JR, Agamanolis DP. Congenital hypomyelinating neuropathy, central dysmyelination, and Waardenburg-Hirschsprung disease: phenotypes linked by SOX10 mutation. *Ann Neurol*. 2002; 52(6):836–842. [PubMed: 12447940]
- Inoue K, Tanabe Y, Lupski JR. Myelin deficiencies in both the central and the peripheral nervous systems associated with a Sox10 mutation. *Ann Neurol*. 1999; 46(3):313–318. [PubMed: 10482261]
- Irrthum A, Devriendt K, Chitayat D, Matthijs G, Glade C, Steijlen PM, Fryns JP, Van Steensel MA, Vikkula M. Mutations in the transcription factor gene Sox18 underlie recessive and dominant forms of hypotrichosis-lymphedema-telangiectasia. *Am J Hum Genet*. 2003; 72(6):1470–1478. [PubMed: 12740761]
- Iwamoto K, Bundo M, Yamada K, Takao H, Iwayama-Shigeno Y, Yoshikawa T, Kato T. DNA methylation status of SOX10 correlates with its downregulation and oligodendrocyte dysfunction in schizophrenia. *Journal of Neuroscience*. 2005; 25(22):5376–5381. [PubMed: 15930386]
- Kamachi Y, Cheah KSE, Kondoh H. Mechanism of regulatory target selection by the SOX high-mobility group domain proteins as revealed by comparison of SOX1/2/3 and SOX9. *Molecular and Cellular Biology*. 1999; 19(1):107–120. [PubMed: 9858536]
- Kamachi Y, Uchikawa M, Kondoh H. Pairing SOX off with partners in the regulation of embryonic development. *Trends Genet*. 2000; 16:182–187. [PubMed: 10729834]
- Kamachi Y, Uchikawa M, Tanouchi A, Sekido R, Kondoh H. Pax6 and SOX2 form a co-DNA-binding partner complex that regulates initiation of lens development. *Genes Dev*. 2001; 15(10):1272–1286. [PubMed: 11358870]
- Kan L, Israsena N, Zhang Z, Hu M, Zhao LR, HJalali A, Sahni V, Kessler JA. Sox1 acts through multiple independent pathways to promote neurogenesis. *Dev Biol*. 2004; 269(2):580–594. [PubMed: 15110721]
- Kan L, Jalali A, Zhao L-R, Zhou X, McGuire T, Kazanis I, Episkopou V, Bassuk AG, Kessler JA. Dual function of Sox1 in telencephalic progenitor cells. *Dev Biol*. 2007; 310:85–98. [PubMed: 17719572]
- Kanai-Azuma M, Kanai Y, Gad JM, Tajima Y, Taya C, Kurohmaru M, Sanai Y, Yonekawa H, Yazaki K, Tam PPL, Hayashi Y. Depletion of definitive gut endoderm in Sox17-null mutant mice. *Development*. 2002; 129:2367–2379. [PubMed: 11973269]
- Kawakami Y, Tsuda M, Takahashi S, Taniguchi N, Esteban CR, Zemmyo M, Furumatsu T, Lotz M, ZBelmonte JC, Asahara H. Transcriptional coactivator PGC-1 α regulates chondrogenesis via association with Sox9. *Proc Natl Acad Sci*. 2005; 102:2414–2419. [PubMed: 15699338]
- Kim J, Lo L, Dormand E, Anderson DJ. SOX10 maintains multipotency and inhibits neuronal differentiation of neural crest stem cells. *Neuron*. 2003; 38:17–31. [PubMed: 12691661]
- Lai T, Jabaudon D, Molyneaux BJ, Azim E, Arlotta P, Menezes JR, Macklis JD. SOX5 controls the sequential generation of distinct corticofugal neuron subtypes. *Neuron*. 2008; 57(2):232–247. [PubMed: 18215621]
- Lee CJ, Appleby VJ, Orme AT, Chan WI, Scotting PJ. Differential expression of Sox4 and Sox11 in medulloblastoma. *J Neurooncol*. 2002; 57(3):201–214. [PubMed: 12125983]
- Lefebvre V, Li P, de Crombrughe B. A new long form of Sox 5(L-Sox5), Sox6 and Sox9 are coexpressed in chondrogenesis and cooperatively activate the type II collagen gene. *EMBO Journal*. 1998; 17:5718–5733. [PubMed: 9755172]
- Liu Y, Assakura M, Inoue H, Nakamura T, Sano M, Niu Z, Chen M, Schwartz RJ, Schneider MD. Sox17 is essential for the specification of cardiac mesoderm in embryonic stem cells. *Proc Natl Acad Sci*. 2007; 104(10):3859–3864. [PubMed: 17360443]
- Lobjois V, Bel-Vialar S, Trousse F, Pituello F. Forcing neural progenitor cells to cycle is insufficient to alter cell fate decision and timing of neuronal differentiation in spinal cord. *Neural Develop*. 2008; 3

- Lyssiotis CA, Walker J, Wu C, Kondo T, Schultz PG, Wu X. Inhibition of histone deacetylase activity induces developmental plasticity in oligodendrocyte precursor cells. *Proc Natl Acad Sci.* 2007; 104(38):14982–14987. [PubMed: 17855562]
- Ma Y, Certel K, Gao Y, Niemitz E, Mosher J, Mukherjee A, Mutsuddi M, Huseinovic N, Crews ST, Johnson WA, Nambu JR. Functional interactions between *Drosophila* bHLH/PAS, Sox, and POU transcription factors regulate CNS midline expression of the *Slit* gene. *J Neurosci.* 2000; 20(12): 4596–4605. [PubMed: 10844029]
- Matsui T, Kanai-Azuma M, Hara K, Matoba S, Hiramatsu R, Kawakami H, Kurohmaru M, Koopman P, Kanai Y. Redundant roles of Sox17 and Sox18 in postnatal angiogenesis in mice. *J Cell Sci.* 2006; 119:3513–3526. [PubMed: 16895970]
- Melichar HJ, Narayan K, Der SD, Hiraoka Y, Gardiol N, Jeannet G, Held W, Chambers CA, Kang J. Regulation of gammaDelta versus alphaBeta T lymphocyte differentiation by the transcription factor SOX13. *Science.* 2007; 315:230–233. [PubMed: 17218525]
- Miyagi S, Masui S, Niwa H, Saito T, Shimazaki T, Okano H, Nishimoto M, Muramatsu M, Iwama A, Okuda A. Consequence of the loss of Sox2 in the developing brain of the mouse. *FEBS Lett.* 2008; 582(18):2811–2815. [PubMed: 18638478]
- Murakami A, Ishida S, Thurlow J, Revest JM, Dickson C. SOX6 binds CtBP2 to repress transcription from the Fgf-3 promoter. *Nucleic Acids Research.* 2001; 29:3347–3355. [PubMed: 11504872]
- Niimi T, Hayashi Y, Futaki S, Sekiguchi K. Sox7 and Sox17 regulate the parietal endoderm-specific enhancer activity of mouse laminin alpha1 gene. *J Biol Chem.* 2004; 279(36):38055–38061. [PubMed: 15220343]
- Nishimoto M, Fukushima A, Okuda A, Muramatsu M. The gene for the embryonic stem cell coactivator UTF1 carries a regulatory element which selectively interacts with a complex composed of Oct-3/4 and Sox-2. *Molecular and Cellular Biology.* 1999; 19:5453–5465. [PubMed: 10409735]
- Panda DK, Miao D, Lefebvre V, Hendy GN, Goltzman D. The transcription factor SOX9 regulates cell cycle and differentiation genes in chondrocytic CFK2 cells. *Journal of Biological Chemistry.* 2001; 276:41229–41236. [PubMed: 11514554]
- Park K-S, Wells JM, Zorn AM, Wert SE, Whitsett JA. Sox17 influences the differentiation of respiratory epithelial cells. *Developmental Biology.* 2006; 294:192–202. [PubMed: 16574095]
- Patterson ES, Addis RC, Shambloot MJ, Gearhart JD. SOX17 directly activates Zfp202 transcription during in vitro endoderm differentiation. *Physiol Genomics.* 2008; 34(3):277–284. [PubMed: 18523156]
- Phi JH, Park S-H, Kim S-K, Paek SH, Kim JH, Lee YJ, Cho B-K, Park C-K, Lee D-H, Wang K-C. Sox2 expression in brain tumors: a reflection of the neuroglial differentiation pathway. *Am J Surg Pathol.* 2008; 32(1):103–112. [PubMed: 18162777]
- Pingault V, Bondurand N, Kuhlbrodt K, Goerich DE, Prehu MO, Puliti A, Herbarth B, Hermans-Borgmeyer I, Legius E, Matthijs G, Amiel J, Lyonnet S, Ceccherini I, Romeo G, Smith JC, Read AP, Wegner M, Goossens M. SOX10 mutations in patients with Waardenburg-Hirschsprung disease. *Nat Genet.* 1998; 18(2):171–173. [PubMed: 9462749]
- Potzner MR, Griffel C, Lutjen-Drecoll E, Bosl MR, Wegner M, Sock E. Prolonged Sox4 expression in oligodendrocytes interferes with normal myelination in the central nervous system. *Molecular and Cellular Biology.* 2007; 27(15):5316–5326. [PubMed: 17515609]
- Powers JF, Evinger MJ, Zhi J, Picard KL, Tischler AS. Pheochromocytomas in Nf1 knockout mice express a neural progenitor gene expression profile. *Neuroscience.* 2007; 147(4):928–937. [PubMed: 17582688]
- Ragge NK, Lorenz B, Schneider A, Bushby K, de Sanctis L, de Sanctis U, Salt A, Collin JR, Vivian AJ, Free SL, Thompson P, Williamson KA, Sisodiya SM, van Heyningen V, Fitzpatrick DR. SOX2 anophthalmia syndrome. *Am J Med Genet.* 2005; 135(1):1–7. [PubMed: 15812812]
- Rex M, Church R, Tointon K, Scotting PJ. Combination of non-isotopic in situ hybridisation with detection of enzyme activity, bromodeoxyuridine incorporation and immunohistochemical markers. *Histochem Cell Biol.* 1997; 107:519–523.

- Roh J, Cho EA, Seong I, Limb JK, Lee S, Han SJ, Kim J. Down-regulation of Sox10 with specific small interfering RNA promotes transdifferentiation of Schwannoma cells into myofibroblasts. *Differentiation*. 2006; 74(9-10):542–551. [PubMed: 17177851]
- Sandberg M, Kallstrom M, Muhr J. Sox21 promotes the progression of vertebrate neurogenesis. *Nat Neurosci*. 2005; 8(8):995–1001. [PubMed: 15995704]
- Schepers GE, Teasdale RD, Koopman P. Twenty pairs of Sox: extent, homology, and nomenclature of the mouse and human Sox transcription factor gene families. *Developmental Cell*. 2002; 3:167–170. [PubMed: 12194848]
- Schlierf B, Friedrich RP, Roerig P, Felsberg J, Reifemberger G, Wegner M. Expression of SoxE and SoxD genes in human gliomas. *Neuropathol Appl Neurobiol*. 2007; 33(6):621–630. [PubMed: 17961134]
- Schmidt K, Glaser G, Wernig A, Wegner M, Rosorius O. Sox8 is a specific marker for muscle satellite cells and inhibits myogenesis. *Journal of Biological Chemistry*. 2003; 278:29769–29755. [PubMed: 12782625]
- Schmidt K, Schinke T, Haberland M, Priemel M, Schilling AF, Mueledner C, Rueger JM, Sock E, Wegner M, Amling M. The high mobility group transcription factor Sox8 is a negative regulator of osteoblast differentiation. *J Cell Biol*. 2005; 168(6):899–910. [PubMed: 15753123]
- Sekiya I, Tsuji K, Koopman P, Watanabe H, Yamada Y, Shinomiya K, Nifuji A, Noda M. SOX9 enhances aggrecan gene promoter/enhancer activity and is up-regulated by retinoic acid in a cartilage-derived cell line, TC6. *Journal of Biological Chemistry*. 2000; 275:10788–10744. [PubMed: 10753871]
- Shen S, Li J, Casaccia-Bonnel P. Histone modifications affect timing of oligodendrocyte progenitor differentiation in the developing rat brain. *Journal of Cell Biology*. 2005; 169:577–589. [PubMed: 15897262]
- Shen S, Sandoval J, Swiss VA, Li J, Dupree J, Franklin RJ, Casaccia-Bonnel P. Age-dependent epigenetic control of differentiation inhibitors is critical for remyelination efficiency. *Nature Neuroscience*. 2008; 11(9):1024–1034.
- Sinner D, Kordich JJ, Spence JR, Opoka R, Rankin S, Lin S-CJ, Jonatan D, Zorn AM, Wells JM. Sox17 and Sox4 differentially regulate beta-catenin/T-Cell factor activity and proliferation of colon carcinoma cells. *Journal of Biological Chemistry*. 2007; 27(22):7802–7815.
- Sinner D, Rankin S, KLee M, Zorn AM. Sox17 and beta-catenin cooperate to regulate the transcription of endodermal genes. *Development*. 2004; 131:3069–3080. [PubMed: 15163629]
- Smits P, Dy P, Mitra S, Lefebvre V. Sox5 and Sox6 are needed to develop and maintain source, columnar, and hypertrophic chondrocytes in the cartilage growth plate. *J Cell Biol*. 2004; 164(5):747–758. [PubMed: 14993235]
- Sohn J, Natale J, Chew L-J, Belachew S, Cheng Y, Aguirre A, Lytle J, Nait-Oumesmar B, Kerninon C, Kanai-Azuma M, Kanai Y, Gallo V. Identification of Sox17 as a transcription factor that regulates oligodendrocyte development. *Journal of Neuroscience*. 2006; 26:9722–9735. [PubMed: 16988043]
- Stolt CC, Lommes P, Friedrich RP, Wegner M. Transcription factors Sox8 and Sox10 perform non-equivalent roles during oligodendrocyte development despite functional redundancy. *Development*. 2004; 131:2349–2358. [PubMed: 15102707]
- Stolt CC, Lommes P, Hillgartner S, Wegner M. The transcription factor Sox5 modulates Sox10 function during melanocyte development. *Nucleic Acids Research*. 2008 DOI:10.1093/nar/gkn527.
- Stolt CC, Lommes P, Sock E, Chaboissier M-C, Schedl A, Wegner M. The Sox9 transcription factor determines glial fate choice in the developing spinal cord. *Genes Dev*. 2003; 17:1677–1689. [PubMed: 12842915]
- Stolt CC, Rehberg S, Ader M, Lommes P, Riethmacher M, Schachner U, Wegner M. Terminal differentiation of myelin-forming oligodendrocytes depends on the transcription factor Sox10. *Genes Dev*. 2002; 16:165–170. [PubMed: 11799060]
- Stolt CC, Schlierf A, Lommes P, Hillgartner S, Werner T, Kosian T, Sock E, Kessaris N, Richardson WD, Lefebvre V, Wegner M. SoxD proteins influence multiple stages of oligodendrocyte

- development and modulate SoxE protein function. *Dev Cell*. 2006; 11:697–710. [PubMed: 17084361]
- Taylor K, LaBonne C. SoxE factors function equivalently during neural crest and inner ear development and their activity is regulated by SUMOylation. *Developmental Cell*. 2005; 9:593–603. [PubMed: 16256735]
- Tziaferi V, Kelberman D, Dattani MT. The role of Sox2 in hypogonadotropic hypogonadism. *Sex Dev*. 2008; 2(4-5):194–199. [PubMed: 18987493]
- Uchikawa M, Kamachi Y, Kondoh H. Two distinct subgroups of Groups B Sox genes for transcriptional activators and repressors: their expression during embryonic organogenesis of the chicken. *Mech Dev*. 1999; 84(1-2):103–120. [PubMed: 10473124]
- Ueda R, Yoshida K, Kawakami Y, Kawase T, Toda M. Expression of a transcription factor, SOX6, in human gliomas. *Brain Tumor Pathol*. 2004; 21(1):35–38. [PubMed: 15696967]
- Wang TW, Stromberg GP, Whiteney JT, Brower NW, Klymkowsky MW, Parent JM. Sox3 expression identifies neural progenitors in persistent neonatal and adult mouse forebrain germinative zones. *J Comp Neurol*. 2006; 497(1):88–100. [PubMed: 16680766]
- Wang Y, Bagheri-Fam S, Harley VR. SOX13 is upregulated in the developing mouse neuroepithelium and identifies a subpopulation of differentiating neurons. *Brain Res Dev Brain Res*. 2005; 157(2):201–208.
- Wegner M. From head to toes: the multiple facets of Sox proteins. *Nucleic acids research*. 1999; 27(6):1409–1420. [PubMed: 10037800]
- Weigle B, Ebner R, Temme A, Schwind K, Schmitz M, Kiessling A, Rieger MA, Schackert G, Schackert HK, Rieber EP. Highly specific overexpression of the transcription factor Sox11 in human malignant gliomas. *Oncol Rep*. 2005; 13:139–144. [PubMed: 15583815]
- Wibmuller S, Kosian T, Wolf M, Finzsch M, Wegner M. The high-mobility-group domain of Sox proteins interacts with DNA-binding domains of many transcription factors. *Nucleic Acids Res*. 2006; 34:1735–1744. [PubMed: 16582099]
- Wilson M, Koopman P. Matching SOX: partner proteins and co-factors of the SOX family of transcriptional regulators. *Curr Opin Gen Dev*. 2002; 12:441–446.
- Yi Z, Cohen-Barak O, Hagiwara N, Kingsley PD, Fuchs DA, Erickson DT, Epner EM, Palis J, Brilliant MH. Sox6 directly silences epsilon globin expression in definitive erythropoiesis. *PLoS Genetics*. 2006; 2(2):e14. [PubMed: 16462943]
- Yokota N, Mainprize TG, Taylor MD, Kohata T, Loreto M, Ueda S, Dura W, Grajkowska W, Kuo JS, Rutka J. Identification of differentially expressed and developmentally regulated genes in medulloblastoma using suppression subtraction hybridisation. *Oncogene*. 2004; 23(19):3444–3453. [PubMed: 15064731]
- Young N, Hahn CN, Poh A, Dong C, Wilhelm D, Olsson J, Muscat GE, Parsons P, Gamble JR, Koopman P. Effect of disrupted SOX18 transcription factor function on tumor growth, vascularization, and endothelial development. *J Natl Cancer Inst*. 2006; 98(15):1060–1067. [PubMed: 16882943]
- Yuan H, Corbi N, Basilico C, Dailey L. Developmental-specific activity of the FGF-4 enhancer requires the synergistic action of Sox2 and Oct-3. *Genes Dev*. 1995; 9:2635–2645. [PubMed: 7590241]
- Zhou G, Zheng Q, Engin F, Munivez E, Chen Y, Sebald E, Krakow D, Lee B. Dominance of SOX9 function over RUNX2 during skeletogenesis. *Proc Natl Acad Sci*. 2006; 103:19004–19009. [PubMed: 17142326]

Table 1

Activator functions of *Sox* proteins

Family	Function	Reference
<i>SoxB1</i>	<i>SoxB1</i> members activate differentiation of telencephalic precursors into neurons	(Economou et al. 2005)
	<i>Sox1</i> enhances neurogenin expression	(Kan et al. 2004)
	<i>Sox2</i> activates cyclinD1 expression with beta-catenin in breast cancer	(Chen et al. 2008)
	<i>Sox1/Sox2</i> activate crystallin genes	(Uchikawa et al. 1999)
<i>SoxC</i>	<i>Sox4</i> and <i>Sox11</i> induce neuronal phenotype, and activate neuronal class III beta-tubulin (<i>Tubb3</i>) gene promoter	(Bergsland et al. 2006)
	<i>Sox4</i> supports glucokinase expression	(Goldsworthy et al. 2008)
	<i>Sox4</i> enhances beta-catenin signaling	(Sinner et al. 2007)
<i>SoxD</i>	<i>Sox5</i> recruits co-activators to <i>Sox9</i> target genes	(Hattori et al. 2008)
	<i>Sox5</i> and <i>Sox6</i> co-stimulate <i>Sox9</i> target genes in chondrocytes	(Han and Lefebvre 2008)
<i>SoxE</i>	Promote neural crest multipotentiality	(Kim et al. 2003)
	Promote glial development of neural crest progenitor cells	(Britsch et al. 2001)
	<i>Sox9</i> promotes progenitor commitment, promotes expression of <i>Aggrecan</i> , <i>Col11a2</i> , <i>Col2a1</i> .	(Bridgewater et al. 1998; Kawakami et al. 2005; Sekiya et al. 2000)
	<i>Sox9</i> promotes <i>Sox10</i> expression in Neuro2A cells	(Stolt et al. 2003)
	<i>Sox9</i> and <i>Sox10</i> maintain PDGFRalpha+ cells	(Finzsch et al. 2008)
<i>SoxF</i>	Promote <i>FoxA</i> and <i>HNF1beta</i> expression	(Sinner et al. 2004)
	Promote <i>laminin alpha 1</i> expression	(Niimi et al. 2004)
	Promote <i>VCAM1</i> expression	(Matsui et al. 2006)
	Promote <i>FGF-3</i> expression	(Sinner et al. 2004)
	Promotes endoderm development	(Kanai-Azuma et al. 2002)
	Promotes hair development	(Irrthum et al. 2003)
	Promotes cardiogenesis	(Liu et al. 2007)
	Promotes angiogenesis	(Young et al. 2006)
	Promotes transdifferentiation to epithelial cells	(Park et al. 2006)
	Stimulates activity of <i>mFoxj1</i> promoter	(Park et al. 2006)
	<i>Sox17</i> induces expression of <i>Zfp202</i> zinc finger protein	(Patterson et al. 2008)
	<i>Sox17</i> and <i>Sox7</i> co-activate beta-catenin target genes in endoderm	(Sinner et al. 2004)
	<i>Sox17</i> promotes myelin gene expression	(Sohn et al. 2006)

Table 2

Repressor functions of *Sox* proteins

Family	Function	Reference
<i>SoxB1</i>	Repress neuronal differentiation and maintain progenitor-specific expression	(Bylund et al. 2003; Graham et al. 2003; Holmberg et al. 2008)
	Binds beta-catenin and inhibits beta-catenin signaling	(Kan et al. 2004)
<i>SoxB2</i>	Inhibits activation of <i>delta-crystallin DC5</i> enhancer	(Sandberg et al. 2005)
	Counteracts activities of <i>SoxB1</i> to promote neurogenesis	(Sandberg et al. 2005)
<i>SoxC</i>	<i>Sox4</i> repress oligodendrocyte development	(Pötzner et al. 2007)
	<i>Sox11</i> represses oligodendrocyte development	(He et al. 2007)
<i>SoxD</i>	<i>Sox5</i> prevents premature development of neurons	(Lai et al. 2008)
	<i>Sox5</i> represses SPARC	(Huang et al. 2008)
	<i>Sox5</i> and <i>Sox6</i> repress IHH signaling, <i>FGFR3</i> and <i>Runx2</i>	(Smits et al. 2004)
	<i>Sox5</i> represses <i>Sox10</i> targets <i>Mitf</i> and <i>Dct</i>	(Stolt et al. 2008)
	<i>Sox5</i> and <i>Sox6</i> suppress premature oligodendrocyte generation.	(Stolt et al. 2006)
	<i>Sox6</i> co-recruited to <i>Sox10</i> site on <i>MBP</i> promoter at E16.5	
	<i>Sox5</i> and <i>Sox6</i> repress <i>Sox9</i> -induced <i>Sox10</i> expression in Neuro2A	(Stolt et al. 2006)
	<i>Sox5</i> and <i>Sox6</i> interact with Olig2 and Neurogenin 2	(Stolt et al. 2006)
	<i>Sox6</i> represses Ca ²⁺ alpha1c promoter	(Cohen-Barak et al. 2003)
	<i>Sox6</i> represses epsilon globin expression	(Yi et al. 2006)
	<i>Sox6</i> represses insulin II gene expression	(Iguchi et al. 2005)
	<i>Sox6</i> suppresses cyclin D1 promoter activity	(Iguchi et al. 2007)
	<i>Sox13</i> suppresses alphaBeta T lymphocyte differentiation	(Melichar et al. 2007)
	<i>Sox13</i> antagonizes TCF1 function and cell proliferation	(Melichar et al. 2007)
<i>SoxE</i>	<i>Sox8</i> prevents premature osteoblast maturation	(Schmidt et al. 2005)
	<i>Sox9</i> suppresses neuronal markers <i>Pax6</i> , <i>Pax7</i> , <i>Nkx6</i> , <i>Irx3</i>	(Cheung and Briscoe 2003)
	<i>Sox8</i> and <i>Sox9</i> prevent precocious myotube differentiation	(Schmidt et al. 2003)
	<i>Sox 10</i> overcomes BMP2 and TGFbeta signaling to maintain gliogenic potential	(Kim et al. 2003)
	<i>Sox 10</i> prevents Schwannoma from differentiating into myofibroblasts	(Roh et al. 2006)
	<i>Sox9</i> inhibits osteoblast development	(de Crombrughe et al. 2001; Hill et al. 2005)
	<i>Sox9</i> inhibits Wnt signaling inhibiting beta-catenin transcriptional activity directly and by affecting its stability.	(Akiyama et al. 2004; Topol et al. 2009)
	<i>Sox9</i> reduces ERK1 levels	(Panda et al. 2001)
	<i>Sox9</i> inhibits Runx2 function	(Zhou et al. 2006)
	<i>Sox9</i> suppresses proliferation in intestinal epithelium	(Bastide et al. 2007)
	<i>Sox9</i> suppresses generation of spinal cord motorneurons, V2 interneurons and astrocytes	(Stolt et al. 2004; Stolt et al. 2003; Stolt et al. 2002)
	<i>Sox 10</i> inhibits beta-catenin-mediated transcription	(Sinner et al. 2007)

Family	Function	Reference
<i>SoxF</i>	Represses <i>mSftpc</i> gene expression in alveolus	(Park et al. 2006)
	<i>Sox17</i> represses <i>HNFa</i> expression	(Patterson et al. 2008)
	<i>Sox7</i> inhibits cell proliferation in colon cancer	(Guo et al. 2008)
	<i>Sox17</i> antagonizes <i>Wnt</i> signaling	(Sinner et al. 2007; Zorn et al. 1999)
	<i>Sox17</i> represses cell proliferation in oligodendrocyte progenitor cells	(Sohn et al. 2006)