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SOX Genes and Cancer

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Abstract

Transcription factors play a critical role in regulating the gene expression programs that establish and maintain specific cell states in humans. Deregulation of these gene expression programs can lead to a broad range of diseases including cancer. SOX transcription factors are a conserved group of transcriptional regulators that mediates DNA binding by a highly conserved high-mobility group (HMG) domain. Numerous evidence has recently demonstrated that SOX transcription factors critically control cell fate and differentiation in major developmental processes, and that their upregulation may be important for cancer progression. In this review, we discuss recent advances in our understanding of the role of SOX genes in cancer.

Keywords: transcription factors, cancer, SOX2, SOX4, SOX9, SOX11

1. Introduction

Cancer is caused by alterations in the control and activity of genes that in turn regulate cell growth and differentiation, leading to abnormal cell proliferation [1]. It is a multi-step process leading to profound metabolic and behavioral changes in a cell. The hallmarks of cancer include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, activating invasion and metastasis, genome instability, inflammation, reprogramming of energy metabolism and evading immune destruction [2]. Most human malignancies are caused by somatic alterations within the cancer genome either through gain-of-function mutations in proto-oncogenes or loss-of-function mutations in tumor suppressor genes. Remarkable progress in cancer research has been made in the last 10 years. However, the detailed molecular mechanisms of cancer remain largely un-elucidated.

A transcription factor (TF) might be defined as any molecule participating, alone or as part of a complex, in the binding to a gene's enhancer response element or promoter, with the

ultimate outcome being the up- or down-regulation of expression of that gene [3]. TFs are key genes involved in the regulation of gene expression. The human genome encodes over 2000 different TF-coding genes, many of which are expressed in a cell type-specific manner to coordinate gene expression programs underlying a vast array of cellular processes [4]. TFs are commonly deregulated in the pathogenesis of human cancer. For instance, *TP53* and *MYC*, which encode the TFs p53 (tumor suppressor protein 53) and c-Myc respectively, are among the most frequently changed genes across all cancers [5, 6].

Sex determining region Y (SRY)-related high-mobility group (HMG) box (SOX) family comprises more than 20 members, which have been shown to involve in regulation of many biological processes such as embryonic development, cell-fate decision, lineage commitment, determination and differentiation [7–9]. This transcription factor family is divided into 10 subgroups based on the level of amino acid conservation within the HMG box and the presence of other motifs. In this review, we discuss the current understanding on the association between SOX genes and cancer. We particularly emphasize the role of several representative SOX subgroup proteins (SOX2, SOX4, SOX9 and SOX11) in cancer initiation and development.

2. The biological functions of SOX gene family

SOX genes are part of a larger family of HMG proteins. SOX proteins bind similar DNA motifs [(A/T)(A/T)CAA(A/T)G] through their HMG domain, which is highly conserved among SOX gene family. Due to the low affinity between SOX proteins and DNA, cofactors are usually required to stabilize their interactions with DNA [9]. Based on the degree of conservation of their HMG-box and the presence of defined HMG-independent structural domains, SOX proteins are organized into 10 subfamilies: SOXA-SOXJ. For example, the SOXA group consists only of SRY; SOXB group comprises of two subgroups (SOXB1 and SOXB2); SOXB1 includes SOX1, SOX2, and SOX3, whereas SOXB2 proteins include SOX14 and SOX21; SOXC group includes SOX4, SOX11, and SOX12; SOXD group includes SOX5, SOX6, and SOX13; SOXE group includes SOX8, SOX9, and SOX10; and SOXF group includes SOX7, SOX17, and SOX18; SOXG (SOX15) and SOXH (SOX30) proteins are structurally related to SOXB1 and SOXD proteins, respectively [10–13]. Individual members within the same SOX group share similar biochemical properties and thus have overlapping biological functions. However, SOX proteins from different groups have distinct biological functions [9]. SOX gene family has been demonstrated to play important roles in various biological processes including, but not limited to development, tissue homeostasis and regeneration, reprogramming [9, 14–16].

In vertebrates, SOX genes are well known regulators of numerous developmental processes. Accumulating evidences have shown that SOX proteins are co-expressed in various developing tissues in an overlapping manner and show functional redundancy. The transcriptional activities of SOX proteins are regulated via three major pathways: (1) the expression levels of SOX proteins are regulated in specific cell types and tissues with precise timing (2) SOX proteins are regulated by posttranslational modification (3) the partners

of SOX proteins are regulated to not only influence the specific recognition of the binding sites of SOX-partner complexes on the target genes, but also determine transcription activities and significantly enhance the activation/repression potential. For instance, SOXB1 and SOXB2 proteins are important for the development of the central nervous system and foregut system [17–19]. SOXD proteins are important for the development of cartilage tissues. In mouse embryos, SOX5, SOX6, SOX9 and collagen II are co-expressed in all cartilaginous sites at around 12.5 dpc. After 17.5 dpc, the chondrocytes become hypertrophic in the growth plate cartilages, the expression of above SOX genes are inhibited and disappear in the hypertrophic chondrocytes [20]. The expression patterns of SOXE genes are important for the development of reproductive system. SOX8, SOX9 and SOX10 are expressed in the overlapping temporal and spatial expression patterns during gonads development, indicating the overlapping roles of these genes in mammalian sex determination and subsequent male sexual development [21, 22]. The members of SOXF group play important roles in the development of cardio-vascular system and extraembryonic endoderm. SOX7 and SOX17 are crucial endoderm lineage-determining regulators and are involved in the later stage of extraembryonic differentiation [23–25].

SOX2 is an important marker for stem and progenitor cell populations in many adult tissues. SOX2 positive cells have been detected in progenitors of various tissues such as adult retina, trachea, tongue epithelium, dermal papilla of the hair follicle, adult testes, forestomach, glandular stomach, anus, cervix, esophagus, lens and dental epithelium [26–30]. Conditional SOX2 deletion significantly influences cell proliferation. In trachea, SOX2 expression is required to sustain tissue homeostasis by controlling the number of proliferating epithelial cells as well as the proportion of basal, ciliated and Clara cells [28]. However, whether SOX2 expression is required for homeostasis in other adult tissues needs further investigation. In addition to maintaining tissue homeostasis, SOX2 plays an important role for tissue regeneration and repair. For instance, the basal stem cells could repair the damaged tracheal epithelium in mice within 7–10 days. The number of basal stem cells was significantly lower in the trachea with SOX2-deficiency. Therefore, the injured trachea was unable to undergo efficient tissue repair. SOX2 is also important for peripheral nerve regeneration. When there is injury, mature adult Schwann cells dedifferentiate to a progenitor cell-like state by re-expressing Sox2 [31].

The expression of four transcription factors, Oct4/Sox2/cMyc/Klf4, was able to convert differentiated cells to pluripotent cells [32]. SOX2 is indispensable for the success of this reprogramming process. However, the biological function of SOX2 seems to be closely correlated with its levels. SOX2 overexpression can promote differentiation and reduce the reprogramming efficiency of neural progenitor cells. In addition to SOX2, SOX1 and SOX3, which are also members of SOXB1 family, can replace SOX2 during the reprogramming process. SOX15 or SOX18 was also able to generate the pluripotent cells but less efficient than SOXB1 family [33].

Many members of SOX gene family have been demonstrated to be closely correlated with tumorigenesis [34, 35]. Below, we discuss the involvement of several SOX genes that have been most extensively studied in human malignancies so far. **Table 1** listed these SOX genes and their clinical relevance in cancers.

SOX genes	Deregulation	Potential clinical significance	Reference
SOX2	Lung, esophagus and oral cancer↑	Promote tumor progression	[36]
	Melanoma↑	Enhance the self-renewal capacity of cancer stem cells	[37]
	Glioblastoma ↑	Associated with tumor aggressiveness and worse prognosis	[38, 39]
	Gastric cancer↓	Promote tumor progression	[40]
SOX4	Oral cancer ↑	Promote tumor initiation and development	[41, 42]
	Prostate cancer↑	Associated with worse prognosis	[43, 44]
	Leukemia↑	Promote tumor progression	[45]
	Primary gallbladder carcinoma↓	Associated with worse prognosis	[46]
SOX9	Papillary thyroid cancer↑	Promote tumor progression	[47]
	Breast cancer ↑	Associated with chemoresistance	[48]
	Gastric cancer ↑	Promote tumorigenesis	[49]
	Cervical carcinoma↓	Promote tumor progression	[50]
SOX11	Breast cancer↑	Promote tumor progression	[51]
	Mantle cell lymphoma↑	Promote tumor progression	[52–54]
	Epithelial ovarian cancer↓	Associated with worse prognosis	[55]
	Gastric cancer↓	Associated with worse prognosis	

Table 1. Deregulation of typical SOX genes and their clinical relevance in cancers.

3. SOX2 and cancer

The SOX2 gene is located on chromosome 3q26.3–q27, it belongs to the SOXB1 group and encodes for 317 amino acids [56, 57]. SOX2 is one of the key transcription factors for induced pluripotent stem cells establishment, stem cell maintenance, and lineage fate determinant. Deregulation of SOX2 has been associated with various diseases such as anophthalmia-esophageal-genital (AEG) syndrome and bilateral anophthalmia/microphthalmia, anterior pituitary hypoplasia, hypogonadotropic hypogonadism hypothalamic hamartoma, sensorineural hearing loss, and esophageal atresia [58, 59]. In addition to the above diseases, increasing evidence has revealed there is a strong relationship between SOX2 and cancer. Cancer stem cells are key drivers of tumorigenesis and may be responsible for tumor initiation, growth and spawning metastases. SOX2-positive cancer stem cells were able to drive tumor initiation and therapy resistance in various types of cancers, indicating that it is a common phenomenon that SOX2 might mastermind the tumor initiating potential of cancer cells [60].

SOX2 silencing significantly suppresses the tumorigenicity of glioblastoma tumor-initiating cells (TICs) [38]. Importantly, high levels of SOX2 have been associated with tumor aggressiveness and worse prognosis in glioblastoma, indicating targeting SOX2 might be an

effective strategy for the treatment of glioblastoma [39]. SOX2 is also amplified in squamous cell carcinomas of the lung, the esophagus, and the oral cavity. SOX2 amplification and SOX2 protein overexpression might be responsible for the tumor initiation and progression in squamous cell carcinomas derived from different organ sites [36]. SOX2 was found to be critical for maintaining the sphere-forming capacity of DU145 prostate cancer stem cells (PCSCs). It promoted the self-renewal of the PCSC population by regulating downstream of EGFR signaling [61]. Similarly, SOX2 was highly expressed in melanoma stem cells. SOX2 suppression remarkably inhibited self-renewal in melanoma spheres and in putative melanoma stem cells with high aldehyde dehydrogenase activity. On the contrary, SOX2 overexpression in melanoma cells enhanced their self-renewal *in vitro*. Animal models showed that SOX2 was critical for tumor initiation and continuous tumor growth. These data suggested that SOX2 was an important factor for self-renewal and tumorigenicity of melanoma-initiating cells [37].

There are conflicting results regarding the role of SOX2 in gastric cancer. For instance, SOX2 was dispensable for self-renewal of gastric stem cells. In addition, loss of SOX2 promoted tumor formation in Apc-deficient gastric cells *in vivo* and *in vitro* by inducing Tcf/Lef-dependent transcription and upregulating intestinal metaplasia-associated genes, suggesting SOX2 acted as a tumor suppressor in gastric cancer [62]. In addition, the expression level of SOX2 expression was frequently downregulated in gastric cancers. Ectopic expression of SOX2 inhibited cell growth through cell-cycle arrest and apoptosis in gastric cells. Moreover, the gastric cancers with SOX2 methylation had a significantly worse survival than those without this methylation [40]. However, SOX2 was found to enhance the tumorigenicity and chemoresistance of cancer stem-like cells derived from gastric cancer, suggesting SOX2 plays an oncogenic role in gastric cancer [63]. SOX2 inhibition reduced cell proliferation and migration, promoted apoptosis and induced changes in cell cycle *in vitro* as well as suppressed the tumorigenic potential of gastric cancer cells *in vivo* [64]. The contradictory findings regarding the role of SOX2 in gastric cancer further support the fact that the outcome of SOX2 activation is closely correlated with tumor origin and cellular context. Future experiments with lineage tracing and gain-and loss-of-function mouse models are required to clarify the role of SOX2 in gastric cancer. SOX2 is frequently regarded as an oncogene in lung SCCs, but previous studies indicated that higher SOX2 levels predicted favorable outcome in lung SCCs [65, 66]. The underlying reasons accounting for the contradictory role of SOX2 in lung SCCs warrant further exploration.

4. SOX4 and cancer

SOX4, one of group-C SOX genes, plays an important role in the regulation of transcription during developmental processes such as embryonic cardiac development, nervous system development, osteoblastic differentiation, and thymocyte development [67]. SOX4 gene is located on 6p22.3 and encodes a protein of 474 amino acids with three distinguishable domains: an HMG box, a glycine-rich region, and a serine-rich region. SOX4 is considered as one of the members of epithelial-mesenchymal transition (EMT)-transcriptional inducers. EMT is a key developmental program that is often activated during organismal development and the progression of epithelial tumors to metastatic cancers and may promote therapeutic resistance, indicating that SOX4 might be a potential therapeutic target for cancer treatment.

Recently, multiple studies have reported altered expression of SOX4 in human cancers. Our group demonstrated that SOX4 was significantly upregulated when oral lichen planus (OLP) progressed to oral squamous cell carcinoma (OSCC). In addition, downregulation of SOX4 suppressed the proliferation, migration and invasion of oral cancer cells. These findings suggest that SOX4 might play a critical role in the progression of OLP to OSCC [41]. Similarly, the expression level of SOX4 was remarkably overexpressed in OSCC tissues compared to adjacent normal mucosa. Also SOX4 was important for maintaining the oncogenic phenotypes of oral cancer cells by promoting cell survival and increasing chemoradioresistance [68]. High SOX4 expression levels were positively correlated with adverse clinicopathological parameters of OSCC, indicating that SOX4 might be significantly associated with poor prognosis of OSCC [42]. In addition to OSCC, SOX4 plays an oncogenic role in other malignancies. SOX4 was overexpressed in prostate cancer (PCa) and higher SOX4 levels predicted unfavorable prognosis [43]. Upregulation of SOX4 in PCa was mechanistically induced by PTEN loss due to the activation of PI3K-AKT-mTOR signaling [44]. SOX4 was able to directly regulate the expression of the epigenetic modifier Ezh2 in breast cancer, indicating SOX4 might be indispensable for tumor progression [69]. SOX4 might combine with oncogenic Ras together to promote tumorigenesis *in vivo* [70]. SOX4 was a direct target of C/EBP α and SOX4 suppression reduced the self-renewal of leukemic cells and restored their differentiation, indicating that SOX4 overexpression resulting from inactivation of C/EBP α promoted leukemia development [45].

However, it should be noted that SOX4 might also function as a tumor suppressor in tumorigenesis. For instance, SOX4 was indispensable for p53 activation in response to DNA damage. In addition, SOX4 could stabilize p53 protein by inhibiting Mdm2-mediated p53 ubiquitination and degradation, suggesting that SOX4 might suppress the progression DNA damage response-associated cancer [71]. In primary gallbladder carcinoma (PGC), SOX4 upregulation was significantly associated with favorable clinical parameters. In addition, SOX4 overexpression predicted better survival [46]. The expression level of SOX4 was significantly reduced in metastatic melanoma compared with that in dysplastic nevi and primary melanoma. In addition, SOX4 suppression promoted the migration and invasion of melanoma cells in an NF- κ B p50-dependent manner [72]. Taken together, these findings indicate that the concrete role of SOX4 is closely associated with tumor microenvironment and might be tissue specific.

5. SOX9 and cancer

The SOXE group comprises three members named SOX8, SOX9 and SOX10. SoxE proteins are important for the development of nervous system and neural crest progenitors. SOX9 was first described as a candidate gene for campomelic dysplasia (CD), a genetic condition that affects the development of the skeleton and reproductive system [73]. SOX9 has been demonstrated to greatly contribute to the organogenesis and development of many tissue types, such as the stomach, pancreas, tooth and craniofacial tissues. In addition, SOX9 is also a master regulator of cartilage development. It is indispensable for roles in the chondrogenic lineage progression of mesenchymal stem cells [74].

Recent studies have reported that SOX9 is aberrantly expressed in several types of cancers. Higher expression levels of SOX9 are correlated with a poor prognosis in patients with Chordoma. In

addition, SOX9 downregulation suppressed the oncogenic behaviors of Chordoma cell *in vitro*, suggesting that SOX9 might function as an oncogene in Chordoma [75]. The expression of SOX9 was upregulated in papillary thyroid cancer (PTC) tissues and cell lines. Downregulation of SOX9 inhibited the proliferation, colony formation, migration, invasion, as well as EMT phenotype of PTC cells. ER α -RUNX2 complex activated the SOX9 expression and promoted endocrine resistance and metastases [76]. In breast cancer, up-regulation of SOX9 expression was closely correlated with tamoxifen (TAM) resistance [77]. The SOX9 levels were significantly higher in osteosarcoma tissues compared with the adjacent normal tissues. However, CLDN8 expression was significantly lower in osteosarcoma tissues. Knockdown of SOX9 inhibited the proliferation and migration but promoted the apoptosis of human osteosarcoma cell lines by downregulating CLDN8 [47]. FOXK2 was overexpressed in colorectal cancer tissues and associated with poor prognosis. In fact, FOXK2 was shown to be transcriptionally activated by SOX9, suggesting that SOX9-FOXK2 axis plays a critical role in the development of colorectal cancer [48]. SOX9 upregulation was associated with *Helicobacter pylori* infection, elevated carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) and gastrokine 1 (GKN1) inactivation. SOX9 knockdown suppressed the tumorigenic capacity of gastric cancer cells by inhibiting the downstream β -catenin signaling pathway [49]. Interestingly, SOX2 was expressed in highly proliferative but minimally invasive lung cancer cells; in contrast, cells with highly invasiveness capacity exhibited increased SOX9 expression but reduced SOX2 expression. The switch between SOX2 and SOX9 expression is epigenetically controlled and is important for determining cancer cell plasticity and metastatic progression [78]. Ectopic expression of SOX9 enhanced growth, invasion, and angiogenesis, whereas silencing of endogenous SOX9 markedly impaired tumor growth in prostate cancer. High SOX9 levels drove tumorigenesis by reactivating the Wnt/ β -catenin signaling in a subset of prostate cancer, indicating WNT inhibition might be beneficial for the effective treatment of prostate cancer [79]. SOX9 was critical for maintaining proliferation, self-renewal, and tumorigenicity in liver cancer stem cells (CSCs), and SOX9 overexpression was positively correlated with worse survival in HCC patients [80]. Although most studies showed that SOX9 played an oncogenic role in cancer development. Ectopic expression of SOX9 was found to suppress cell growth, clonal capacity and colonosphere formation by inhibiting Wnt/ β -catenin signaling pathway and c-myc expression in colorectal cancer, suggesting that SOX9 might be a tumor suppressor in colorectal cancer [81]. SOX9 expression was progressively decreased in cervical carcinoma *in situ* and especially in invasive cervical carcinoma, compared with normal cervix tissue. Lastly, SOX9 overexpression in cervical carcinoma cells inhibited cell growth *in vitro* and tumor formation *in vivo*, and *vice versa* [50].

6. SOX11 and cancer

Similar to SOX4, SOX11 is also a transcriptional activator that falls in the subgroup C. The Sox11 gene is mapped at chromosome 2p25.3 and the human SOX11 protein has 441 amino acids and 46.7 kDa molecular weight. It contains two functional domains: a HMG box DNA-binding domain and a transactivation domain [82]. SOX11 plays an important role in embryogenesis and tissue remodeling. Sox11 expression in most tissues is transient and thus little SOX11 expression has been found in terminally differentiated adult tissues. The role of SOX11 in the tumor microenvironment is cancer type-dependent.

Our recent studies have demonstrated that SOX11 plays a tumor promotion role in the development of head and neck cancer (HNC) [83]. We have employed a liquid chromatography–tandem mass spectrometry (LC–MS/MS) based approach to identify novel targets that may interact with SOX11 in HNC cells. The proteins that strongly bind to SOX11 in HNC cells may be important for maintaining the activity, stability and function of SOX11 or be regulated by SOX11. Gene ontology and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis indicated that many potential SOX11-binding partners were associated with protein synthesis, cell metabolism and cell–cell adhesion. We speculated that upregulation of SOX11 might firstly activate the aggressive phenotypes of HNC cells by modulating the oncoprotein synthesis and altering cellular metabolism. Then it might further promote invasion and metastasis by affecting cell–cell adhesion system and formation and release of extracellular exosomes. One of the identified proteins, heat shock protein 90 alpha (HSP90 α), was selected for further investigation. A biochemical interaction is validated between SOX11 and HSP90 α through the co-immunoprecipitation with Western blot analysis. In addition, we have found that downregulation of HSP90 α inhibits the malignant phenotypes of HNC cells and HSP90 α upregulation is significantly associated with worse clinical outcome of HNC, suggesting HSP90 α might serve as a potential prognostic biomarker and therapeutic target for HNC [84].

Aberrant expression of SOX11 has been reported in other types of cancer. SOX11 levels were negatively correlated with the tumorigenic capacity of glioma-initiating cells [85]. Similarly, epithelial ovarian cancer patients with lower SOX11 suffered poorer recurrence-free survival [55]. SOX11 mRNA was downregulated in both gastric cancer (GC) cell lines and primary GC tissues. SOX11 gene promoter hyper-methylation was significantly associated with worse clinical parameters and poorer prognosis, suggesting that SOX11 might function as a tumor suppressor in gastric cancer [86]. The methylation frequency of serum SOX11 promoter in hepatocellular carcinoma (HCC) patients was significantly higher than that in chronic hepatitis B (CHB) patients. In addition, significant difference of serum SOX11 promoter methylation in HCC patients with vascular invasion and those without vascular invasion was found. Moreover, serum SOX11 promoter methylation was found to be more sensitive than serum alpha-fetoprotein for discriminating HCC from CHB [87]. Previous studies also reported SOX11 functions an oncogene during tumorigenesis. SOX11 upregulation can promote oncogenic behaviors of ductal carcinoma in situ (DCIS) cells both *in vitro* and *in vivo*, indicating that SOX11 contributes to the progression of ductal carcinoma in situ to invasive breast cancer [88]. Similarly, SOX11 is an important regulator of multiple basal-like breast cancers (BLBCs) phenotypes, including growth, migration, invasion, and expression of signature BLBC genes. In addition, high SOX11 expression was also found to be a poor prognostic indicator of survival in women with breast cancer [51].

SOX11 is expressed in virtually all aggressive mantle cell lymphoma (MCL) and at lower levels in a subgroup of Burkitt and acute lymphoblastic lymphomas, but not in other lymphoid neoplasms. The *in vivo* tumorigenic potential of SOX11 in a MCL xenograft model has been demonstrated, indicating that SOX11 functions as an oncogene in MCL [52]. In addition, SOX11 can block the terminal B-cell differentiation through direct positive regulation of PAX5 and promote angiogenesis in MCL through regulating platelet-derived growth factor

A [52, 53]. Patients with SOX11-negative MCL exhibited more frequent non-nodal presentation and better survival compared with patients with SOX11-positive MCL [54]. However, there is contradictory result about the association between SOX11 and survival in MCL. The overall survival was shorter in patients with SOX11-negative MCL compared to the patients with SOX11-positive MCL [89]. The relationship between SOX11 expression and survival of patients with MCL remains uncertain.

7. Conclusion

In conclusion, recent studies have started to uncover important functions of the SOX genes as regulators of cancer initiation and progression. Our understanding of the role of SOX genes is, however, still at its infancy. Contradicting results regarding the role of SOX genes have been reported in different types of cancer. This suggests that the molecular functions of SOX genes in tumorigenesis need to be examined carefully in tissue-specific setting.

Abbreviation list

SOX	sex determining region Y box
HMG	high mobility group
MCL	mantle cell lymphoma
HNC	head and neck cancer
EMT	epithelial-mesenchymal transition
TF	transcription factor
HSP90 α	heat shock protein 90 alpha
KEGG	Kyoto Encyclopedia of Genes and Genomes
LC-MS/MS	liquid chromatography-tandem mass spectrometry

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