**SOX4: Epigenetic Regulation and Role in Tumorigenesis**

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**Abstract**

Sex-determining region Y-related (SRY) high-mobility group box 4 (*SOX4*) is a member of the group C subfamily of SOX transcription factors and promotes tumorigenesis by endowing cancer cells with survival, migratory, and invasive capacities. Emerging evidence has highlighted an unequivocal role for this transcription factor in mediating various signaling pathways involved in tumorigenesis, epithelial-to-mesenchymal transition (EMT), and tumor progression. During the last decade, numerous studies have highlighted the epigenetic interplay between SOX4-targeting microRNAs (miRNAs), long noncoding RNAs (lncRNAs) and SOX4 and the subsequent modulation of tumorigenesis, invasion and metastasis. In this review, we summarize the current state of knowledge about the role of SOX4 in cancer development and progression, the epigenetic regulation of SOX4, and the potential utilization of SOX4 as a diagnostic and prognostic biomarker and its depletion as a therapeutic target.

**Keywords**

SOX4, cancer, epigenetic regulation, microRNA, lncRNA, EMT

**Introduction**

SOX4 is a member of the SOX (Sry-related high-mobility group (HMG) box) family of transcription factors, which are characterized by a transactivation domain (TAD) located at the C-terminus. SOX4 binds to the minor groove of DNA *via* its HMG box domain, leading to alterations in chromatin architecture and changes in functional and transcriptional activities of downstream genes [1, 2].

*SOX4*, like most of *SOX* genes, is expressed with a spatial and temporal pattern and plays pivotal roles in various biological processes at different life stages. In mammals, SOX4 expression is limited to embryonic structures and certain adult tissues, such as pancreas, intestine, lymphoid organs and skin [3]. For instance, the expression of SOX4 and SOX9 in cholangiocytes is required for normal development of bile duct by controlling the expression of Notch, mediators of the transforming growth factor-β (TGF-β) and Hippo-Yap signaling pathways [4]. Consistently, adult SOX4/SOX9*loxP/loxP* mice show cholestasis, deficient development of peripheral bile ducts, ductular reactions and liver fibrosis [4]. In children, certain SOX4 HMG domain missense variants are incapable of transactivating downstream genes and cause neurodevelopmental disease and facial dysmorphism [5]. In addition, SOX4 controls early stage of B lymphocyte differentiation by inducing gene rearrangements of immunoglobulin heavy chain through transcriptionally activating the *Rag1* and *Rag2* genes, and suppression of Wnt signaling by inducing the expression of casein kinase 1ε [6]. A growing list of reports has correlated increased expression of SOX4 with tumorigenesis and progression in numerous cancer types, including colorectal [7], breast [8], prostate [9, 10] and gastric [11] cancer. This elevated expression of SOX4 promotes different aspects of cancer development and progression by the transcriptional activation of downstream genes in cancer-associated signaling pathways, such as TGF-β/SMAD [12] and Wnt/β-catenin [13], thus endowing malignant cells with apoptosis resistance and promoting epithelial-to-mesenchymal transition (EMT) [14].

EMT is a fundamental developmental process enabling the acquisition of mesenchymal features by epithelial and cancer cells. These features include the increased expression of the mesenchymal markers fibronectin, N-cadherin and vimentin, which enhances the motility and invasive potential of the cells [14, 15]. Therefore, EMT is a critical process for cancer development and progression through the regulation of cellular migration, invasion and metastasis. Several studies have identified central roles of forkhead box protein C2 (FOXC2), twist-related protein 1 (TWIST1), zinc finger E-box binding homeobox 1 (ZEB1), snail family zinc finger 1 (SNAI1) and SNAI2 in tumors through the regulation of EMT programs [16-19]. Moreover, a recent consensus has suggested SOX4 as a master regulator of EMT in various types of cancer, such as breast, prostate and colorectal cancer (CRC) [12, 20, 21]. Through orchestrating the EMT program, SOX4 regulates target genes encoding proteins associated with mesenchymal features, including N-cadherin, tenascin-C (TNC), frizzled-5 (FZD5), ADAM10, transmembrane protein-2 (TMEM2), neuropilin-1, and semaphorin-3A, and thus enhances cancer cell migration, invasion and metastasis [22-24].

In recent years, a growing body of evidence has highlighted the posttranscriptional regulation of SOX4 by a large class of small noncoding RNAs (ncRNAs; ~20 nt) called microRNAs (miRNAs). To date, dozens of miRNAs have been reported to control cancer development and progression by targeting the 3' untranslated region (3'UTR) of *SOX4* mRNA. Ectopic expression of SOX4-targeting miRNAs has been shown to impair the proliferation and motility of CRC cells by inhibiting the EMT program and thus reinstating the expression of the epithelial markers E-cadherin and zona occludens 1 (ZO-1) [25, 26]. Furthermore, emerging evidence has identified long noncoding RNAs (lncRNAs), a class of RNAs with lengths greater than 200 nt, as new players in tumorigenesis and tumor progression and as key regulators of SOX4 expression. The lncRNAs modulate EMT programs and apoptosis by acting as competing endogenous RNAs (ceRNAs) for SOX4-targeting miRNAs [27] and by directly targeting the SOX4 promoter [28]. In this review, we highlight the role of SOX4 in the context of tumorigenesis and malignant transformation. A particular emphasis is placed on the modulation of SOX4 expression and function by miRNAs and lncRNAs and the subsequent modulation of cancer-associated signaling pathways and cancer phenotypes.

**2. SOX4-mediated cancer development and progression**

Meta-analysis of cancer microarray data has classified *SOX4* as a ‘cancer signature’ gene, suggesting its fundamental role in cancer development [29]. SOX4 may promote cancer development and progression *via* various mechanisms: (i) directly regulating the expression, transcription and/or epigenetic reprogramming of numerous genes implicated in EMT, including enhancer of zeste homolog 2 (*EZH2*), E-cadherin (*CDH1*), N-cadherin (*CDH2*), vimentin (*VIM*) and *TGFB*; (ii) targeting gene networks involved in miRNA processing and posttranscriptional regulation; (iii) enhancing proliferative signals in tumors and potentially activating the signal transduction phosphatidylinositol-3 kinase (PI3K)/Akt pathway through targeting growth factor receptors; (iv) interacting with and activating developmental pathways such as the Wnt, Notch and Hedgehog pathways; and (v) inhibiting differentiation *via* the repression of transcription factors and induction of homeobox (HOX) gene expression.

***2.1. Role of SOX4 during tumorigenesis***

The tumorigenesis-promoting roles of SOX4 have been attributed primarily to the inhibition of apoptosis and stimulation of cell survival in various cancer types, the direct coordination of the induction of mesenchymal markers and the indirect regulation and activation of other EMT inducers. Figure 1 provides a schematic presentation of the role of TGF-β-SMAD2/3-mediated SOX4 activation and the subsequent induction of numerous SOX4 target genes involved in cancer cell proliferation, survival, stemness, and EMT. Accumulating evidence has shown that the downregulation of SOX4 induces apoptosis and reduces the survival rate of various types of cancer cells, including prostate cancer [30], lymphoblastic leukemia [31], melanoma [32], triple negative breast cancer [33], lung cancer [34] and osteosarcoma [35, 36]. For example, SOX4 inhibition has been reported to induce apoptosis in melanoma cells through the downregulation of the nuclear factor-κB (NF-κB) and p65 subunit signaling pathway [32]. Moreover, depletion of SOX4 by RNA interference reduced proliferation potential of lung carcinoma cells, hence suppressing Krüppel-like factor 5 (KLF5)-mediated tumorigenesis [37]. Similarly, SOX4 silencing in osteosarcoma reduced cell proliferation, migration and invasion and increased apoptosis [38]. These cellular effects were associated with a significant increase in the protein expression of B cell lymphoma 2 (Bcl2)-associated X protein (Bax), caspase-3 and p53, along with a reduction in the expression of Bcl-2, matrix metalloproteinase-2 (MMP2), and MMP9 [38]. Consistent with these observations, the inhibition of SOX4 in lung cancer cells induced apoptosis *via* the upregulation of caspase-3 [39]. Mechanistically, SOX4 depletion modulated the expression of critical genes involved in apoptosis and cell cycle control [40, 41]. For instance, in adult prostate epithelium, the deletion of SOX4 in the absence of phosphatase and tensin homolog (PTEN) inhibited tumor progression through the prevention of phosphoinositide-3,4,5-trisphosphate (PIP3) accumulation and thus the deactivation of the kinase Akt/PKB and its downstream effectors [30].

SOX4 is highly expressed in stem cells and early progenitor cells from various tissues. Through interaction with and regulation by TGF-β and its downstream signaling molecules SMAD2/3, SOX4 induces the expression of the stem cell marker SOX2 [42]. In addition, SOX4 mediated the promoting role of TGF-β/SMAD2/3 in aggressive tumor-initiating cell (TIC) phenotypes in glioma [43]. SOX4 depletion suppressed TGF-β-induced EMT in gastric cancer cells [11], and delayed the expression of mesenchymal markers in breast cancer cells [12]. In addition, SOX4 ablation led to a significant reduction in primary tumor growth in murine breast cancer cells [44]. In lines, mice model with reduced whole-body SOX4 expression showed accelerated aging and reduced cancer incidence [3]. In summary, SOX4 depletion in a variety of cancer cell models highlights vital roles for SOX4 in regulating tumorigenesis. However, the efficacy of SOX4 depletion as a therapeutic strategy in clinical trials is not yet tested.

***2.2. SOX4-directed and -coordinated EMT programs***

During EMT, transcription factors play vital roles in controlling several cellular events such as cell proliferation, survival, differentiation, adhesion, and migration [11, 14, 45-48]. Numerous recent studies have demonstrated important interplay between the transcription factor SOX4 and various EMT regulators [14]. For instance, SOX4 acts as a central component of TGF-β signaling to mediate EMT in various types of cancer (reviewed by [14]). The TGF-β signaling pathway is a prime inducer of EMT through the transcriptional modulation of transcription factors that suppress epithelial but enhance mesenchymal features [49], and the activation of this signaling pathway mediates the expression of SOX4 [14, 20, 50]. In addition, SOX4 enhances the transcription of the EMT regulators Snail, ZEB, and TWIST through intermediate protein or epigenetic modifications, as demonstrated in a murine breast cancer cell model [44], or through the direct induction of these transcription factors, as demonstrated in human gastric cancer cells, leading to enhanced expression of the genes encoding N-cadherin and vimentin and hence promoting EMT [11]. SOX4 also interacts with the histone methyltransferase EZH2, a component of the polycomb (PcG) repressive complex 2 (PRC2). In SOX4-deficient cells, EZH2 was shown to complement SOX4 during EMT and regulate the expression of numerous genes downstream of SOX4 [44]; furthermore, in an experimental animal model, SOX4 deficiency inhibited breast cancer cells from undergoing EMT and metastasizing to the lungs [51].

Recently, cross-platform analyses of genomic and proteomic data have identified and validated SOX4 as a mediator of the PI3K/Akt signal transduction pathway [52]. The PI3K/Akt pathway is one of the most commonly dysregulated pathways in cancer; this pathway can affect EMT programs through several mechanisms to influence tumor aggressiveness [53]. In parallel, SOX4 stimulates Wnt signaling through the inhibition of β-catenin protein degradation *via* a casein kinase 2 (CK2)-dependent mechanism [54]. Akt can phosphorylate and inhibit the kinase GSK3β, increasing the activity of Wnt pathway mediators and β-catenin and thus facilitating the induction of tumor invasion [55, 56]. Additionally, SOX4 expression was induced in PTEN-deficient prostate cancer cells through the phosphorylation of Akt at serine 473 [30]. Moreover, a significant reduction in activated β-catenin was observed in prostate tissue from PTEN/SOX4 conditional double-knockout mice [30]. Concordantly, SOX4 targets growth factor receptors such as the epidermal growth factor receptor (EGFR) and fibroblast growth factor receptor-like 1 (FGFRL1), and insulin-like growth factor 2 receptor (IGF2R) to enhance tumor cell proliferation through the activation of the PI3K/Akt pathway [57]. In summary, SOX4 seems to be critical modulator of various signaling pathways and possibly for crosstalk between pathways and to be involved in cell proliferation and differentiation, cell cycle arrest, EMT and cancer.

***2.3. SOX4 as a mediator of tumor migration and invasion***

SOX4 exerts its promotive effects on primary tumor growth and cell metastasis *via* the direct regulation of genes encoding key components of developmental and growth factor signaling pathways, including *TNC*, integrin alpha-V (*ITGAV*), Rac family small GTPase 1 (*Rac1*), paxillin (*PXN*), *EGFR,* *FZD5*, heat shock protein 70 (*HSP70*),patched-1(*PTCH1*), delta-like *1* (*DLL1*)*,* lysine methyltransferase 2A(*KMT2A*),forkhead box A1(*FOXA1*)*,* zinc finger protein 281(*ZNF281*)*,* as well asNK3 homeobox 1 (*NKX3.1*) [57, 58], as summarized in Figure 1. In addition, SOX4 augments metastasis and invasion through the inhibition of terminal differentiation *via* the repression of NKX3.1 and activation of mixed-lineage leukemia 1 (MLL1), which subsequently activate HOX gene expression, leading to EMT [58, 59]. SOX4 and SOX9 are the only two SOX family members linked to TGF-β and EMT; SOX4 deficiency was sufficient to prevent TGF-β-mediated EMT in normal and malignant mammary epithelial cells (MECs), and thus inhibited mammary tumor growth and metastasis [44]. Upregulated expression of SOX4 promotes the migration and invasion of melanoma cells [60]. These promotive effects are attributed to the activation of the NF-κB/p65 signaling pathway [32] and MMP9 and MMP2, members of the metalloprotease family responsible for the breakdown of the extracellular matrix (ECM) microstructure, a hallmark of tumor invasion and metastasis [61]. Moreover, ectopic expression of SOX4 was sufficient to increase the expression of TMEM2, a transmembrane protein that mediates metastatic migration and invasion of breast cancer cells [24].

**3.0 Epigenetic regulation of SOX4**

Various genetic mechanisms such as DNA amplification, deletion, or mutation; or epigenetic mechanisms (i.e. DNA and histone modification) can lead to alter SOX4 expression. Interestingly and despite its documented overexpression in various human malignancies, SOX4 promoter hypomethylation or gene amplification is only observed in a few cancer types [31, 62]. This has suggested the existence of other regulatory mechanism, such as miRNA and lncRNA-dependent mechanisms, leading to its upregulated expression in human cancers.

***3.1 miRNA biogenesis and function in cancer***

MiRNAs are a class of small and highly conserved noncoding RNAs that orchestrate the posttranscriptional regulation of protein expression; hence, they are implicated in regulating numerous biological processes under normal and pathological conditions. MiRNA genes are encoded in various regions of the genome; approximately 40% of miRNAs are found embedded within introns of protein-coding genes, while approximately 10% are located within introns of long ncRNA transcripts [63]. With some exceptions, a general downregulation of miRNAs is observed in cancers, mostly due to chromosomal anomalies, epigenetic alterations or altered functioning of the miRNA biogenesis machinery [64]. Interestingly, more than half of all miRNA genes are located at fragile sites, in cancer-associatedgenomic regions, and in minimal regions of amplification or loss of heterozygosity, hence are more prone to altered expression [65].

MiRNAs have emerged as dominant regulators of gene expression in different human cancers [66, 67]. During tumorigenesis, miRNAs can function as oncogenes (oncomiRs) or as tumor suppressors, depending on the type of malignancy and the specific miRNA [68]. Although the vast majority of studies have focused on studying individual miRNA targets, most miRNAs orchestrate their effects by targeting multiple mRNA transcripts, some of which may reside in the same or in other related pathways [69, 70]. For example, let-7 is the first identified tumor suppressor mammalian miRNA that is normally expressed in epithelial tissues and is frequently downregulated during transformation [71]; Let-7 targets many mRNA transcripts such as those of RAS [72] and LIN28, an inhibitor of miRNA processing, and itself is a target of negative feedback regulation by LIN28 [73]. MiR-21 is an oncomiR that is overexpressed in the majority of human cancers and inhibits several tumor suppressor genes, thus promoting cancer cell proliferation and invasion and tumor metastasis [74, 75].

***3.2 miRNA-mediated SOX4 regulation in human cancers***

Accumulated evidence revealed a close relationship between miRNA and SOX4 expression in cancers of epithelial and non-epithelial origin. Many miRNAs have been found to target SOX4 through direct binding to the *SOX4* 3'UTR, thus regulating a plethora of vital processes in cancer cells, such as proliferation, migration, invasion, EMT, and tumor progression. This finding is not surprising given that SOX4 has a relatively large 3`UTR (4241 nt; TargetScan Human). SOX4 targeting by miRNAs slows EMT in various ways, including (i) preventing the SOX4/EZH2 axis from inducing the epigenetic modification of major EMT molecules; (ii) inhibiting the Wnt/β-catenin signaling pathway, which further suppresses cell proliferation and migration and promotes apoptosis; (iii) suppressing TGF-β-induced EMT; and (iv) decreasing the levels of p-PI3K, p-Akt, p-SMAD2 and p-SMAD3. SOX4 interacts directly with β-catenin [76], and the deletion or miRNA-mediated inhibition of SOX4 reduces the level of active β-catenin *in vivo*; this reduction led to a significant reduction in Akt phosphorylation in cancer cells *in vitro* [30, 52]. In this section, we will summarize the current state of knowledge about the regulation of SOX4 by miRNAs in various human malignancies. The SOX4-miRNA-lncRNA network in different human cancers is presented in Figure 2.

The SOX4-targeting miRNAs frequently altered in human cancers are summarized in Table 1. In breast cancer, miR-335 was found to suppress metastasis and invasion through targeting the transcription factor SOX4 and the extracellular matrix component TNC [77]. Furthermore, in a cohort of 368 breast cancer patients, those with primary breast tumors that were positive for the miR-335 signature showed unfavorable metastasis-free survival [77]. MiR-93, a member of the miR-106b-25 cluster, was found to induce mesenchymal-to-epithelial transition (MET) and to moderate the proliferation and differentiation state of breast cancer stem cells (BCSCs) through targeting SOX4 and several additional genes, such as high-mobility group AT-hook 2 (*HMGA2*), *AKT3*, *EZH1*, Janus kinase 1 (*JAK1*), and signal transducer and activator of transcription 3 (*STAT3*) [78]. MiR-338-3p is downregulated in breast cancer tissues; this downregulation was negatively correlated with lymph node metastasis and tumor-node-metastasis (TNM) stage [79]. MiR-191-5p was identified as an oncomiR in different human malignancies [80-82]. Interestingly, miR-191-5p was shown to be a target for P53 suppression, and itself can indirectly target P53 expression through inhibition of SOX4 [83]. Hence, anti-miR-191-5p promoted breast cancer apoptosis in response to doxorubicin, through SOX4 and P53 induction [83]. Therefore, the p53-miR-191-5p-SOX4 axis has a major impact on apoptosis and drug resistance in breast cancer. MiR-320 is also frequently downregulated in breast cancer, correlating with elevated SOX4 expression [84].

Our group first identified SOX4 as a target of the miR-212/132 cluster in breast cancer cell lines [85]. We found that the activation of the aryl hydrocarbon receptor (Ahr) by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) transcriptionally activates the SOX4-targeting miR-212/132 cluster, thus suppressing cancer cell migration, invasion and metastasis [85]. Similarly, the activation of Ahr by flavipin suppressed the migration and invasion of breast cancer cell lines by inducing the miR-212/132- SOX4 axis [86]. Moreover, the activation of Ahr by TCDD or 6-methyl-1,3,8-trichlorodibenzofuran (MCDF) induced the expression of the SOX4-targeting miR-335 and inhibited lung metastasis [87]. These observations suggest ligand-activated Ahr as a potential strategy to downregulate SOX4 *via* miRNAs.

Numerous studies in CRC have identified several SOX4-miRNA circuits. Our group first identified the downregulation of the miR-320 family in CRC [88]. We subsequently identified SOX4, forkhead box M1 (FOXM1), and FOXQ1 as *bona fide* targets of miR-320c, that promote cell migration and chemotherapy resistance in CRC cells lacking miR-320c [69]. Moreover, in CRC, miR-187 downregulation was linked to tumor metastasis and poor prognosis, which was found to target SOX4 [26]. MiR-363-3p and miR-539 were also found to target SOX4 in CRC [25, 89]. Reduced expression of miR-539 correlated with lymph node metastasis and TNM stage in CRC patients, and miR-539 expression was found to attenuate cell proliferation and invasion *in vitro* *via* SOX4 suppression [89].

In addition, many SOX4-miR circuits have been identified in several other human cancers. For instance, miR-129-5p downregulation was found to be associated with poor prognosis in bladder cancer and to promote cell death *via* targeting SOX4 [90]. Similarly, Zhang and colleagues demonstrated a tumor suppressor role for miR-129-5p in chondrosarcoma [91]. MiR-129-2 was found to be epigenetically silenced in endometrial, gastric, esophageal, and hepatocellular carcinoma, leading to increases in SOX4 expression and cell proliferation [92-95]. In ovarian cancer, miR-138 and the miR-212/132 cluster were shown to function as tumor suppressors through targeting SOX4 [96, 97]. In addition, SOX4 was found to be targeted by the miR-212/132 cluster and miR‑25‑3p in osteosarcoma [35, 36, 98, 99] and by miR-30a and the miR-212/132 cluster in prostate cancer [100, 101]. In VCaP prostate cancer cells, metformin upregulated miR-30a, which in turn repressed SOX4 expression and subsequently inhibited TGF-β-induced EMT, as manifested by inhibiting the increase in N-cadherin and vimentin, and the reduction in E-cadherin and β-catenin [100]. Similarly, miR-19a-3p overexpression decreased the levels of SOX4 mRNA and protein, subsequently suppressing the migration and invasion of prostate cancer cells [10]. In esophageal cancer, miR-31 and miR-133a were found to target SOX4, hence suppressing tumorigenesis [102, 103]. In gastric cancer, miR-211 downregulation led to enhanced SOX4 expression and tumor cell growth and invasion [104]. Additionally, miR-338-3p was shown to suppress lung cancer *via* targeting SOX4 [34].

In hematological malignancies, miR-204 was found to be underexpressed and to target SOX4 in T cell acute lymphoblastic leukemia [105]. Interestingly, the miR-212/132 cluster was found to regulate B cell development. In particular, miR-132 was found to target SOX4; hence, the re-expression of miR-132 inhibited B cell cancer development in a c-Myc expression model [106].

While the literature presented thus far has highlighted a role for several miRNAs in regulating SOX4 expression in various human malignancies, SOX4 has also been found to control the transcription of Dicer in cutaneous melanoma cells through binding to its promoter and increasing its activity, leading to the expression of a substantial number of cancer-associated miRNAs [68, 107]. Concordantly, a previous study showed that SOX4 can directly regulate the miRNA processing machinery in prostate cancer cells through targeting Argonaute 1, Dicer, and RNA helicase A [57]. The PRC2 is responsible for the methylation of lysine 27 on histone 3 (H3K27) [108]. PRC2 can mediate mono-, di- and trimethylation of H3K27; the later is associated with heterochromatin formation and the repression of key transcriptional factors [109]. The catalytic subunit of PRC2 is the SET domain-containing protein EZH2 (or EZH1) can be functional only in the context of the full PRC core complex [109]. The SOX4/EZH2 complex repressed the expression of the miR-212/132 cluster through direct recruitment to the promoter regions of members of this cluster and the deposition of H3K27me3 epigenetic repressive marks (Fig. 1) [97]. SOX4/EZH2 axis-mediated H3K27me3 epigenetic silencing highlighted the reciprocal crosstalk between miR-129-5p and SOX4 expression in breast cancer [110]. Similarly, the corepressor complex composed of SOX4, EZH2 and histone deacetylase 3 (HDAC3) enhanced the proliferation and invasion of esophageal tumor cells through epigenetic silencing of miR-31 by H3K27me3 [102]. Taken together, these findings indicate that SOX4-mediated EZH2 expression induces the epigenetic modification of major EMT molecules to promote EMT and metastasis. Therefore, there appears to be a reciprocal relationship between SOX4 and the miRNA biogenesis and silencing pathway.

Interestingly, Bu and colleagues reported a positive feedback loop in CRC, in which TGF-β induced miR-1269a expression through SOX4 activation and miR-1269a in turn enhanced TGF-β signaling through targeting SMAD7 and HOXD10 [21]. TGF-β treatment significantly enhanced the expression of SOX4, while SOX4 silencing (as with miRNA targeting) reversed the TGF-β-induced invasion and sphere formation abilities of gastric cancer cells [11]. Moreover, SOX4 overexpression promoted the EMT phenotype in VCaP prostate cancer cells [111], while the treatment of prostate cancer cells with TGF-β led to epigenetic modifications in the ETS-related gene (ERG) and SOX4 promotors that were associated with the direct binding of ERG to the SOX4 promotor [20]. Silencing both genes restored the epithelial characteristics and reduced the migration and invasion of prostate cancer cells [20].

It is apparent that SOX4 is subjected to complex miRNA-mediated regulatory mechanisms. Notably, few miRNAs play crucial role in regulating SOX4 expression across multiple cancer types such as miR-204, miR-132 and/or miR-212 and miR-129-3p. In addition, miR-320 plays an important role in targeting not only SOX4, but also FOXM1 and FOXQ1, in colorectal and breast cancer. Collectively, these results suggest broad roles for these miRNAs in regulating SOX4-mediated tumorigenesis.

**3.3 *LncRNA-dependent SOX4 regulation***

LncRNAs interact with RNA-binding proteins during chromatin remodeling, hence modulating various dynamic and epigenetic processes. These ncRNAs act at the transcriptional, posttranscriptional and translational levels [112] and also may modulate their function by acting as ceRNAs for mRNA-targeting miRNAs (Fig. 2) [113]. Jiao and colleagues reported that lncRNA-UCA1 promoted esophageal cancer cell proliferation through functioning as a ceRNA for miR-204, hence inhibiting the interaction between miR-204 and the *SOX4* 3'UTR and leading to elevated SOX4 expression [114]. Similarly, androgen receptor negatively induced lncRNA (ARNILA) acted as a ceRNA for miR-204 to upregulate SOX4 expression, induce EMT and promote invasion and metastasis in triple negative breast cancer cells [115]. Moreover, elevated expression of ARNILA was found to correlate with poor progression-free survival in triple negative breast cancer patients. In hepatocellular carcinoma, STAT3 signaling was found to induce the expression of lncRNA HOXD-AS1, which in turn sequestered miR-130a-3p, thus inhibiting miR-130a-3p-mediated SOX4 repression and leading to enhanced hepatocellular carcinoma metastasis [116]. In addition, lncRNA-PAGBC was also reported to activate the Akt/mammalian target of rapamycin (mTOR) pathway and to promote gallbladder tumor metastasis through the downregulation of miR-133b and miR-511, leading to the elevated expression of SOX4 and phosphoinositide-3-kinase regulatory subunit 3 (PIK3R3), respectively [117]. Similarly, colon cancer-associated transcript-1 (CCAT1) promoted cisplatin resistance in lung cancer cells through the downregulation of miR-130a-3p and the subsequent induction of SOX4 expression [118]. In a recent study, lncSOX4 was found to initiate the expression of SOX4 through directly interacting with and recruiting STAT3 to the SOX4 promoter, promoting the self-renewal of liver TICs [28]. MiR-381 is known to target SOX4 in gastric cancer [119]. Interestingly, Zhang and colleagues reported that lncRNA taurine-upregulated gene 1 (TUG1) sequestered endogenous miR-381, promoting the metastasis of gastric cancer cells *via* SOX4 upregulation [119]. In RUNX1-rearranged acute leukemia, lncRNA CASC15 enhanced SOX4 expression through the recruitment of Yin and Yang-1 (YY1) to the SOX4 promoter [120]. In lung adenocarcinoma, lncRNA cancer susceptibility candidate 2 (CASC2) inhibited EMT through SOX4 downregulation, although the exact mechanism by which CASC2 downregulated SOX4 expression was not revealed [121]. LncBRM promoted ovarian cancer cell proliferation, migration and invasion through the suppression of miR-204 and the subsequent upregulation of SOX4 expression [122]. LncRNA ABHD11-AS1 was shown to promote CRC development through acting as a ceRNA for miR-133a and hence promoting SOX4 expression [123].

Notably, while miR-204 plays a crucial role in regulating SOX4 expression in leukemia, breast, ovarian, and gastric cancer, miR-204 itself is subjected to additional layer of negative regulation by ARNILA and UCA1. This complex regulatory network highlights an important role for the fine-tuning of SOX4 expression to prevent tumorigenesis in multiple cancer types.

**4. SOX4 as a potential prognostic biomarker in human cancers**

Since the initial discovery of SOX4, several studies have identified SOX4 as a potential prognostic biomarker in most human cancers, correlating its higher expression in tumor tissues with malignancy and poor prognosis in cancer patients [7, 8, 124, 125]. Increased expression of SOX4 in different types of human cancers is often associated with unfavorable clinical outcomes. Based on a meta-analysis including more than 1300 cancer patients, high expression of SOX4 correlates with poor prognosis, suggesting that SOX4 is a pan-cancer prognostic biomarker [124]. Computational analysis revealed a significant correlation between elevated SOX4 expression and poor metastasis-free survival in a cohort of 200 early-stage lymph node-negative breast cancer patients [44]. In prostate cancer, elevated SOX4 expression was associated with a poor clinical outcome [111]. In a multivariate analysis conducted in 148 breast cancer patients, elevated SOX4 expression was significantly associated with poor clinical outcome, regardless of tumor stage, tumor size, lymph node metastasis and distant metastasis [8]. Moreover, in a cohort of 168 gastric cancer patients, elevated nuclear SOX4 expression correlated with a number of clinical parameters, including stage, invasion depth, vascular invasion status, nodal status, distant metastasis, and poor disease-free survival [126]. Analysis of the microarray expression profiles of 424 CRC samples and subsequent validation in two independent cohorts of stage II CRC patients revealed that high SOX4 expression was correlated with an increased risk of recurrence (HR 2.7, P=0.01) [127]. Immunohistochemical examination of SOX4 expression in tumor tissues from 263 patients with colon cancer revealed nuclear SOX4 overexpression correlated with tumor stage, depth of invasion, and distant metastasis [128]. In a multivariate analysis, increased SOX4 expression was suggested as an independent predictor of poor prognosis in non-small cell lung cancer (NSCLC) patients [129]. Taken together, these data warrant further investigation, and a side-by-side comparison with existing biomarkers, for potential development of SOX4-based molecular signatures for cancer diagnosis and prognosis.

**5. Conclusion**

Cancer development and progression are mediated by alterations in transcriptional and posttranscriptional networks, leading to a disturbed balance in the activity of oncogenes and tumor suppressor genes. In this context, SOX4 promotes different aspects of cancer development and progression through the transcriptional activation and epigenetic modification of downstream genes and, thus endowing malignant cells with a proliferation and survival advantage and with EMT and invasion capabilities. A large body of data also correlates elevated SOX4 expression with advanced stages of malignancy and poorer clinical outcomes, suggesting a potential opportunity for combating cancer by targeting SOX4. Indeed, numerous preclinical studies have suggested the efficacy of targeted SOX4 depletion as a therapeutic opportunity in various human cancer models.

Increasing number of studies have identified numerous SOX4-targeting miRNAs and highlighted the consequences of altered miRNA expression on the modulation and/or inhibition of cancer progression. In fact, we observed more than 25 miRNAs to target SOX4 in various human malignancies, which is not frequently seen in various biological systems. One plausible explanation is that SOX4 has relatively large 3`UTR region spanning more than 4000 nt, thus allowing the binding of dozens of miRNAs. SOX4 also induces the expression of a number of genes involved in miRNA biogenesis and maturation (i.e. Dicer), thus causing global changes in miRNA expression in cancer cells. On the other hand, SOX4 represses the expression of several miRNAs through EZH2-mediated H3K27me3 epigenetic modification. A number of lncRNAs also play a role in this complex regulatory network (summarized in figure 1 and figure 2). LncRNAs enhance SOX4 expression, or they can act as ceRNAs to sequester SOX4-targeting miRNAs. This complex regulatory network highlights a pivotal role for SOX4 and the level of regulation required to keep this master regulator fine-tuned to prevent tumorigenesis.

Abundant preclinical data have shown the feasibility of utilizing miRNA-based therapies *in vivo* in various disease models [130-132]. Notably, miravirsen, a miR-122 inhibitor previously shown to reduce the hepatitis C viral load in a primate hepatitis C virus infection model, has entered clinical trials [131]. In the context of cancer therapeutics, MRX34, a miR‑34 mimic, is the first to enter multicenter phase I clinical trial to treat 47 patients with advanced stage IV cancers (multiple cancer types) [133]. The results from the trial showed that MRX34 treatment, with dexamethasone premedication, exerts antitumor activity in a subset of patients with refractory advanced solid tumors [133]. However this study was subsequently terminated due to immune-related adverse effects [134]. Zandwijk and colleagues explored the efficacy of miR-16-based miRNA mimic, packaged in an EnGeneIC Dream Vector (EDV), targeting EGFR-expressing mesothelioma cells *via* bispecific antibodies in patients with advanced pleural mesothelioma [135]. The authors reported that only a patient out of 22 patients achieved an objective response [135]. Therefore, the translation of the *in vitro* and preclinical findings into clinical trials is just beginning. Additionally, the development of small molecule inhibitors targeting SOX4 as more efficient therapeutic strategies and the translation of preclinical data into the clinic are needed.

Despite the wealth of information on the role of SOX4 during tumorigenesis and epigenetic regulation, a number of outstanding questions pertaining to its epigenetic regulation and its therapeutic potential remains to be addressed. For instance, what is the biological relevance of the identified miRNAs and lncRNAs in regulating SOX4 expression and tumorigenesis under physiological conditions? Employing a conditional and tissue-specific gain and loss of function approaches in various cancer animal models could provide some insight on the contribution of ncRNAs-SOX4 circuits during tumorigenesis *in vivo*. Is it plausible to target SOX4 as a therapeutic strategy in cancer patients? Developing clinical-grade small molecule and tumor tissue-directed inhibitors for SOX4 could hold the key to answering these questions.

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**Figure 1. TGF-β-mediated SOX4 expression and downstream effects on gene expression and tumorigenesis.** Activation of TGFβ signaling leads to SMAD2/3 phosphorylation and translocation to the nucleus, leading to SOX4 expression. Various SOX4-containing transcription complex (SOX4, β-catenin, ERG) directly induced the expression of EZH2, leading to increased H3K27me3 and gene silencing. SOX4 represses NKX3.1 and induces the expression of a number of genes involved in tumor survival, EMT, metastasis, and stemness, hence promoting tumorigenesis.

**D:\Padma\2019\June\29.6.19\YSCBI_1601\Figure 2.tif**

**Figure 2. MiRNA-mRNA-SOX4 network in human cancers.** Schematic representation of the interaction of the indicated lncRNAs, miRNAs, and SOX4 in breast, colorectal, ovarian, gastric, esophageal, liver, other epithelial cancers, hematological, and sarcomas. Arrow-headed and bar-headed lines indicate activation or inhibition, respectively.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Table. 1. SOX4-targeting miRNAs and lncRNAs in different human cancers** | | | | | |
| **miRNA** | **Patient samples** | ***In vitro* models** | ***In vivo***  **models** | **Validated functions** | **Ref.** |
| **Breast cancer (BC)** | | | | | |
| miR-335 | 82 pairs of primary BCs | MDA-MB-231 cells | NOD/SCID female mice (NCI), 6-8-week-old were used for lung colonization, tumor growth and orthotopic metastasis xenograft assays. | Inhibited metastatic cell invasion through targeting SOX4 and extracellular matrix component tenascin-C. | [77] |
| miR-93 (member of mir106b-25 cluster) | N/A | SUM159 and HCC1954 cells | NOD/SCID mice | Inhibited tumor growth and metastasis in the adjuvant setting. Overexpression of miR-93 increased the CSC population and accelerated tumor growth in luminal subtype MCF7 cells. MiR-93 downregulated stem cell regulatory genes in BC-CSCs. It increased proliferation of SUM159 by 29%. Promoted MET in SUM159 cells. Maintains normal BC-CSCs in an epithelial state. | [78] |
| miR-338-3p | 32 pairs of primary BCs | MCF-10A, MCF7, MDA-MB‑231, MDA-MB-453 and BT-549 cells | Twenty female BALB/c mice (18-20-g, 4-5-week-old) | Inhibited cell proliferation, colony formation, migration and invasion, induced cell apoptosis, cell cycle arrest at G1/G0 stage and suppressed tumor growth. MiR‑338-3p targeted SOX4 3'UTR. | [79] |
| miR-212/132 | N/A | MDA-MB-231 and T47D cells | Female BALB/c athymic nude mice, 6–8 weeks old. Mammary fat pad injection followed by lung metastasis | Inhibited cell proliferation, migration and metastasis. | [85] |
| miR-191-5p | N/A | MCF7, ZR-75, and T47D cells | N/A | P53 down-regulated miR-191-5p, miR-191-5p functions as an anti-apoptotic miRNA, its targets SOX4 and brings about downregulation of p53 levels. Anti-miR-191 treatment sensitizes BC cells to doxorubicin-mediated apoptotic death. | [83] |
| miR-320 | 15 pairs aged between 40 to 65 years (mean age, 53 years) | MCF7, T47D, MDA‑MB‑231, MDA‑MB‑468 and 293FT cells | N/A | Knockdown of miR‑320 in BC cells promoted cell proliferation and invasion *in vitro*, whereas miR‑320 overexpression had the opposite effect. MiR‑320 targeted *SOX4* 3'UTR, and the restoration of SOX4 in miR‑320‑overexpressing cells attenuated the tumor‑suppressive effects of miR‑320. | [84] |
| miR-204 | 88 TNBC patients. Age of 18 years or older. no distant metastasis and neoadjuvant chemotherapy | MDA-MB-231, MDA-MB-436 and Hs578T cells | Female BALB/c  nude mice aged 4 weeks | AR-negatively induced lncRNA (ARNILA) acted ceRNA for miR-204 to upregulate SOX4 expression, and induced EMT and promoted TNBC invasion and metastasis. | [115] |
| miR-129-5p | N/A | MCF7 cells | N/A | MiR-129-5p and SOX4 *via* the SOX4/EZH2 complex mediated H3K27me3 modification in BC cells and thus modulating EMT and multi-drug resistance (MDR). Overexpression of miR-129-5p suppressed SOX4, N-cadherin and Vimentin expression and restored E-cadherin expression. | [110] |
| **Colorectal cancer (CRC)** | | | | | |
| miR-187 | 40 paired stage II CRC and adjacent normal mucosa tissue | LS174T, RKO, HT29, HCT116, SW480, SW620, SW480/M5, and NCM460 cells | A subcutaneous nude mice tumor model | Inhibited cell proliferation and migration *in vitro* and tumor formation *in vivo*. Downregulation of miR-187 induced EMT by activating SMAD pathway. SOX4, NT5E and PTK6 are direct targets for miR-187. | [26] |
| miR-320c | 13 pairs of CRC and adjacent normal samples | HCT116 cells | SCID 6-8 weeks-old for xenograft experiments | MiR-320 family is downregulated in CRC and their overexpression reduces HCT116 cell growth and migration. MiR-320c targeted SOX4, FOXM1 and FOXQ1 in CRC. Forced expression of miR-320c increased sensitivity of CRC cells to 5-fluorouracil. | [69] |
| miR-363-3p | 39 pairs of fresh CRC tissue and paired adjacent no tumor | SW480, SW620, HCT116, HT29, LoVo, and 293T cells | BALB/c-nu/nu nude mice, 5-weeks-old | Downregulation of miR-363-3p promoted cell migration and invasion, and induced EMT *in vitro* and *in vivo*. miR-363-3p 140 targets *SOX4* 3'UTR. Downregulation of miR-363-3p increased SOX4 expression and induced EMT. | [25] |
| miR‑539 | 49 pairs of CRC tissues and normal adjacent tissues | LoVo, HCT116, HT29, SW480, SW620, and FHC cells | N/A | Attenuated cell proliferation and invasion *in vitro*. MiR‑539 targeted *SOX4* 3'UTR. Upregulation of SOX4 partially restored the tumor suppressive effects of miR‑539 on cell proliferation and invasion. | [89] |
| miR-133a | 132 pairs of CRC tissues and normal adjacent tissues | SW480, HT-29, LoVo, HCT-116, HCT-8, SW620, Caco-2, and HcoEpiC cells | N/A | ABHD11-AS1 directly interacted with miR-133a, and SOX4 was found to be a downstream target of miR-133a. ABHD11-AS1 subsequently exerted its biological effects *via* modulating the expression of SOX4 in CRC cells. | [123] |
| **Gastric cancer (GC)** | | | | | |
| miR-129-3p | 70 paired patients with GC | SGC-7901 cells | N/A | Upregulation of SOX4 was inversely associated with the epigenetic silencing of miR-129-3p and restoration of miR-129-3p downregulated SOX4 expression. Inactivation of SOX4 and restoration of miR-129-3p induced apoptosis. | [93] |
| miR-138 | 48 paired patients with GC | HGC-27, MGC-803, SGC-7901 and BGC-823, and GES-1 cells | ALB/c nude mice 6 weeks-old. | Overexpression of miR-138 impaired GC cell proliferation, colony formation, migration and invasion *in vitro*, as well as suppressed tumor growth *in vivo*. | [136] |
| miR-140 | 20 paired patients with GC (10 males and 10 females) aged from 42 to 81 years (60.3±9.8) | HGC-27, BGC-823, SGC-7901 and GES-1 cells | N/A | Overexpression of miR-140 inhibited HGC-27 cell viability and colony formation and resulted in G0/G1 arrest. MiR-140 targets *SOX4* 3'UTR. | [137] |
| miR-204 | 54 paired patients with GC | AGS cells | *In situ* hybridization | Suppressed proliferation, migration, invasion of GC Cells. MiR-204 was associated with no lymph node metastasis and early tumor stages GC patients showed, whereas SOX4 was associated with lymph node metastasis and advanced tumor stages. miR-204 was expressed lower and SOX4 expressed higher in GC tissues than normal. | [138] |
| miR-211 | 20 paired patients with GC | BGC-823, AGS, HGC-27, MKN-45, and GES-1 cells | N/A | Inhibited cell proliferation and migration. miR-211 targets SOX4 3'UTR. SOX4 is inversely expressed with miR-211 in GC patients. Knockdown of SOX4 inhibited the proliferation and invasion in BGC-823 cells. | [104] |
| miR‑381 | 60 paired patients with GC (36 males and 24 females). The age range between 45 and 73 years, and the median age was 54 years | GES‑1, BGC‑823, MGC‑803, SGC‑7901 and MKN28 cells | N/A | Upregulation of miR‑381 inhibited the migration and invasion of GC SGC‑7901 cells through SOX4‑mediated EMT. | [119] |
| miR-204 | N/A | SGC-7901/MKN45 GC cells | N/A | Suppressed migration, invasion and proliferation of SGC-7901 and MKN45 cells. Ectopic miR-204 expression decreased SOX4 expression at the mRNA and protein levels in the GC cell line. MiR-204 targeted *SOX4* 3'UTR and inhibited EMT. | [139] |
| **Hepatocellular carcinoma (HCC)** | | | | | |
| miR-449 family (miR- 449a, miR-449b, miR-449c) | RNA of human HCC tissues (n = 61) and of normal livers (n = 4) collected | HLE, HLF, Huh7, Hep3B, HepG2, and THLE-2 and THLE-3 cells | Injected subcutaneously into the left flank of six-week-old nu/nu mice (N = 6 for each condition) | Transfection of miR-449a, miR-449b, and/or miR-449c inhibited cell proliferation and migration, induced apoptosis, and reduced tumor growth to different extents. MiR-449a, miR-449b, and, to a lesser degree, miR-449c directly targeted *SOX4* 3'UTR, and thereby inhibited TGF-β-mediated cell migration. | [140] |
| miR-129-3p | 75 paired tumor and normal liver tissues from HCC patients with serum HBsAg positive were collected | HepG2 cells | N/A | SOX4 level in the HCC tissues was significantly higher than that in non-tumor tissues (P = 0.0174) and normal liver tissues (P = 0.0077), correlated reversely with miR-129-3p level (P = 0.0105). Overexpression of miR-129-2 reduced cell proliferation and clonogenicity, while co‐expression with SOX4 could partially reverse its antitumor effects. SOX4 in HepG2 cells enhanced β‐catenin/TCF activity by increasing β‐catenin level. Methylation‐mediated repression of miR‐129‐2 may enhance oncogenic SOX4 expression and involve in HCC tumorigenesis. | [95] |
| miR-130a-3p | 120 patients | SNU449, Huh28, SMMC-7721, Huh7 and Hep3B cells | Huh7 cells infected with shRNA-HOXD-AS1 or empty vector and injected into BALB/c-nu/nu mice through the tail vein | Downregulation of miR-130a-3p by HOXD-AS1 led to increased SOX4 expression. | [116] |
| **Esophageal cancer (EC)** | | | | | |
| miR-31 | N/A | ESCC, EAC, TE8, TE1, TE11, TE7, TE12, TE2, TE3, TE5 and TE9 cells | N/A | Inhibited cell growth, migration and invasion. miR-31 targeted *SOX4* 3'UTR. MiR-31 regulated EZH2 and HDAC3 indirectly. SOX4, EZH2 and HDAC3 levels inversely correlated with miR-31 expression in ESCC cell lines. Ectopic expression of miR-31 in ESCC and EAC cell lines led to downregulation of SOX4, EZH2 and HDAC3. Conversely, pharmacologic and genetic inhibition of SOX4 and EZH2 restore miR-31 expression showed that SOX4, EZH2 and HDAC3 form a co-repressor complex that binds to the miR-31 promoter, repressing miR-31 through an epigenetic mark by H3K27me3 and by histone acetylation. | [102] |
| miR-129-3p | 42 pairs of EC and normal tissues | NMC109 cells | N/A | It was downregulated in 27 of 31 primary EC, while the expression of SOX4 was upregulated (P<0.001). Restoration of miR-129-3p led to a decrease in SOX4 expression, which was accompanied by reduced migration and proliferation of the cancer cells. | [94] |
| miR-133a | 45 pairs of EC and normal tissues | ESCC, KYSE-150, KYSE - 510, EC-9706 and SHEE cells | Nude mouse. (Four in each group, 6-8 weeks age) | Inhibited the cell proliferation, migration and invasion. Downregulation of miR-133a contributed to ESCC progression in nude mouse xenograft model. MiR-133a targeted *SOX4* 3'UTR. | [103] |
| **Lung cancer (LC)/ Non - small cell lung cancer (NSLC)** | | | | | |
| miR-212 | 115 pairs from NSLC patients | H292, H1299, A549, SPC-A1 and BEAS-2B cells | N/A | Inhibited cell migration, invasion and EMT, while downregulated miR-212 reversed the effect. SOX4 expression reversed the functional effects of miR-212. | [141] |
| miR-338-3p | 90 pairs of NSCLC specimens, all patients had not received radiation or chemotherapies prior to surgery | L9981, NL9980 cells | Four in each group, 6-8 weeks age, and cells were injected into left side of the posterior flank of nude mouse. | Inhibited the migration and invasion of LC cells *in vitro* *and in vivo*. MiR-338-3p targeted *SOX4* 3'UTR. Overexpressing or silencing SOX4 could elevate or inhibit the migration and invasion of LC cells. | [34] |
| miR-130a-3p | N/A | BEAS-2B, parental NSCLC A549, H1299, and (Cisplatin) DDP-resistant NSCLC A549/DDP cells | N/A | CCAT1 and SOX4 were upregulated, and miR-130a-3p was downregulated in DDP-resistant NSCLC cells. CCAT1 directly interacted and negatively regulated miR-130a-3p expression. MiR-130a-3p targeted *SOX4* 3'UTR. Knockdown of SOX4 reversed the miR-130a-3p-inhibition-induced increase of DDP resistance and ABCG2 expression. | [118] |
| **Ovarian cancer (OC)** | | | | | |
| miR-138 | N/A | SKOV-3 and TOV-112D cells | Cells were injected intrabursally into 8- to 10-week-oldCB17/lcr-Prkdc scid/Crl mice | Inhibited the cell migration and invasion. Xenograft mouse model demonstrated that the expression of miRNA-138 inhibited OC metastasis. MiR-138 directly targeted SOX4 and HIF-1α, and overexpression of SOX4 and HIF-1α effectively reversed the miR-138-mediated suppression of cell invasion. | [96] |
| miR-212 and miR-132 | N/A | SKOV-3 and OV2008 cells | N/A | Overexpression of EZH2 and SOX4 repressed miR-212 and miR-132 expressions in SKOV3 and OV2008 cells. Interactions among SOX4, EZH2, and H3K27me3, and significant enrichment of EZH2 and H3K27me3 in the promoter region of miR-212/132 were reported. Both pri-miR-212 and -132 decreased after enforced EZH2 or SOX4 expression. Western blot and dual-luciferase assay confirmed that miR-212 and miR-132 targeted *SOX4* 3'UTR and suppressed its expression in OC cells. MiR-132 or miR-212 overexpression or knockdown of endogenous SOX4 reduced EMT-like properties. | [97] |
| miR-204 | 80 OC patients | A2780, TOV112D, HO-8910, OVCAR-3, and SKOV3 cells | NA | lncBRM promoted OC cell proliferation, migration and invasion though suppression of miR-204 and subsequent upregulated SOX4 . | [122] |
| **Endometrial cancer (EC)** | | | | | |
| miR-129-3p | Tissue specimens (117 tumors and 8 uninvolved controls) from EC patients | ECC-1 and Ishikawa cells | N/A | SOX4 was computationally predicted to be the target of a miR-129-3p. When compared to the matched endometria, the expression of miR-129-3p was lost in 27 of 31 primary endometrial tumors that also showed a concomitant gain of SOX4 expression (P<0.001). This was associated with hyper methylation of the miR-129-3p CpG island, which was observed in EC cell lines and 68% of 117 EC tumors. Reactivation of miR-129-3p by pharmacological induction of histone acetylation and DNA demethylation resulted in decreased SOX4 expression. Restoration of miR-129-3p led to decreased SOX4 expression and reduced proliferation. | [92] |
| **Prostate cancer (PC)** | | | | | |
| miR-30a | 84 PC patients | Vcap, DU-145, Lncap, PC-3, RWPE, and HEK293T cells | N/A | Inhibited proliferation and EMT process of VCaP cells. MiR30a targeted *SOX4* 3'UTR. SOX4 overexpression is significantly associated with decreased levels of miR-30a in PC cases. | [100] |
| miR-19a-3p | N/A | DU145 cells | N/A | Overexpression of miR-19a-3p downregulated SOX4, MMP9, N-cadherin, Vimentin and α-SMA in DU145 cells. MiR-19a-3p inhibited migration, invasion and EMT of DU145 cells. | [10] |
| **B and T cell leukemia** | | | | | |
| miR-132 | N/A | Mice splenic and bone marrow cell populations and 70Z/3 cells | C57BL/6 WT and miR-212/132 mice were bred and housed | Overexpression of miR-132 blocked B cell development and induced apoptosis in primary bone marrow B cells. Loss of miR- 212/132 accelerated B cell recovery after antibody-mediated B cell depletion. SOX4 with miR-132 rescued the defect in B cell development from overexpression of miR-132 alone. | [106] |
| miR-204 | 32 pairs of T-cell acute lymphoblastic leukemia patients and healthy controls | Jurkat and MOLT-3 cells | N/A | Overexpression of miR-204 suppressed cell proliferation, migration and invasion. MiR-204 targeted *SOX4* 3'UTR. | [105] |
| **Osteosarcoma (OS)** | | | | | |
| miR-25 | 36 pairs of OS and normal tissues (located >3 cm from the tumor) | Saos-2, HOS, U2OS, MG63, hFOB 1.19 cells | U2OS cells injected subcutaneously into the dorsal flanks of 6-week-old male nude mice. | Inhibited proliferation, colony formation, migration and invasion of OS cells *in vitro* and retarded tumor growth *in vivo*. Inhibited EMT process and evidenced by bioinformatics analysis predicted and luciferase reporter assay. | [36] |
| miR-25‑3p | 27 pairs of OS and normal tissues (male, 19; female, 8; age range, 16‑53 years) | MG‑63, SAOS‑2, HOS, U2OS, and hFOB 1.19 cells | N/A | Inhibited proliferation, colony formation, migration, and invasion of OS cells *in vitro*. MiR-25-3p targeted *SOX4* 3'UTR. | [99] |
| miR-132 | N/A | MG63, HOS, SaOS-2, 143B, U2OS, and hFOB1.19 cells | N/A | Inhibited proliferation, invasion, induces G1-phase arrest and cell apoptosis in SaOS-2 and 143B cells. Downregulation of SOX4 had similar effects with miR‑132 overexpression. Suppression of SOX4 is essential for miR‑132-inhibited cell proliferation, invasion and EMT in OS cells. | [98] |
| miR-212 | 28 pairs of OS and normal tissues | MG63 and U2OS cells | Male BALB/c nude mice aged 4 weeks | Inhibited cell proliferation, invasion and tumor growth in the nude mice. MiR-212 targeted *SOX4* 3'UTR. Knockdown of SOX4 showed similar effects with miR-212 overexpression. SOX4 re-introduction reversed the anti-proliferative roles of miR-212. | [35] |
| **Chondrosarcoma (CS)** | | | | | |
| miR-30a | 107 CS and 59 chondroma paraffin tissue samples. | SW1353 cells | N/A | MiR-30a targeted *SOX4* 3'UTR. Clinically, miR-30a expression was negatively correlated with SOX4 expression in CS cases. Identified that SOX4 was oncogenic in CS and negatively regulated by miR-30a *in vitro*. | [142] |
| miR-129-5p | 92 patients (47 males and 45 females) | JJ012, SW1353, and CHON-002 cells | Sixty SCID nude mice at an average age of 4 weeks | Upregulation of SOX4 and downregulation of miR-129-5p in CS tissues and cells was reported. MiR-129-5p inhibited Wnt/β-catenin pathway by targeting SOX4. MiR-129-5p suppressed proliferation, migration and promoted apoptosis of CS cells. | [91] |
| **Gallbladder cancer (GBC)** | | | | | |
| miR-133b | 77 GBC tumor samples | GBC-SD and SGC-996 GBC cells | NOZ cells with lncRNA-PAGBC were injected into the spleen to establish liver metastasis | lncRNA-PAGBC downregulated miR-133b which activated SOX4 and AKT pathway. MiR‐133b targeted *SOX4* 3'UTR. lncRNA‐PAGBC plays important roles in regulating SOX4 expression by competitively binding to miR‐133b. | [117] |
| **Urinary bladder carcinoma (UBC)** | | | | | |
| miR-129-5p | 11 normal and 106 UBC samples | T24, SW780, HT1376, RT4, J82, HU609, and CV29 cells | In situ hybridization. | Inhibited cell proliferation and induced cell death. A direct link between miR-129 and the two putative targets GALNT1 and SOX4 was reported. | [90] |
| **Renal cell carcinoma (RCC)** | | | | | |
| miR-138 | 67 pairs of RCC tissues and normal | HK-2, ACHN, 786-O, and SN12-PM6 cells | Nude mice, 4-6 weeks old, cells were subcutaneously injected into nude mice | Overexpression of miR-138 inhibited, whereas downregulation of miR-138 promoted, the proliferation, migration and invasion. MiR-138 targeted *SOX4* 3'UTR. Ectopic expression of miR-138 repressed tumor growth *in vivo*. | [143] |