The potential role of SOX2 in the anti-apoptosis property of cancer cells

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SOX2, a member of the SOX family, plays important roles in the maintenance of pluripotency and self-renewal of embryonic stem cells, as well as adult tissue progenitor cells. Recent studies have revealed ectopic expression of SOX2 in a number of cancer types and disclosed vital contributions of SOX2 to the stemness property of cancer stem cells and tumor progression. Despite with some controversy, most researchers have reached a consensus that SOX2 works as an anti-apoptosis factor in cancer cells. This review will discuss recent advances in elucidating the regulatory effect of SOX2 on survival and anti-apoptosis property of cancer cells. These studies support the concept that SOX2 regulates intricate apoptosis-related proteins and signal pathways. Delineation of these pathways may help to develop novel therapy strategies targeting cancer stem cells.

Keywords: SOX2; apoptosis; cancer; cancer stem cells


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Introduction

The transcription factor SOX2 belongs to the SOX (Sex-related HMG Box) family \textsuperscript{11}. It has been found to play a significant role in maintaining the unique characters such as clonogenicity, pluripotency and self-renewal of embryonic stem cells (ESCs) as well as tissue progenitor cells, and is also indispensable in the process of organogenesis \textsuperscript{1-4}. Moreover, SOX2 is one of the pivotal transcription factors capable of reprogramming differentiated somatic cells to induced pluripotent stem cells (iPSCs) \textsuperscript{7-10}.

Recent studies pointed out the potential contribution of SOX2 to cancer progression. Although there is still some controversy \textsuperscript{11}, elevated SOX2 expression has been detected in a number of cancer types, such as breast cancer, lung cancer, ovarian cancer and prostate cancer \textsuperscript{12-15}. According to our previous studies, SOX2 expression is correlated with the histological grade and TNM stage in human breast cancer \textsuperscript{15}, and Gleason scores in human prostate cancer \textsuperscript{14}. In
addition, predominantly higher expression of SOX2 was found in both of small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) than in normal or paracarcinoma tissues [12]. Cancer stem cells (CSCs), which have been proposed as tumor-initiating cells in recent years, possess a series of the same characteristics as ESCs [16, 17]. CSCs exhibit much higher resistance to apoptosis than their differentiated counterparts, and this radio- and/or chemoresistance nature of CSCs makes them to be the source of cancer recurrence [18-21]. It is found that SOX2 is highly expressed in isolated CSCs [12, 22-24], and contribute to tumorigenesis and/or recurrence of certain cancers [22-27]. Several groups including us have revealed that SOX2 contributes significantly to the anti-apoptosis property of cancer cells by using different tumor models [14, 22, 24, 28]. Nevertheless, the mechanism by which SOX2 regulates apoptosis signals still need to be extensively explored and discussed. In this brief review, we will summarize the recent studies focusing on the potential role of SOX2 in the anti-apoptosis property of human cancer, and also further discuss our recent published results on the regulation of apoptosis by SOX2 through MAP4K4-Survivin signaling pathway.

Role of SOX2 in apoptosis of cancer cells

In our recent study, we found that suppression of SOX2 expression in distinct human lung cancer cell models similarly results in apoptosis [28]. This observation suggests SOX2 to be a critical gene for the survival of human cancer cells, which is consistent with our previous finding that SOX2 enhances the anti-apoptotic and chemotherapeutic resistance property of prostate cancer cells [14]. Similar results have been discovered by several other research groups using different tumor models independently. In ovarian cancer, SOX2 overexpression conferred enhanced resistance to apoptosis in response to conventional chemotherapies and TRAIL [29]. However, in their study, modulation of SOX2 expression did not alter cultured ovarian cancer cell proliferation, which is different to our results in prostate cancer [14]. In human gastric cancer, there are controversial reports on the role of SOX2. Yuasa’s group reported that SOX2 expression is down-regulated in some human gastric carcinomas compared to normal gastric mucosae [11]. And they further demonstrated that SOX2 suppresses cell proliferation and induces apoptosis in gastric cell lines [11]. Hütz et al. also verified that most gastric cancer cell lines show no or marginal expression of SOX2 mRNA [30]. Distinct to Yuasa’s group, however, Hütz et al. chose AZ-521 cell line for their further investigation, which expresses the highest SOX2 transcriptional activity in all the gastric cancer cell lines they screened [30]. Using this SOX2 high-expression cell line, they came to the very opposite conclusion that blocking SOX2 transcriptional activity leads to the inhibition of cell proliferation, partly due to the induction of apoptosis [30]. The different observations may be as the results of the facts that the expression of SOX2 is only detected in a subset of gastric cancers, and different cell lines were used in different studies.

The mechanism by which SOX2 regulates cancer cell survival and prevents apoptosis

Despite with some controversy, most researchers have reached a consensus that SOX2 mainly works as an anti-apoptosis factor in human cancer. However, the results indicate that SOX2 may regulate different downstream genes in different cancer models.

In our study, we found silencing of SOX2 in human NSCLC induced apoptosis via activation of both ‘extrinsic’ and ‘intrinsic’ apoptotic signaling pathways, which was reflected by the activation of p53, overexpression of TNF-α, Bax, Bad, release of cytochrome C from mitochondria to the cytosol, reduced expression of Survivin and cleavage of Procaspsase 3 and Procaspsase 8 [28]. Similar to our results, it was also reported that SOX2 regulates apoptosis signals by direct regulation of Bcl-2 family members [31]. Chou et al. discovered that silencing of SOX2 in lung adenocarcinoma cells causes marked apoptosis as well as autophagy with down-regulation of BCL2L1 [31]. They further demonstrated the direct binding of SOX2 to the promoter of BCL2L1 [31]. Besides these finding, our previous study showed that overexpression of SOX2 in human prostate cancer cells reduces the store-operated calcium entry activity, which may contribute to the anti-apoptotic effect of SOX2 [14]. SOX2 was also reported to increase the tamoxifen resistance of breast cancer cells through activation of WNT signal pathway [27]. Those studies revealed the possible mechanisms and signal pathways that contribute to anti-apoptotic property of SOX2.

SOX2 gene has been shown to be amplified at chromosome 3q26.3 in esophageal squamous cell carcinoma (ESCC) and lung squamous cell cancer (LSCC) [32-34]. It has been reported that SOX2 is correlated with a series of signaling pathways which are significant in cancer cell survival and proliferation. Gen et al determined that SOX2 can activate AKT/mTORC1 after investigating several signaling pathways through phosphoprotein assay, and the ability of SOX2 to promote the proliferation of ESCC cells depends on AKT/mTORC1 activation [34]. Justilian et al. focused on the cooperation effect of PRKCI and SOX2 on Hedgehog (Hh) signaling pathway activation.
in LSCC, which are coamplified on chromosome 3q26 [35]. SOX2 can be phosphorylated by protein kinase C \( \alpha \) (PKC\( \alpha \)), and the PKC\( \alpha \)-mediated SOX2 phosphorylation is required for the expression of Hedgehog acyltransferase (HHAT) to catalyze the production of Hh ligand, which is the rate-limiting procedure [35]. In primary LSCC tumors, PRKCI and SOX2 are frequently coamplified and coordinately overexpressed, and the PKC\( \alpha \)-SOX2-Hh signaling axis plays a significant role in the maintenance and survival of CSCs-like populations in primary human LSCC [35]. In primary melanoma cells, SOX2 is reported to be regulated by Hh signaling via direct binding of transcription factors GLI1 and GLI2 to the proximal promoter region of SOX2 [24]. It remains unclear whether there is a positive feedback loop between SOX2 and Hh signaling. Watanabe et al. further compared the gene profiles regulated by SOX2 in squamous cell carcinoma (SCC) cell lines with those in ESCs by applying ChIP-seq analysis. They found that SOX2 preferentially interacts with p63 in SCCs, but in ES cells, it tends to be more inclined to interact with OCT4 [36]. Moreover, SOX2 and p63 jointly regulated a series of genes, including ETV4, which mediate the proliferation and anchorage-independent growth of SCC cells [36].

**SOX2 regulates apoptosis through MAP4K4-Survivin signaling pathway**

Our recent work revealed MAP4K4 as one of the key proteins in the apoptotic cascade following SOX2 silencing [28]. We found that the mRNA expression level of MAP4K4 and its downstream genes such as MAP2K4, ERK1 and JNK1 were all increased in human NSCLC cell lines (including A549, H1299 and H460) after down-regulation of SOX2, supporting the activation of MAP4K4 signals. Blocking the expression of MAP4K4 can effectively inhibit the apoptosis of NSCLC induced by SOX2 silencing, with reduced expression of p53, P-p53, cytosolic cytochrome C and TNF-\( \alpha \). We also found that activated MAP4K4 induced down-regulation of Survivin, and ectopic expression of Survivin in A549 cells rescued the apoptotic effect induced by SOX2 silencing. Consistent with our finding, Lin’s study disclosed that SOX2 regulates the expression of Survivin in human prostate cancer cells [37]. Given that the traditional opinion viewed MAP4K4 to be implicated in cancer cell growth in hepatocellular carcinoma and pancreatic cancer [38, 39], we tend to believe that the apoptosis triggered by MAP4K4 activation in NSCLC may be context-dependent [28].

Although obvious cell death were observed in human NSCLC, down-regulation of SOX2 did not showed significant apoptosis effect but only cell growth inhibition in many other cancer cell types, including certain types of prostate and breast cancer cell lines, such as DU145, MCF7, 4T1, EO771 et al. from our published or unpublished studies [14, 15], possibly due to different SOX2 silencing efficiency and different gene background in these cells.

**Concluding remarks**

In summary, mounting evidences have identified SOX2 as an important anti-apoptotic gene that plays an important role in tumor recurrence in many cancer types both in vitro and in vivo. However, the signal pathway mediating the apoptotic effect of SOX2 silencing may vary depending on cancer cell types, and a further disclosure of the molecular mechanism by which SOX2 regulates apoptosis may lead to effective strategy to induce the apoptosis in cancer stem cells and prevent recurrence of cancers.

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**Conflict of interests**

The authors declare that they have no conflicting interests.

**References**


