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SOX4: The Unappreciated Oncogene

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Abstract

SOX4 is an essential developmental transcription factor that regulates stemness, differentiation, progenitor development, and multiple developmental pathways including PI3K, Wnt, and TGFβ signaling. The *SOX4* gene is frequently amplified and overexpressed in over 20 types of malignancies, and multiple lines of evidence support that notion that SOX4 is an oncogene. Its overexpression is due to both gene amplification and to activation of PI3K, Wnt, and TGFβ pathways that SOX4 regulates. SOX4 interacts with multiple other transcription factors, rendering many of its impacts on gene expression context and tissue-specific. Nevertheless, there are common themes that run through many of the effects of SOX4 hyperactivity, such as the promotion of cell survival, stemness, the epithelial to mesenchymal transition, migration, and metastasis. Specific targeting of SOX4 remains a challenge for future cancer research and drug development.

Keywords

SOX4; Cancer; Metastasis; EMT; Wnt; TGFβ; PI3K

SOX4 in normal development

The SRY-related High Mobility Group (HMG) box or SOX family of transcription factors plays numerous roles in normal development. The founding member of the family, SRY, is located on the Y-chromosome, and is essential for sex fate determination and male sexual development [1-3]. There are 20 members of the SOX family, which are found in all vertebrates, and the family is subdivided into nine subgroups ranging from SOXA to SOXH [4]. SOX family transcription factors play critical developmental roles in most organs and tissues in the endoderm, ectoderm, mesoderm, and germline, including the central nervous system, the retina, bone, cartilage, heart, pancreas, hematopoietic system, vasculature, and lymphatic system (reviewed in [4, 5]). A number of developmental genetic syndromes, or 'SOXopathies,' have been described [6] that include effects on the muscular system, central

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and peripheral nervous systems, cardiovascular system, auditory and ocular systems, reproductive system, hair and skin, kidney, and bone. Many of these syndromes are highly sensitive to genetic dosage and result from haploinsufficiency of SOX proteins [6]. SOX proteins are also key regulators of cell fate and stemness [7-9]. SOX2, in particular, has been shown to be essential for generation of induced pluripotent stem cells [8, 9], and alterations in expression levels of SOX2 can impact proper differentiation of multiple tissues including Schwann cells [10] in the CNS and the foregut endoderm [11, 12]. The two SOX factors most extensively studied in relation to cancer are SOX9 [13-15] and SOX4 [16-20], although many other SOX proteins, including SOX2 [21], SOX7 [22, 23], and SOX17 [24] have also been associated with various cancers (reviewed in [25]).

SOX4 is an essential developmental transcription factor that regulates stemness, differentiation, progenitor development, and multiple developmental pathways [24, 26]. The SOX4 protein is encoded by a single-exon gene and contains a highly conserved high-mobility group (HMG) DNA binding domain related to the TCF/LEF family of transcription factors that play important roles in the Wnt pathway. *SOX4* is an essential gene, as embryonic total knockout of murine *Sox4* is lethal due to cardiac developmental defects [27]. SOX4 null embryos also show impaired B lymphocyte development with a block at the pro-B cell stage [27]. SOX4 is expressed in stem cells [28], and modulates stem cell activation [29] and likely also plays a role in stem cell maintenance, possibly through activation of expression of SOX2 [30, 31]. Overexpression of Sox4 in the murine myeloid cell line 32Dcl3 markedly inhibited cytokine-induced granulocyte maturation, suggesting a differentiation block [32]. Moreover, prolonged Sox4 expression in cells of the oligodendrocyte lineage in the central nervous system (CNS) inhibits development of a fully mature phenotype, suggesting that Sox4 may normally prevent premature terminal differentiation [33]. In the adult mouse hippocampus, expression of Sox4, and its close relative Sox11, is initiated around the time of neuronal commitment of adult neural stem cells (NSCs) and is maintained in immature neurons, and expression of Sox4 promotes and is necessary for *in vitro* neurogenesis from adult NSCs [34]. Sox4 functions as a pro-survival factor during spinal cord development [35], and ensures the survival of tyrosine hydroxylase-expressing cells in the developing sympathetic nervous system [36]. Thus, the normal function of SOX4 appears to be to promote early differentiation and expansion and survival of transit amplifying progenitor cells, while inhibiting terminal differentiation, which are functions highly compatible with the development of malignancies.

Amplification and overexpression of SOX4 in cancer

Although SOX4 is rarely mutated, the *SOX4* gene, located on chromosome 6p22.3 is amplified in 1-3% of lung cancers [37], 10% of ovarian cancers, 16-24% of bladder cancers (BLCA), and roughly 10% of triple-negative breast cancers (TNBC) [38-40] (Figure 1A), strongly supporting its role as an oncogene. Much like the *MYC* oncogene, SOX4 expression is increased in cancers with SOX4 amplification (Figure 1B-D). While amplification does not always result in increased expression, in general, mRNA expression in amplified cases is higher than in diploid cases [41]. In lung cancer, SOX4 is overexpressed due to gene amplification and SOX4 exhibits functional oncogenic properties by significantly increasing the transforming ability of the weakly oncogenic RHOA-Q63L

mutation [37]. The SOX4 6p22.3 amplification is the most significant focal amplification in BLCA [42-44]. Moreover, cBioPortal analysis of public datasets indicates that SOX4 is amplified or overexpressed in 41% of metastatic PCa [45, 46], although SOX4 amplification is less common in studies of primary localized prostate cancer (e.g. TCGA). *SOX4* mRNA is overexpressed in many types of human cancers, including leukemias [47], melanomas [48], glioblastomas [49], medulloblastomas [50], and cancers of the prostate [51], bladder [52], lung [53], and breast [54, 55]. When comparing cancer to normal tissues in the Oncomine database [56], SOX4 is overexpressed in 107 (23%) of 462 unique studies in over 20 types of cancer (Table 1), whereas MYC and SOX9 are each upregulated in only 41 (9%) of these studies. In prostate cancer, upregulation of SOX4 mRNA and protein is correlated with Gleason score or tumor grade [51]. This observation was confirmed in a meta-analysis of 1,321 human prostate cancer gene expression profiles [57] and is shown in Figure 2. SOX4 also plays an important role in myeloid leukemias by cooperating with Mef2c [58] and with CREB [59] in myeloid leukemogenesis. C/EBPα inactivation results in Sox4 overexpression, which contributes to the development of leukemia with a distinct acute myeloid leukemia (AML) leukemia-initiating cells (LICs) phenotype [60]. A meta-analysis examining the transcriptional profiles of over 3700 human cancers found *SOX4* to be one of 64 genes uniquely upregulated as a general “Cancer Signature” [61], suggesting that it has a fundamental role in multiple tumor types. SOX4 expression is induced by many pathways that are commonly activated in cancers, including PI3K signaling [18], Wnt signaling [62], TGFβ signaling [63, 64], and deletion of the BMP1 receptor [65], which activates Wnt signaling and the PI3K-AKT pathway.

SOX4 in cancer progression and PI3K signaling

Our laboratory was the first to demonstrate that *SOX4* can act as an oncogene in human prostate cancer, showing that SOX4 expression was essential for anchorage independent growth of immortalized RWPE-1 prostate epithelial cells [51]. Moreover, conditional deletion of Sox4 in adult stem cells of stratified epithelia results in increased skin stem cell quiescence and resistance to chemical carcinogenesis [29], suggesting a role of SOX4 in development and initiation of cancers. Our lab has also shown that tissue-specific homozygous deletion of *Sox4* in the adult murine prostate epithelium strongly inhibits tumor progression initiated by homozygous loss of the *Pten* tumor suppressor gene [18]. Mechanistically, Sox4 ablation reduced activation of both AKT and β-catenin, leading to an attenuated invasive phenotype, and arresting cancer progression at the high-grade prostatic intraepithelial neoplasia (HGPIN) precancerous stage [18]. Furthermore, in the mouse prostate, SOX4 expression was induced by *Pten* loss as a result of the activation of PI3K-AKT-mTOR signaling, suggesting a positive feedback loop between SOX4 and PI3K-AKT-mTOR activity [18]. In acute lymphoblastic leukemia (ALL), mouse genetic studies have also demonstrated that Sox4 is a critical activator of PI3K/AKT and MAPK signaling in ALL cells [66]. Also, *in silico* analyses of breast cancer patients followed by *in vitro* confirmation using RNAi in breast cancer cells have also shown that SOX4 amplification promotes PI3K/AKT signaling [67]. Recently, several studies have identified *PTEN* as not only a critical tumor suppressor gene, but also as a metastasis-suppressor gene [68, 69], which is consistent with many of the functional roles of SOX4 in cancer.

SOX4 protein-protein interactions and target genes

SOX4 has been shown to have many protein interaction partners and a wide variety of target genes. Transcription factors that have been shown to interact with SOX4 include p53 [70], β-catenin [24], plakoglobin [62], TCF4 [24], KLF5 [71], SMAD3 [72], ERG [73], EVI1 [32], and NSD3 [74]. In hepatocellular carcinoma, SOX4 modulates the transcriptional activity of p53 and leads to the inhibition of p53-mediated apoptosis [75], including significant repression of p53-induced Bax expression and subsequent repression of p53-mediated apoptosis induced by gamma-irradiation [76]. On the other hand, in pancreatic cancer, Klf5 cooperates with Sox4 in oncogenesis and prevents Sox4-induced apoptosis [71], suggesting context-dependent functions of Sox4 that are tissue-specific. As another example of context specific function, in colon cancer cells, Sox4 may function to stabilize β-catenin protein [24], whereas when prostate and breast cancer cells are stimulated with WNT3A, the interaction between SOX4 and plakoglobin is significantly increased and the activity of β-catenin reporter constructs is reduced [62]. Recently, it has been shown by ChIP-seq that SOX4 and SMAD3 co-occupy a large number of genomic loci [72], and that SOX4 expression was required for TGFβ-mediated induction of a subset of SMAD3/SOX4-co-bound genes that regulate migration and extracellular matrix-associated processes in claudin^{low} MDA-MB-231 breast cancer cells [72]. Protein-protein interactions screens have also identified NSD3 (WHSC1L1), DACH1, CDKN2A, and AURKA as protein-protein interaction partners with SOX4, although the functional significance of these interactions have yet to be demonstrated [74].

Regarding downstream targets of SOX4, a number of studies have identified genes regulated by SOX4 [20, 71, 72, 77, 78], but there is relatively little overlap between them, which is consistent with the variety of protein partners and context-specific nature of SOX4 transcriptional activation activity. Tenascin C (TNC) is an extracellular matrix protein associated with TGFβ signaling and migration that has been identified as a SOX4 target in five separate studies [16, 71, 72, 77, 79]. Another direct transcriptional target of SOX4 in breast cancer cells is the transmembrane protein TMEM2 [80], which mediates pro-migratory and pro-invasive phenotypes. Sox4 also directly regulates the expression of Ezh2 [17], the catalytic subunit of the polycomb repressive complex that mediates tri-methylation of H3K27 residues in repressive chromatin. We identified 282 high-confidence direct SOX4 target genes in prostate cancer cells, including DICER, EGFR, FOXA1, NKX3-1, and many regulators of pivotal cancer signaling networks of differentiation, cell survival, and apoptosis including the Wnt (e.g. FZD4, FZD5, FZD8) and PI3K pathways (e.g. PIK3R1, PIK3R4) [77]. These results are supported by another recent study in mouse models of leukemia showing that SOX4 regulates expression of Pik3r2, Pik3r3, and Mtor [66]. In SOX4-amplified lung cancer cells, SOX4 regulates genes involved in neuronal development such as PCDHB, MYB, RBP1, and TEAD2 [78], whereas in endothelial cells, SOX4 directly regulates endothelin-1 (ET-1) expression, potentially promoting tumor-induced angiogenesis [20].

SOX4 in Wnt signaling

As noted above, SOX4 is important for Wnt signaling [24, 26, 81], and interacts directly with β-catenin [24, 62, 77, 82], although there are clearly SOX4-independent aspects of the Wnt pathway that are mediated by TCF/LEF factors. While the precise role of SOX4 in the Wnt pathway is still unclear, SOX4 can interact directly with β-catenin in a cooperative way to activate gene expression [24, 77]. Induction of β-catenin/TCF activity by Sox4 is caused by stabilization of the β-catenin protein, not by induction of β-catenin transcription [82]. We recently demonstrated that combined inhibition of Wnt signaling and SOX4 inhibits proliferation and migration and induces apoptosis of triple negative BT-549 breast cancer cell lines [83]. This same Wnt inhibitor (iCRT3) was also shown to interfere with androgen receptor (AR) activity and to inhibit growth of prostate cancer xenografts [84]. Several lines of evidence suggest that Wnt signaling is important for the progression and metastasis of castration-resistant prostate cancer (CRPC) based on numerous studies [85-97]. Clinical studies indicate that at least a subset of patients with CRPC exhibit activation of Wnt signaling [86, 88-90, 92, 94, 97]. Our data [18] show that genetic deletion of *Sox4* reduces levels of active β-catenin *in vivo* in prostate cancers, but the mechanisms of how Sox4 loss inhibits β-catenin activation remains to be determined. One potential mechanism is that SOX4 stimulates β-catenin activity indirectly via maintenance of active AKT. It is well established that there is crosstalk between the PI3K-AKT and Wnt-β-catenin pathways via AKT phosphorylation and inhibition of GSK3β [98-100]. Moreover, PI3K-AKT and β-catenin can cooperate to stimulate AR signaling in CRPC [101-103], and β-catenin can interact directly with AR [104, 105]. Thus, SOX4 may play an important role at the intersection of PI3K and Wnt signaling in metastatic prostate cancer.

SOX4, TGFβ, and the Epithelial to Mesenchymal Transition (EMT)

Several studies have indicated that SOX4 also plays a critical role in regulation of the Epithelial to Mesenchymal Transition, or EMT, which is a frequent (although not absolutely necessary [106]) step for metastasis of solid tumors. In breast cancers, Sox4 is essential for EMT and cell survival *in vitro* and for primary tumor growth and metastasis *in vivo* [17]. Moreover, Sox4 regulation of Ezh2 is critical to Sox4 control of EMT in this model [17]. Other groups have also shown that SOX4 overexpression induces EMT in breast cancer cells [107], which in turn induces stem cell markers and enhances formation of mammospheres [108]. SOX4 positively regulates expression of known EMT inducers, and plays an important function in mediating activation of the TGFβ pathway to contribute to EMT [72, 107]. Several studies have also shown that SOX4 itself is induced by TGFβ [63, 64, 107]. SOX4's role in EMT has also been demonstrated in prostate cancer cells, where ERG and SOX4 have cooperative roles in TGFβ1-induced EMT [73] and SOX4 inhibition reversed EMT [109]. A model of the role of SOX4 in EMT and cancer is depicted in Figure 3. Consistent with this model, nuclear expression of SOX4 has been shown to be associated with depth of invasion, metastasis, stage, and poor disease free survival in colon cancer patients [110]. In fact, a meta-analysis of 1348 cancer patients found that SOX4 overexpression is a poor prognostic factor for human cancers including colon and gastric cancers [111].

SOX4 and Metastasis

SOX4 knockdown has been shown to reduce migration of cancer cells in many studies [16, 72, 73, 83, 107, 112]. In addition to regulation of EMT and migration, SOX4 is critical for metastasis, since shRNA knockdown of SOX4 inhibits lung metastases of breast cancer xenografts [16]. The microRNA miR-335 also suppresses lung metastasis and migration of breast cancers through repression of SOX4 and TNC [16]. In hepatocellular carcinoma (HCC) tumor metastasis, RNAi knockdown of SOX4 reduces tumor cell migration, invasion, *in vivo* tumorigenesis and metastasis [112]. It is interesting that SOX4 is most frequently amplified in bladder cancer, which is defined by its ability to invade one of the most impenetrable barriers in the body, the basement membrane and stromal muscle of the bladder. Thus, it is clear that SOX4 is critical for several aspects of aggressive cancer progression including EMT, migration, and metastasis, making SOX4 a potential drug target for advanced disease.

Targeting SOX4 in cancer

While the literature strongly supports the notion that SOX4 is an oncogene that promotes stemness, cancer cell survival, angiogenesis, migration, EMT, and metastasis, targeting of SOX4 remains a challenge. Because SOX4 is relatively unstructured outside of its HMG DNA binding domain (DBD) [113], it is difficult to generate crystal structures that could lead to rational drug targeting. Moreover, the SOX4 DBD is highly homologous to other SOX family transcription factors, thus making target specificity an issue for any small compound that targets the SOX4 DBD. However, the FDA has recently approved the first siRNA treatment for the treatment of peripheral nerve diseases [114], and thus it is conceivable that with proper, targeted delivery to cancer cells, siRNA targeting of SOX4 could be effective. However, the fact that SOX4 regulates DICER and AGO1 [77], at least in prostate cancer cells, could make the siRNA approach challenging. Furthermore, even successful targeting of SOX4 could have undesirable side effects such as immunosuppression due to inhibition of proliferation of B lymphocytes.

Another approach to targeting SOX4 could be to identify compounds that disrupt SOX4 protein-protein interactions (PPIs). Such compounds might have more specificity than drugs that target SOX4-DNA interactions and could even target only a subset of the many functions that SOX4 plays within the cell, or that are important only in specific cell types of interest. Since SOX4 plays a critical role in such a wide variety of malignancies, high-throughput screening of compounds that disrupt SOX4 PPIs could ultimately lead to therapies that target many aggressive forms of cancer.

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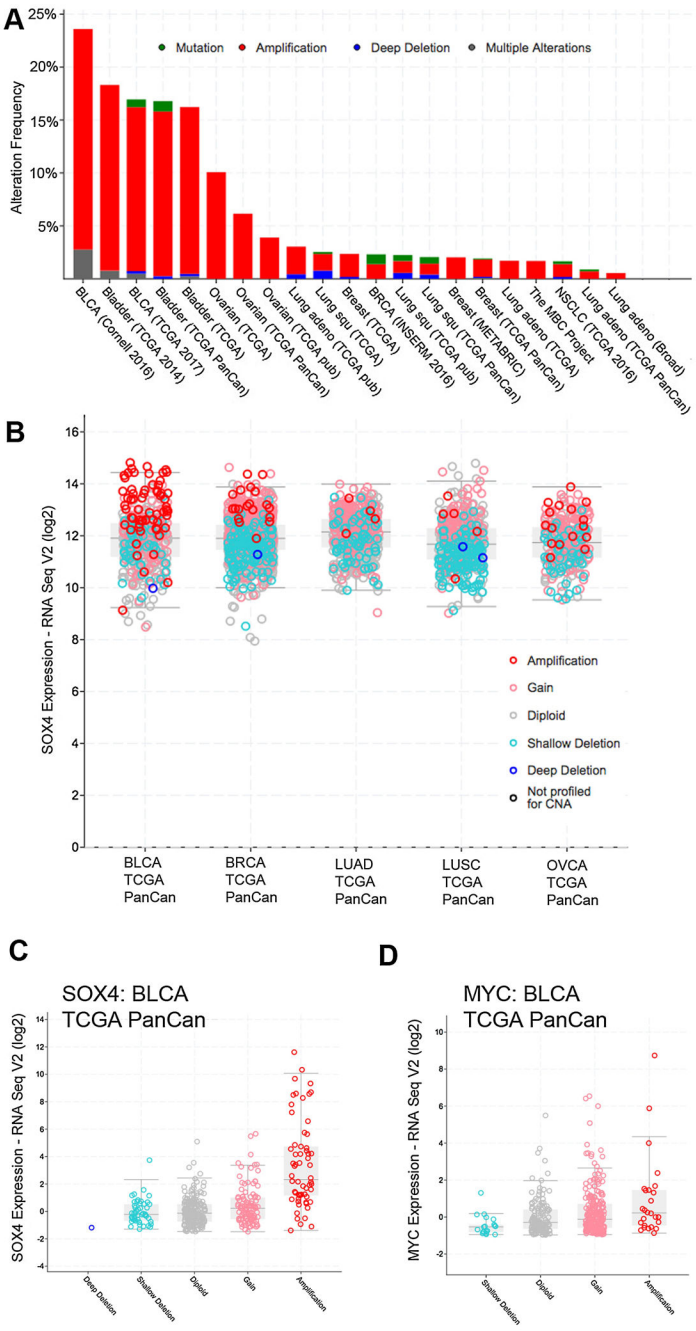

Figure 1:

(A) cBioPortal analysis of SOX4 amplification in Bladder, Ovarian, Lung, and Breast Cancers. Amplifications are shown in red, mutations in green, deletions in blue, and multiple alterations in grey. (B) cBioPortal analysis of SOX4 mRNA expression in TCGA PanCan data shows strong correlation of SOX4 mRNA with gene amplification. (C) cBioPortal analysis of SOX4 mRNA in BLCA supports association of SOX4 amplification with gene expression. (D) Similar cBioPortal analysis of MYC amplification and mRNA in BLCA.

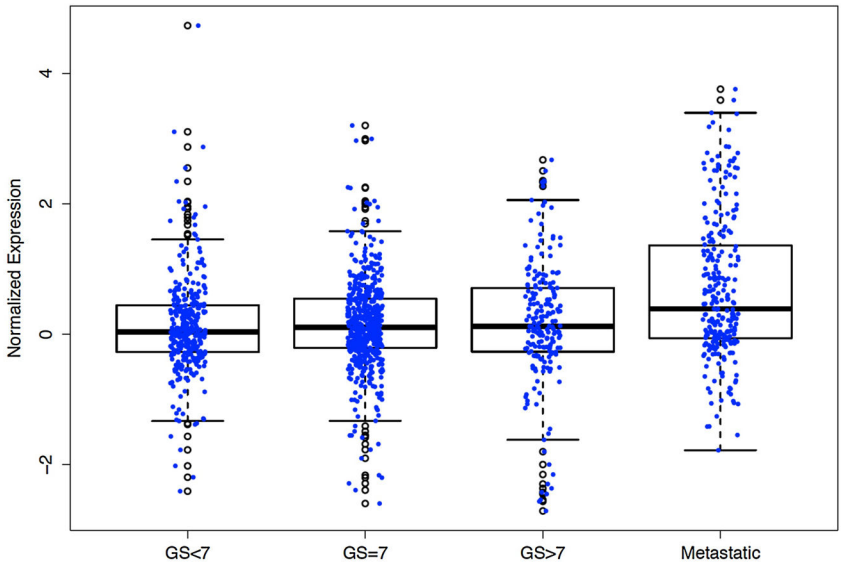

Figure 2:

Normalized SOX4 expression across 1,321 prostate cancer samples. Indolent prostate cancers have gleason scores (GS) < 7, while aggressive prostate cancers have GS ≥ 7. SOX4 expression is sharply increased in prostate cancer metastases.

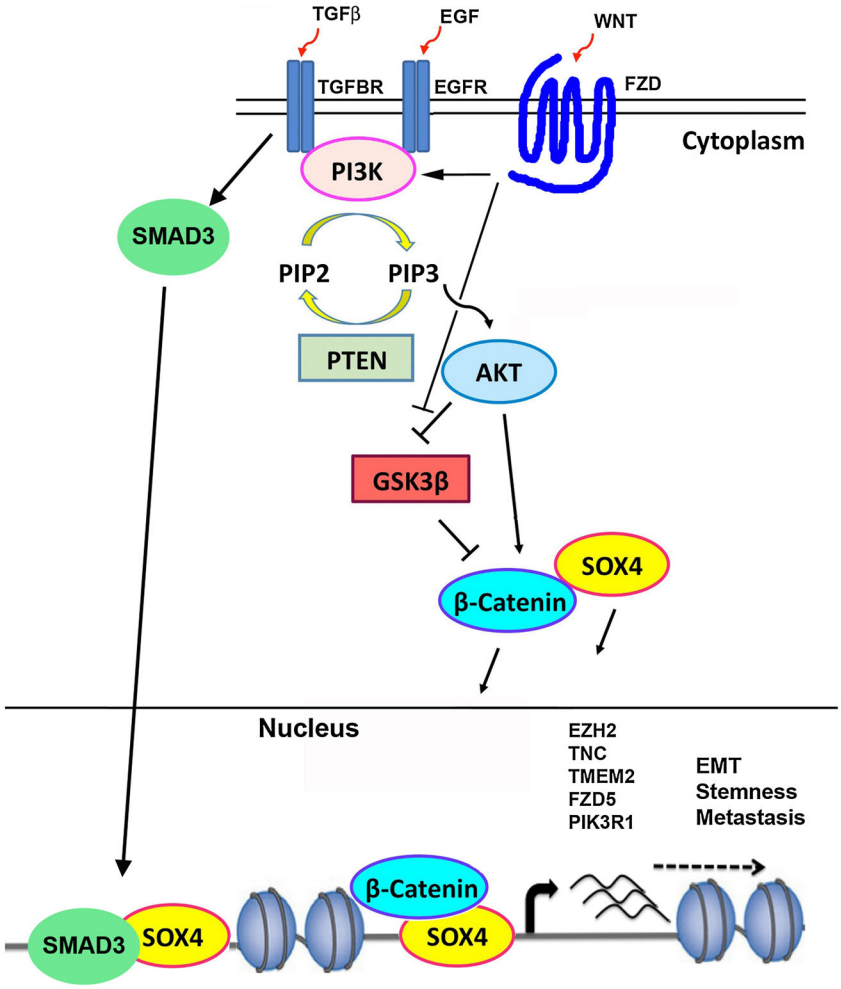

Figure 3:

Model of SOX4 role in cancer. TGFβ 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 EMT.

Table 1:

Cancer vs. Normal studies in the Oncomine database showing significant SOX4 changes in mRNA expression. SOX4 is upregulated in 107 of 462 unique studies across over 20 types of malignancies. In contrast, MYC was found upregulated in only 41 studies, as was SOX9. The SOX factor SOX3, which has little association with cancer, was upregulated in only two studies, and downregulated in three (not shown).

Cancer Type	# Studies with SOX4 Upregulated	# Studies with SOX4 Downregulated	# Studies with MYC Upregulated	# Studies with MYC Downregulated	# Studies with SOX9 Upregulated	# Studies with SOX9 Downregulated
Bladder	4	-	-	-	1	-
Brain	10	-	7	1	5	-
Breast	1	-	1	10	-	
Cervical	4	-	-	-	-	-
Colorectal	13	-	20	-	17	-
Esophageal	6	-	-	-	2	-
Gastric	2	-	-	-	1	-
Head & Neck	8	-	2	-	-	-
Kidney	2	1	2	-	2	-
Leukemia	15	5	-	3	-	-
Liver	6	-	-	1	6	-
Lung	9	-	-	-	1	-
Lymphoma	1	2	2	2	-	1
Melanoma	1	-	-	-	-	1
Myeloma	-	1	1	-	-	-
Other	9	-	1	1	-	5
Ovarian	-	-	-	-	4	-
Pancreatic	3	-	-	-	-	-
Prostate	6	-	5	-	-	-
Sarcoma	8	-	-	4	2	1
Significant Unique Analyses	107	9	41	22	41	8
Total Unique	462		470		437	