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Control of Cell Fate and Differentiation by Sry-related High-mobility-group Box (Sox) Transcription Factors

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Abstract

Maintain stemness, commit to a specific lineage, differentiate, proliferate, or die. These are essential decisions that every cell is constantly challenged to make in multi-cellular organisms to ensure proper development, adult maintenance, and adaptability. *SRY*-related high-mobility-group box (Sox) transcription factors have emerged in the animal kingdom to help cells effect such decisions. They are encoded by twenty genes in humans and mice. They share a highly conserved high-mobility-group box domain that was originally identified in *SRY*, the sex-determining gene on the Y chromosome, and that has derived from a canonical high-mobility-group domain characteristic of chromatin-associated proteins. The high-mobility-group box domain binds DNA in the minor groove and increases its DNA binding affinity and specificity by interacting with many types of transcription factors. It also bends DNA and may thereby confer on Sox proteins a unique and critical role in the assembly of transcriptional enhanceosomes. Sox proteins fall into eight groups. Most feature a transactivation or transrepression domain and thereby also act as typical transcription factors. Each gene has distinct expression pattern and molecular properties, often redundant with those in the same group and overlapping with those in other groups. As a whole the Sox family controls cell fate and differentiation in a multitude of processes, such as male differentiation, stemness, neurogenesis, and skeletogenesis. We review their specific molecular properties and in vivo roles, stress recent advances in the field, and suggest directions for future investigations.

Keywords

Sox; transcription factor; stem cell; differentiation; HMG

1. Introduction

Proper development and maintenance of multi-cellular organisms requires that cells be constantly able to make decisions regarding lineage commitment, differentiation, proliferation and death status. Intense research is geared nowadays towards uncovering how developing and adult organisms maintain stem cells, i.e., cells with both infinite self-renewal capacity and unrestricted fate potential. Equally important is research on how stem cells commit to specific cell lineages, and how lineage-committed cells progress along their differentiation program. The decision of a cell to change status is effected in a large part by cell-specific transcription factors that modulate or switch expression of selected gene subsets. While a decade or two ago

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the notion was prevalent that a single master transcription factor would be necessary and sufficient to control cell fate decisions and differentiation into each lineage, it has now been abundantly demonstrated that sets of transcription factors from various families act in concert to fulfill such roles. These factors include basic-helix-loop-helix, POU domain, Runt domain, homeodomain, forkhead, and Sox proteins. This review will specifically focus on the Sox family. Its members exhibit properties of classical transcription factors, synergize with many types of transcription factors, and are believed to possess a unique role in the assembly of transcriptional enhanceosomes. They play critical roles in cell fate and differentiation decisions in a large variety of lineages. We first review how this family has evolved from high-mobility-group (HMG) domain ancestors to twenty unique proteins, and then review their molecular properties and in vivo roles. We end with an evaluation of current knowledge and with suggestions for future research directions.

2. The Sox family within the high-mobility-group domain superfamily

A brief recapitulation of the discovery of HMG domain and Sox proteins is useful at the start of this review to understand the evolution, classification, and distinguishing features of Sox, HMG, HMG domain, and HMG box proteins (reviews in Bustin, 1999; Wegner, 1999; Bianchi and Beltrame, 2000). Non-histone chromosomal proteins were originally sorted by SDS-PAGE and classified according to their mobility (Goodwin et al., 1973). The proteins forming a high-mobility group (HMG) were found to belong to at least three totally unrelated families of DNA-binding proteins: the HMG1/2 or HMG domain family, the HMG-I(Y) or AT-hook family, and the HMG- 14/17 or nucleosome-binding protein family. The HMG domain proteins, the only ones related to Sox proteins (see below), are abundantly expressed in all eukaryotic cells. They feature two or more copies of a so-called canonical HMG domain. This domain of about 80 residues has a twisted L-shape containing three alpha helices and an N-terminal beta strand (review in Weiss, 2001). It binds linear DNA with little, if any, sequence specificity and also binds unusual DNA structures, such as four-way junctions and kinks (Grosschedl et al., 1994). While most other types of DNA-binding proteins contact the DNA major groove and only induce minor changes of the DNA conformation, the two arms of the L-shaped HMG domain bind DNA in the minor groove, intercalate amino acid side chains between DNA base pairs, and induce a significant bend of the DNA helix. The minor groove is widened and the major groove compressed. HMG domain proteins are thus unique in their ability to alter the conformation of DNA and to increase its protein accessibility and plasticity. They thereby facilitate the formation of enhanceosomes, i.e., functionally active complexes of transcription factors on gene enhancer sequences.

Proteins were later identified that harbor a non-canonical HMG domain, also called the HMG box domain. These proteins fall into two families: the Sox family and the T-cell factor (TCF)/lymphoid enhancer binding factor (LEF-1) family. They are present only in the animal kingdom and must therefore have evolved from canonical HMG domain proteins. Unlike HMG domain genes, HMG box genes are expressed at a low level and in a restricted number of cell types, and their proteins contain only one HMG box domain. This domain is only ~20% identical to the canonical HMG domain, but the amino acids that confer the ability to alter the DNA conformation are conserved. The domain has acquired the ability to bind DNA with some sequence specificity and to bend DNA at a flexible angle rather than a fixed angle through changes in just a few residues (Murphy et al., 1999).

Sry was the first *Sox* gene identified (Sinclair et al., 1990; Gubbay et al., 1990). Its discovery ended a long search for the gene responsible for male differentiation on the Y chromosome (*Sry* stands for sex-determining region on the Y chromosome). This important discovery then prompted several groups to specifically embark on searches for genes with a high degree of identity to *Sry* in the HMG box (Gubbay et al., 1990; Denny et al., 1992; Wright et al., 1993).

They gave vertebrate genes the acronym *Sox*, for "Sry-related HMG box", followed by a number corresponding to the order of discovery. The efforts of these groups and those of others led, at the turn of the 20th century, to the cloning of many Sox genes in multiple species from the fruit fly to humans, with *Sox30* receiving the highest number (Ozaki et al., 1999). With the goal of obtaining a definitive enumeration and classification of *Sox* genes, in 2002 Schepers and collaborators searched the first whole-genome sequences that became available and reached a final count of only twenty *Sox* genes in mice and humans (Schepers et al., 2002). They found that several Sox acronyms had been assigned to orthologues in different species (for instance, *Sox12* and *Sox22*).

Protein sequence comparisons showed that *Sox* genes fall into eight groups, A to H, with two B subgroups, B1 and B2 (Figure 1). Sox proteins within the same group share a high degree of identity (generally 70-95%) both within and outside the HMG box, whereas Sox proteins from different groups share partial identity (≥46%) in the HMG box domain and none outside this domain. While most *Sox* genes feature one to three exons and give rise to a single protein product, the *SoxD* and *SoxH* genes are split into multiple exons and give rise to several splice variants with different properties (Wunderle et al., 1996;Lefebvre et al., 1998;Hiraoka et al., 1998;Osaki et al., 1999). Drosophila melanogaster and Caenorhabditis elegans have only five and eight *Sox* genes, respectively, but interestingly, each *Sox* gene in these species corresponds to a different vertebrate *Sox* group or subgroup (for further details on the *Sox* gene phylogeny, see the review by Bowles et al., 2000).

3. Molecular properties

Most Sox proteins harbor several functional domains (Figure 1). The HMG box domain alone fulfills the functions of DNA binding, DNA bending, protein interactions, and nuclear import or export (Figures 2 and 3). These properties are reviewed in the next four subsections, but before we describe them, we would like to mention that these properties are mediated by sequences highly conserved in all Sox proteins. Therefore, considering that the HMG box domains of Sox proteins are virtually identical within each group but only ~50% identical between groups, one can postulate that the HMG box domain of each Sox group has evolved either to fulfill other unique functions, or to undergo unique modes of regulation. This domain may thus fulfill even more functions than we know today. Most Sox proteins also feature one or several other functional domains outside the HMG box. These domains have generally been highly conserved among orthologues as well as among members of the same group, and they are totally different between proteins from distinct groups. They include transactivation, transrepression and dimerization domains. Sry, however, is an intriguing exception. Sry orthologues show hardly any conservation outside the HMG box domain, which has led to the proposal that either Sry has no other functional domain than the HMG box or that it has been under pressure of rapidly undergoing species-specific adaptative changes. In support of the former notion, at least for human SRY, is the observation that virtually all *SRY* mutations that cause sex reversal cluster within the HMG box (Whitfield et al., 1993;Cameron and Sinclair, 1997). Supporting the latter notion, at least in some species, is the demonstration that the Sry protein of the mouse subspecies Mus musculus molossinus features a unique C-terminal extension that includes a potent transactivation domain (Dubin et al., 1995). However, the importance of this domain and other putative domains described outside the HMG box of Sry proteins from other species has not been demonstrated in vivo. It thus remains likely that, at least in humans, the HMG box is the most critical region of SRY.

3.1. DNA binding

As mentioned earlier, the Sox and Tcf/Lef-1 proteins have acquired the ability to bind DNA with some sequence specificity upon evolution from HMG domain proteins. This property must allow them to concentrate on restricted panels of target genes despite their low abundance

in any given cell type. Sequence specificity was convincingly demonstrated in vitro through DNA site selection studies. In these studies all Sox proteins that were tested exhibited a preference for the hexameric core sequence 5′-WWCAAW-3′, where W indicates A or T (Denny et al., 1992; van de Wetering et al., 1993; Harley et al., 1994; Mertin et al., 1999). This preferred Sox site is highly related to the TCF/LEF-1 consensus site 5′- TWWCAAAG-3′ (Love et al., 1995; Werner et al., 1995). Preferences for the nucleotides directly adjacent to this consensus vary among Sox proteins (Mertin et al., 1999). For instance, Sox9 and Sox17 prefer 5′AG nucleotides, whereas Sry prefers 5′WW and Sox5 5′TW. Further, Sox9 prefers 3′ GG nucleotides, Sox17 prefers 3′G, Sry 3′AG, and Sox5 3′A. Dictated by the HMG box domain, these preferences likely allow Sox proteins in the same group to target the same DNA sites in vivo, whereas Sox proteins in other groups either target other sites or compete with the former for the same sites. Supporting the notion that both mechanisms exist in vivo is the demonstration that L-Sox5 (a long protein isoform of the *Sox5* gene) and Sox6 (SoxD) cooperate with Sox9 (SoxE) to activate a chondrocyte-specific *Col2a1* enhancer harboring several recognition sites (Lefebvre et al. 1998), but have opposite functions and compete with Sox9 and Sox10 (SoxE) for recognition sites in the promoter of oligodendrocyte-specific myelin protein zero (*Mpz*) and myelin basic protein (*Mbp*) genes (Stolt et al., 2006).

It is important to stress here that several Sox proteins have been shown to bind DNA sequences in major target genes that only partially match the in vitro Sox consensus. Since imperfect Sox binding sites are abundantly found on DNA, it is clear that DNA sequence is not the only factor that directs Sox proteins to their target genes in vivo. L-Sox5, Sox6, and Sox9, for instance, control the abundant and specific expression of the *Col2a1* gene in cartilage by binding to a cluster of four sites that each feature only 4 or 5 nucleotides of the 6bp Sox consensus (Lefebvre et al., 1997 and 1998). Like their HMG domain relatives, Sox proteins may use the DNA configuration as one of several criteria to select their target genes. Supporting this argument is the observation that the four Sox binding sites present on the *Col2a1* enhancer overlap two 11bp inverted repeats that may arrange into a non-linear DNA arrangement (Lefebvre et al., 1996). The notion that Sox proteins bind in vivo to DNA sequences that only partially match their in vitro consensus implies that, in practice, searching for the binding sites of Sox proteins on putative target genes can be a challenging task. Indeed, these sites cannot be predicted based solely on DNA sequence, as for most other transcription factors. This task will remain challenging until we understand all the criteria which Sox proteins obey when selecting target sites.

3.2. DNA bending

The Sox cousin Lef1 was demonstrated more than ten years ago to have an essential architectural role in the assembly of a functional enhanceosome on the T cell receptor-alpha (TCR□) gene (Travis et al., 1991; Giese et al., 1995). This architectural role relies largely on the ability of Lef1 to induce a sharp bend of DNA upon binding in the middle of this enhancer. This bend allows transcription factors bound to non-adjacent sites on either sides of Lef1 to interact with each other and thereby to form an active transcriptional complex. Sox proteins also have the ability to bend DNA, but surprisingly, even though their primary role could also be to assemble enhanceosomes, this role has not been demonstrated for any Sox protein yet. However, in support of the notion that DNA bending is an essential Sox function, *SRY* and *SOX2* mutations have been described in humans that selectively interfere with DNA bending, not with DNA binding, and that cause a disease phenotype (Pontiggia et al., 1994; Scaffidi and Bianchi, 2001). The DNA bending angle induced by Sox proteins varies from as little as 30° up to as much as 110°, which has led to their qualification as “floppy” proteins (Weiss, 2001). This is due to the fact that the angular surface of the L-shaped HMG box domain is flexible. It becomes fixed upon binding of the Sox protein to DNA, with the Sox domain instructing DNA how to bend and DNA instructing the protein how to complete its tertiary

fold. The design of this flexible domain may represent a strikingly economical strategy by Mother Nature to use less than two dozen proteins to organize various types of enhanceosomes in many cell lineages.

3.3. Protein interactions

Sox proteins not only bind DNA with low sequence specificity, they also bind DNA with a lower affinity (Kd ~ 10^{-7} to 10^{-9}M) than most other transcription factors (Kd ~ 10^{-9} to 10^{-11}M) when tested in isolation. As mentioned above, they may increase their DNA binding efficiency by selecting non-linear DNA configurations, but this latter property remains to be demonstrated in vivo. Another important property, which has been convincingly demonstrated for several Sox proteins, is the ability to pair off with various types of transcription factors. (reviews in Kamachi et al., 2000; Wilson and Koopman, 2002). The first described, and today's best-characterized example, is that of an *Fgf4* enhancer specifically expressed in embryonic stem cells and embryonal carcinoma cells (Yuan et al., 1995). This enhancer features adjacent recognition sites for Sox and POU domain proteins. Sox2 and the POU domain factor Oct3/4 are co-expressed in these cells and synergize in activating the enhancer. They do so by heterodimerizing with each other on DNA through their DNA-binding domains (Remenyi et al., 2003). The two proteins similarly synergize for the activation of other stem cell-specific genes, including the *Sox2* gene itself (Tomioka et al., 2002). Interestingly, Sox2 pairs off with other partners in other cell lineages, such as Pax6 in lens cells (Kamachi et al., 1998 and 2001) and Brn2 in neural primordium (Tanaka et al., 2004). Several other examples of Sox proteins synergizing with other transcription factors were also described, such as Sox9 and SF1 in Sertoli cells (De Santa Barbara et al., 1998). In all cases, the Sox protein and its partner interact through their DNA-binding domains. That such interactions occur efficiently on DNA is likely related to the fact that the Sox HMG box contacts the minor groove of DNA, whereas the DNA-binding domain of most other transcription factors contacts the major groove of DNA. Further, Sox proteins were shown in the yeast and in vitro to pair off with DNA-binding proteins from many families, including homeodomain proteins, zinc finger proteins, basic helix-loop-helix and leucine zipper proteins (Wissmüller et al., 2006). In every case, heterodimerization occurred via the C-terminal part of the Sox HMG box domain and the DNA-binding domain of the other partner (Remenyi et al., 2003; Wissmüller et al., 2006). The Sox HMG box domain may thus organize biologically active transcriptional complexes through DNA bending as well as through direct interactions with various types of transcription factors.

3.4. Nuclear transport

The Sox HMG box domain contains two nuclear localization domains that are independent of each other and that have been highly conserved in all Sox proteins (Südbeck and Scherer, 1997). The SoxE HMG box domain also features a nuclear export signal (Gasca et al., 2002; Rehberg et al., 2002). Whether nuclear import and export constitute a general mechanism to regulate Sox protein activity in vivo is a question that has only been addressed for a few Sox proteins so far. Sox9 is cytoplasmic in the sexually indifferent gonad of young embryos and in the early differentiating female gonad (Morais da Silva et al., 1996) and Sox2 is cytoplasmic in blastocyst cells outside the inner cell mass (Avilion et al., 2003). Otherwise these two proteins and other Sox proteins have been described to be nuclear.

3.5. Transactivation and transrepression

The Sox B1, C, E and F proteins, which account for 12 of the 20 Sox proteins, feature a potent transactivation domain in their C-terminal region, and this domain in Sox2 and Sox9 physically interacts with the transcriptional co-activator CBP/p300 (Nowling et al., 2003; Tsuda et al., 2003). These proteins therefore must contribute to the activity of enhanceosomes not only through architectural roles, but also through direct interaction with partners of the

transcriptional machinery. The Sox B group is of particular interest in that it has evolved into a B1 subgroup of three transcriptional activators (Sox1, Sox2, and Sox3) and a B2 subgroup of two transcriptional repressors (Sox14 and Sox21; Uchikawa et al., 1999). The five proteins are highly related to each other in the HMG box domain and have overlapping expression patterns, such that the B2 transrepressors act in vivo to specifically repress the activity of their SoxB1 relatives (see later). Sequences C-terminal to the HMG box domain are required for transcriptional repression by the B2 proteins, indicating that these proteins must act not only by competing for DNA binding with the B1 proteins, but also through protein interactions in the C-terminal region. Sox15, the only member of the SoxG subgroup, has also been described to induce transcriptional repression through a domain located in its C-terminal half (Beranger et al., 1999). Interestingly, the SoxD proteins may modulate transcription both as co-activators and as repressors. They cooperate with Sox9 to activate specific genes in cartilage (Lefebvre et al., 1998). Since they have no intrinsic transactivation domain and do not interact directly with Sox9, their roles may be architectural or involve interactions with other proteins. Distinct mechanisms have been proposed for their transrepression action. In otic vesicle cells, Sox6 interacts with the transcriptional co-repressor CtBP2 through a short PLNLSS motif outside the HMG box. In pancreatic beta cells, it interacts with the transcription factor Pdx1 through its HMG box domain. In oligodendrocytes, L-Sox5 and Sox6 directly compete for DNA binding with SoxE proteins (Stolt et al., 2006). Finally, Sox13 represses T lymphocyte-specific genes by directly binding and possibly sequestering Tcf1, but the Sox13 region involved in this activity has not been mapped (Melichar et al., 2007). These data thus strongly suggest that the SoxD proteins may be highly versatile, fulfilling variable roles and using several mechanisms to fulfill these roles. Their mode of action may depend both on the cellular context and on the target gene context.

3.6. Homodimerization

Sox D proteins are further unique in that they harbor two highly conserved leucine-zipper coiled-coil domains, with the major one being associated to a glutamine-rich segment (Lefebvre et al., 1998). These coiled-coil domains mediate protein homodimerization in the absence or presence of DNA, resulting in high-efficiency binding to pairs of adjacent recognition sites on DNA. SoxD proteins were thus suggested to be their own partners, but since they do not interact with each other via the HMG box domains, they may additionally pair off with other transcription factors through their HMG box domain. Sox E proteins are also able to homodimerize and thereby to increase their DNA-binding affinity to pairs of adjacent binding sites (Peirano and Wegner, 2000; Schlierf et al., 2002). This is achieved through a conserved region located N-terminal to the HMG box domain. They dimerize only upon binding to DNA and provided that the DNA sequence features a pair of binding sites. Mutations in this domain in human SOX9 were shown to cause Campomelic Dysplasia but not XY sex reversal, supporting the notion that this mode of protein activity regulation is cell type-dependent (Bernard et al., 2003; Sock et al., 2003; see also later).

3.7. Posttranslational modifications

As for other regulatory factors, the activity of Sox proteins is likely modulated by various types of posttranslational modifications. Many Sox proteins feature putative phosphorylation sites for various types of kinases, but only Sox9 has yet been shown to undergo phosphorylation. Phosphorylation by protein kinase A on two sites that flank the HMG box domain results in increasing Sox9's efficiency of binding to DNA in vitro (Huang et al., 2000). Sox9 is a target of this kinase in cartilage (Huang et al., 2001) and in the developing male gonad, where this modification allows its nuclear translocation (Malki et al., 2005). Sox3, Sox4, Sox6, and SoxE proteins can be sumoylated or ubiquitinated in vitro, with variable consequences for protein stability, nuclear localization, DNA-binding efficiency and transactivation potential (Savare et al., 2005; Fernandez-Lloris et al., 2006; Girard and Goossens, 2006; Hattori et al., 2006;

Pan et al., 2006). For instance, SoxE proteins share two sumoylation sites, one N-terminal to the dimerization domain and one in the C-terminal transactivation domain (Taylor and LaBonne, 2005). These sites interact with the small ubiquitin-like modifier SUMO-1 and the E2 SUMO-conjugating enzyme Ubc9. Evidence that SUMOylation occurs in vivo and has important functional consequences was provided by showing in Xenopus embryos that SoxE mutants that cannot be SUMOylated, or mutants that mimic constitutive SUMOylation, are each able to mediate a subset of the diverse activities of the wild-type proteins in neural crest development (Taylor and LaBonne, 2005). These data open the way for a potentially important and widespread mode of regulation of Sox proteins.

4. In vivo roles and molecular functions

Since the discovery of *SRY* and its major role in male differentiation, essential functions have been identified for many *Sox* genes in multiple developmental and physiological processes in vivo, including milestone discoveries in just the last few years. Reviewing all the data currently available is no longer feasible in a single review. We have therefore assembled two tables highlighting major pieces of information. Table I provides an overview of *Sox*'s known functions in vivo and Table II lists all human diseases due to *SOX* mutations and one disease due to Sox auto-antibodies. The next paragraphs summarize some of the best-known and most critical roles of *Sox* genes in major processes.

4.1. Sex differentiation

Sex and *Sox* have become closely associated key words for both sexologists and soxologists since *SRY* and *SOX9* were found to specify male differentiation (reviewed in Koopman, 2005). *SRY* mutations lead to XY sex reversal in humans, and XX mice harboring an *SRY* transgene develop as fertile males (Sinclair et al., 1990; Koopman et al., 1991). *SOX9* heterozygous mutations often cause XY sex reversal in humans (Foster et al., 1994; Wagner et al., 1994) and mouse *Sox9*-null XY undifferentiated gonads develop into ovaries in vitro (Chaboissier et al., 2004). *Sry* exists only in mammals and is located on the Y chromosome. Besides expression in some areas of the brain (Lahr et al., 1995), it is expressed exclusively in the initially bipotential XY gonad, where it induces the differentiation of Sertoli cells and thereby testis development. *Sox9* is expressed shortly after *Sry* in pre-Sertoli cells and is both required and sufficient for male determination. It is believed, but not yet proven, that Sry's main role is to activate *Sox9*. Other *Sox* genes have roles in sex differentiation and function. *Sox3*, the closest relative of *Sry*, is located on the X chromosome in the pseudoautosomal X-Y homologous region (Graves, 1998; Katoh and Miyata, 1999). It is thus the likely ancestor of *Sry*. In humans, *SOX3* mutations cause significant gonadal defect, including small testes, in addition to X-linked hypopituitarism, recessive hypoparathyroidism, and mental retardation (Rousseau et al., 1991; Laumonnier et al., 2002). Similarly, *Sox3* is not required for gonad determination in the mouse, but is needed for normal oocyte development and for male testis differentiation and gametogenesis (Weiss et al.; 2003). *Sox8*, a close relative of *Sox9*, starts to be expressed soon after *Sox9* in the differentiating mouse gonad, where it can partly substitute for *Sox9* (Chaboissier et al., 2004).

4.2. Stemness

In light of today's high enthusiasm for stem cell research a high-profile *Sox* gene is undoubtedly *Sox2*. This protein functions cell-autonomously in both the epiblast and the extraembryonic ectoderm of the early embryo to maintain the pluripotency of the stem cells that later give rise to all embryonic and trophoblast cell types (Avilion et al., 2003). It is also required to maintain the pluripotency of embryonic stem cells in vitro. As mentioned earlier, Sox2 acts in synergy with the POU domain protein Oct3/4 to directly activate essential genes in embryonic stem cells, such as *Fgf4* (Yuan et al., 1995). Moreover, it was recently shown to form with Oct3/4,

c-Myc, and Klf4 a quartet of transcription factors that are sufficient to induce pluripotent stem cell properties in embryonic and adult fibroblasts (Takahashi and Yamanaka, 2006). *Sox2* is thus a stemness master gene. It is worth mentioning that heterozygous mutations of *SOX2* in humans result in a complex syndrome that reflects essential roles for *Sox2* in multiple processes at later stages of development (Fantes et al., 2003; Kelberman et al., 2006; Williamson et al., 2006). These roles are still incompletely known, but appear to consist of maintaining cell stemness, for instance in neural cells (see later), as well as in promoting cell differentiation, for instance in lens cells (Kamachi et al., 2001). *Sox15* is also expressed in embryonic stem cells, but its inactivation in the mouse has not revealed obvious functions in the cells or in mouse development and normal physiology (Maruyama et al., 2005; Lee et al., 2004). Redundancy with other Sox genes may explain this apparent lack of function. Indeed, even though Sox15 is the only member of the *SoxG* group, it has a high degree of identity with SoxB proteins in the HMG box domain and behaves similarly to Sox2 in DNA-binding in vitro (Koopman et al., 2004; Maruyama et al., 2005). Like *Sry*, *Sox15* is found only in mammals. In contrast to *Sry*, it is possible that this newly evolved gene may not have acquired essential functions yet.

4.3. Neurogenesis and gliogenesis

The development of the nervous system best exemplifies *Sox* genes' critical functions and interactions (reviews in Episkopou, 2005; Pevny and Placzek, 2005; Wegner and Stolt, 2005). Many *Sox* genes are expressed in the developing and adult nervous system. Their expression patterns are overlapping and together cover virtually all cells from the neural stem cell stage until terminal maturation of neurons and macroglia. The *SoxB1* genes, *Sox1*, *Sox2*, and *Sox3*, are panneurally expressed and have redundant roles in maintaining the broad developmental potential and identity of neural stem cells. Their inhibition in the vertebrate embryo results in premature differentiation of neural precursors and their overexpression results in inhibition of neurogenesis (Kishi et al., 2000; Cremazy et al., 2000; Overton et al., 2002; Avilion et al., 2003; Graham et al., 2003; Bylund et al., 2003). The three proteins counteract the functions of proneural basic helix-loop-helix transcription factors (Bylund et al., 2003; Pevny and Placzek, 2005). The *SoxB1* genes continue to be expressed and to maintain neural stem cells in the adult brain, as supported by the observation that reduced expression of *Sox2* in adult mice results in a loss of neuronal precursors and in neurodegeneration as observed in the Huntington and Alzheimer diseases (Ferri et al., 2004; Ekonomou et al., 2005; Wang et al., 2006; Sottile et al., 2006). Neurogenesis (development of neurons), is initiated in the embryo when proneural proteins upregulate expression of the *SoxB2* genes *Sox14* and *Sox21* (Malas et al., 1999). As mentioned earlier, these two genes encode transcriptional repressors that interfere with the activity of the SoxB1 transcriptional activators (Sandberg et al., 2005). Proneural proteins also activate expression of the *SoxC* genes *Sox4* and *Sox11* (Bergsland et al., 2006). These two genes establish neuronal properties mainly redundantly by activating panneuronal gene expression. Gliogenesis (development of oligodendrocytes, astrocytes, and Schwann cells) in the central nervous system and peripheral nervous system relies on *SoxE*, and *SoxD* genes (Wegner, 2005; Stolt et al., 2003, 2004, and 2005). *Sox9* and, to a lesser extent, *Sox8* specify the gliogenic fate of neuronal precursors. The three *SoxE* genes are co-expressed and have redundant functions during oligodendrocyte proliferation. *Sox10* and, to a lesser extent, *Sox8* are expressed during terminal differentiation and required for myelination. The *SoxD* genes *Sox5* and *Sox6* are expressed downstream from the *SoxE* genes and, as mentioned earlier, their protein products directly interfere with transactivation of cell maturation markers by the SoxE proteins (Stolt et al., 2006). Finally, the *SoxF* gene, *Sox17*, may also be involved in gliogenesis. It is expressed in the oligodendrocyte lineage in vivo and has been shown in vitro to control oligodendrocyte progenitor cell cycle exit and differentiation (Sohn et al., 2006).

4.4. Neural crest development

The neural crest is a unique cell population that delaminates from the lateral borders of the neural plate shortly after neural tube closure and migrates into specific regions of the embryo to contribute to the development of a number of important structures, including the heart, great vessels, peripheral nervous system, craniofacial skeleton, eyes, and melanocytes. Interestingly, the same *SoxB*, *C*, *D*, and *E* genes that are expressed in neurogenic cells are also expressed in these cells and their derivatives, emphasizing the notion that they act in concert in a number of distinct processes (review in Hong and Saint-Jeannet, 2005). The *SoxE* gene *Sox10* was first found to play a key role in the neural crest. Heterozygous mutations in *SOX10* cause the human Waardenburg–Hirschsprung syndrome (Pingault et al., 1998), characterized by enteric agangliogenesis, pigmentation defects, and deafness. Similarly, the *Sox10 Dom* mutation in the mouse results in megacolon due to absence of neural crest-derived enteric nervous ganglia (Herbarth et al., 1998). Sox10 synergizes with Pax3 in neural crest derivatives to activate the gene for the melanocyte master transcription factor Mitf (Bondurand et al., 2000) and the gene for the enteric ganglia essential *c-ret* transcription factor (Lang et al., 2003). The other *SoxE* genes *Sox9* and *Sox8* are also expressed in the developing neural crest and act at least in part in redundancy with *Sox10* (Taylor and LaBonne, 2005; Maka et al., 2005). The *SoxC* genes *Sox4* and *Sox11* are needed for heart outflow tract proper formation and *Sox11* is also needed for proper development of other structures that, like the heart outflow tract, derive in part from the neural crest (Schilham et al., 1996; Sock et al., 2004). Like neurogenesis, neural crest development is thus also controlled by numerous *Sox* genes, but it is likely that we have uncovered so far only a subset of their actual contributions.

4.5. Skeletogenesis

Skeletogenesis is initiated in the embryo upon establishment of pluripotent mesenchymal cells at the presumptive sites of skeletal elements. *SoxC* and *SoxE* genes are expressed in these cells, but their roles remain largely unknown (Ng et al., 1997; Jay et al., 1997; Sock et al., 2004). Overt skeletogenesis is initiated when mesenchymal cells commit to the chondrocyte fate and undergo early steps of differentiation (review in Lefebvre and Smits, 2005). *Sox9* has a master role in this process. The first clue that it critically controls chondrogenesis came from the finding that heterozygous mutations in *SOX9* cause the severe human skeleton malformation syndrome known as Campomelic Dysplasia (Foster et al., 1994; Wagner et al., 1994). This syndrome is mainly characterized by underdevelopment and malformation of the cartilage primordia of most definitive bones. *Sox9* is highly expressed in the chondrocyte lineage from the mesenchymal cell precursor stage (Ng et. al., 1997; Zhao et al., 1997) and is required for chondrocyte lineage commitment and differentiation (Bi et al., 1999; Akiyama et al., 2002). As in the oligodendrocyte lineage, *Sox9* activates *Sox5* and *Sox6*, but while L-Sox5/Sox6 counteract the action of SoxE proteins, including Sox9, in oligodendrocytes, they cooperate with Sox9 to activate major cartilage-specific genes (Lefebvre et al., 1998). Inactivation of *Sox5* and *Sox6* in the mouse has revealed essential, redundant roles for the two genes in promoting chondrocyte early differentiation, proliferation, and terminal maturation (Smits et al., 2001 and 2004). The three *Sox* genes are not only required for chondrogenesis, but were also shown to be sufficient to induce chondrocyte differentiation of mesenchymal cells (Ikeda et al., 2004). Osteogenesis (bone formation) occurs when pluripotent mesenchymal cells commit to the osteoblast lineage, differentiate, and start replacing cartilage by bone or establish bone models de novo. *Sox9* has been proposed to prevent osteoblast differentiation of osteochondrogenic mesenchymal cells (Mori-Akiyama et al., 2003), and its close relative *Sox8* was shown to prevent osteoblast differentiation (Schmidt et al., 2005). *Sox8* and *Sox9* may thus work together in this function. Mouse fetuses lacking *Sox11* show a delay in ossification, suggesting a role for this *SoxC* gene in osteogenesis (Sock et al., 2004). Skeletogenesis is thus another important process critically controlled by a battery of *Sox* genes.

4.6. Hematopoiesis

Hematopoiesis is a complex process whereby hematopoietic stem cells are maintained throughout life while constantly giving rise to progenitors that develop into multiple blood cell types. In contrast to other processes, few Sox proteins have been reported to be expressed and to have roles in this process. *Sox4* is highly expressed in the thymus and promotes pro-B lymphocyte expansion and T lymphocyte differentiation (Schilham et al., 1996 and 1997). The *SoxD* gene *Sox13* acts further downstream in the same pathway to promote delta-gamma T-cell development while opposing alpha-beta T-cell differentiation (Melichar et al., 2007). As mentioned above, Sox13 works by inhibiting transactivation of lineage-specific genes by TCF1 downstream of the Wnt signaling pathway. Another *SoxD* gene, *Sox6*, is expressed in definitive erythroid cells. It enhances the ability of the erythropoietin signaling to promote cell survival and proliferation and also promotes erythroid cell maturation (Dumitriu et al., 2006). It directly inhibits expression of embryonic globin genes (Yi et al., 2006). Based on the essential roles that Sox genes have in maintaining stemness and in determining lineage fate and cell differentiation in other processes, it will be worth exploring in future projects the possibility that multiple Sox genes are involved in various aspects of hematopoiesis, as they are in many other processes.

4.7. Endoderm and hair development, cardiogenesis, and angiogenesis

Until now, we have reviewed functions for all *Sox* groups, but have hardly mentioned the *SoxF* group. This group of three genes, *Sox7*, *Sox17*, and *Sox18*, has essential roles in processes that are mostly distinct from those controlled by other *Sox* genes. This notion, however, may only reflect the limit of our current knowledge. Namely, they are involved in definitive endoderm development, cardiogenesis angiogenesis, and also hair development. The definitive endoderm of the early embryo gives rise to the entire gastrointestinal tract, glandular structures of the pharynx, the respiratory tract, liver and pancreas and other associated visceral organs (reviews in Tam et al., 2003). Studies in Xenopus and mouse embryos have demonstrated that *Sox17* function is essential for the survival and differentiation of the definitive endoderm and thereby for proper development of the fore-, mid- and hindgut (Hudson et al., 1997; Kanai-Azuma et al., 2002). Sox17 acts in this process by interacting with beta-catenin in its C-terminus and by directly transactivating such targets as the genes for the transcription factors Foxa1, and Foxa2 and the gene for the major basement membrane component laminin-alpha1 (Sinner et al., 2004; Niimi et al., 2004). Further, the three *SoxF* genes are highly expressed in vascular endothelial cells and the developing heart and have important, likely redundant roles in vasculogenesis and cardiogenesis. This conclusion is supported by the effect of dominant-negative *Sox18* mutations on the cardiovascular systems of *ragged* and *ragged-like* mice (Pennisi et al., 2000; Downes and Koopman, 2001; James et al., 2003), by defective cardiogenesis in Xenopus mutants (Zhang et al., 2005), and by vascular abnormalities in postnatal *Sox17/Sox18* double null mice (Matsui et al., 2006). Sox18, and likely its close relatives, has been shown to mediate its functions in endothelial cells by interacting with the MADS box transcription factor Mef2C and by directly activating the gene for the vascular cell adhesion molecule VCAM1 (Hosking et al., 2001 and 2004). Finally, *Sox18* is also required for normal hair follicle development, as supported by the observation of a sparse coat in *ragged* mice and by the fact that mutations in *SOX18* cause the hypotrichosis-lymphedema-teleangiectasia syndrome, characterized by sparse hair, absence of eyebrows and eyelashes, edema, and vascular anomalies (Irrthum et al., 2003).

5. Conclusions, questions, and future directions

Sox research has kept progressing at a fast pace since it was born less than two decades ago, leading to the now well-established concept that *Sox* genes critically control cell fate and differentiation in a multitude of key developmental and physiological processes. These

processes include embryonic and neural cell stemness, sex determination, neurogenesis, cardiogenesis, skeletogenesis, as well as many more. In many processes, *SoxB1* genes control stem cells, whereas *Sry* (*SoxA*), *SoxC, SoxE* and *SoxF* genes work downstream to specify lineage fate and early differentiation, and *SoxD* genes act even further downstream to promote or inhibit terminal maturation. The importance of *Sox* genes is such that mutations in several of them cause complex syndromes in humans. Notable examples are XY sex reversal due to *SRY* mutations, campomelic dysplasia due to *SOX9* mutations, and Hirschsprung disease due to *SOX10* mutations. Even though the number of roles that have already been identified for Sox genes is overwhelming, it is expected from expression pattern and in vitro studies that numerous important roles remain to be uncovered for most Sox genes and that additional human diseases may be caused by *SOX* mutations. Sox proteins have unique key functions in lineage-specific gene transcription, several of which are fulfilled by their highly conserved HMG box domain. This domain binds DNA, bends DNA, and directly interacts with various types of transcription factors. It thereby confers to Sox proteins a central role in the organization and activity of transcriptional complexes. Most Sox proteins also participate in transcription by contributing a potent transcriptional activation or repression domain. The first and foremost best characterized example is that of Sox2, which synergizes with the Oct3/4 POU domain transcription factor through binding to enhancers on several genes expressed in embryonic stem cells. Other examples are those of L-Sox5, Sox6, and Sox9 that cooperate with each other to activate chondrocyte-specific enhancers, but compete with each other to control glial cell-specific enhancers. The identification of the binding sites of Sox proteins on target genes remains a challenging task as these proteins bind DNA with low sequence specificity. It should become easier as new advances are made to identify their DNA configuration preferences and protein partners. A few Sox proteins have recently been shown to undergo posttranslational modifications, such as SUMOylation and phosphorylation of Sox9. These modifications significantly affect the protein stability and activity. These new findings should stimulate further investigations to learn how such modifications may affect other Sox proteins. Finally, how the expression of the Sox genes themselves is controlled is a question that we have hardly discussed in this review and that remains largely unanswered. Progress in this area will contribute in the future to a more complete understanding of the major impact that Sox genes have in the control of cell fate and differentiation.

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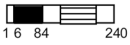
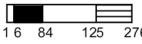
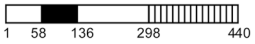
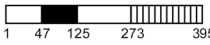
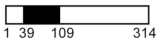
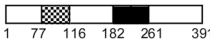
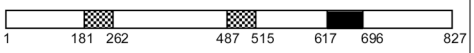
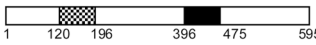
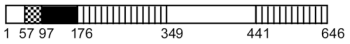
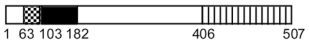
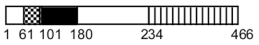
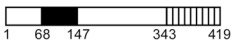
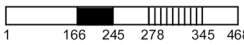
Group	Gene	Locus	Schematic	References
A	*Sry*	YC3		Gubbay et al., 1992 Dubin et al., 1995
B1	*Sox1*	8 A1-A2		Collignon et al., 1996 Kamachi et al., 1999
	Sox2	3 A2-B		Collignon et al., 1996 Kamachi et al., 1999
	Sox3	X A7.3-B		Collignon et al., 1996
B2	*Sox14*	9 E3.3		Hargrave et al., 2000
	Sox21	14 E4		Uchikawa et al., 1999
C	*Sox4*	13 A3-A5		van de Wetering et al., 1993
	Sox11	12 A3		Kuhlbrodt et al., 1998
	Sox12	2 G3		NCBI - CAM23207
D	*Sox5*	6 G3		Denny et al., 1992 Lefebvre et al., 1998
	L-Sox5	6 G3		Lefebvre et al., 1998 Hiroaka et al., 1998
	Sox6	7 F1		Lefebvre et al., 1998 Takamatsu et al. 1995 Connor et al., 1995
	Sox13	1 E4		Kido et al., 1998
E	*Sox8*	17 A3		Schepers et al., 2000
	Sox9	11 E2		Sudbeck et al., 1996 Wright et al., 1995
	Sox10	15 E1		Pusch et al., 1998 Kuhlbrodt et al., 1998
F	*Sox7*	14 C3		Taniguchi et al., 1999 Takash et al., 2001
	Sox17	1 A1		Kanai et al., 1996
	Sox18	2 H4		Dunn et al., 1995 Hosking et al., 2001
G	*Sox15*	11 B3		Beranger et al., 2000
H	*Sox30*	11 B1.1		Osaki et al., 1999

Figure 1.

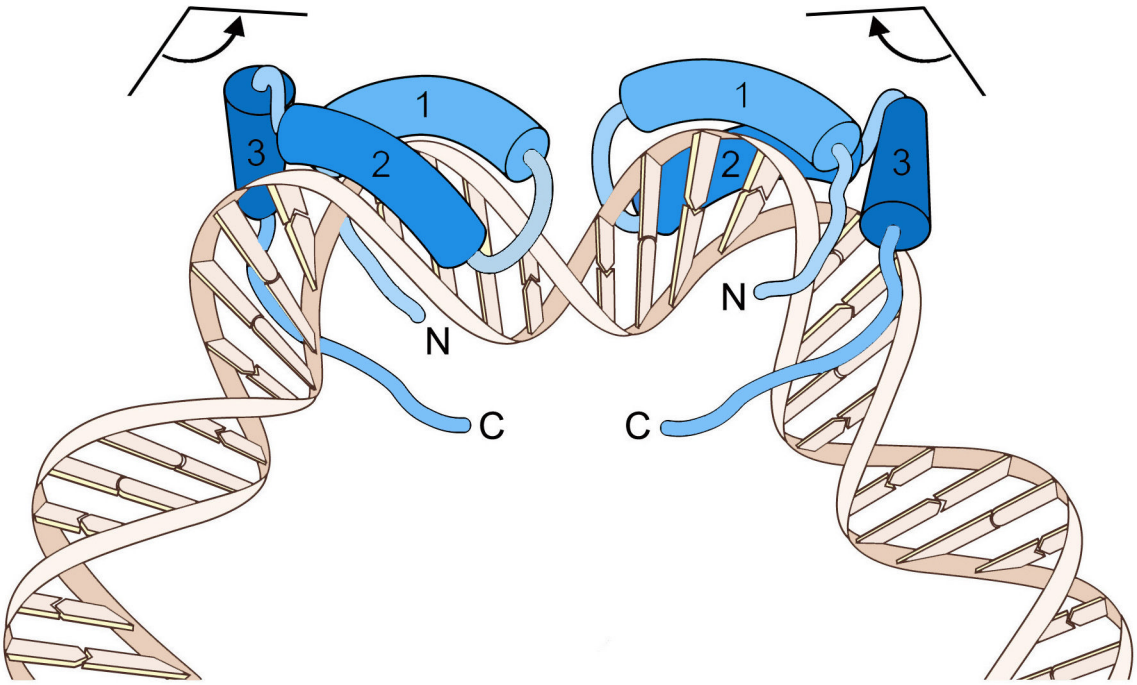


Figure 2.

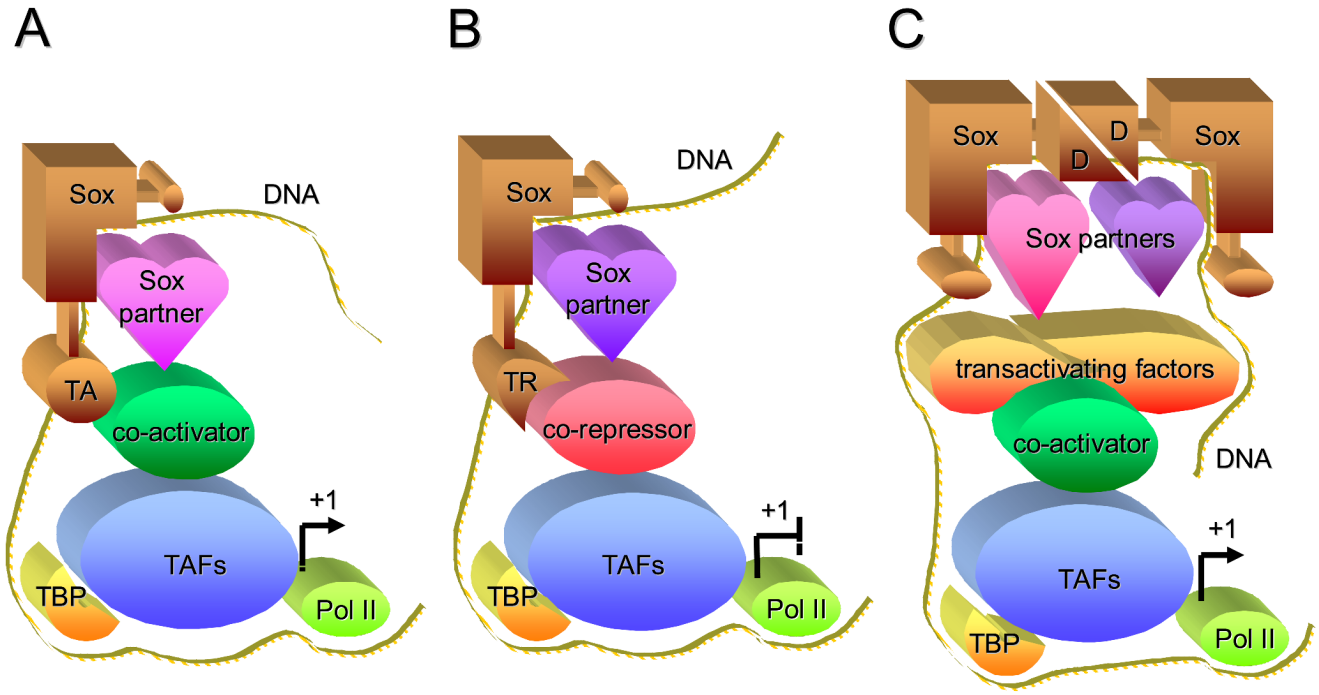


Figure 3.

Table I

In vivo roles of Sox genes

Group	Gene	Roles
A	*Sry*	• Sex determination: Sertoli cell differentiation in the male embryo (Polanco and Koopman, 2007) • Brain activity: regulation of dopaminergic neurons of the nigrostriatal system in the adult male (Dewing et al., 2006)
B1	*Sox1*	• Eye development: induction of lens fiber cell differentiation (Nishiguchi et al., 1998; review in Kondoh et al., 2004) • Neurogenesis: specification and maintenance of neural stem cell identity (Bylund et al., 2003; Pevny and Placzek, 2005; Wegner and Stolt, 2005)
	Sox2	• Embryonic stem cells: maintenance of identity and pluripotency (Avilion et al., 2003) • Neurogenesis: specification and maintenance of neural stem cell identity (Graham et al., 2003; Pevny and Placzek, 2005; Wegner and Stolt, 2005) • Eye development: induction of lens fiber cell differentiation (Kamachi et al., 1998; Kondoh et al., 2004) • Anterior pituitary development: expression of various hormones (Kelberman et al. 2006) • Taste bud: differentiation of endodermal progenitor cells into sensory cells versus keratinocytes (Okubo et al., 2006)
	Sox3	• Neurogenesis: specification and maintenance of neural stem cell identity (Bylund et al., 2003; Pevny and Placzek, 2005; Wegner and Stolt, 2005) • Eye development: induction of lens fiber cell differentiation (Kamachi et al., 1998; Kondoh et al., 2004) • Pituitary development: Rathke's pouch development and hypothalamo-pituitary axis function (Rizzoti et al., 2004) • Gonadogenesis: oocyte proper development, male differentiation and spermatogenesis (Weiss et al., 2003)
B2	*Sox14*	• Neurogenesis: counteraction of Sox1-3 to promote neuronal differentiation (Sandberg et al., 2005)
	Sox21	• Neurogenesis: counteraction of Sox1-3 to promote neuronal differentiation (Sandberg et al., 2005)
C	*Sox4*	• Cardiogenesis: outflow tract formation (Schilham et al., 1996) • Lymphopoiesis: pro-B-cell expansion and T-cell differentiation (Schilham et al., 1997) • Pancreas formation: normal development of pancreatic islets (Wilson et al., 2005) • Neurogenesis: panneuronal gene activation during neuronal maturation (Bergsland et al., 2006)
	Sox11	• Cardiogenesis: outflow tract formation (Sock et al., 2004) • Development of multiple organs, including lung, stomach, pancreas, spleen, eye and skeleton (Sock et al., 2004) • Neurogenesis: panneuronal gene activation during neuronal maturation (Bergsland et al., 2006)
	Sox12	• Unknown
D	*Sox5*	• Skeletogenesis: chondrocyte differentiation, extracellular matrix production, and proliferation (Smits et al., 2001) • Neural crest development: enhancement of neural crest cell production and development (Perez-Alcala et al., 2004) • Gliogenesis: repression of specification and terminal differentiation of oligodendrocytes (Stolt et al., 2006)
	Sox6	• Cardiac conduction: proper function (Hagiwara et al., 2000) • Skeletogenesis: chondrocyte differentiation, extracellular matrix production, and proliferation (Smits et al., 2001) • Gliogenesis: repression of specification and terminal differentiation of oligodendrocytes (Stolt et al., 2006) • Erythropoiesis: erythroid cell survival, proliferation, and maturation (Dumitriu et al., 2006; Yi et al., 2006)
	Sox13	• Lymphopoiesis: regulation of gammadelta versus alphabeta T lymphocyte differentiation (Melichar et al., 2007)
E	*Sox8*	• Gliogenesis: oligodendrocyte specification and terminal maturation (Stolt et al., 2004 and 2005) • Testis development: gonadal precursor cell differentiation into Sertoli cells (Chaboissier et al., 2004) • Osteogenesis: inhibition of osteoblast differentiation (Schmidt et al., 2005) • Neural crest: initiation of formation and maintenance (Maka et al., 2005; O'Donnell et al., 2006)
	Sox9	• Sex determination: Sertoli cell development, testogenesis, and inhibition of female differentiation (Bishop et al., 2000; Chaboissier et al., 2004; Barrionuevo et al., 2006a; Kobayashi et al., 2005; Koopman, 2005)

Group	Gene	Roles
		• Chondrogenesis: chondrocyte specification and early differentiation (Bi et al., 1999; Akiyama et al., 2002) • Neural crest: survival and epithelial-mesenchymal transition (Cheung et al., 2005; Taylor and LaBonne, 2005) • Gliogenesis: terminal differentiation of oligodendrocytes (Stolt et al., 2003; Wegner and Stolt, 2005) • Notochord cells: survival (Barrionuevo et al., 2006b) • Cardiogenesis: endocardial cushion formation (Akiyama et al., 2004) • Inner ear formation (Taylor and LaBonne, 2005) • Hair follicle: outer root sheath differentiation and the formation of the hair stem cell compartment (Vidal et al., 2005) • Pancreas: progenitor cell pool maintenance (Seymour et al., 2007) • Gut: specification of the pyloric sphincter epithelium (Moniot et al., 2004)
	Sox10	• Neural crest: formation, multipotency maintenance, specification and differentiation into enteric ganglionic cells, peripheral glial cells, oligodendrocytes and melanocytes, (Southard-Smith et al., 1998; Britsch et al., 2001; Stolt et al., 2002; Aoki et al., 2003; Cheung et al., 2005; Wegner and Stolt, 2005; Kelsh et al., 2006) • Inner ear formation (Taylor and LaBonne, 2005)
F	*Sox7*	• Cardiogenesis (Zhang et al., 2005)
	Sox17	• Endoderm formation (Hudson et al., 1997; Kanai-Azuma et al., 2002) • Angiogenesis (Matsui et al., 2006)
	Sox18	• Cardiogenesis (Pennisi et al., 2000; Zhang et al., 2005) • Angiogenesis (Downes & Koopman, 2001; Matsui et al., 2006) • Hair follicle development (Pennisi et al., 2000)
G	*Sox15*	• Skeletal muscle regeneration (Lee et al., 2004; Meeson et al., 2007)
H	*Sox30*	• unknown

Table II

Human diseases due to SOX mutations or auto-antibodies

Group	Gene	Human disease	Gene locus
A	*SRY*	XY sex reversal and XY female type gonadal dysgenesis: SRY point mutations or deletions; XX male syndrome: Y-autosome or Y-X translocations involving Sry (Goodfellow and Lovell-Badge, 1993)	Yp11.3
B1	*SOX1*	None reported	13q34
	SOX2	MCOPS3, microphtalmia, syndromic 3: SOX2 heterozygous mutations; anophthalmia or microphthalmia, anterior pituitary hypoplasia; other central nervous system abnormalities, short stature, esophageal atresia, sensorineural hearing loss, and male genital tract abnormalities (Fantes et al., 2003; Kelberman et al., 2006; Williamson et al., 2006)	3q26.3-q27
	SOX3	MRGH: mental retardation, X-linked, with isolated growth hormone deficiency: Mental retardation, infundibular hypoplasia; hypopituitarism; hypoparathyroidism (Laumonnier et al., 2002)	Xq26.3
B2	*SOX14*	Candidate gene for limb defects associated with BPES, (blepharophimosis, ptosis, and epicanthus inversus syndrome) and for MBS2, Moebius syndrome (Wilmore et al., 2000)	3q23
	SOX21	None reported	13q31-q32
C	*SOX4*	None reported	6p22.3
	SOX11	None reported	2p25
	SOX12	None reported	20p13
D	*SOX5*	None reported	12p12.1
	SOX6	None reported	11p15.3-p15.2
	SOX13	SOX13 protein: insulin-dependent diabetes mellitus (IDDM)-specific human autoantigen (Kasimiotis et al., 2001)	1q32
E	*SOX8*	ATR-16: Alpha-thalassemia/mental retardation syndrome, deletion-type. Deletion in 16p involving SOX8 and alpha globin genes (Pfeifer et al., 2002). SOX8 haploinsufficiency could cause mental retardation.	16pter-p13.3
	SOX9	CMPD: Campomelic dysplasia with autosomal sex reversal. Autosomal dominant; bowing and angulation of long bones; other skeletal defects; heart, kidney, hair, pancreas defects; two-thirds of XY individuals with genital defects or developing as females (Foster et al., 2004; Wagner et al., 2004).	17q24.3-q25.1
	SOX10	PCWH: peripheral demyelinating neuropathy, central dysmyelinating leukodystrophy, Waardenburg syndrome, and Hirschsprung disease. Autosomal dominant; developmental delay; hypotonia, neurologic abnormalities; hypopigmentation, deafness, and ganglionic colon (Inoue et al., 2002).	22q13
F	*SOX7*	None reported	8p22-23
	SOX17	None reported	8q12-13
	SOX18	HLTS: Hypotrichosis-Lymphedema-Teleangiectasia syndrome: sparse scalp and body hair, leg edema and dilation of small blood vessels (Irrthum et al., 2003)	20q13.33
G	*SOX15*	None reported	17p13
H	*SOX30*	None reported	5q33