Reproductive Biology 23 (2023) 100823

Contents lists available at ScienceDirect

Reproductive Biology

journal homepage: www.journals.elsevier.com/reproductive-biology

Regulatory mechanisms of SoxD transcription factors and their influences on male fertility

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ARTICLE INFO

Keywords:
SOXD members
Sry-related-box
High mobility group
Testis
Spermatogenesis

ABSTRACT

Members of the SRY-related box (SOX) subfamily D (SoxD) of transcription factors are well conserved among vertebrate species and play important roles in different stages of male reproductive development. In mammals, the SoxD subfamily contains three members: SOX5, SOX6 and SOX13. Here, we describe their implications in testicular development and spermatogenesis, contributing to fertility. We also cover the mechanisms of action of SoxD transcription factors in gene regulation throughout male development. The specificity of activation of target genes by SoxD members depends, in part, on their post-translational modifications and interactions with other partners. Sperm production in adult males requires the coordination in the regulation of gene expression by different members of the SoxD subfamily of transcription factors in the testis. Specifically, the regulation of genes promoting adequate spermatogenesis by SoxD members is discussed in comparison between species.

1. Introduction

Infertility affects 8–12% of couples, with the male component accounting for about half of these cases [74]. A complete absence of sperm in the ejaculate (azoospermia) or a sperm concentration of less than 15 million sperm/ml are both signs of male infertility (oligozoospermia) [15]. There is a clear need to better understand the molecular pathways that control normal sperm production in mammals. Sex-determining region (Sry)-related box (SOX) proteins play a role in various developmental events of the male embryo, including male sex determination and Sertoli cell differentiation. Several *Sox* genes are differentially expressed in distinct tissues during development. In addition to having a critical function during fetal development, SOX family members have been found in many postnatal organs, including the testis. Indeed, many members of this family are expressed in different cell types of the adult testis and play critical roles in transcriptional regulation contributing to normal spermatogenesis. In this article, we will review the functional characteristics of SOX transcription factors members of the SoxD subfamily, as well as their regulatory mechanisms and implications in the acquisition and maintenance of male reproductive function across species.

2. Classification of the SOX family of transcription factors

The SOX family includes transcription factors with a three-α-helix high mobility group (HMG) DNA binding domain that binds to the consensus DNA sequence (A/T)(A/T)CAA(A/T)G in the minor groove of DNA to bend it [29,42,53,57,67]. The HMG domain of SOX transcription factors contains a highly conserved amino acid sequence (RPMNAFMVW) present in all SOX transcription factors except SRY [7]. This protein motif not only binds to DNA, but also regulates intracellular transport and interactions with partner proteins [53]. The 20 members of the SOX family are divided into nine groups based on amino acid sequence similarity and conserved domains: SoxA, SoxB1, SoxB2, SoxC, SoxD, SoxE, SoxF, SoxG, and SoxH [7] (Table 1). In each group, the Sox proteins have highly conserved amino acid sequences (>70%). In addition, the HMG sequence of the SRY protein shows at least 50% amino acid similarity with the HMG sequences of the other SOX proteins [4]. Importantly, members of the same group tend to be functionally redundant, which limits the potential development of infertility following inactivation of one member. The SoxD group includes members SOX5, SOX6 and SOX13. SoxD proteins are expressed in multiple isoforms by alternative splicing [45] and are characterized by the absence of a transactivation domain [42]. Thus, SoxD proteins can be qualified as long and short isoforms.

Much like the lamprey of the taxon cyclostomata (jawless fish) [60],

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https://doi.org/10.1016/j.repbio.2023.100823
Received 22 September 2023; Received in revised form 31 October 2023; Accepted 1 November 2023
Available online 17 November 2023

Table 1
Classification of SOX transcription factors in mammals based on HMG amino acids sequences comparisons.

Group	Sox members
A	SRY
B1	SOX1, SOX2, SOX3
B2	SOX14, SOX21
C	SOX4, SOX11, SOX12
D	SOX5, SOX6, SOX13
E	SOX8, SOX9, SOX10
F	SOX7, SOX17, SOX18
G	SOX15
H	SOX30

invertebrates such as *Drosophila*, *Caenorhabditis elegans*, and sea urchins have only one gene member for the SoxD group [7]. However, expression of the three SoxD group members, SOX5, SOX6 and SOX13, has been reported in most vertebrates. Like other SOX transcription factors, members of the SoxD group are also able to induce DNA bending by binding to their regulatory elements via their HMG domain [13,18].

Between species, the amino acid sequence of SoxD members is more variable in regions outside the DNA binding domain and the coiled coil domain. As for SOX6, the SOX5 protein sequence is conserved by more than 74% between zebrafish, xenopus, chicken and mammals. However, the protein sequence for SOX13 is less conserved between species with only 55% between zebrafish and xenopus.

Members of the SOX family contain transactivation domains on the C-terminal side of the HMG box. The activity of these transactivation domains is often promoter and partner dependent (Fig. 1). These activator or repressor domains can serve as protein-protein interaction domains and recruit cofactors necessary for activation or repression of the target gene, respectively. Intriguingly, SoxD proteins do not have typical activator or repressor domains. Therefore, their activity may depend on post-translational modifications related to tissue type and developmental stage. In addition, their protein-protein interaction capabilities may rather rely on their coiled-coil domains [30]. Moreover, the function of SOX proteins may also depend on the regulatory context of the promoter and require the cooperation with several transcription factors, ultimately leading to tissue-specific and development-dependent regulation.

In human and mouse, the *Sox5* gene encodes short (S-SOX5) and long (L-SOX5) isoforms where the short isoform lacks the coiled-coil domain [46]. The short transcript of *Sox5* (2 kb) can be found in the adult testis [18], whereas the longer transcript (6 kb) is detected in other tissues [35]. The short isoform of SOX5 lacks the N-terminal motifs essential for transcription factor function and association with SOX6. Recently, a new variant of S-SOX5, having a unique 5'UTR region and an additional exon 9, has been characterized in the mouse testis [93]. Both S-SOX5 variants are increasingly expressed in the mouse testis from postnatal day 21 and may play roles in the formation of round spermatids [93]. SOX5 is also involved in the regulation of *dmrt1* expression and germ cells development in medaka [66], however only one isoform has been characterized in this specie thus far.

3. Regulation of the activity of SOXD members

The choice of protein partners, as well as the post-translational modifications of SOX proteins, contribute to the specificity of their target genes. Indeed, due to their low DNA binding affinity, SOX proteins recruit a wide range of cooperative transcription partners or cofactors to form stable regulatory complexes on SOX-like DNA binding elements. Thus, to achieve their transcriptional regulatory function, SOX proteins must recruit protein partners to DNA regulatory regions [70].

3.1. Dimerization and cofactor recruitments

The specific transcriptional regulation capacity of SOX transcription factors is mainly attributed to their dimerization ability and interactions with other cofactors or transcription factors. The extent of dimerization varies depending on the cell type and target genes for these transcription factors. While most SOX transcription factors form monomers, SOX5 and SOX6 members are an exception as they possess a group-specific N-terminal coiled-coil domain (CC in Fig. 1) involved in DNA independent formation of homo and heterodimers among SOX members [45]. Indeed, only the long isoforms of SoxD members contain a typical N-terminal domain with a leucine zipper and a glutamine-rich region (Q-box), allowing their homodimerization or heterodimerization with other SoxD proteins [35]. In addition, SOX5 and SOX6 can form heterodimers with SOX9 to cooperate and activate genes important for chondrogenesis [46]. Interestingly, SOX9 also regulates the expressions of *SOX6* and *L-SOX5* in human chondrocytes [2].

The structure of the *Sox6* gene dictates its functional versatility [30]. Indeed, SOX6 does not contain any known regulatory domains; rather, it interacts with various cofactors. In addition, the *Sox6* gene has a long 3'-UTR that contains multiple microRNAs' binding sites. Hence, its protein level is precisely determined by cell-type specific microRNAs. However, it is rather the short form (approx. 3 kb) of the *Sox6* transcript lacking the long 3'-UTR that is mainly expressed in the testis [12,46].

As for SOX5, the long isoform of SOX6 contains a leucine zipper in addition to an HMG box [77]. Interestingly, SOX6 has been reported to physically interact with the centromere protein K (CENPK) in the testis [90]. Such interaction may rely on phosphorylation within the leucine zipper region of SOX6 by the Ca^{2+}/calmodulin-dependent protein kinase IV (CAMK4) [90].

Because of the small size of the regulatory element of SOX factors, the choice of cofactors is important to confer their specificity of action.

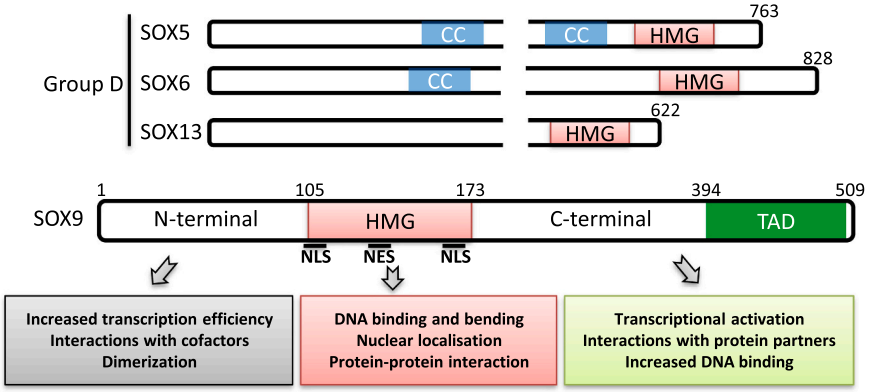

Fig. 1. The structure and functional domains of human SoxD members and of the human SOX9 as a comparison. HMG: high mobility group; TAD: trans-activation domain; CC, coiled-coil domain.

Dimerization of SoxD members facilitates their binding to clustered SOX DNA regulatory elements with a high tolerance for poorly conserved sequences [46,77]. SOX members are capable of interacting with other transcription factors to form major complexes [88]. Binding with co-factors and other transcription factors involves the HMG domain that is conserved in all SOX factors.

SOX proteins can participate in the regulation of signaling pathways, such as the Wnt pathway, by interacting with β-catenin and/or the lymphoid enhancer binding factor TCF/LEF. In the canonical Wnt signaling pathway, SOX proteins can compete with TCF/LEF for binding to β-catenin, leading to inhibition of the Wnt/β-catenin signaling pathway. SOX proteins can also synergize with β-catenin to positively regulate target gene expression [4]. During T cell development, SOX13 interacts directly with TCF/LEF to repress Wnt target gene expression [55]. According to different mouse models, the Wnt signaling pathway is required for normal spermatogenesis [39] and may be regulated by SoxD members. Also influencing their protein-protein interaction capabilities, SOX transcription factors can undergo several post-translational modifications important for the regulation of their target gene expression.

3.2. Post-translational modifications

Post-translational modifications of transcription factors are essential for their protein stability, activities, intracellular localizations, and interactions with protein partners [23]. These modifications include phosphorylation, acetylation, methylation, hydroxylation, or conjugation to small molecules such as ubiquitination or sumoylation. Although various post-translational modifications of SoxD proteins have been reported, their importance in the transcriptional regulation of target gene expression in the testis needs to be investigated further and has been limited to phosphorylation, acetylation, ubiquitination or sumoylation.

3.2.1. Phosphorylation

Phosphorylation is very important in the regulation of the activity of many transcription factors. Phosphorylation by the cyclic AMP-dependent protein kinase (PKA) of SRY on a serine motif in its N-terminal region increases its affinity for DNA and its transcriptional activity [20]. The phosphorylation of mouse SOX6 at T119 by cyclin-dependent kinase 5 (CDK5) promotes its degradation in the brain [65]. The human SOX5 can be phosphorylated by cyclin-dependent kinases at 4 serine residues (S503, S528, S531, S534) between the coiled coil and HMG domains [19]. Interestingly, the human SOX13 can be phosphorylated at seven sites (T307, S308, S309, S312, S382, S385, S386) by cyclin dependent kinases [19,62]. However, the relevance of these phosphorylation sites in the activity of SoxD members in the testis, their contributions to male fertility, and their conservation between species remain to be investigated.

3.2.2. Acetylation

Acetylation of SOX members, such as the residue K136 in human SRY, is essential for their nuclear localization and their role in male sex determination [78]. The residues K595 for SOX5, K155, K159 and K164 for SOX6 and K298 for SOX13 can be acetylated and are conserved between rodents and human [36]. Hence, acetylation/deacetylation of these lysine residues may regulate the nucleocytoplasmic shuttling of SoxD members in the testis.

3.2.3. Ubiquitination

Ubiquitination corresponds to the addition of ubiquitin subunits to the target protein, leading to its cytoplasmic degradation by the proteasome. Very few examples of ubiquitination of SOX proteins have been characterized. TRIP12, a member of the E3 ubiquitin ligase HECT family, physically interacts with the coiled-coil domain of SOX6 and carries out ubiquitination of this SOX member for proteasome-dependent degradation in muscle cells [3]. Specifically, SOX6 can be ubiquitinated at K159 and K340, whereas SOX5 can be ubiquitinated at K147 and K171 in rodents and human [1,36,83]. For SOX13, ubiquitination may play a major role in the regulation of its activity with seven lysine residues being targeted in human and rodents (K101, K117, K124, K183, K200, K378, K389) [1,83]. However, the importance of SOX protein ubiquitination in testis development remains to be investigated.

3.2.4. Sumoylation

Sumoylation of target proteins is the covalent addition of SUMO proteins to a lysine residue by a cascade of specific enzymes. The consequences of sumoylation range from transcriptional repression, alteration of subcellular localization and activity of target proteins, DNA damage repair and signal transduction [24]. In human, the sumoylation of SOX6 at K404/417 by the ubiquitin conjugating enzyme UBC9 inhibits its transcriptional activity [22]. Interestingly, these sumoylation sites are highly conserved in other species such as rodents and chicken. In addition, SOX5 and SOX13 contain highly conserved sumoylation sites at K467 and K139/K514, respectively [33,51]. However, the functional roles of these sumoylation sites in SoxD-dependent transcriptional regulation in the testis remain to be characterized.

3.2.5. Nuclear localization of SOX transcription factors

The regulation of nucleocytoplasmic migration of SOX transcription factors by interaction with karyopherin proteins represents an important mechanism influencing their cellular functions. Two nuclear localization signals (NLS) can be found in the HMG domain: the N-terminal NLS is calcium/calmodulin dependent and involves exportin-4, while the C-terminal NLS is importin β dependent [53]. However, the importance of nucleocytoplasmic shuttling in the regulation of SoxD members' transcriptional activity in the testis remains to be investigated.

4. SoxD members and spermatogenesis

In the testis, *Sox5* and *Sox6* are typically expressed in spermatocytes and spermatids, whereas *Sox13* is mainly expressed in spermatogonia [64]. In other species such as *Macaca mulatta*, *Bos taurus* and *Gallus gallus*, SoxD members are highly expressed in the testis [56]. Hence, these transcription factors may regulate gene expression critical for spermatogenesis in vertebrate species. Since *Sox5* and *Sox6* are expressed in the same cell types of the testis, redundancy may be present between these transcription factors.

In spermatids, the chromatin modeling and level of DNA compaction suggest that transcriptional regulation and gene expression are relatively inactive during spermiogenesis. However, spermatids are characterized by the coordinated expression of cell type-specific genes. Indeed, others have reported that around 5% of mRNAs and 30% of long non-coding RNAs are specifically expressed in spermatocytes and/or spermatids [47,68,71]. More research is needed to clearly determine whether this transcription in spermatids is a secondary, and functionally irrelevant, consequence of chromatin remodeling. Interestingly, the knockout of another SOX family member expressed in round spermatids, SOX30, results in the downregulation and upregulation of 664 and 121 protein coding genes, respectively [91]. As for SOX30, SOX5 and SOX6 may regulate gene expression in spermatocytes and/or spermatids.

Interestingly, *SOX5* haploinsufficiency results in the development of the extremely severe Lamb-Shaffer syndrome, characterized by developmental delay, intellectual disability, speech delay, and distinctive facial appearance [44]. In contrast, an heterozygous inactivating variant of SOX6 is linked to a different [80]. However, it remains unclear whether the fertility of these patients is affected.

4.1. SOX5 regulates gene expression in spermatids

SOX5 and SOX6 are expressed in round spermatids during spermatogenesis [14,18,64]. The immunolocalization of SOX5 in the nucleus of round spermatids from mice testes suggests that this protein

plays a role in regulating spermatogenesis [13]. Indeed, several SOX5 polymorphisms have been associated to nonobstructive azoospermia in a Chinese population [37,94]. In addition, the levels of SOX5 are increased in mice testes from pre-puberty (21 days) to adulthood (4 months) and *Sox5* is mainly expressed in post-meiotic round spermatids [13,18]. In fact, SOX5 may play an important role in transcriptional regulation of different target genes being expressed in spermatids. Indeed, SOX5 binds but does not activate *Lipe* expression in vitro [5], enhances the activation of a *Nfkbib* reporter construct [8], binds to the *Pacap* promoter [17], activates the human and mouse *Spag6* promoter [43], as well as the human *ZNF230* promoter [89]. These target genes are all being critical for normal spermatogenesis in mammals. Interestingly, silencing of *sox5* down-regulates *spag6* expression in the chicken fibroblast cell line DF-1, inhibiting their proliferation and migration [75]. This suggests that SOX5 regulation of target genes may be conserved between species.

According to transcriptomic and protein expression analyses [64], SOX5 is specifically expressed in spermatids. However, several spermatocytes with a perinuclear localization of SOX5 were also reported. Such observation has been reported previously for SOX5 in differentiating chondroblasts [34] and may be related to impaired transcriptional activity. However, further investigation will be required to better define the relevance of this perinuclear localization of SOX5 in spermatocytes. Others have also reported an expression of *Sox5* in mouse spermatogonia and Sertoli cells [63]. However, its role in regulating the expression of genes specific to these cell types has yet to be defined.

Interestingly, SOX5 activates the *Catsper1* promoter by being recruited to the SOX regulatory element at −214 bp within the promoter region [54]. The *Catsper* gene codes for a Ca^{2+} permeable channel required for sperm hyperactivation. In the mouse testis, the *Sox5* and *Catsper1* genes are being co-expressed in post-meiotic pachytene spermatocytes and spermatids [54].

In zebrafish, SOX5 inhibits the expression of the *doublesex* and *mab-3*-related transcription factor 1 (*Dmrt1*), involved in gonadogenesis [27]. High expression of *Dmrt1* generally promotes male sex differentiation. Interestingly, SOX5 DNA regulatory elements in the proximal region of the *Dmrt1* promoter are conserved in other species such as the black rockfish *Sebastes schlegeli* [52], the wrasse *Halichoeres tenuispinis* [38] and medaka *Oryzias latipes* [66]. In addition, inactivation of *sox5* in medaka leads to XX female to male sex reversal [66].

Interestingly, the expression of *Sox5* is highly decreased in male mice harboring an inactivation of SOX30 [21]. The transcription factor SOX30 has been characterized as a critical regulator of spermiogenesis and part of its regulatory mechanism may be attributed to its regulation of *Sox5* expression in post-meiotic germ cells of the adult testis. However, the importance of SOX30 in regulating *Sox5* expression in the testis of species other than the mouse remains to be confirmed.

4.2. Sox6 as a potent regulator of spermatogenesis

SOX6 has been shown to be expressed in mouse [14,77], rat [58] and rainbow trout *Oncorhynchus mykiss* adult testes [77]. Using RNA-Seq analysis, *Sox6* has been confirmed to be highly expressed in spermatids and at a lower level in spermatocytes of both mouse and rat [64], suggesting that SOX6 must have a conserved regulatory function in spermatogenesis. The *Sox6* gene is also expressed in the developing nervous system [14] and acts with retinoic acid to allow neuronal cells differentiation [31]. SOX6 has a suppressive effect on retinoic acid induced apoptosis [32]. Retinoic acid plays an important role in spermatogenesis by initiating meiosis [9]. Thus, regulation of spermatogenesis by retinoic acid and SoxD members may be linked. Indeed, treatment of spermatogonial stem cells with retinoic acid downregulates *Sox13* expression [84]. SOX6 and SOX5 have similar expression profiles in the testis and bind common DNA regulatory elements [14], suggesting that these members of the SoxD group may be functionally redundant in regulating gene expression during spermatogenesis.

Interestingly, chronic sleep restriction in rats has been associated with an increase in *Sox6* gene expression in testes and a decrease in fertility [11]. However, the identification of SOX6 target genes and its importance in the regulation of male spermatogenesis remain to be clarified.

In the developing rat testis, as well as in rat Sertoli cells from adult testis, the expression of SOX6 overlaps with that of NR0B1 (DAX-1), and these transcription factors physically interact to relieve the inhibitory action of NR0B1 on pre-mRNA splicing [59]. However, the implication of SOX6 in Sertoli cells alternative splicing of target genes important for gonadal development and maturation may be species specific. Indeed, the expression of SOX6 has been reported in rat Sertoli cells, but not in mouse Sertoli cells [64]. The identity of target genes for such a pre-mRNA splicing regulatory mechanism remains to be characterized.

Interestingly, SOX6 showed a male-specific expression pattern in a comparison of ovary and testis transcriptomes from the spot-fin porcupine fish (*Diodon hystrix*) [10] and silver sillago (*Sillago sihama*) [79]. Supporting its conserved role in gonadal development and spermatogenesis, *sox6* is also specifically expressed in testes of teleost fishes and seems to be involved in the maturation of spermatids [87]. However, such gonadal male-specific expression of *Sox6* is not conserved among all species. For instance, analyses of the transcriptomes of gonads from juvenile jade perch (*Scortum barcoo*) and Chinese soft-shell turtle (*Peelodiscus sinensis*) revealed a higher expression of *sox6* in the ovaries compared to the testes [49,85,92].

Analyses of publicly available data can enable us to better define the possible roles of SOX6 in regulating the expression of genes important for proper spermatogenesis. Using the Human protein atlas [81], 64 genes were identified as having a similar expression profile to *SOX6* in the testis. These genes were then investigated for potential SOX6 binding sites using the ChIP-Atlas: Target Genes platform [61,95] where 33 among them have an enrichment for SOX6 within 10 kb of their TSS in mouse chondrocytes. Among these genes, 7 have an important functionality in the regulation of spermatogenesis and spermiogenesis. Indeed, *INSL6* plays a role in the maturation of spermatozoa [50]. The *MBD3L1* gene is involved in the post-meiotic development and epigenetic reprogramming of male germ cells [86]. The *RNF32* gene is expressed in spermatids during spermatogenesis [82]. SPACA4 is a sperm membrane surface protein conserved among mammals that appears to be involved in adhesion between the sperm and egg membranes and gamete fusion during fertilization [25]. The SUN3 protein is essential for sperm head formation during mouse spermiogenesis [26]. The *TSKS* gene codes for a testis specific serine kinase substrate important for spermatogenesis and spermiogenesis [69]. In addition, the *ZPBP* gene codes for a protein that accumulates in the acrosome during the maturation of spermatids and participates in the binding between acrosome-reacted sperm and the egg-specific zona pellucida [48].

4.3. Implication of SOX13 in spermatogonia

The gene *Sox13* has been reported to be expressed in spermatogonia of both mouse and rat testes [16,64]. However, although *Sox13* mRNA was not detectable in mouse spermatocytes and spermatids, it is possible that the SOX13 protein is being preserved during the progression of spermatogenesis, whereas the *Sox13* mRNA is being degraded. In other species such as the Chinese soft-shell turtle (*Peelodiscus sinensis*), *sox13*, as for *sox6*, is rather upregulated in the ovary [85,92]. However, the expression of *sox13* is higher in the testis of male juvenile jade perch (*Scortum barcoo*) compared to ovaries [49]. In addition, others have originally detected *Sox13* in the mouse ovary, but not in the testis [41]. The precise function of SOX13 in male reproduction remains to be characterized. However, potential regulatory elements for SOX13 can be found in the regulatory regions of genes important for spermatogenesis such as *Ppp2r2b* [40], *Jarid2* [28], *Msl2* [72], *Dlgap2* [73], and *Cdk8* [76] as determined using bioinformatics analyses of ATAC-Seq and SOX13 ChIP-Seq data [61,95].

Table 2
Overview of SoxD members' target genes in the testis across vertebrate species.

SoxD member	Cell types	Species	Target genes	Ref.
Sox5	Spermatocytes	Mouse	*Catsper1*	[54]
	Spermatids	Mouse	*Lipe*	[5]
			Nfkbib	[8]
			Pacap	[17]
			Spag6	[43]
			Znf230	[89]
	Testis	Medaka	*Dmrt1*	[66]
		Black rockfish	*Dmrt1*	[52]
		Wrasse	*Dmrt1*	[38]
	Undifferentiated gonads	Zebrafish	*Dmrt1*	[27]
Sox6	Spermatocytes / Spermatids	Human	*INSL6*	[50]
			MBD3L1	[86]
			RNF32	[82]
			SPACA4	[25]
			SUN3	[26]
			TSKS	[69]
			ZPBP	[48]
Sox13	Spermatogonia	Mouse	*Ppp2r2b*	[40]
			Jarid2	[28]
			Msl2	[72]
			Dlgap2	[73]
			Cdk8	[76]

5. Conclusions and perspectives

In conclusion, *Sox5* and *Sox6* are typically expressed in spermatocytes and spermatids. Spermatogonia are rather characterized by the expression of *Sox13*. Postnatal expression profiles of these SoxD members suggest that these transcription factors may play different roles and regulate different genes according to cell types from the adult vertebrate testis (Table 2). In humans, there is insufficient data linking SoxD genes' expression to male fertility beyond testicular expression. Further research is therefore required to conclude that SoxD members are involved in the regulation of male fertility in humans. Although the expression profiles of SOX members have been characterized within the testis according to development, numerous questions remain to be addressed: 1) What are the post-translational modifications regulating their activities? 2) What are their interacting partners and are they cell specific? 3) Which target genes do they regulate and what are their implications in male fertility? More research is required to answer these questions and possibly identify causes of currently unexplained cases of male infertility.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Current work was funded by the Natural Sciences and Engineering Research Council of Canada (NSERC), Canada (#05219 to L.J.M).

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