

REVIEW ARTICLE

# SOX9 Up-Regulation Can Change Survival and Anticancer Resistance in Different Cancer Type

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Received: Aug 05, 2023,

Revised: Aug 25, 2023,

Accepted: Aug 30, 2023,

DOI: 10.57238/jbb.2023.7047.1043



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article online

## 1 Introduction

SOX transcription factors were discovered for the first time in mammals in 1990. The family is based on the conserved high migratory group (HMG) box genes of the mammalian testis determinant Sry. SOX proteins are proteins with an HGM domain that share 50% or more amino acid sequences with the HMG [1] This family is divided into eight subgroups, A–H, each with 1–3 members [2] The SOX gene family encodes transcription factors that are conserved across mammals and have important developmental roles [3] This family comprises the Y box 9 (SOX9) sex-determining region [4] SOX9, SOX8, and SOX10

## Abstract

**Background** Y-box member SOX9 determines sex. This family's eight subgroups (A–H) have one to three members each. Sox gene transcription factors are critical for development and conserved across species. Several studies have shown that a tiny percentage of malignant cells, called cancer stem-like cells (CSCs) or tumor-initiating cells, have stem cell traits such self-renewal and differentiation. Self-renewal is thought to cause tumor growth and progression. Mechanistic studies show that SOX9 controls cancer-specific gene networks that are involved in self-renewal, differentiation, and extracellular matrix/cytoskeleton remodeling.

**Objective** This review examines SOX9 as a predictive biomarker and its function in cancer beginnings, progression, and therapeutic resistance across many cancer types. This review discusses genetic/epigenetic SOX9 deregulation in several cancers.

**Results** Multiple cancer types revealed high SOX9 expression and prognosis in the CBIOportal database. SOX9-targeting small molecules may diminish chemotherapy resistance. Finally, SOX9 over-expression, malignant prognosis, and resistance need additional study.

**Keywords:** SOX9; Cancer; Upregulation; Resistance; Prognosis.

are classified as E subgroups based on the amino acid sequences of their HMG domains, transactivation and dimerization domains, and transactivation and dimerization domains [5] SOX9 protein contains an HMG box DNA binding domain that binds to (A/T) CAA (T/A) G DNA sequences and controls target gene expression [6], It also has a transcription activation domain at the C-terminus and is involved in inducing tissue and cell morphogenesis, survival (Shi et al., 2013), and the regulation of many developmental processes [7] including embryonic development, lineage commitment, and stem cell maintenance [8] SOX9 expression is upregulated in a variety of malignancies, including lung, prostate, skin, brain, colorectal, pancre-

atic, and breast cancers [3–5,9] These findings suggest that SOX9 works as an oncogene in a variety of malignancies. Several other investigations have found that SOX9 is important in cancer genesis because an increase in its level promotes stem cell transition. In addition, increased SOX9 levels have been associated with a higher grade of tumor, a poor prognosis, and a lower chance of survival in a variety of cancers [1]. In addition, SOX9 control the downstream gene expression for Sry in direct way [2]. However, key SOX9 regulatory genes in both normal and tumor cells have yet to be found, and they may vary depending on cell type and developmental stage [3]. In other hands, SOX9 show opposite function and suppress the proliferation which make SOX9 actions complex and vary depending on the environment [9]. Consequently, SOX9 undergoes alterations in its expression and function in a wide variety of human malignancies, primarily through its role in regulating the activity of cancer stem cells (CSCs) and, under some circumstances, as a tumor suppressor [1].

## 2 SOX9 expression in cancers

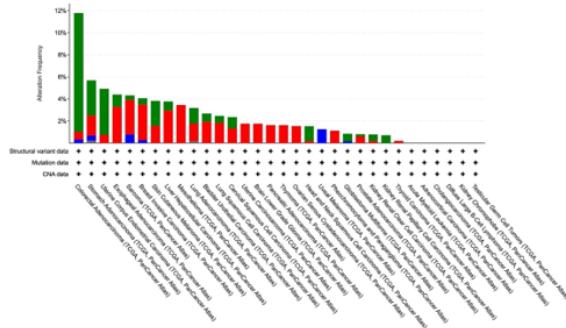
Cancer is a multifaceted disease that continues to be a major cause for concern and human mortality. Most of the cell biology pathways regulated by transcription factors (TFs), for instance, DNA damage repair, energy produce, cells proliferation and differentiation, apoptosis and Cell survival. Many malignancies have been linked to transcription factor dysregulation at some point in their development. Oncogenes and tumor suppressor genes are both encoded by transcription factor genes. These genes are crucial in the development of tumors due to gain or loss of function mutations [4–6]. For instance, they account for roughly 20% of all oncogenes in tumors, as of this writing. Pluripotent, fetal, adult, and progenitor cells all express SOX9, making it a master TF. During embryonic development, SOX9 is expressed initially in pluripotent stem cells and then in the ectoderm, mesoderm, and endoderm that give rise to the many tissues and organs. Significantly, SOX9 upregulate in fully differentiation cells, particularly in the hair follicle and the gut [7]. It's also crucial in fixing damage to endodermal and ectodermal tissues after birth [7]. The opposite is true: abnormal SOX9 expression is linked to cancer development and progression [8].

During embryonic development, the SOX9 gene is essential because of the domains that can bind to DNA and make dimerization domain, and transactivation domain [10,11]. Tissue differentiation and final lineage fate can affect with SOX9 expression which showed sensitive spatial expression and temporal patterns [12]. Many levels of transcription regulation can regulate gene expression in addition to in addition

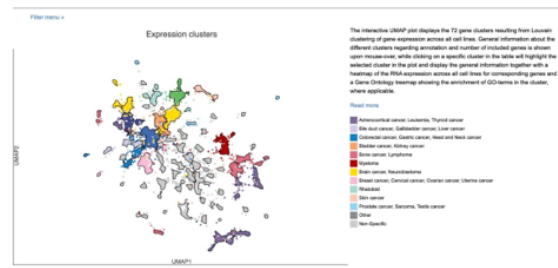
post-translational modifications and miRNA, SOX9 is controlled at the transcriptional and translational levels [7]. It has become clear that SOX9 dysregulation is a key contributor to many types of cancer. Malignant growth has also been linked to its expression, and depending on the kind of cancer, SOX9 can either operate as a proto-oncogene [13–17] or a tumor suppressor gene [18–20]. However, the methods by which SOX9 promotes carcinogenesis at different stages of disease and why, in some cases, it behaves as a tumor suppressor are intriguing issues for further research. Since SOX9 is a proto-oncogene, having more of it in the body raises the risk of developing cancer. Low survival rates, tumor invasion, and metastasis are all associated with high SOX9 expression [13,21–25]. Intestinal tumors, on the other hand, have SOX9 functioning as a tumor suppressor via regulating Wnt/catenin signaling. This is in contrast to other malignancies [26]. A number of cancers, including those of the bladder and cervix, have been linked to an increase in the amount of methylation in the CpG islands of the SOX9 promoter [19,27]. likewise, the promoter region of SOX9 is fully methylated in cervical cancer, whereas in healthy cervical tissue, it is entirely unmethylated. DNA methylating inhibitors, such as 5-azacytidine (5-AZA) and Zebularine, have anti-malignant growth effects on a variety of tumors [19,28]. These drugs can be used to upregulate hypermethylated SOX9 in both types of cancer. As a result, DNA methylation stands out as a promising pathway for deregulating the SOX9 gene in cancer. DNA alterations in the SOX9 gene have been proposed as a potential predictive biomarker in cancer treatment [19,29].

SOX9 has been linked to multiple types of cancer, and it plays a number of roles. Multiple recent investigations [30,31] have demonstrated SOX9's function in relation to the tumor microenvironment (TME). In addition, the transcription factor SOX9, which regulates stem cells, plays a role in the regulation of CSCs in a variety of malignancies [32–34], and hence functions as an oncogene. Evidence is mounting that many malignancies acquire CSC characteristics through abnormal stimulation of the SOX9 signaling pathway [35,36]. In addition to promoting EMT during invasion and migration, SOX9 also provides a stem cell phenotype, predicts a poor prognosis, and is involved in poor clinical outcomes [23,32,35,37]. Despite SOX9's heterogeneity, most research efforts are directed toward figuring out how to defeat drug resistance in it [6,38,39]. SOX9 expression was analyzed in 10,363 patients and 10,377 samples across 32 different cancer types. Most of the changes were upregulation, as indicated in Figure 1, and this could be a sign for cancer progression and resistance to anticancer treatments. The highest levels of SOX9 expression were seen in ovarian serous adenocarcinoma, thymic adenocarcinoma, pancreatic

adenocarcinoma, and low-grade gliomas of the brain. In addition, the interactive UMAP plot displays the 72 gene clusters resulting from Louvain clustering of gene expression across all cell lines as it displays in Figure 2.



**Figure 1:** The expression of SOX9 in the various types of cancer. The majority of cancers have been shown to have an increase in SOX9 expression. Cbioportal.org.



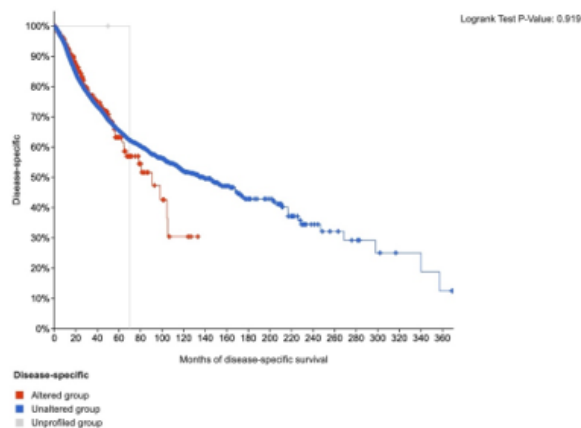
**Figure 2:** The interactive UMAP plot displays the 72 gene clusters resulting from Louvain clustering of gene expression across all cell lines. Human protein atlas website.

The survival curve for this table, which displays the total number of patients that are disease-free and progression-free, may be seen in Table 1.

**Table 1:** Display the percentage of patients that display the disease free and progression free.

| Survival Type    | Number of Patients | # in Altered group | # in Unaltered group | # in Unprofiled group | Median months survival in Altered group (95% CI) | Median months survival in Unaltered group (95% CI) | Median months survival in Unprofiled group (95% CI) | p-Value | q-Value |
|------------------|--------------------|--------------------|----------------------|-----------------------|--|--|---|---------|---------|
| Disease Free     | 5383               | 166                | 5217                 | 0                     | 101.46 (101.46 - NA)                             | NA   | NA  | 0.777   | 0.986   |
| Disease-specific | 10256              | 312                | 9942                 | 2                     | 90.84 (66.57 - NA)                               | 138.80 (120.56 - 162.08)                           | 70.13   | 0.919   | 0.986   |
| Overall          | 10801              | 317                | 10482                | 2                     | 66.57 (55.86 - 81.17)                            | 80.12 (75.16 - 84.59)                              | 70.13   | 0.945   | 0.986   |
| Progression Free | 10611              | 317                | 10292                | 2                     | 49.84 (33.70 - NA)                               | 62.23 (57.37 - 66.08)                              | 33.80 (33.80 - NA)                                  | 0.986   | 0.986   |

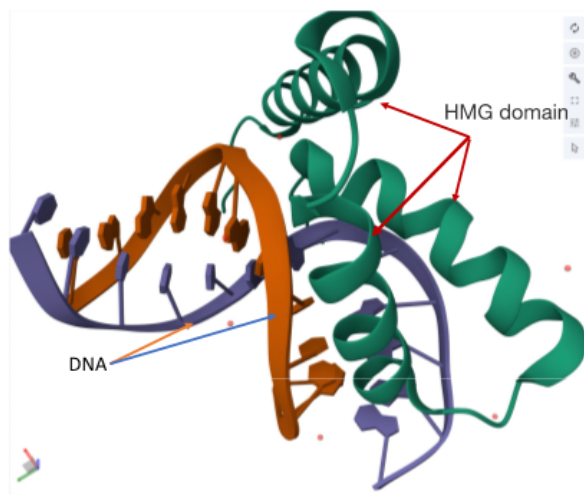
As can be seen in Figure 3, the survival rate of the group that had their behavior altered was much lower in comparison to the group that served as control. The curve went down for 10801 patients, with 312 of them falling into the altered group and 10482 falling into the unaltered group. There were also 2 patients who fell under the unprofiled group.



**Figure 3:** The survival data on patients from different cohorts for 10801 patients, 312 in altered group and 10482 in unaltered group also 2 patients under unprofiled group. Cbioportal.org.

### 3 SOX9 inhibitor

Cancer stem-like cells, also known as tumor-initiating cells, are a minuscule fraction of malignant cells that are suspected to possess stem cell characteristics such as the ability to self-renew and differentiate. Cancer stem-like cells are also known as tumor-initiating cells. It is widely held that the property of self-renewal is the fundamental driving force behind tumor growth and progression. (Wion & Berger, 2006) Some research has pointed to the possibility of cancer stem-like cells, which are also referred to as CSCs. According to the findings of mechanistic analyses, the oncogenicity of SOX9 has been linked to the regulation of a significant number of gene networks that are unique to cancer. These gene networks include those that are involved in self-renewal, differentiation, and extracellular matrix/cytoskeleton remodeling (Larsimont et al., 2015). It has been postulated that the distinct SOX9 regulatory capacities are depending on the unique connections that SOX9 has with the entire genome. According to [35] these interactions could take place either by the indirect binding of SOX9 proximal to the transcriptional start site via the basal transcriptional complex or through the direct binding of SOX9 to numerous enhancer elements via low-affinity SOX9 dimeric motifs. Both of these binding mechanisms involve the basal transcriptional complex. It is not yet understood how variations in the amounts of the SOX9 protein impact the preferred binding distribution of the gene in the genome or the transcriptional activity of the gene. Locating a tiny molecule that can target SOX9 will result in a decrease in malignancy and a rise in resistance. Therefore, it is of the utmost importance to thoroughly investigate the crystal structure of SOX9, as shown in Figure 4.



**Figure 4:** HMG domain of SOX-9 bound to DNA from Homo sapiens .

### 4 Conclusion

Inter- and intra-tumoral heterogeneity contributes to late identification, aggressive progression, and treatment resistance in several malignancies. SOX9 [SRY (Sex determining region Y)-box 9] is a developmental regulator in the SOX family of transcription factors with a conserved HMG DNA-binding domain. SOX9 regulates cell fate, sex, neural crest formation, chondrogenesis, and pancreatic development. SOX9 controls progenitor proliferation and differentiation during embryogenesis to maintain tissue identity, especially in the brain and gut. SOX9 regulates adult stem cells to maintain tissue homeostasis, but it has also been related to multiple differentiated cells in various organs. Using the Cbioportal database, multiple cancer types showed high SOX9 expression and a connection to prognosis. Thus, SOX9-targeting small compounds may reduce chemotherapy resistance. Finally, SOX9 overexpression and tumor prognosis and resistance need further study.

### Acknowledgments

The authors acknowledge College of Basic Education, Misan University.

**Conflict of Interest:** No conflicts of interest exist between the authors and the publication of this work.

**Ethical consideration:** The ethical committee approved the study at College of Basic Education, Misan University, Misan, Iraq.

**Funding:** These authors declare that above-submitted work was not funded by any

governmental or private funding source nor supported by any financial projects.

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#### How to cite this article

Al-Saadi N.; Al-hraishawi H.; SOX9 Up-Regulation Can Change Survival and Anticancer Resistance in Different Cancer Type. *Journal of Biomedicine and Biochemistry*. 2023;2(3):38-44. doi: 10.57238/jbb.2023.7047.1043