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REVIEW

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# *Sex-determining region Y box-containing* genes: regulators and biomarkers in gynecological cancers

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**ABSTRACT** *Sex-determining region Y box-containing* genes are transcription factors with roles in multiple biological processes, including cell differentiation, proliferation, and apoptosis. *Sex-determining region Y box-containing* genes have also been shown to act as regulators and biomarkers in the progression of many different cancers, including gynecological cancers such as ovarian, cervical, and endometrial cancer. In this review, we summarize the contrasting regulatory roles of *Sex-determining region Y box-containing* genes in different gynecological cancers, as promotors with high expression levels or as suppressors with low expression levels. Expression levels of *Sex-determining region Y box-containing* genes were also identified as biomarkers of clinical features, including International Federation of Gynecology and Obstetrics stage, histopathologic grade together with disease-free survival, and treatment efficacy in patients with gynecological cancers. An understanding of the mechanisms whereby *Sex-determining region Y box-containing* genes regulate the progression of gynecological cancers will aid in the development of novel diagnostic and therapeutic strategies, while analysis of *Sex-determining region Y box-containing* expression levels will help to predict the prognosis of patients with gynecological cancers.

**KEYWORDS** *Sex-determining region Y box-containing* gene; gynecological cancer; regulator; biomarker; clinical feature; progression

## Introduction

*Sex-determining region Y box-containing* (*SOX*) genes encode regulatory transcription factors that can act as tumor suppressors or promoters in carcinogenesis. *SOX* genes were shown to be involved in the development of various cancers, including breast[1], lung[2], hepatocellular[3], and gastrointestinal cancers[4]. Due to the increased morbidity and mortality of gynecological cancers (GCs) year by year, the roles of *SOX* genes in GCs, including ovarian (OC), cervical (CC), and endometrial cancer (EC) become a recent focus of researches[5]. Studies investigating the relationship between aberrant expression of *SOX* genes and the development of GCs found that some *SOX* genes with high expression level were expected to act as oncogenic regulators which promoting the progression of GCs, while those with low expression level were regarded as suppressors with the opposite effects[6-11]. Furthermore, regulating expression level of *SOX* genes in certain cancer cell lines could influence cell proliferation and apoptosis *in vitro* but without known mechanisms[12,13]. Additionally, analysis of abnormal *SOX* genes expression in patient samples contributed to the detection of early GC lesions[14-16]. Expression level of *SOX* genes was also considered as biomarkers associated with clinical features in patients with GCs, including International Federation of Gynecology and Obstetrics (FIGO) stage, histopathologic grade, and disease-free survival (DFS), as well as treatment response[10,15,17-19]. Understanding the mechanisms whereby *SOX* genes regulate the progression of GCs is therefore valuable and may facilitate the development of novel diagnostic, therapeutic, and prognostic strategies which aimed at improving the prognosis of women with GCs. This review provides a systematic summary of the *SOX* genes' roles in the progression of GCs, and highlights future directions for research.

## Classification and functions of *SOX* genes

### Classification of *SOX* genes

*SOX* genes encode a conserved group of regulatory transcription factors comprising about 414-amino-acid

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polypeptides with a highly conserved high-mobility group (HMG) box[20,21]. This box encodes around 79-amino-acid DNA-binding domain, with two L-shaped arms that can bind to ATTGTT or related DNA sequence motifs in the minor groove by recognizing the sequence 5′-(A/T)(A/T)CAA(A/T)-3′, resulting in widening of the minor groove, unwinding of the DNA helix, and DNA bending[22]. This domain was first identified in SRY, as a crucial factor involved in determining male sex of mammals. Genes that encode proteins containing an HMG domain with at least 50% amino acid similarity to the SRY HMG domain are considered as *SOX* genes[23]. To date, mammalian genomes have been found to include approximately 30 different *SOX* genes, which can be classified into 10 subgroups (A–J) based on the degree of homology of the amino acid sequence inside the HMG domain, the presence of conserved motifs outside the HMG domain, and their full-length structures (**Figure 1**)[24-26]. In this review, we summarize the roles of some GC-related *SOX* genes, including *SOX1*, *SOX2*, *SOX3*, *SOX4*, *SOX7*, *SOX8*, *SOX9*, *SOX11*, *SOX14*, *SOX15*, *SOX17*, and *SOX18*.

## Functions of *SOX* genes

The activities of the various subgroups of *SOX* genes are multi-faceted. Fundamentally, *SOX* genes are involved in sex determination and the development of the testis, prostate, endothelial cells, and the vascular, lymphatic, and nervous systems during vertebrate embryonic development[24,27]. However, the multiple functions of *SOX* genes in the development of these various systems alerted researchers to their potential roles in the development of diseases, especially cancers[12]. Most recent studies of *SOX* genes focused on their involvement in gastric cancer, lung cancer, hepatocellular carcinoma, and prostate cancer[2-4,28,29]. Studies indicated that most *SOX* genes played their roles in these cancers through the Wnt/β-catenin signaling pathway, as the so-called 'canonical' Wnt pathway mediated by β-catenin[12,13]. Activation of the Wnt/β-catenin signaling pathway decreases phosphorylation of β-catenin in the cytoplasm and increases β-catenin transfer into the nucleus. Consequently, it activates the nuclear complex of β-catenin/T cell factor/lymphoid enhancer factors, and enhances expression level of cell cycle-related molecules such as cyclin-D1 and c-Myc[12,30]. Thus, a discussion of how *SOX* genes act in the progression of GCs *via* different signaling pathways, especially the Wnt/β-catenin signaling pathway is presented below.

# *SOX* genes in GCs

Numerous studies currently focus on the roles of *SOX* genes in GCs. In this review, OC, CC, and EC are selected to be representative GCs due to their high incidence and mortality. In general, *SOX* genes have been identified as regulators influencing the progression of GCs, as well as biomarkers of clinical features. Clinical, cellular, and animal experiments have shown that some *SOX* genes act as oncogenes while others act as tumor suppressor genes in these three cancers (**Figure 2**). General depiction of the expression level of *SOX*

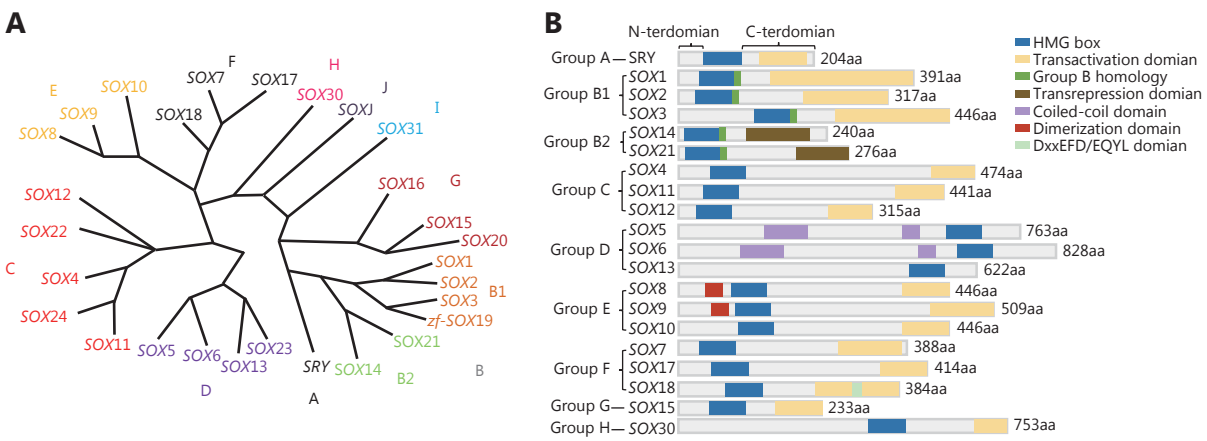


**Figure 1** Classifications and structures of *SOX* families. (A) *SOX* genes contain approximately 30 different *SOX* genes which are classified into ten subgroups (A–J). These various groups are highlighted by different colors. Origins and connection between branches are based on the structures and function of *SOX* protein encoded by *SOX* genes. (B) Schematic representation of the structures of some known *SOX* protein. The HMG box, transactivation/repression domain and other functional domains are indicated along with the length of *SOX* proteins. Groups and representative protein members are indicated to the left. N-terminal and C-terminal domains of *SRY* are depicted at the top. The sizes in amino acids (aa) of the various *SOX* proteins are shown to the right.

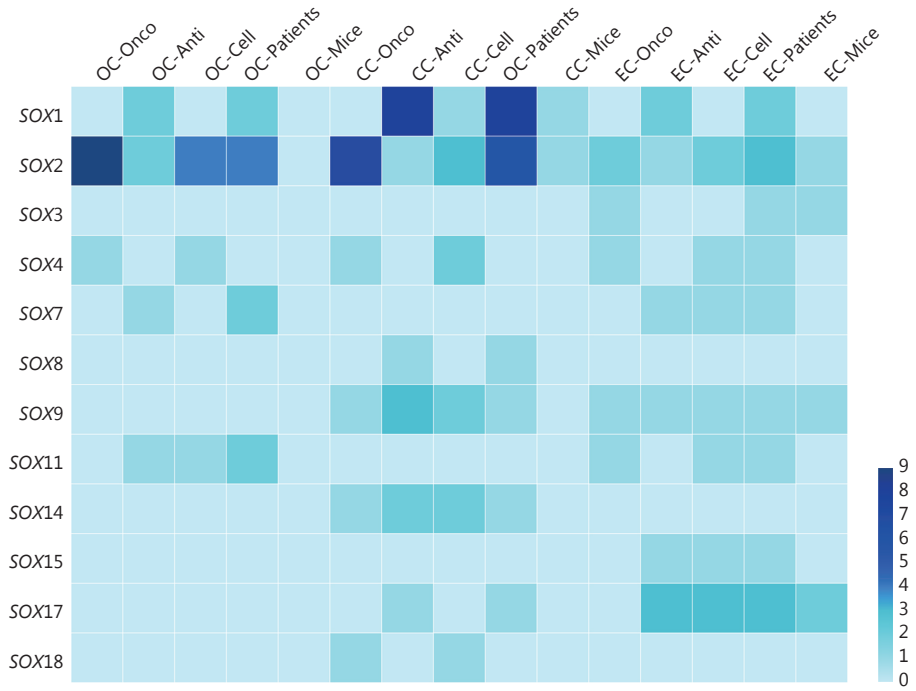


**Figure 2** General summary of the researches on *SOX* genes in GCs. Darker blue coloration means more researches in the corresponding area as indicated in the legend on the right side of the heatmap. The number represents the corresponding number of researches. Onco: *SOX* that plays as an oncogene. Anti: *SOX* that plays as a tumor suppressor gene. Cell: researches based on cell lines. Patients: researches based on patients' samples. Mice: researches based on nude mice.

genes in GCs and mechanisms of how they perform effectively are shown in **Figure 3**.

## *SOX* genes in OC

OC is one of the three most common cancers in women, with an estimated 22,240 new diagnoses and 14,070 deaths in the United States in 2018[5]. Due to lack of specific symptoms and reliable screening methods, approximately 70% of patients with OC are diagnosed at advanced stage with metastasis beyond the ovary, which contributes to its high mortality[31,32]. Thus, there is an urgent need to find novel diagnostic biomarkers for detecting OC at a premalignant stage[33]. *SOX* genes are identified as such biomarkers that can contribute to early screening and the prediction of clinical features in patients with OC, and regulation of *SOX* gene expression could influence cell proliferation and treatment efficacy at the cellular level[9,10,16,18,31,34].

### *SOX genes as clinical biomarkers for OC*

Regarding their roles as clinical biomarkers, multiple studies analyzed the relationships between *SOX* gene expression level in OC samples and clinical features, including FIGO stage, histopathologic grade, and DFS (**Table 1**). Researchers identified *SOX1*, *SOX7*, and *SOX11* as tumor suppressor genes, with low expression level in patient samples due to aberrant CpG island hyper-methylation or unclear mechanisms[17,18]. Low expression level of these genes in cancerous tissues or serum was detected more frequently in patients with more advanced stage, higher grade, more aggressive tumor behavior, and shorter recurrence-free survival (RFS), while higher level was associated with the opposite clinical features[10,17,18,35,40]. These results suggested that analyzing *SOX* gene expression might be a good biomarker for predicting the prognosis of patients.

However, in addition to tumor suppressor role of *SOX* genes, *SOX2* was shown to play dual roles in OC, with high expression level identified as a poor prognostic biomarker in some cases, but as a favorable factor in other cases. On one hand, high *SOX* expression level in fallopian tube epithelium was exploited as a biomarker for OC screening, especially in *BRCA1* or *BRCA2* mutation carriers or in women with serous OC in high grade[16]. High expression level of *SOX2* in patient samples was also shown to be related to high grade, advanced FIGO stage, and decreased DFS[36,37]. On the other hand, Pham et al.[38] demonstrated that high expression level of *SOX2* was a favorable biomarker indicating longer DFS and overall survival (OS) in patients with stage II–IV high-grade

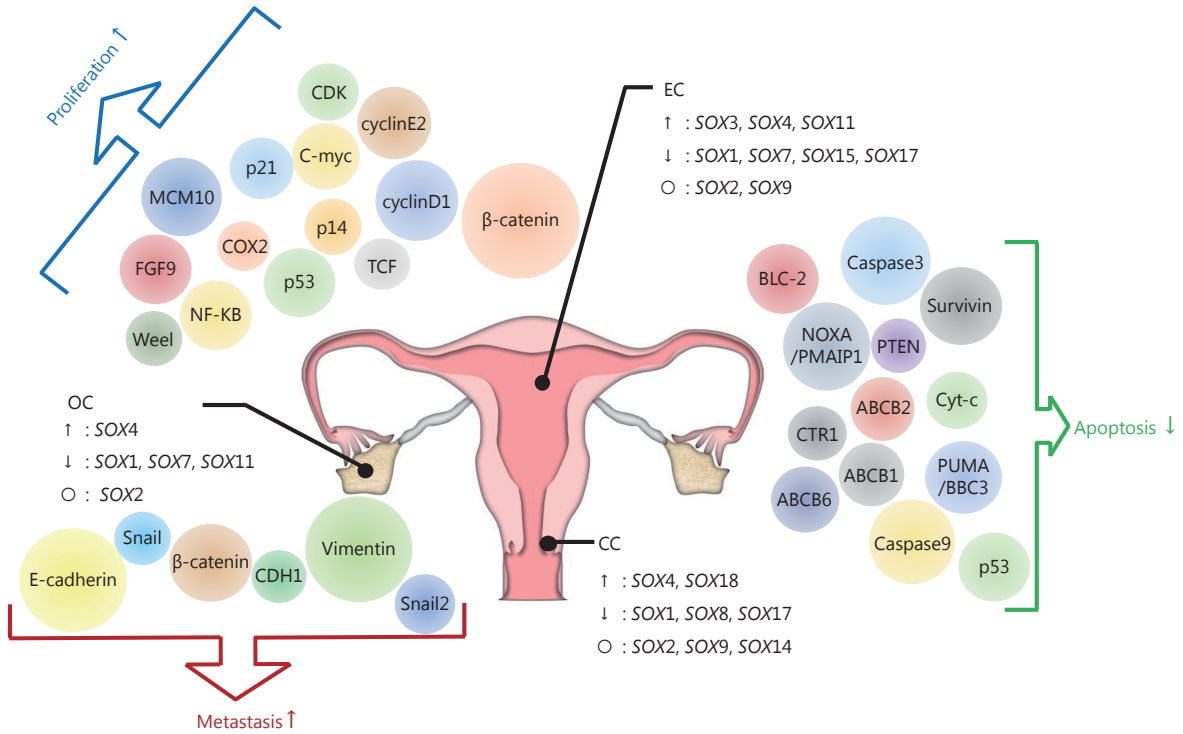


**Figure 3** Comprehensive depiction of the roles of *SOX* genes performed in GCs. *SOX* genes play different roles in different GCs. The black upward arrows indicate high expression level of *SOX* genes in the corresponding cancers, which play as promoters. The black down arrows indicate low expression of *SOX* genes the corresponding cancers, which play as inhibitors. The black circles indicate that the roles of *SOX* genes are controversial. The genes or molecules shown in the surrounding colored circles are among the pathways through which *SOX* genes play in GCs to promote cell proliferation, inhibit apoptosis, and enhance cell metastasis.

serous OC among 215 cases of OC. Other researchers also affirmed the good prognostic effects of *SOX2* in 570 samples from patients with ovarian serous cystadenocarcinoma[39]. The mechanisms responsible for these different effects of *SOX2* may be due to various factors, such as feedback mechanisms of *SOX2* expression, interactions between *SOX2* in the cytoplasm and nucleus, or differences between patient spectra and measuring methods. These flexible and bidirectional roles of *SOX2* suggest that *SOX2* could be a 'double-edged sword' depending on how scientists choose to utilize it. However, analyzing expression level of *SOX* gene in tissues is still generally considered to be a valuable approach for predicting clinical features in patients with OC.

## *SOX genes as regulators in the progression of OC*

In addition to their role as clinical biomarkers, accumulating evidence from *in vitro* studies indicated that *SOX* genes acted as vital regulators in the progression of OC, including in cell proliferation, apoptosis, and metastasis (**Figure 4**). *SOX2* was considered as an oncogene at the cellular level, and up-regulation of *SOX2* in OC cell lines promoted cell proliferation and tumor sphere formation *via* hypoxic treatment and overexpression of the intracellular domain of Notch[9]. Moreover, transduction of *SOX2* into OC cell lines also enhanced resistance to cell apoptosis through overexpression of the anti-apoptotic gene *BCL2* and simultaneous down-regulation of the pro-apoptotic genes *PUMA/BBC3* and *NOXA/PAMAIP1*[34]. Overexpression of *SOX2* also accelerated cell migration by down-regulating E-cadherin and up-regulating vimentin expression[31]. These results at the cellular level were not as the same as the results based on clinical samples, which suggested that *in vitro* studies could not imitate the environment in the body completely. And more animal studies are needed to clarify the role of *SOX2* in the progression of OC. In addition to *SOX2*, up-regulation of *SOX4* in OC cell lines by the long non-coding RNA BRM promoted cell proliferation, migration, and invasion *via* an unknown mechanism[62]. More researches are therefore also needed to investigate the mechanisms and potential of *SOX4* in OC.

*SOX7* and *SOX11*, which are considered as tumor suppressor genes at both the clinical and molecular level,

**Table 1** Abnormal expression of *SOX* genes and their potential clinical implications in gynecological cancers

| *SOX* genes | Potential clinical implication in gynecological cancers | References |
|---|---|---|
| | **OC** | |
| *SOX1* | Methylation of *SOX1* was a clue to detect premalignant OC and predict recurrence as well as worse survival | 17, 35 |
| *SOX2* | ① High expression level of *SOX2* was exploited as a biomarker for screening OC | 9, 16, 31, 36-39 |
| | ② High expression level of *SOX2* implied advanced FIGO stage together with shorter DFS | |
| | ③ *SOX2* could improve cell resistance to chemo-treatment | |
| | ④ High expression of *SOX2* indicated favorable DFS and OS in stage II to IV high-grade serous OC | |
| *SOX7* | High expression level of *SOX7* was regarded as a good prognostic marker | 10 |
| *SOX11* | High expression level of *SOX11* was associated with improved recurrence-free survival | 18, 40 |
| | **CC** | |
| *SOX1* | Hyper-methylation of *SOX1* was an effective biomarker that can discriminate early lesions of CC from normal tissues | 14, 41-46 |
| *SOX2* | ① High expression level of *SOX2* was associated with higher grade along with poorer differentiation | 7, 47-51 |
| | ② Higher expression level of *SOX2* indicated bigger tumor size, more metastasis and invasion as well as shorter OS and RFS | |
| | ③ High expression level of *SOX2* implied radiation resistance and unfavorable prognosis | |
| | ④ High expression level of *SOX2* indicated favorable DFS together with OS compared with low expression of it | |
| *SOX4* | *SOX4* increased cell resistance to cisplatin and contributed to progression of CC | 52 |
| *SOX8* and *SOX17* | Hyper-methylation of *SOX8* along with *SOX17* was detected more frequently in CIN3+ lesions | 53 |
| *SOX9* | ① *SOX9* enhanced CC cell resistance to chemo-treatment | 54, 55 |
| | ② High methylation level of *SOX9* could be used as an early screening marker and indicated poor behavior of CC | |
| | **EC** | |
| *SOX1* | Analysis of high methylation index of *SOX1* in patients' tissues was demonstrated as a potential method for detection of EC hidden in atypical hyperplasia | 56, 57 |
| *SOX2* | ① Low level of *SOX2* due to hyper-methylation of CpG island upstream in promoter region indicated type Ⅱ serous or clear cell adenocarcinoma and short survival | 11, 15, 58 |
| | ② High expression level of *SOX2* was associated with high grade, tumor metastasis and local recurrence which implied poor outcome | |
| *SOX7* | Low or absent expression level of *SOX7* in tissues was associated with high grade EC | 19 |
| *SOX9* | High expression level of *SOX9* inhibited cell proliferative but implicated high histologic grade due to a feedback system | 59 |
| *SOX17* | ① Loss of *SOX17* indicated more advance stage, higher grade and shorter recurrence free-survival of patients with EC | 21, 60, 61 |
| | ② High expression level of *SOX17* in tissues indicated that patients might own increased sensitivity and toxicity to cisplatin | |

inhibited the progression of OC. Low level of *SOX7* together with increased cyclooxygenase-2 and cyclin-D1 were detected in tissues from patients with epithelial OC, especially in patients with advanced serous cystadenocarcinoma[10]. This suggested that *SOX7* might regulate cell proliferation by influencing the Wnt/β-catenin signaling pathway. Transduction of *SOX11* into OC cell lines was also reported to inhibit cell proliferation, though the mechanism remained unclear[18]. These members of the *SOX* gene family all contribute to the progression of OC, and their various

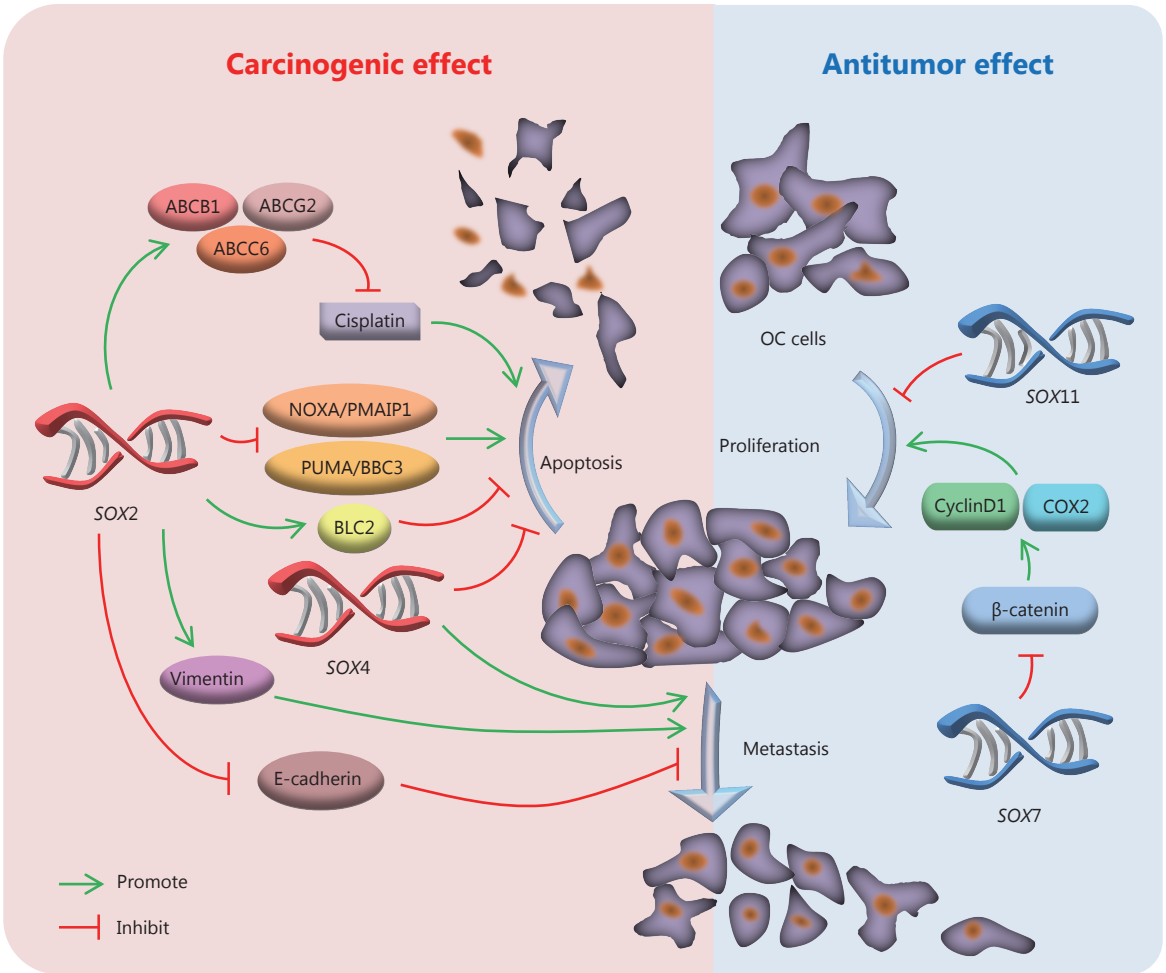


**Figure 4** Roles of *SOX* genes (*SOX2*, *SOX4*, *SOX7* and *SOX11*) in the progression of OC. *SOX2* and *SOX4* performed as oncogenes in red color. *SOX7* and *SOX11* acted as tumor suppressor genes in blue color. Small green arrows indicate promotion and small red arrows indicate inhibition. Cyclin D1 and Cyclooxygenase2 (COX2) are promoting factors in the cell cycle. E-cadherin is an intercellular adhesion molecule, and vimentin is a protein that helps epithelial cells maintain characteristics of fibroblasts such as weaken adhesion and enhance mobility.

mechanisms warrant more detailed investigation. These results also suggested that controlling the expression of certain *SOX* genes may be a promising therapeutic target in the near further.

### *SOX genes influence treatment efficacy in OC*

In terms of treatment, overexpression of *SOX2* was shown to enhance chemoresistance of OC cell lines to cisplatin through activating the expression of the drug efflux transporter genes *ABCB1* and *ABCG2*[9]. Knockdown of *SOX2* in cell lines accordingly decreased chemoresistance to cisplatin *via* down-regulating expression of *ABCB1*, *ABCG2*, and *ABCC6*[31]. These results were accordance with those of researches on the roles of *SOX2* based on OC cell lines, but not with researches based on patients' samples in other cases[9,31,34,38,39]. Further simultaneous *in vitro* and *in vivo* researches into *SOX2* are therefore needed to develop its role as a promising new therapeutic target for patients with OC.

## *SOX* genes in CC

CC is a common GCs considered to be an accidental endpoint of persistent infections with certain types of human papillomavirus (HPV), especially HPV16 and HPV18[5,63]. Some investigators found that *SOX2* regulated HPV16 transcription by inhibiting activity of its long control region and finally decreasing expression of the E6 and E7 oncogenes in CC carcinogenesis[64]. Furthermore, mounting evidence

implicated other members of the *SOX* genes family in the regulation of CC progression (**Figure 5**) and identified their roles as biomarkers for predicting the prognosis of patients with CC (**Table 1**).

### *SOX genes as screening biomarkers and prognostic factors in CC*

Analysis of the aberrant expression level of *SOX1*, *SOX8*, *SOX9*, *SOX14*, and *SOX17* were identified as a novel early screening method for distinguishing between early CC lesions and normal tissues by methylated-CpG island recovery assay (**Table 1**). Higher methylation level of these genes was accompanied by more severe cervical squamous cell lesions[14,41-46,55]. Moreover, the sensitivity and specificity of this early screening method was increased by the combined detection of the methylation level of more than one *SOX* gene, such as *SOX1* and *SOX14*, or *SOX8* and *SOX17*[53,65]. Further studies are therefore needed to determine if analyzing the expression level of all *SOX* genes combined might increase their sensitivity as screening biomarkers for CC.

In terms of prognostic biomarkers, *SOX2* was identified as a dual-effect gene, with its expression level having different implications for clinical features in different studies. Four studies detected high level of *SOX2* in tissues from CC patients and concluded that high *SOX2* expression was associated with higher grade, poorer differentiation, advanced stage, and poorer survival[7,48-50] (**Table 1**). However, the opposite effects were observed in other studies. For example, Kim et al.[47] detected *SOX2* expression in tissue samples from normal cervical epithelium, cervical intraepithelial neoplasia, and CC by immunohistochemistry, and found that high expression level of *SOX2* were correlated

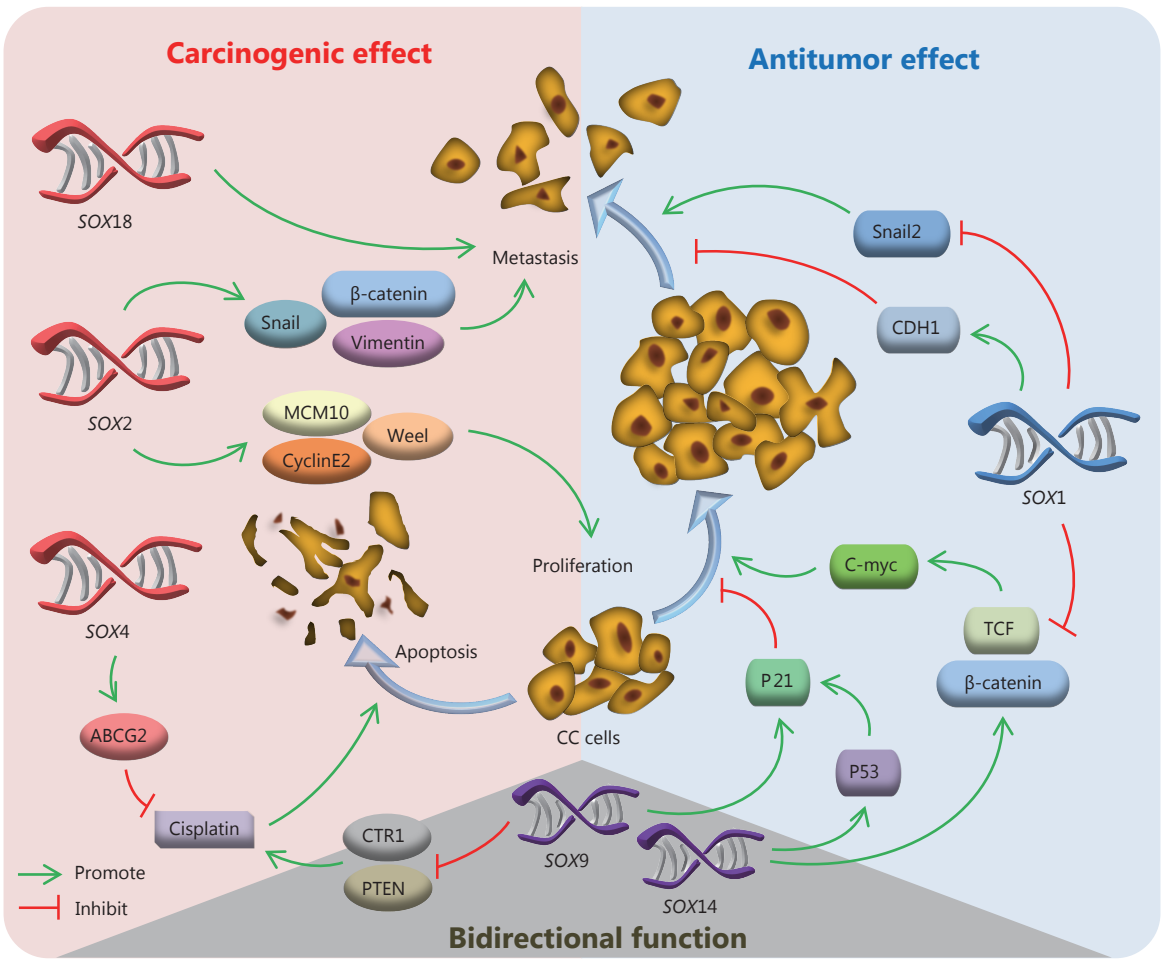


**Figure 5** Roles of *SOX* genes (*SOX1*, *SOX2*, *SOX4*, *SOX9*, *SOX14* and *SOX18*) in the progression of CC. Oncogenes included *SOX4*, *SOX2* and *SOX18* in red color. *SOX1* was regarded as suppressor gene in blue color. *SOX9* and *SOX14* played bidirectional roles in purple color. Small green arrows indicate promotion and small red arrows indicate inhibition. There were few studies of *SOX4* and *SOX18* yet. *P21*$^{WAF1/CIP1}$ is a main kind of cyclin-dependent kinase inhibitor in cell cycle.

with favorable DFS and OS. The unknown mechanisms behind this phenomenon may help to account for the roles of *SOX2* in OC at the clinical level. Nevertheless, more researches are needed to elucidate the precise mechanisms responsible for the effects of *SOX2*.

### *SOX genes regulate progression of CC*

Similar to their roles in OC, numerous studies investigated the involvement of *SOX* genes in regulating the progression of CC (**Figure 5**). Consistent with an oncogenic role, some studies found that transduction of CC cell lines with *SOX2*, *SOX4*, and *SOX18* promoted cell proliferation, metastasis, and invasion[52,66-68]. Specifically, endogenous overexpression of *SOX2* or *SOX4* in CC cell lines drove the cell cycle from G0/G1 to S stage by promoting expression of cell cycle promoters, such as cyclinE2, minichromosome maintenance protein 10 (MCM10), and weel protein kinase[52,66]. Overexpression of *SOX2* in CC cell lines also promoted metastasis and invasion by augmenting the expression of epithelial–mesenchymal transition-promoted molecules, such as vimentin, β-catenin, and Snail[67]. However, the action of *SOX2* at the cellular level did not necessarily reflect the same behavior in clinical samples because of the absence of the body's internal environment. *SOX18* promoted the development of CC without clear mechanisms, so further studies are needed to clarify the mechanisms responsible for the oncogenic role of *SOX18*[68].

In contrast, *SOX1* is considered as a tumor suppressor gene, in line with its activity in clinical samples as mentioned above. Up-regulation of *SOX1* inhibited the growth of CC cells both *in vitro* and *in vivo* by impeding the transcriptional activity of T cell factor in the Wnt/β-catenin signaling pathway. It also promoted metastasis by up-regulating the cancer metastasis suppressor gene *cadherin 1* (*CDH1*) and simultaneously down-regulating *Snail2*, the inhibitor of E-cadherin transcription[6]. Future researches should focus on exploring how *SOX1* influence cell apoptosis and treatment efficacy.

Intriguingly, although *SOX9* and *SOX14* were regarded as tumor suppressor genes with low expression level detected in patients' samples due to methylation, these two *SOX* genes presented dual functions based on research on cell lines. As oncogenes, some researchers reported that overexpression of *SOX9* in CC cell lines promoted cell proliferation by down-regulating the expression of *PTEN*, which prevents cells from growing too quickly[54]. And overexpression of *SOX14* were proved to boost cell proliferation and invasion by activating the Wnt/β-catenin signaling pathway along with high level of β-catenin[69]. In contrast, as tumor suppressor genes, up-regulation of *SOX9* or *SOX14* could block the cell cycle transition by activating the expression of $p21^{WAF1/CIP1}$ and p53, resulting in suppression of cell growth and tumor formation *in vitro*. Overexpression of *SOX14* also induced apoptosis by promoting the expression of Bax and cleaved-poly ADP-ribose polymerase[8,70]. These interesting results indicated the need for more thorough investigations to compare and combine the effects of different experimental conditions on outcomes.

### *Effects of SOX genes on treatment efficacy in CC*

In terms of treatment, *SOX2* and *SOX4* are considered as oncogenes accordance with their roles in the progression of CC. Superficially, expression level of *SOX2* was higher in tissues from patients with radiation-resistance compared with those with radiation-sensitivity, suggesting that *SOX2* was a biomarker of unfavorable therapeutic reactivity[51]. Overexpression of *SOX* genes, such as *SOX4*, in Caski cell lines also decreased the treatment efficacy of cisplatin by up-regulating the drug efflux transporter gene *ABCG2*[52]. And more investigations are required to explore how *SOX* genes influence treatment efficacy in patients with CC. In addition to *SOX2* and *SOX4*, one study implied that high expression of *SOX9* in CC cell lines enhanced cell resistance to cisplatin through combining with the promoter region of miR-130a and down-regulating expression of *copper transporter protein 1* (*CTR1*), which is a significant factor affecting the activity of cisplatin[54]. However, this result was in contrast to the action of *SOX9* in the progression of CC, and the function of *SOX9* in the treatment of CC still needs clarification.

In conclusion, *SOX* genes play significant roles in CC, and *SOX* members may act as promising biomarkers or therapeutic targets in clinical practice in the near future.

## *SOX* genes in EC

EC, with an estimated 63,230 new cases and approximately 11,350 deaths, was regarded as the most common female reproductive system malignancy in the United States in 2018[5]. Despite extensive research focusing on exploring the genetic and epigenetic characteristics of EC, its pathogenesis and progression remain unclear. Recently, some studies indicated the important roles for *SOX* genes in regulating the progression of EC (**Figure 6**) and in indicating clinical features and treatment efficacy of patients with EC (**Table 1**)[19,21,58,71,72].

### *SOX genes as biomarkers of clinical features in EC*

Many researchers explored the roles of *SOX* genes in indicating the clinical features of patients with EC (**Table 1**).

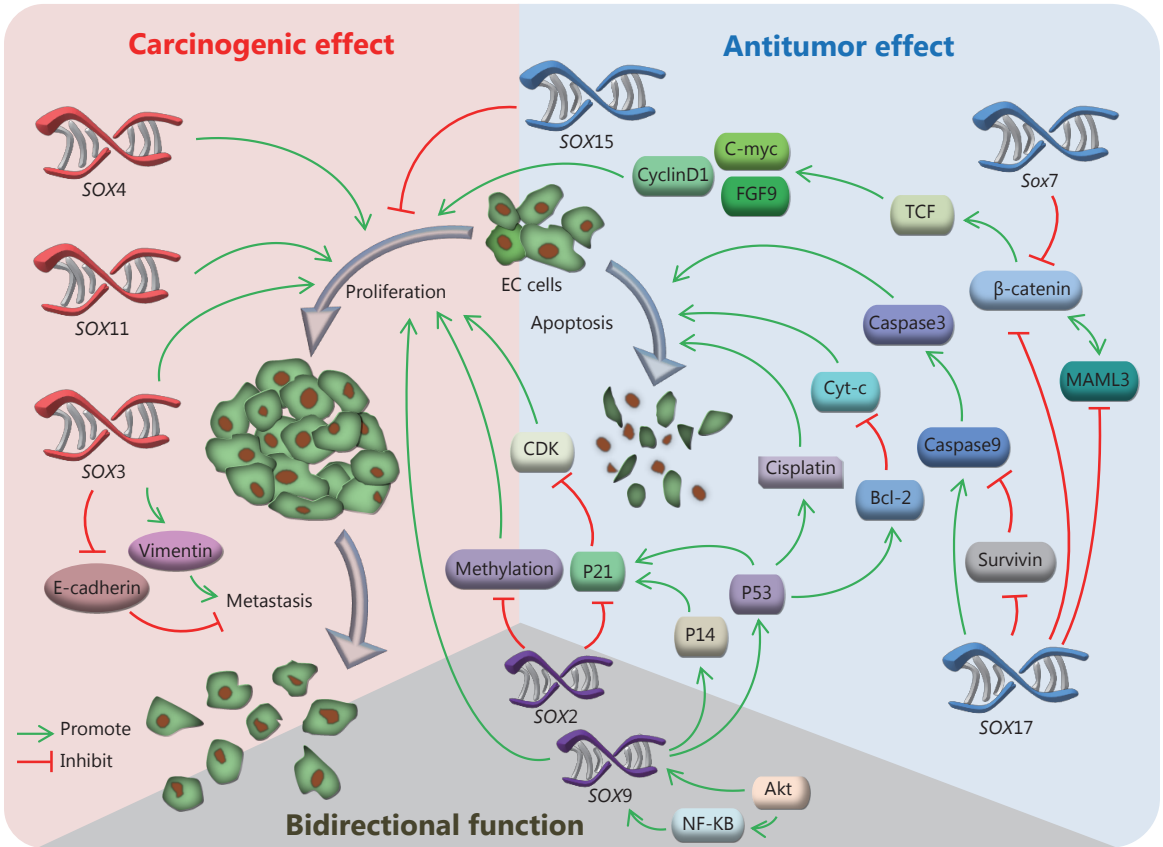


**Figure 6** Mechanisms of *SOX* genes (*SOX2*, *SOX3*, *SOX4*, *SOX7*, *SOX9*, *SOX11*, *SOX15* and *SOX17*) in the development of EC. Oncogenes included *SOX3*, *SOX4* and *SOX11* in red color. Tumor suppressor genes consisted of *SOX7*, *SOX15* and *SOX17* in blue color. *SOX2* and *SOX9* played bidirectional roles in purple color. Small green arrows indicate promotion and small red arrows indicate inhibition. The mechanisms of *SOX4*, *SOX11* and *SOX15* have only been mentioned in a few researches yet. Akt promote growth factor-mediated proliferation and survival of cells both directly and indirectly. NF-κB is a protein complex that controlled transcription of DNA, cytokine production and cell survival. BCL2-associated X protein functions as an apoptotic activator. Cleaved caspase-3 is an executioner of apoptosis. Caspase-9 is an initiator of apoptosis. Survivin is an inhibitor of apoptosis. Mastermind like3 (MAML3) is a co-activator of β-catenin-mediated transcription.

Low expression level of tumor suppressor *SOX* genes, such as *SOX1*, *SOX7*, *SOX9*, and *SOX17*, due to methylation and other mechanisms, could be considered as novel prognostic biomarkers of EC. For example, low expression level of *SOX1*, *SOX7*, and *SOX17* was shown to be potential biomarkers for detecting EC masked by atypical hyperplasia, and indicated advanced stage, higher grade, and shorter RFS[19,21,56,57,60]. Additionally, high expression level of *SOX17* in tissues indicated increased toxicity of cisplatin and high therapeutic sensitivity of patients[61]. However, *SOX9* expression showed a significant stepwise increase from normal tissues through grade 1 to grade 2/3 cancer tissues, probably due to a hidden feedback system[59]. This study suggested that detecting the detailed mechanisms of *SOX9* will provide valuable information.

Interestingly, *SOX2* is identified as a bi-functional gene in EC, as in OC and CC. Pityński et al.[15] analyzed expression level of *SOX2* in samples from EC patients and found higher expression level of it in high-grade (G3) compared with moderate-grade (G2) and low-grade (G1) of EC. High expression level of *SOX2* in tissues was also associated with poorer outcomes of patients with advanced-stage EC[11]. In contrast, Wong et al.[58] proposed that *SOX2* was a tumor suppressor gene inhibiting the progression of EC, and low level of it was identified as an indicator of type II serous, clear cell adenocarcinoma as well as shorter survival. These phenomena suggested that further exploration of the molecular mechanisms of *SOX2* should be carried out in relation to clinical management of EC.

## *SOX genes regulate progression of EC*

In relation to the progression of EC, researchers regulated the

expression of *SOX* gene in EC cell lines by transduction with the corresponding *SOX* genes. Through this method, they found that overexpression of *SOX3*, *SOX4*, and *SOX11* promoted cell proliferation while overexpression of *SOX7*, *SOX15*, and *SOX17* inhibited cell growth and accelerated apoptosis. Meanwhile, *SOX2* and *SOX9* were regarded as dual-function genes in the progression of EC (**Figure 6**).

As oncogenes, up-regulation of *SOX3*, *SOX4*, and *SOX11* in EC cell lines was associated with accelerated cell proliferation *via* unknown mechanisms, while silencing of these genes had the inverse effects[72-74]. Moreover, *SOX3* also promoted EC cell metastasis *in vitro* by down-regulating the epithelial marker E-cadherin and up-regulating the mesenchymal marker vimentin[72]. However, the roles of *SOX4* and *SOX11* in promoting cell metastasis and invasion remain unclear.

*SOX7*, *SOX15*, and *SOX17*, regarded as tumor suppressor genes, inhibited cell proliferation through different signaling pathways. Enforced expression of *SOX7* and *SOX17*, both belonging to *SOX* subgroup F, played inhibitory roles in the growth and colony formation of EC cell *in vitro* by suppressing the accumulation of β-catenin in the Wnt/β-catenin signaling pathway[19,21]. *SOX7* also inhibited the downstream factors of β-catenin, such as cyclinD1, c-Myc and fibroblast growth factor 9 (FGF9), in the Wnt/β-catenin signaling pathway[19]. Cell lines with elevated *SOX17* expression also demonstrated high apoptosis and low proliferation rates through up-regulating wild-type p53, Bcl2-associated X protein, and cleaved caspase-3 and caspase-9, while simultaneously down-regulating the level of survivin and mastermind like-3[21,61]. Conversely, down-regulation of *SOX17* increased the rate of cell proliferation in cell lines, and suggested that the low expression level of *SOX17* may be due to frequent mutations, including missense, frameshift, and hotspot missense changes. They also detected a moderate increase in β-catenin, as a key regulator of EC, following transfection of EC cell lines with mutated *SOX17*[21,60]. These results suggest that the regulation of *SOX17* may vary in the progression of EC. In addition to the above genes, *SOX15* is a novel and vital gene in EC. And the expression level of it was at significantly lower level in EC tissues compared with adjacent uninvolved tissues from the same patient[75]. And up-regulation of *SOX15* in EC cell lines suppressed cell proliferation and viability by inducing cell-cycle arrest in G0/G1 stage, promoting cell apoptosis, and weakening cell migration, whereas knockout of *SOX15* had the opposite effects. More researches are therefore needed to clarify the detailed mechanisms of *SOX15*[75].

Apart from these oncogenes above, *SOX2* and *SOX9* are considered as bi-directionally regulated genes in EC. Overexpression of *SOX2* in cells promoted cell proliferation by inhibiting expression of p21[11], while low level of *SOX2* in tissues caused by promoter hyper-methylation was conversely accompanied by initiation of EC[58]. These phenomena reflecting the role of *SOX2* as a biomarker of clinical features in patients with EC was possibly due to different locations of *SOX2* and its currently unclear mechanisms. Regarding *SOX9*, Behringer et al.[71] found that overexpression of *SOX9* in uterine epithelial cells in a progesterone receptor-Cre mouse model promoted the formation of more simple and complex cystic glandular structures. However, the results differed at the cellular level. Stable overexpression of *SOX9* in EC cell lines served as a negative regulator of cell proliferation, particularly in the exponential growth phase, through activation of the $p14^{ARF}$/p53/$p21^{WAF1}$ pathway and interactions with nuclear factor-κB and Akt[59]. These results revealed that *SOX9* behaved differently *in vitro* and *in vivo*, waiting for further investigations. The roles of *SOX2* and *SOX9* in EC thus remain largely uncertain.

### *Effects of SOX genes on treatment efficacy in EC*

In relation to treatment of EC, only *SOX17* was demonstrated an association with the chemosensitivity of EC cells to cisplatin. Zhang et al.[61] overexpressed *SOX17* in HEC-1B cells and found that cells with elevated expression of *SOX17* had higher sensitivity to cisplatin, lower cell viability, and higher cell apoptosis rate when treated with cisplatin. These results suggest that *SOX17* may be a promising target for gene treatment of EC.

## Similarities of *SOX* genes in GC and prospective challenges

In this review, we classified *SOX* genes and emphasized their critical roles as regulators in the progression of GCs. And *SOX* genes were also considered as biomarkers of clinical features, including FIGO stage, histological grade, treatment efficacy, and prognosis of patients with GCs. *SOX* genes owned the potential to assist gynecologists in making precise clinical decisions. There were some similarities in *SOX* genes among GCs. 1) Methylation analysis of the tumor suppressor *SOX1* gene in patients' samples was regarded as a novel method for early screening and as a biomarker of clinical features. 2) Expression level of the dual-acting *SOX2* gene revealed low level in some cases and high level in other cases, indicating different prognostic values in different patients, and highlighting the need for more research to clarify its role.

3) At a cellular level, transduction of the oncogene *SOX4* in cell lines promoted the progression of GCs by enhancing cell proliferation and metastasis. 4) *SOX7* and *SOX17*, both belong to subgroup F *SOX* genes, acted as tumor suppressor genes which were associated with decreased rate of progression. Given that *SOX3* belongs to subgroup B with *SOX1* and *SOX2*, meanwhile, *SOX18* belongs to subgroup F with *SOX7* and *SOX17*. Researchers could investigate the roles of *SOX3* and *SOX18* in GCs to see if they play similar roles to other members from the same subgroups.

The current review was limited to studies of the three most common GCs and certain histological subtypes, such as cervical squamous cell carcinoma, epithelial OC, and unexplained EC. Therefore, larger population-based studies of other kinds and subtypes of GCs, such as uterine myoma, uterine sarcoma, tumors of the fallopian tube, and vulvar squamous cell carcinoma, are warranted to further our understanding of the associations between *SOX* genes and the progression of GCs. Although studies to date only scratched the surface in terms of understanding the biological and clinical functions of *SOX* genes in GCs, these pre-clinical studies held promise and provided the basis for future studies aiming at elucidating the detailed functions of these genes.

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## Conflicts of interest statement

No potential conflicts of interest are disclosed.

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