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Journal of
Reproductive Healthcare
and Medicine

ISSRF
Indian Society for the Study of Reproduction & Fertility

Review Article

SOX4 expression in cancer: Insights from developmental regulation and deregulation in tumorigenesis

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Received: 15 April 2024
Accepted: 05 June 2024
Published: 29 July 2024

DOI
10.25259/JRHM_8_2024

Quick Response Code:

ABSTRACT

The burden of cancer is on a rapid rise globally. Deregulated gene expression profiles may lead to the development of cancer. Master regulators are the regulatory checkpoints that define and control the intricate networks of gene and protein interactions that make up cell physiology. The molecular programs that generate particular cellular phenotypes depend on master regulators. *SOX4* gene is a master regulator that controls the expression of other genes responsible for tumorigenesis and plays a crucial role in multiple signaling pathways. The expression of SOX4 is upregulated in various malignancies. Increased proliferation of cancer cells, survival, apoptosis, and epithelial-to-mesenchymal transition leading to metastasis have all been linked to SOX4 expression in cancer. Elevated levels of SOX4 also possess a correlation with poor prognosis in various cancer types. Recently, SOX4 has surfaced as a possible target for cancer therapeutics. Furthermore, it has been shown that targeting SOX4 could inhibit tumor growth and enhance the efficacy of conventional cancer therapies. The present review summarizes the current status of SOX4 in the initiation and progression of various human cancers.

Keywords: Cancer, Master regulator, SOX4, Prognosis, Therapeutic

INTRODUCTION

The sex-determining region Y (*SRY*) gene is located on the Y chromosome and is crucial for the determination of sex-specific fates and the development of male sexuality.[1-3] The *SOX* gene family comprises 20 members, which are divided into nine subgroups, varying from SOXA to SOXH.[4] A comparison among various members of the SOX family has been illustrated in Table 1.[5-57] SRY-related high-mobility-group-box 4 (SOX4) belongs to the C subfamily of SOX transcription factors and has a significant role in the growth and differentiation of cells and organs during early development. SOX4 is also linked to the initiation and progression of various human malignancies.[4,58] The *SOX4* gene is found on chromosome 6p22.3 in humans. It encodes for a 47 KDa protein constituting 474 amino acids and is highly conserved in vertebrates. In addition to being crucial for the development of bones, islets, and the heart, SOX4 also plays a crucial role in cancers, osteoporosis, and other diseases. SOX4 executes its impact on context-specific gene expression regulation and tissue-specific tumorigenesis by interacting with numerous other transcription factors. Several investigations about the medical relevance of SOX4 in cancer suggest its function in tumor growth and development.[59] Increased expression of SOX4 in various human cancers is frequently linked to poor clinical outcomes. SOX4 also

Table 1: Physiological function of SOX4 family members and their role in cancer.

Subfamily	Member	Chromosomal position	Physiological function	Role in cancer	References
Group A	SRY	Yp11.2	Sex determination	Prognostic biomarkers in head and neck SCC	[5,6]
Group B1	SOX1	13q34	Involved in brain development	SOX1 overexpression inhibits cell proliferation, invasion, and tumor formation in hepatocellular, cervical, lung, gastric and breast cancer	[7,8]
	SOX2	3q26.33	Maintains stemness of embryonic cells	High expression with poor prognosis in breast, oral, lung, ovarian and prostate cancer	[9]
	SOX3	Xq27.1	Development of pituitary and CNS	Promotes malignant behaviour of glioblastoma cells Induces EMT in osteosarcoma	[10-12]
Group B2	SOX14	3q22.3	Neuronal development	High expression associated with increased growth and metastasis in cervical cancer	[13,14]
	SOX21	13q32.1	Neural stem cell differentiation	Induces apoptosis of GBM and glioma	[15,16]
Group C	SOX4	6q22.3	Development of heart, reproductive system and CNS	Upregulated in breast, lung and cervical cancer Induces EMT in breast and gastric cancer	[17-20]
	SOX11	2p25.2	Development of cerebral cortex, kidney, lung and spinal cord	Elevated expression is associated with B-lineage malignancies	[21,22]
	SOX12	20p13	Differentiation of lymphocytes	Associated with progression and poor prognosis in breast cancer Promotes growth of multiple myeloma cells	[23-25]
Group D	SOX5	12p12.1	Chondrogenesis and neural cell development	Promotes invasion and metastasis in gastric cancer Contributes to EMT and metastasis in prostate cancer	[26-28]
	SOX6	11p15.2	Differentiation of erythroid cells Regulates adipogenesis	Inhibits proliferation, migration, tumor growth and metastasis in pancreatic cancer Low expression associated with poor prognosis in lung adenocarcinoma	[29-32]
	SOX13	1q32.1	Brain development Cartilage development	Promotes metastasis in colorectal cancer Promotes breast cancer cell growth and glycolysis	[33-35]
Group E	SOX8	16p13.3	Maintenance of gonadal function Testis determination	Promotes tumor growth and predicts poor prognosis in Tongue SCC Associated with tumor invasion in colorectal cancer	[36-38]
	SOX9	17q24.3	Development of pancreas and intestine Cartilage and lung development	Master regulator of breast cancer cell survival and metastasis Promotes pancreatic cancer progression by regulating EMT	[39-42]
	SOX10	22q13.1	Differentiation of neural crest cells	Prognostic marker for human nasopharyngeal carcinoma Prmotes proliferation ability of melanoma cells	[43-45]
Group F	SOX7	8p23.1	Heart development	Tumor suppressor in lung cancer and glioblastoma	[46-48]
	SOX17	8q11.23	Hematopoetic development from Stem cells	Immunomarkers for ovarian and endometrial cancer Inhibits metastasis in endometrial cancer	[49-51]
	SOX18	20q13.33	Development of blood and lymphatic vessels	Promotes metastasis in gastric cancer	[52,53]
Group G	SOX15	17p13.1	Population of myogenic progenitor cells and regeneration	inhibit the proliferation, migration and invasion and induce cells apoptosis in colorectal cancer	[54]
Group H	SOX30	5q33.3	Development of testis and male fertility	Prognostic marker for ovarian cancer Inhibits migration and invasion in lung cancer	[55-57]

CNS: central nervous system, EMT: Epithelial-to-mesenchymal transition, SCC: Squamous cell carcinoma, GBM: Glioblastoma multiforme

mediates several signaling pathways which contribute to tumorigenesis and tumor progression. Several pathways regulated by SOX4 are depicted in Figure 1.

The interaction between SOX4 targeting microRNAs (miRNAs) and long non-coding RNAs (lncRNA) and the consequent epigenetic regulation of tumorigenesis has gained attention in recent years and is employed in cancer therapeutics.

SOX4 AS AN ESSENTIAL DEVELOPMENTAL TRANSCRIPTION FACTOR

The crucial transcription factor SOX4 controls progenitor development, differentiation, stemness, and a variety of pathways contributing to development.[17,60,61] It has been observed that the knockout of SOX4 *in vivo* led to embryonic lethality due to cardiac failure.[62] Moreover, in SOX4 deficient embryos, the development of B lymphocytes is hindered as there is a halt at the pro-B cell stage.[62] In addition to being expressed in stem cells, SOX4 regulates stem cell activation[63] and also contributes to stem cell maintenance, possibly by activating the expression of SOX2.[20,64,65] The cytokine-induced granulocyte maturation in the 32Dcl3 murine myeloid cell line was significantly suppressed by SOX4 overexpression, indicating a differentiation block.[66] Furthermore, the establishment of a fully mature phenotype is inhibited by prolonged SOX4 expression in the cells of the central nervous system, indicating that premature terminal differentiation may be prevented by SOX4.[67] Around the time when adult neural stem cells (NSCs) commit to a neuron, SOX4 expression is initiated in the adult mouse hippocampus and is restored in immature neurons. SOX4 expression also facilitates and is required for the generation of neurons from adult NSCs *in vitro*.[68] SOX4 protects tyrosine hydroxylase-expressing cells by acting as a pro-survival factor throughout the development of the spinal cord.[69] Therefore,

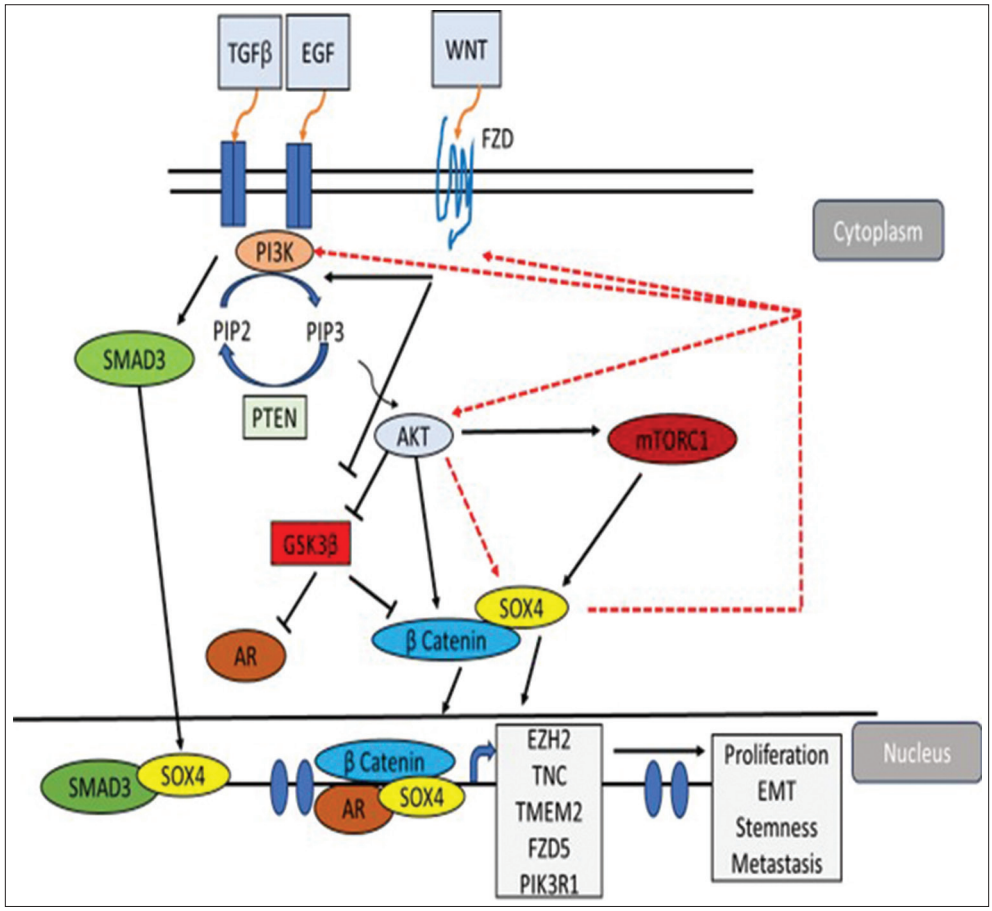

Figure 1: Schematic diagram illustrating how SOX4 interacts with PI3K-AKT, Wnt/β-catenin, SMAD3, and AR signaling pathways, and how the PI3K-AKT-mTOR pathway regulates the expression of SOX4 in cancer progression. A potential positive feedback loop is indicated by the red dashed line. Transforming growth factor-β and Wnt activate PI3K/AKT to induce and stabilize SOX4 protein. SOX4 recruits β-catenin and interacts with SMAD3 at promoters of genes critical for proliferation, stemness, epithelial-to-mesenchymal transition, and metastasis.

it can be concluded that SOX4 is a crucial transcription factor for development, which promotes stemness, early differentiation, growth, and survival of transit-amplifying progenitors and regulates multiple pathways corresponding to normal development.

ASSOCIATION OF SOX4 WITH VARIOUS MALIGNANCIES

SOX4 transcription factor is involved in tumorigenesis and regulates various aspects of cancer development. SOX4 was found to be 1 of 64 genes which are upregulated as a "general cancer signature" in transcriptional profiles of human cancers,[70] highlighting the function of SOX4 in malignancies.

Multiple studies have shown that aberrant expression of SOX4 is linked to the progression of various cancers. SOX4 protein is upregulated in cancers of the prostate,[71] endometrial,[72] and breast[73] and exerts an oncogenic function, whereas a reduced expression of SOX4 is detected in cutaneous melanoma,[74] primary gallbladder carcinoma (PGC),[75] and colon cancer,[76] where SOX4 plays the role of cancer suppressor gene.

Several facets of cancer development and progression are promoted by elevated expression of SOX4 and it also regulates expression of many downstream genes and signaling pathways. SOX4 contributes to the malignant phenotypes of cancer cells by regulating processes such as epithelial-to-mesenchymal transition (EMT) and cell death through apoptosis. Several evidences have shown that SOX4 knockdown resulted in apoptosis in adenoid cystic carcinoma (ACC),[77] melanoma cells,[78] and lung cancer[79] and contrary to that SOX4 overexpression promoted cell cycle and apoptosis in colon cancer[76] and hepatocellular carcinoma (HCC).[80] SOX4 overexpression increased cell invasion and metastasis by inducing EMT in renal cell carcinoma[81] and gastric cancer (GC)[20], whereas SOX4 knockdown increased EMT in bladder cancer.[82]

SOX4 expression is a prognostic factor in determining cancer patient outcomes. Higher expression of SOX4 is seen to be associated with better prognosis in HCC,[80] medulloblastoma,[83] and bladder cancer[84] patients but shorter survival in patients of prostate cancer,[85] GC,[86] and colon cancer.[87]

SOX4 is known to serve as a specific predictor of chemotherapy response in cancer. One of the important findings suggests that ectopic expression of SOX4 increases the susceptibility of breast cancer cells to paclitaxel[88], whereas the cell death induced by cisplatin reduced sharply with SOX4 overexpression in cervical cancer[89] and oral squamous cell carcinoma (OSCC).[90]

SOX4 in Adenoid Cystic Carcinoma (ACC)

Microarray analysis of RNA gene expression profiling in ACC shows that SOX4 is one of the most upregulated genes. SOX4 protein was upregulated in ACC patients, as revealed by immunohistochemistry of 20 normal tissues and 28 primary cancers. Silencing SOX4 protein reduced cell viability with an increase in apoptosis, suggesting that SOX4 contributes to tumorigenesis by promoting ACC cell survival. Cell morphology, DNA fragmentation, and flow cytometry were used to confirm apoptosis. Overall, these findings suggested that SOX4 is overexpressed in ACC patients and promotes the survival of ACC cells by contributing to the malignant phenotypes.[77]

SOX4 in Bladder Cancer

Whole-genome expression analysis of bladder tumor tissue samples and normal tissues was used to determine the involvement of SOX4 in bladder cancer disease. SOX4 expression was five-fold higher in bladder tumor tissues as compared to normal tissues. Tissue microarray analysis with clinical annotation was used to evaluate SOX4 protein expression in bladder cancers, and a relation between SOX4 expression and improved patient survival was observed. In the HU609 bladder cancer cell line, overexpression of SOX4 significantly reduced cellular viability and increased apoptosis.[84] In another study, SOX4 expression was investigated in bladder cancer and normal bladder tissues. In comparison to normal tissue, expression of the *SOX4* gene was 2.2-fold upregulated in bladder tumor tissues. A significant variation was also observed in immunostaining between normal bladder and bladder tumor tissues. SOX4 was strongly expressed in tumor tissues. These results suggested that SOX4 might be involved in bladder cancer tumorigenesis.[91]

SOX4 in Breast Cancer

Various studies have shown a correlation of SOX4 transcription factor with increased tumor size, facilitating migration and invasion, leading to metastasis and poor overall survival (OS) in breast cancer patients.[92] Another study revealed that there was an aberrant overexpression of SOX4 which correlated with the triple-negative breast cancer (TNBC) (ER−/PR−/HER−) subtype in human breast cancer specimens.[73]

Transforming growth factor-β (TGF-β) directly targets SOX4. SOX4 induces TGF-β and is essential for TGF-β-induced EMT. Ectopic expression of SOX4 n mammary epithelial cells upregulated the expression of inducers of EMT and TGF-β pathway. It has also been demonstrated that conditional activation of SOX4 could not induce complete EMT. Silencing of SOX4 using short hairpin RNA

(shRNA) approach, delayed messenger RNA (mRNA), and protein expression of TGF-β induced mesenchymal markers. Collectively, these findings indicate that in human primary epithelial cells, TGF-β-mediated increased expression of SOX4 was essential to induce a mesenchymal phenotype during EMT.[58]

mRNA and protein expression of SOX4 was evaluated in breast cancer tissues and adjacent non-cancer tissues and its relation with clinical features of breast cancer patients was studied. Compared to adjacent normal mammary tissues, it was seen that mRNA and protein expression of SOX4 was upregulated in breast cancer tissues and correlated positively with clinical stages, tumor-node-metastasis (TNM) classification, hormone receptor status, and histological grades of breast cancer patients. Overexpression of SOX4 protein was an unfavorable prognostic factor and biomarker, regardless of tumor size, clinical stage, lymph node, or distant metastasis in breast cancer patients.[93]

Our group has also shown SOX4 protein expression in different breast cancer cell lines (unpublished data). We have observed that gene silencing of SOX4 in BT-474 breast cancer cells resulted in increased apoptosis and promoted autophagy (unpublished data).

SOX4 in Cervical Cancer

According to recent reports, SOX4 is highly expressed in cervical cancer cells and tissues. In CaSki cervical cancer cells, overexpression of SOX4 promotes the formation of tumor clones, increases cellular proliferation, and accelerates the cell cycle. On the other hand, silencing of SOX4 using the shRNA approach in CaSki cells inhibited cellular proliferation and decreased the progression of the cell cycle, suggesting the contribution of SOX4 in tumorigenesis. In addition, overexpression of SOX4 by gene transfer decreased the sensitivity of CaSki cells toward the chemotherapeutic drug cisplatin, whereas silencing SOX4 expression using an RNA interference approach increased the sensitivity of CaSki cells in response to cisplatin. Moreover, *ABCG2,* which is a multiple drug resistant gene, was upregulated by overexpression of SOX4 whereas SOX4 downregulation inhibited expression of *ABCG2*. All these findings collectively show that SOX4 modulates the proliferation of cancer cells by cell cycle regulation and inhibition of cancer cell sensitivity toward therapeutic drugs through upregulating *ABCG2*.[89] Therefore, it could be concluded that SOX4 might serve as a focus molecule for cervical cancer treatment.

SOX4 in Chondrosarcoma

It has been shown that SOX4 is overexpressed in 30.4% of interpretable chondrosarcoma patients as compared to 6.9% of interpretable chondroma cases. SOX4 overexpression significantly correlated with both histological grade and tumor recurrence in chondrosarcoma for patients with low histological grade chondrosarcoma; SOX4 was an unfavorable independent prognostic factor. Downregulation of SOX4 *in vitro* suppressed the proliferation migration and invasion capability of SW1353 cells, suggesting the oncogenic function of SOX4 in chondrosarcoma. Clinically, miR-30a and SOX4 expression are negatively correlated in chondrosarcoma cases. In conclusion, SOX4 serves as an unfavorable prognostic factor for low histological grade chondrosarcoma patients.[94]

SOX4 in Esophageal Cancer

Activation of SOX4 is associated with downregulation of miRNA in esophageal carcinoma. Esophageal tumor samples collected from patients who underwent primary surgical resection showed an elevated expression of SOX4 as compared to controls. SOX4 expression was upregulated, whereas expression of miR-129-2 was low in primary esophageal tumors. This finding revealed that dysregulation of miR-129-2 causes aberrant SOX4 expression, and miRNA restoration suppresses the oncogenic target of SOX4 in esophageal cancer.[95]

One of the genes that miR-133a directly targets is SOX4. miR-133a expression was seen to be lowered in cells and tissues of esophageal squamous cell carcinoma (ESCC). Expression of SOX4 correlated inversely with ESCC tissue samples. Furthermore, ablation of SOX4 led to a reversal in the increased migration and invasion mediated by anti-miR-133 in ESCC.[96]

Around 90% of cancer-related deaths occur due to metastasis of tumors. According to a recent report, to ablate miR-31, SOX4 cooperates with EZH2 and HDAC3 to activate and stabilize a co-repressor complex, hence promoting the growth and invasion of esophageal tumor cells. On binding of this co-repressor complex to the miR-31 promoter, epigenetic repression of miR-31 occurs. Clinical samples also show increased expression of SOX4, EZH2, and HDAC3 in metastatic ESCC tissues in comparison to adjacent normal tissues.[97]

SOX4 in Gallbladder Cancer

Recently, the role of SOX4 and its prognostic significance in PGC was investigated in 136 PGC tissues. SOX4 expression was observed in 75% of PGC tissues but not in normal gallbladder epithelium. In addition, SOX4 overexpression was significantly associated with low pathologic T stage, early clinical stage, and histologic grade. Tissues of PGC with positive nodal metastasis had lower levels of SOX4 immunostaining than tissues without metastasis. Furthermore, Kaplan–Meier curves revealed that SOX4

overexpression was substantially associated with better overall and disease-free survival (DFS). In PGC patients, SOX4 overexpression served as a sole predictor of improved overall DFS and correlated significantly with positive clinicopathologic characteristics.[75]

SOX4 in Gastric Cancer (GC)

In GC tissues, the relation of SOX4 expression with patient survival and other clinicopathological features was examined. SOX4 overexpression correlated significantly with stage, nodal status, vascular invasion, distant metastasis, and poorer DFS rate. Overexpression of SOX4 serves as a prognostic biomarker for GC and can be exploited to determine the outcome of GC patients.[86]

Another study shows that SOX4 promotes GC progression by regulating EMT and acquiring stemness through the activation of transcription factors and the Wnt signaling pathway. TGF-β signaling targets SOX4 and induces EMT and stem cell features of GC cells, revealing that the TGF-β/SOX4 axis regulates the malignant behavior of GC cells.[20]

Subgroup analyses revealed that overexpression of SOX4 was a poor predictor of OS for GC patients and recurrence-free survival for colorectal cancer (CRC) patients. In conclusion, it can be determined that SOX4 may be a beneficial prognostic biomarker for GC in humans.[98]

SOX4 in Head and Neck Cancer

The impact of SOX4 on oncogenic behavior and responsiveness to chemotherapy and radiation therapy in cells of head and neck squamous cell carcinoma (HNSCC) was assessed. SOX4 ablation decreased cellular proliferation and induced apoptosis through activation of caspase-3, caspase-7, and poly-ADP ribose polymerase and inhibiting X-linked inhibitor of apoptosis protein in HNSCC cells. Moreover, it promoted apoptosis induced by radiation/cisplatin and downregulated migration and invasion of HNSCC cells. SOX4 protein expression was also significantly elevated in OSCC tissues as compared to adjacent normal mucosa. It was concluded that SOX4 may contribute to malignant phenotypes of HNSCC cells by enhancing their survival.[90]

SOX4 in Hepatocellular Carcinoma (HCC)

The gene regulation and function of the SOX4 were investigated in metastatic HCC. RNAi-mediated silencing of SOX4 reduced migration and invasion of tumor cells, suggesting that SOX4 regulates tumor metastasis and also *in vivo* tumorigenesis. Silencing of two target genes of SOX4 – *Semaphorin 3C* and *Neuropilin 1*, reduced migration ability in HCC cells indicating SOX4 also exerts some of its effects through regulating downstream target genes.[99]

SOX4 also contributed to carcinogenesis by inhibiting apoptosis mediated by p53, and its overexpression may function as a beneficial prognostic marker for better management of HCC.[80]

SOX4 in Leukemia

It was discovered that primary adult T-cell leukemia (ATL) cells consistently expressed SOX4. Knockdown of SOX4 expression suppressed the growth of ATL leukemia cells.[100] C/EBPα directly targets SOX4, and its expression inversely correlates with C/EBPα activity. Leukemic cells that self-renewal were abrogated by downregulation of SOX4, and their differentiation was restored. This data demonstrates the development of leukemia with a distinct phenotype by SOX4 expression mediated by C/EBPα inactivation.[101] Poor outcome was predicted by high levels of SOX4 expression in acute lymphoblastic leukemia (ALL) cells at the time of diagnosis in a pediatric clinical trial (COG P9906). These studies justify that SOX4 centrally mediates oncogenic signaling in ALL.[102]

SOX4 in Lung Cancer

SOX4 gene mutation was investigated in non-small-cell lung cancer (NSCLC) tissues[103], and it was not associated with the histopathology of tumors but related to pathological stages. The rate of mutation increased gradually with a positive relation in advanced-stage NSCLC. The results revealed that mutations in the *SOX4* gene contribute to lung carcinogenesis.[103]

mRNA expression levels of SOX4 were compared in lung cancer cell lines.[104] In cells with gene amplification, there was an overexpression of the *SOX4* gene by a factor of 10. The fraction of primary lung tumors and lung cancer cell lines expressed SOX4 more strongly. Results showed that overexpression of SOX4 is due to the amplification of genes and provided the basis for the malignant role of SOX4 in lung cancer.[104]

SOX4 gene is directly targeted by miR-132. Biological functions and molecular mechanisms of miR-132 were evaluated in human lung cancer cells. Expression levels of miR-132 were downregulated in lung cancer cell lines A549, YTMLC-9, and H460. Furthermore, miR-132 led to significant downregulation in *in vitro* migration and invasion ability of lung cancer cells. Overexpression of miR-132 also inhibited the *in vivo* growth of the tumor. Reintroducing SOX4 reversed miR-132's anti-invasion function.[105]

SOX4 expression analysis and its relationship with clinicopathological characteristics were evaluated in NSCLC.[106] As compared to normal tissues, mRNA and protein expression of SOX4 was higher in NSCLC tissues and correlated positively with the status of degree of

differentiation, clinical stage, and TNM classification. Moreover, elevated expression of SOX4 was related to poor OS in NSCLC patients, indicating a crucial role of SOX4 in the advancement and prognosis of NSCLC.[106]

SOX4 in Melanoma

SOX4 expression was evaluated in 180 melanocytic lesions using a tissue microarray. Expression of SOX4 was lower in metastatic melanoma, in comparison to primary melanoma and dysplastic nevi and significantly related with a poorer disease-specific survival of melanoma patients. Knockdown of SOX4 increased migration and invasion abilities and also upregulated stress fiber formation of melanoma cells. Results suggested that SOX4 regulates the invasion and migration of melanoma cells and could be used as a prognosis indicator and possible treatment target for human melanoma.[74]

SOX4 in Pancreatic Cancer

According to recent reports, SOX4 regulates several EMT master regulators, such as *Twist*, *Zeb, and Snail,* and is essential for EMT both *in vivo* and *in vitro*. In addition, SOX4 promotes EMT and metastasis by reprogramming the cancer epigenome by inducing the transcription of Ezh2 (histone methyltransferase). In pancreatic cancer, Exh2 and miR-335 regulate the expression of SOX4 epigenetically. The prognosis for DFS was worse for SOX4-positive patients, and the prognosis for OS was similarly significantly lower for Ezh2-positive individuals. It has been discovered that the SOX4/Ezh2 axis influences prognosis in pancreatic cancer patients.[107]

SOX4 in Prostate Cancer

Expression of SOX4 correlated highly with Gleason score at gene and protein levels in prostate tumor samples. Silencing of SOX4 induced apoptosis of prostate cancer cells, indicating that SOX4 could serve as a therapeutic target for prostate cancer.[71]

Expression of SOX4 was higher in castration-resistant prostate cancer (CRPC) tumors as compared to hormone-dependent prostate cancer. The androgen-depleted environment promotes prostate cancer cell proliferation mediated by 17β-estradiol. In addition, *SOX4* gene silencing attenuates the proliferation migration and invasion ability of prostate cancer cells. Thus, it could be concluded that identification and prevention of the onset of CRPC may be aided by SOX4 overexpression.[108]

EPIGENETIC REGULATION OF SOX4

Various epigenetic mechanisms, such as DNA or histone methylation, can lead to altered SOX4 expression. Although SOX4 is overexpressed in a number of malignancies, *SOX4* gene amplification is reported in only a few cancer types.[102,104] Other regulatory mechanisms, such as lncRNA and miRNA-mediated processes, lead to elevated expression of SOX4 in cancer.

miRNA mediation regulation of SOX4 in human cancers

In human malignancies, miRNAs are potent regulators of gene expression. These can function as oncogenes (oncomiRs) or tumor suppressors, depending on the particular malignancy and miRNA involved. While most research has focused on individual targets of miRNAs, they actually influence multiple genes at once, often in connected pathways. This complex web of interactions makes miRNAs important players in cancer biology.[59]

It has been discovered that a large number of miRNAs directly bind to the 3'untranslated region (UTR) of SOX4 to target it. This regulates several critical processes in cancer cells, including tumor growth, proliferation, invasion, migration, and EMT. A recent study has shown that miR-355 suppresses invasion and metastasis, targeting the SOX4 in breast cancer.[109] Another study identified miR-191-5p as an oncogene in various human cancers.[110-112] miR-187 targets SOX4, and its inhibition was linked to metastasis and dismal prognosis in CRC.[113] Overexpression of miR-138 in GC inhibited tumor growth *in vivo* and suppressed *in vitro* cell proliferation, colony formation, migration, and invasion.[114] In HCC, epigenetic inhibition of miR-130a-3p resulted in increased SOX4 expression.[115] MiR-133a directly targets 3'UTR in esophageal cancer and its downregulation aids in the development of ESCC.[96] In prostate cancer, also miR-30a directly targets SOX4 3'UTR, and reduced miR-30a levels are linked to SOX4 overexpression, which also inhibits PC cell growth and the EMT process.[116] In osteosarcoma, miR-25-3p reduced cell proliferation, colony formation, migration, and invasion *in vitro* and slowed tumor growth *in vivo* through targeting SOX4 3'UTR.[117]

lncRNAs-mediated regulation of SOX4 in human cancers

During chromatin remodeling, lncRNAs and RNA-binding proteins work together to regulate a range of dynamic and epigenetic processes. lncRNAs work at the transcriptional, posttranscriptional, and translational levels.[118] They can also influence the activity of mRNA-targeting miRNAs by functioning as competing endogenous RNAs (ceRNAs).[119] In a recent study, lncRNA-UCA1 acted as ceRNA for miR-204, which prevented it from attaching to the SOX4 3'UTR and, elevated SOX4 expression, and accelerated the growth of esophageal cancer cells.[120] Similarly, androgen receptor negatively induced lncRNA (ARNILA) served as a ceRNA for miR 204 in TNBC cells, increasing SOX4

expression, inducing EMT, and facilitating invasion and metastasis.[121] It was shown that in HCC, STAT3 signaling induces the production of HOXD-AS1 lncRNA, which inhibits the repression of SOX4 mediated by miR-130a-3p by sequestering it and leads to increased metastasis.[115] In addition, it has been shown that lncRNA-PAGBC stimulates the Akt/mammalian target of the rapamycin pathway and facilitates the metastasis of gallbladder tumors by downregulating miR-133b and miR 511, which, in turn, results in the upregulation of SOX4 and phosphoinositide 3-kinase regulatory subunit 3, respectively.[122] LncRNA ABHD11-AS1 has been demonstrated to stimulate CRC formation by facilitating SOX4 expression by acting as a ceRNA for miR-133a.[122]

Numerous studies have found miRNAs that target SOX4 and have drawn attention to the effects of changing miRNA expression on the regulation and/or suppression of cancer growth. Indeed, across a variety of human cancers, over 25 miRNAs that target SOX4 have been discovered, which is uncommon in other biological systems. SOX4 might be vulnerable to miRNA regulation because it has an unusually long 3'UTR over 4000 nucleotides long. This extended UTR provides more space for many different miRNAs to attach and potentially control SOX4 activity. LncRNAs either function as ceRNAs to sequester miRNAs that target SOX4, or they can increase SOX4 expression. This intricate network of regulatory networks emphasizes the critical importance of SOX4 and the level of regulation needed to maintain the optimal balance of this master regulator to avoid tumorigenesis. Even though SOX4's function in tumorigenesis and epigenetic regulation has been extensively studied, there are still many unanswered concerns about this protein's epigenetic regulation and possible therapeutic applications.

SOX4 AS A POTENTIAL PROGNOSTIC BIOMARKER FOR HUMAN CANCERS

SOX4 plays a complex role in cancer, with its expression differing depending on the cancer type. In many cancers, such as those of the bladder,[84] prostate,[71] endometrium,[72] and liver,[80] SOX4 expression is elevated. However, contrary to that expression of SOX4 is lower in melanoma[74] and gallbladder cancer.[75] Numerous investigations have examined the relationship between nuclear SOX4 expression and clinicopathologic markers as well as the implications of nuclear SOX4 to predict prognosis of cancer patients.

Nuclear SOX4 expression was elevated in colon cancer and correlated with stage, distant metastasis, and depth of invasion. In addition, it was linked to a worse DFS rate. Compared to patients with low expression levels, those with high nuclear SOX4 expression levels had a 5-year DFS rate of 44.8%. Nevertheless, in multivariate analysis, when other known prognostic factors such as nodal status, stage, and degree of differentiation were included, the correlation between overexpression of nuclear SOX4 and survival was not statistically significant ($P = 0.425$), whereas distant metastasis (Hazard Ratio [HR] = 0.052, 95% confidence interval [CI] = 0.024–0.111, $P \leq 0.001$] was prognostically independent.[87]

In GC, the following parameters showed significant correlations with nuclear SOX4 overexpression: Depth of invasion, nodal status, distant metastasis, stage, and vascular invasion. SOX4 overexpression was linked to a considerably lower disease-free survival. Patients with higher nuclear SOX4 expression levels had a 5-year DFS rate of 45.6%, while those with lower SOX4 expression levels had a higher DFS rate of 66.5%. Nevertheless, no statistically significant correlation between nuclear SOX4 overexpression and survival was found in multivariate analysis. Prognostic factors in multivariate analysis included nodal status (HR = 3.901, 95% CI = 1.589–9.580, $P = 0.003$), distant metastasis (HR = 15.453, 95% CI = 6.419–37.114, $P = 0.001$), depth of invasion (HR = 2.091, 95% CI = 1.073–4.077, $P = 0.030$), and vascular invasion (HR = 1.849, 95% CI = 1.058–3.229, $P = 0.031$).[86]

Patients with strong or moderate nuclear SOX4 immunopositivity (overexpression) were found to have a better prognosis than those with weak or negative nuclear SOX4 expression in cases of HCC, whereas clinicopathological parameters and SOX4 expression did not correlate.[80]

In laryngeal squamous cell carcinoma (LSCC), pathological differentiation, lymphatic invasion, and pathological TNM were all associated with SOX4 expression. Multivariate analysis revealed that lymphatic invasion and positive SOX4 expression were independent predictors of the OS time of LSCC patients following surgery.[123]

PROGNOSTIC MODELS BASED ON SOX4-ASSOCIATED GENES

It is commonly known that a combination of genetic, environmental, dietary, and physical factors can shape a tumor. The development of reliable models that can predict the prognosis is critically important. As it is widely known, aberrant DNA damage, EMT, M6A methylation, hypoxia, energy metabolism, and ferroptosis are important processes frequently involved in tumor development and progression.[124-129] Thus, based on the SOX4-associated genes, six multi-gene prognostic models have been developed to predict the prognosis of liver HCC. These models include genes linked to DNA damage repair, EMT, M6A methylation, hypoxia, energy metabolism, and ferroptosis. The estimated 1-, 3-, and 5-year survival probability was calculated with the help of nomograms. The area under the receiver operating characteristic curves (AUCs) for the 1, 3, and 5-year survival

rates also showed that all models displayed good predictive discrimination.[130]

To establish the prognostic model based on the SOX4-associated genes related to energy metabolism, ferroptosis, hypoxia, EMT, DNA damage repair, and hypoxia, a thorough literature search was carried out. Cluster heatmaps were then used to visualize the correlations between these genes and SOX4 expression in a variety of tumor types. To identify the genes with non-zero coefficients, the least absolute shrinkage, and selection operator regression approach was applied. Independent risk factors for OS, two-sided $P < 0.05$, were identified using a multivariate logistic regression, and the risk was then predicted using a nomogram model based on associated genes. The AUC of the receiver operating characteristic curve was used to measure the nomogram's prediction accuracy. The Kaplan–Meier survival analysis was utilized to determine the OS of LHIC patients.[131] Risk factors of SOX-4 associated genes based on multivariate analysis are shown in Tables 2-7.

The STRING database (version 11, Swiss Institute of Bioinformatics, Lausanne, Switzerland) provided a number of proteins that frequently linked with SOX4, which were obtained to explore *SOX4* gene-related pathways that may be involved in different kinds of malignancies [Figure 2]. TP53, POU3F3, TCF7, TCF7L1, TCF7L2, CTNNB1, and PTEN were among the predicted interacting proteins with high confidence. The investigation of KEGG pathways demonstrated that specific functional protein partners belonged to pathways associated with the WNT signaling network, the cell cycle signaling route, the p53 signaling pathway, the Hippo signaling pathway, and multiple other pathways linked to cancer.[131]

Table 2: Multivariate logistic regression analysis of risk factors for SOX4 associated DNA damage-related genes.

Variable	Model		
DNA damage-related genes	**β-coefficient**	**Odds Ratio (95% CI)**	***P*-value**
RFC3	−0.574	0.563 (0.415, 0.763)	<0.001
RAD54B	0.876	2.401 (1.006, 5.728)	0.048
MUTYH	0.407	1.503 (1.010, 2.236)	0.044
MGMT	−0.418	0.658 (0.509, 0.851)	0.001
HAP1	0.582	1.789 (1.232, 2.598)	0.002
UVSSA	−0.456	0.634 (0.411, 0.978)	0.039

CI: Confidence interval

Table 3: Multivariate logistic regression analysis of risk factors for SOX4 associated EMT.

Variable	Model		
EMT-related genes	**β-coefficient**	**Odds Ratio (95% CI)**	***P*-value**
ACTA2	−0.235	0.791 (0.671, 0.933)	0.005
PHLDA2	0.186	1.204 (1.070, 1.355)	0.002
SGCB	0.262	1.299 (1.118, 1.509)	<0.001
NKX3-2	0.403	1.497 (1.059, 2.116)	0.022

EMT: Epithelial-to-mesenchymal transition, CI: Confidence interval

Table 4: Multivariate logistic regression analysis of risk factors for SOX4-associated M6A methylation.

Variable	Model		
M6A methylation-related genes	**β-coefficient**	**Odds Ratio (95% CI)**	***P*-value**
ZC3H13	−0.456	0.634 (0.476, 0.843)	0.002
YTHDF2	0.669	1.951 (1.207, 3.154)	0.006

CI: Confidence interval.

Table 5: Multivariate logistic regression analysis of risk factors for SOX4-associated hypoxia.

Variable	Model		
Hypoxia-related genes	**β-coefficient**	**Odds Ratio (95% CI)**	***P*-value**
CUL2	0.405	1.500 (1.019, 2.208)	0.04
EPO	0.148	1.160 (1.059, 1.270)	0.001
UBB	−0.443	0.642 (0.450, 0.916)	0.014

CI: Confidence interval

Table 6: Multivariate logistic regression analysis of risk factors for SOX4-associated energy metabolism.

Variable	Model		
Energy-metabolism-related genes	**β-coefficient**	**Odds Ratio (95% CI)**	***P*-value**
GGT3P	2.596	13.410 (2.186, 82.250)	0.005
LDHA	0.305	1.356 (1.015, 1.813)	0.04
NQO2	0.236	1.266 (1.031, 1.556)	0.025

CI: Confidence interval

Table 7: Multivariate logistic regression analysis of risk factors for SOX4-associated ferroptosis.

Variable	Model		
Ferroptosis-related genes	**β-coefficient**	**Odds Ratio (95% CI)**	***P*-value**
SAT1	−0.283	1.115 (0.576, 0.986)	0.039
SLC7A11	0.192	1.212 (1.029, 1.426)	0.021
CISD1	0.354	1.425 (1.020, 1.992)	0.078

CI: Confidence interval

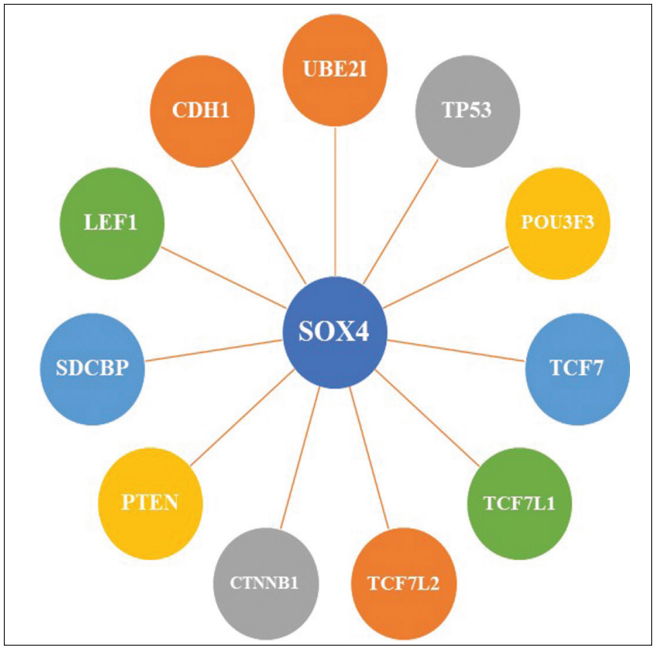

Figure 2: Functional protein partners of SOX4.

FUTURE PROSPECTIVE

Recently, many studies have put forth evidence that SOX4 plays a significant role in cancer development and progression and relates to poor clinical outcomes in cancer patients. Since SOX4 has been shown to promote the growth and spread of many human cancers by mediating cell survival, stemness, angiogenesis, movement, and metastasis, it holds promise as a target for new cancer therapies. SOX4 is a protein with potential applications in cancer treatment. However, it is challenging to design drugs that target SOX4 effectively for two reasons. First, SOX4 is relatively unstructured outside its HMG DNA binding domain (DBD), making it difficult to create crystals for studying its properties. Second, SOX4 DBD is very similar to other proteins in the SOX family. This similarity makes it difficult to develop drugs that target only SOX4 and no other SOX proteins. Specificity and selectivity remain key issues; therefore, further research is needed to address these concerns.

Numerous studies have identified miRNAs that target SOX4 and have brought attention to the effects of changing miRNA expression on the regulation and suppression of cancer growth. There is a wealth of preclinical data that show miRNA-based therapeutics that are being used *in vivo* in a variety of disease models. In regard to cancer, therapeutics miRNA mimics have entered into clinical trials and shown plausible results. Research shows promise for turning epigenetic therapies into cancer treatments, but more work is needed to develop therapies that are precise and have minimal side effects. Specifically, creating small molecule inhibitors targeting SOX4 and ensuring a smooth transition from preclinical data to clinical trials are important next steps.

By controlling the expression of multiple other genes and the downstream signaling pathways these genes activate, SOX4 mediates development and carcinogenesis and may be a useful target for cancer treatment. Even though it has been demonstrated that numerous SOX proteins are critical for cell survival, tumor cell growth and proliferation, and a multitude of other tumor features, there are still a number of concerns to be addressed, such as the difficulty of therapeutically blocking transcription factors.

Subsequent investigations will yield a further understanding of the interactome and gene regulatory networks of the SOX4 protein in relation to cancer. Without a doubt, these findings will contribute to the creation of new treatment approaches for this extremely diverse disease with fewer available treatments. Few promising findings point to the potential of SOX4 in cancer management but warrant further research, which may be valuable for the management of the overall burden of cancer.

CONCLUSION

By transcriptional activation and altering downstream genes epigenetically, SOX4 facilitates various facets of cancer development and progression, giving malignant cells an edge in proliferation and survival. The idea that SOX4 is an oncogene that governs angiogenesis, migration, EMT, metastasis, stemness, and cancer cell survival is well supported by the literature. Thus, targeting SOX4-mediated pathways may provide therapeutic opportunities for various highly aggressive human cancers.

Therefore, an improved comprehension of the roles of SOX4 in various cancers and its underlying mechanisms may offer newer insights into tumor development and progression and facilitate in discovery of potent anti-cancer therapies.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

Patient consent was not required as there are no patients in this study.

Financial support and sponsorship

Financial Support provided by National Institute of Immunology, New Delhi and Mahatma Gandhi University of Medical Sciences and Technology, Jaipur.

Conflicts of interest

Dr. Nirmal Kumar Lohiya is on the editorial board of the journal.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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How to cite this article: Arora S, Godha M, Lohiya NK, Jagadish N. SOX4 expression in cancer: Insights from developmental regulation and deregulation in tumorigenesis. J Reprod Healthc Med. 2024;5:5. doi: 10.25259/JRHM_8_2024