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Review

SOX2 in development and cancer biology

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ABSTRACT

The transcription factor SOX2 is essential for embryonic development and plays a crucial role in maintaining the stemness of embryonic cells and various adult stem cell populations. On the other hand, dysregulation of SOX2 expression is associated with a multitude of cancer types and it has been shown that SOX2 positively affects cancer cell traits such as the capacity to proliferate, migrate, invade and metastasize. Moreover, there is growing evidence that SOX2 mediates resistance towards established cancer therapies and that it is expressed in cancer stem cells. These findings indicate that studying the role of SOX2 in the context of cancer progression could lead to the development of new therapeutic options. In this review, the current knowledge about the role of SOX2 in development, maintenance of stemness, cancer progression and the resistance towards cancer therapies is summarized.

1. Introduction

In 1990, a new transcription factor with a distinctive DNA-binding domain was described to be involved in testis determination. The gene encoding for this protein was found to be located on the sex-determining region of the Y chromosome and was therefore termed *sex-determining region Y* (*SRY*) gene [1,2]. The Sry protein binds to specific DNA sequences with its high-mobility-group (HMG) domain. Since its discovery a new gene family has been established on the basis of sequence similarities to this HMG domain (Fig. 1). The so-called Sry-related HMG box (SOX) proteins contain an HMG domain with at least 50% sequence similarity to the HMG domain of Sry. Up to the present day, 20 different *SOX* genes have been found in the murine and human genome which in turn have been divided into eight subgroups based on sequence identity and similar functions [3,4]. In this review, we will focus on SOX2, a member of the SOXB1 subgroup.

Among all *SOX* genes, *SOX2* is probably the most recognized due to its role in reprogramming somatic cells into induced pluripotent stem cells (iPSCs) [5]. The human *SOX2* gene is situated on chromosome 3 at the position q26.3–27 and encodes for a protein of 317 amino acids [6]. The structural centerpiece of SOX2 is its HMG domain that is highly conserved among species. Apart from binding to specific DNA consensus sequences, this domain also contains a nuclear localization and a nuclear export signal. The function of the C-terminal transactivation domain is to recognize and bind the promoters of target genes and by doing so activating or repressing gene expression [7].

2. SOX2 in development

SOX2 is expressed already very early in embryonic development. Pan and Schultz reported the presence of SOX2 at the 2-cell stage of murine embryos with increasing levels up to the blastocyst stage [8]. Indeed, SOX2 plays an essential role in the emergence of the pluripotent inner cell mass during early embryonic development since its absence results in embryonic lethality [9]. While SOX2 is homogeneously expressed in the inner cell mass, it becomes restricted to certain cell populations when the embryo undergoes the transformation from a single-layered to a multi-layered structure during gastrulation. After this process, SOX2 expression characterizes primordial germ cells, gut endoderm, presumptive neuroectoderm, sensory placodes and pharyngeal arches [10,11]. The specification of the neural lineage in early embryonic development strongly relies on the activity of SOX2. SOX2 exerts this effect by antagonizing transcription factors that would favor the development of non-neural cell lineages. By suppressing the transcription factor brachyury SOX2 shifts the decision pro neuroectoderm and against mesendoderm [12,13]. The antagonism between SOX2 and TBX6 regulates the differentiation of bipotential axial stem cells. SOX2 induces the differentiation of axial stem cells to the neural plate which

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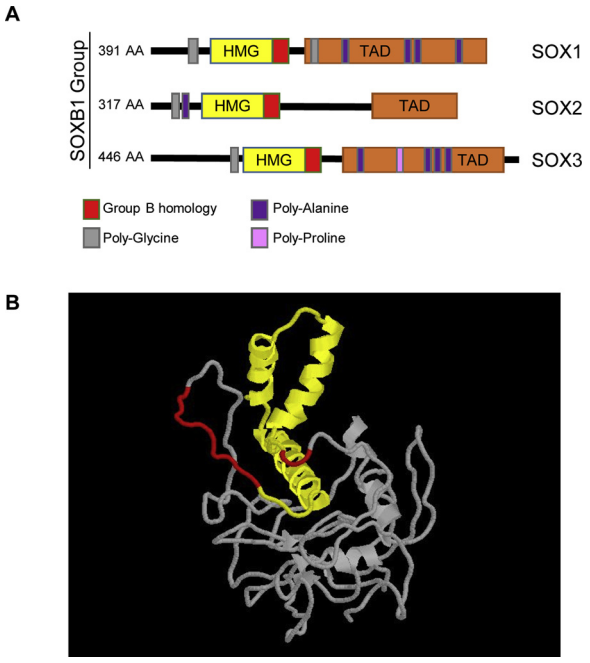

Fig. 1. Schematic drawing and crystal structure of SOX2. A: SOX2 belongs together with SOX1 and SOX3 to the SOXB1 group of the SOX family. All family members have the DNA-binding HMG domain in common. **B**: Crystal structure of SOX2 modulated with RasMol. The yellow and red part is reconstructed based on NMR results while the grey part is a theoretical model based on IntFOLD calculations with a global model quality score of 0.3263. The HMG domain is labeled in yellow.
(HMG: High-mobility-group box DNA-binding domain; TAD: Transactivation domain)

later gives rise to the central nervous system (CNS). When TBX6 is present, it blocks a specific enhancer of the SOX2 gene and thereby inhibits SOX2 expression. Consequently, the influence of TBX6 drives the differentiation of the axial stem cells towards paraxial mesoderm from which the vertebral column, the skeletal musculature and the dermis are derived [14]. Throughout further fetal development SOX2 impacts the proliferation and differentiation of progenitor cells of the CNS and the peripheral nervous system (PNS) [15,16]. Complete absence of SOX2 expression in retinal progenitor cells (RPCs) abrogates their proliferation capacity and the ability to differentiate. Even decreased SOX2 expression already affects RPCs leading to microphthalmia in mice. It could be demonstrated that SOX2 directly activates Notch1 in RPCs and that the disruption of this axis is responsible for the described phenotype [17]. In Schwann cell precursors (SCPs), the crosstalk between SOX2 and the melanocyte-specific transcription factor MITF decides whether these cells commit to a glial or melanocytic fate. SOX2 directly suppresses the transcription of MITF and hence causes SCPs to adopt a glial phenotype [18]. However, SOX2 was also reported to prohibit the terminal differentiation of SCPs emphasizing its dual role in promoting determination and maintaining the precursor phenotype [19]. Interestingly, in the case of GABAergic neurons, SOX2 has a differentiation promoting effect. *In vitro* and *in vivo* studies have revealed that a lack of SOX2 interferes with the differentiation of GABAergic neurons. Newborn SOX2 hypomorphic and knockout mice showed less GABAergic interneurons in their cortex and olfactory bulb [20,21]. Further tissues and organs originating from the ectoderm and relying on SOX2 expression for proper development comprise the dental epithelium and the inner ear [22,21,24]. The involvement of SOX2 in the control of developmental processes is not limited to cell lineages of ectodermal origin. Several studies revealed a role of SOX2 in the formation of endoderm-derived structures. The differentiation of tracheal cartilage, the emergence of the lung from the primary lung bud and the development of taste bud sensory cells in the embryonic tongue are examples for this [25–28]. Furthermore, the contribution of SOX2 to the origination of organs from the embryonal foregut endoderm was described in detail. High levels of SOX2 in the anterior foregut induce the formation of forestomach and esophagus. On the other hand, low SOX2 levels are associated with the emergence of the posterior stomach and the trachea. Remarkably, abnormally decreased SOX2 levels in the

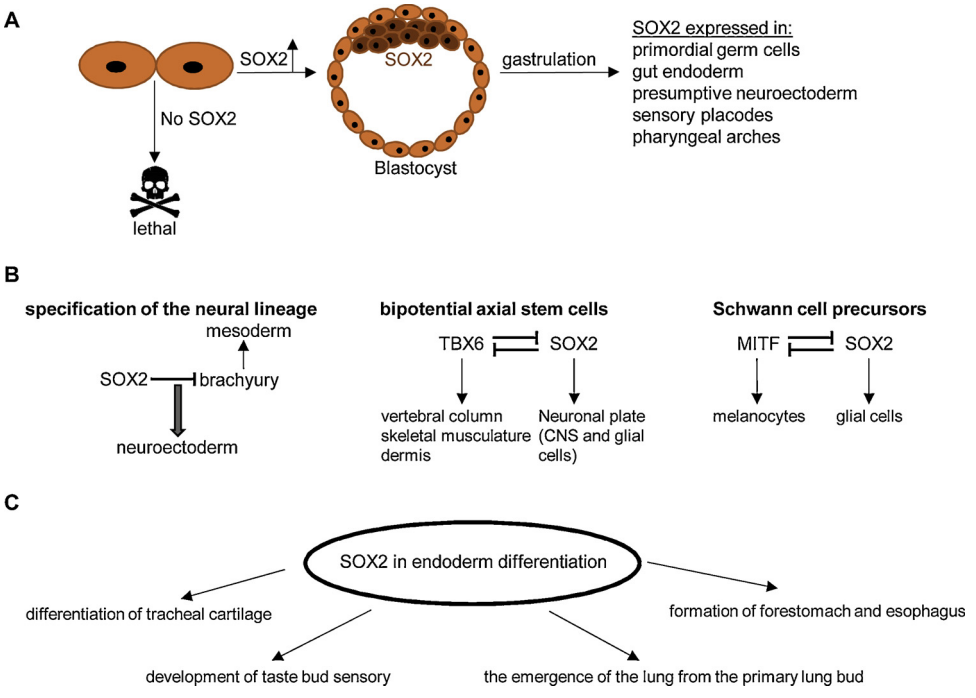

Fig. 2. SOX2 in development. A: Role of SOX2 in embryonic development. **B:** SOX2 in neuronal lineage differentiation. **C:** SOX2 in the formation of endoderm-derived structures.
(TBX6 = T-Box Protein 6; MITF = Microphthalmia-Associated Transcription Factor; CNS = central nervous system)

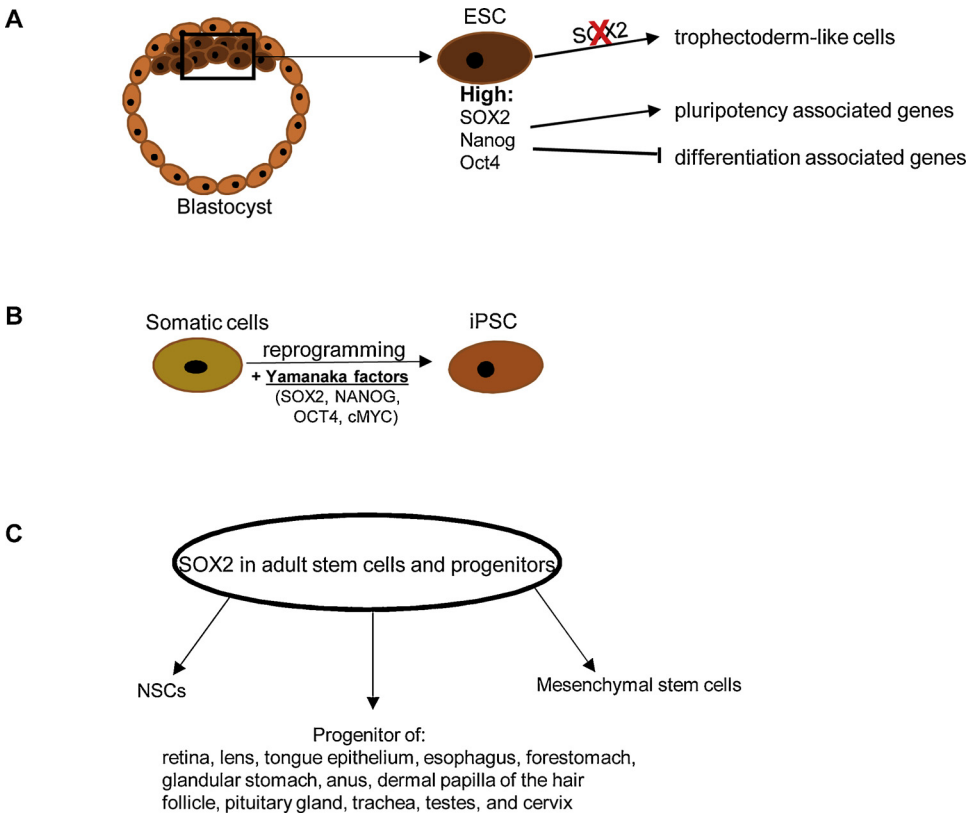

Fig. 3. SOX2 in embryonic and adult stem cells. A: The role of SOX2 in maintaining the pluripotency of ESCs. **B:** SOX2 is a Yamanaka factor enabling reprogramming of somatic cells into iPSCs. **C:** SOX2 is important to maintain adult stem cells in an undifferentiated state. (ESC = embryonic stem cells; iPSC = induced pluripotent stem cells; NSC = neural stem cells)

foregut result in a transformation of esophagus into trachea. Apart from that SOX2 hypomorphic mouse embryos showed an abnormal phenotype of the forestomach with glandular instead of the normal keratinized, squamous histology [29]. Much less is known about SOX2 in cells of mesodermal origin. Although SOX2 initially suppresses the differentiation of mesendoderm in favor of neuroectoderm [12,13], some studies suggest that SOX2 nevertheless also plays a role in cells of the mesodermal lineage. The dermal sheath and dermal papilla (DP) of hair follicles arise from dermal condensates which are populations of mesenchymal cells that express SOX2 [30,31]. The established opinion that DPs solely arise from neural crest cells has been disproved by Jinno and colleagues showing that only facial DP cells derive from the neural crest while DPs of the trunk are derived from mesodermal somites [32] (Fig. 2).

3. The role of SOX2 in embryonic and adult stem cells

As already mentioned above, SOX2 is highly expressed in pluripotent cells of the inner cell mass of a developing embryo. It is no surprise that this is also true for embryonic stem cells (ESCs) which are derived from the inner cell mass [9]. The importance of SOX2 for the maintenance of the stem cell phenotype of ESCs could be demonstrated by deleting SOX2 in these cells resulting in their differentiation to trophectoderm-like cells [33]. The preservation of stemness of pluripotent stem cells is achieved by the so-called core transcriptional network consisting of SOX2 and the transcription factors OCT4 and Nanog. These three factors cooperate functionally in order to promote the expression of pluripotency-associated genes (Nanog, OCT4, SOX2 among others) and to suppress the expression of genes associated with differentiation [34,35]. Interestingly, SOX2 and OCT4 synergistically bind OCT4/SOX2 consensus binding sites in the promoters or enhancers of their target genes showing their close functional connection. Moreover, a loss of SOX2 can to some extent be compensated by overexpression of OCT4, suggesting that SOX2 contributes to the maintenance of stemness by sustaining OCT4 expression [33]. In 2006, Takahashi and Yamanaka succeeded in reprogramming somatic cells to iPSCs by ectopically overexpressing four transcription factors termed as Yamanaka factors. Knowing about the role of SOX2 and OCT4 in sustaining the stemness of ESCs, it is not unexpected that both are among these Yamanaka factors [5]. During the reprogramming process, ectopically expressed SOX2 induces the transcription of endogenous SOX2 and other genes associated with pluripotency. That way, the endogenous core transcriptional network is established and a stable pluripotent state is reached [36]. Additionally, cells subjected to reprogramming undergo global epigenetic remodeling which resets their epigenome to a state which is very similar to the one found in ESCs [37]. Of note, cells expressing SOX2 endogenously can be reprogrammed without additional ectopic SOX2 expression. In this way, neural progenitor cells (NPCs), melanocytes and even melanoma cells were converted to bona fide iPSCs [38–40]. Despite being associated with ESCs, SOX2 also undertakes important functions in later stages of fetal development and in the adult organism. As already mentioned before, SOX2 expression is detectable in embryonic NPCs [15,16], but also persists in adult neural stem cells (NSCs) and NPCs in the neurogenic regions in the subventricular zone (SVZ) of the lateral ventricle, the subgranular zone (SGZ) of the hippocampus and the ependyma of the adult central canal [20,41]. SOX2-expressing NPCs could be stably cultured *in vitro* without losing their self-renewal capacity and their ability to differentiate to neuronal or glial cells [41,42]. Knocking down SOX2 in NPCs *in vitro*significantly reduces their capability to differentiate to neurons [21]. Similarly, conditional deletion of SOX2 in the brains of mice leads to a depletion of NPCs and decreased cell proliferation in the dentate gyrus [20,43]. SOX2-positive stem cell populations have been detected in several other adult tissues. Remarkably, these tissues also depend on SOX2 during development. Among these cell populations are progenitors of the retina, lens, tongue epithelium, esophagus, forestomach, glandular stomach, anus, dermal papilla of the hair follicle, pituitary gland, trachea, testes, and cervix [17,23,28,31,44–47]. Moreover, mesenchymal stem cells (MSCs) from different sources have been found to rely on SOX2 expression for the

maintenance of stemness, proliferation and proper differentiation [48–50]. In an interesting study, Vilas and colleagues depleted SOX2-positive adult stem cells *in vivo* and observed several signs of premature aging in their mice like kyphosis, hair graying and reduced fat mass demonstrating that SOX2 plays an essential role in the maintenance of adult stem cells [51] (Fig. 3).

4. The role of SOX2 in disease and cancer

4.1. SOX2 in developmental disorders and cancer progression

SOX2 is essential for the normal progress of numerous developmental processes. Its importance is evident by the fact that SOX2-deficient embryos die straight after implantation [9]. Moreover, even heterozygous deletions of SOX2 have severe consequences. Fantes and colleagues were the first to link SOX2 loss-of-function mutations to bilateral anophthalmia [52]. In addition, the well characterized autosomal dominant anophthalmia-esophageal-genital (AEG) syndrome results from a heterozygous loss-of-function mutation of SOX2. AEG syndrome manifests itself in ocular malformations such as microphthalmia or even anophthalmia, brain abnormalities, hearing loss, trachea-esophageal fistula, abnormalities in the hypothalamo-pituitary-gonadal axis and testicular atrophy [53,54].

Dysregulation of SOX2 expression is also an important factor contributing to cancer pathogenesis. Numerous studies have shown an amplification of the SOX2 gene locus and an increased SOX2 expression that in turn affects cancer progression (Table 1). SOX2 controls several features of cancer cells such as proliferation, epithelial-to-mesenchymal transition (EMT), migration, invasion, metastasis, sphere and colony formation, tumor initiation, cancer stem cell formation as well as resistance to apoptosis and therapy [4,55], (Fig. 4). Interestingly, the effect exerted by SOX2 can vary depending on the cancer type. Bass and colleagues were able to show that the SOX2 locus is amplified in esophageal and lung squamous cell carcinomas (SCCs), which results in increased SOX2 expression enhancing proliferation and anchorage-independent growth of SCCs [56]. Lung SCCs with high SOX2 levels express also factors that are usually found in ESCs. This is not surprising since SOX2 is part of the transcriptional network that controls pluripotency [34]. Remarkably, patients with tumors expressing these ESC-associated factors exhibited better survival compared to patients whose tumors did not express these factors [56]. In a follow-up study, Watanabe and colleagues discovered that SOX2 interacts with p63 in different SCC lines to jointly activate gene expression. One of their targets is the oncogene ETV4 that is necessary for SCC cell survival [57]. This study nicely demonstrates that SOX2 exerts different effects in different cell lineages based on its interaction partners. In ESCs, for instance, SOX2 cooperates with OCT4 to regulate transcription [58]. SOX2 was also found to aberrantly activate Hedgehog (Hh) signaling in lung SCC. SOX2 and protein kinase Cι (PRKCI) are often coamplified and overexpressed in primary lung SCCs. Upon being phosphorylated by PRKCI, SOX2 enhances the transcription of the Hh acyltransferase (HHAT). Elevated HHAT expression levels result in increased Hh ligand production which in turn activates Hh signaling and fosters lung SCC tumorigenesis [59]. An amplification of the SOX2 gene and an increased expression of SOX2 could be demonstrated for different subtypes of sinonasal carcinoma. The data analyzed in this study clearly indicate that patients with tumors with SOX2 amplification relapse significantly more often. Beyond that, there was a tendency for a lower overall survival rate for SOX2-amplified patients. Of note, the authors could not detect a correlation between relapse and SOX2 expression levels [60]. In gliomas, SOX2 expression and malignancy grade correlate positively with the highest levels of SOX2 found in the hypercellular and hyperproliferative areas of glioblastomas (GBMs). The SOX2 gene locus was amplified in 14.4% of GBMs and 11.1% of anaplastic oligodendrogliomas [61]. The study from Alonso and colleagues revealed that although only a small percentage of patient GBM samples exhibited an amplification of the gene locus, all of them showed increased SOX2 expression. This is due to an aberrant hypomethylation of the SOX2 promoter [62]. A more recent publication reported that all grades of pediatric gliomas express SOX2. Moreover, SOX2-specific T cells were found in tumor and blood samples of pediatric glioma patients indicating that SOX2 might be used as a target in immunotherapy [63]. In non-small cell lung cancer (NSCLC), an amplification of the SOX2 gene locus has been detected. Interestingly, this amplification correlated with an increased median overall survival (OS) of patients with early stages of this disease. At later stages there is no difference in the median OS between patients with SOX2-positive and –negative tumors [64]. Another study confirmed this observation by showing that patients with tumors expressing high levels of SOX2 have a significantly better prognosis than patients with tumors that only express low amounts of SOX2 [65]. On the other hand, Chou and colleagues report that SOX2 expression is associated with later stages of NSCLC and that SOX2-positive tumors go along with lower overall survival rates. SOX2 was found to induce the expression of EGFR and BCL2L1 and thereby promoting proliferation and survival of tumor cells. Moreover, SOX2 expression augmented chemoresistance [66]. In melanoma, the role of SOX2 is still debatable. Weina and colleagues discovered that TGF-beta induces the expression of SOX4 which in turn elevated the expression of SOX2, resulting in an increased invasive capacity of melanoma cells [67]. On the other hand, Schaefer and colleagues observed that the deletion of the *SOX2* gene in human melanoma cells or the conditional inactivation of *SOX2* in a melanoma mouse model do not alter melanoma initiation, growth or metastasis formation [68]. These contradictory observations could be due to different genetic backgrounds of the melanoma cells and models used for the studies. According to that, SOX2 could influence different cellular mechanisms depending on the regulatory network present in a particular cell. Also for ovarian cancer, the most severe gynecologic cancer, a contradictory impact of SOX2 has been reported. Two studies found SOX2 to be expressed grade dependently with higher levels in more advanced stages of ovarian tumors. In line with this, strong SOX2 expression correlates with decreased disease-free survival [69,70]. On the other hand, Belotte and colleagues reported that SOX2 gene amplification goes along with a significantly longer median overall survival time [71]. However, it was not

Table 1
List of cancer types with aberrant SOX2 expression and the corresponding prognosis. Arrows in the middle column indicate an increased (↑) or decreased (↓) expression. Arrows in the right column indicate a poor prognosis/high tumor grade (↘) or good prognosis/low tumor grade (↗). Adapted from Wuebben and Rizzino, 2017 [160].

Cancer type	Increased SOX2 expression	Poor prognosis/high tumor grade
Breast	↑ [141,142],	↘ [84,142],
Colorectal	↑ [143]	↘ [106,151],
Esophageal	↑ [56,143,144],	↘ [107]
Glioblastoma	↑ [61,62,145,146],	↘ [61,152],
Liver	↑ [111]	↘ [111]
Lung adenocarcinoma	↑ [108]	↘ [108]
Nasopharyngeal	↑ [110]	↘ [110]
Oral SCC	↑ [147]	↘ [109]
Prostate	↑ [120,148],	↘ [120,153],
Sinonasal	↑ [60]	↘ [60]
Small cell lung	↑ [149,150],	↘ [149,150],
	Increased SOX2 expression	Good prognosis/low tumor grade
Lung, squamous cell	↑ [56,108,123,154,155],	↗ [156]
	Increased SOX2 expression	Contradictory prognoses
Head and neck SCC	↑ [95]	↘ [94] / ↗ [125]
Non-small cell lung	↑ [66]	↘ [94] / ↗ [64,65],
Ovarian	↑ [69–71]	↘ [69,105],/ ↗ [71]
	Decreased SOX2 expression	Poor prognosis/high tumor grade
Gastric	↓ [72,73,74], [158,159],	↘ [73,74,122],

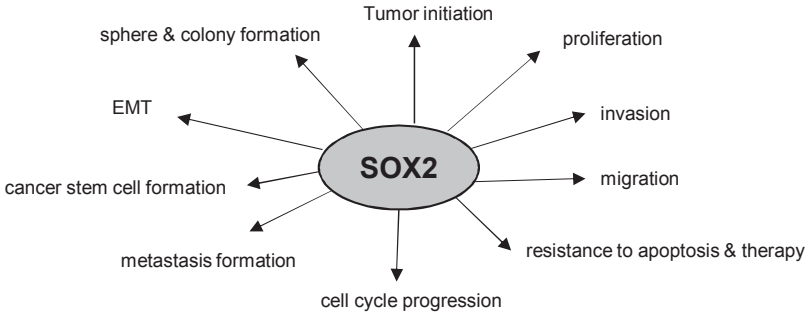

Fig. 4. Role of SOX2 in cancer. SOX2 affects different features of cancer cells and thereby promotes tumorigenesis and cancer progression. (EMT = epithelial-to-mesenchymal transition).

mentioned if the gene amplification also resulted in higher SOX2 expression. While many studies show that SOX2 promotes cancer cell proliferation, the opposing effect was observed in gastric cancer. Several groups reported that SOX2 expression is downregulated in gastric cancer cells in contrast to normal gastric mucosae. Otsubo and colleagues discovered that SOX2 exerts an antiproliferative effect on gastric cancer cells by inducing cell-cycle arrest. Furthermore, SOX2 has a proapoptotic effect. Downregulation of SOX2 in gastric cancer was found to be due to hypermethylation of the SOX2 gene. The survival time of patients with SOX2 gene methylation was significantly shorter compared to patients with non-methylated SOX2 gene [72]. Wang and colleagues demonstrated that low SOX2 levels are associated with poor patient prognosis. They could show that SOX2 exerts an antiproliferative, antimetastatic and pro-apoptotic effect on gastric cancer cells by directly regulating the PTEN/AKT pathway [73]. Another study revealed that SOX2 reduces the migratory and invasive potential of gastric cancer cells by upregulating p21 expression. Accordingly, patients with tumors with high SOX2 expression had less lymph node metastases and responded better to treatment [74]. SOX2 controls the expression of a plethora of genes and thereby affects a lot of pathways and cellular processes. The examples mentioned above reflect this versatility and stress the importance of investigating the role of SOX2 in cancer.

4.2. SOX2 in cancer stem-like cells

Over the years, it has become more and more evident that tumors are complex structures with a cellular heterogeneity and hierarchy. Genetic mutations, interactions with the tumor microenvironment and the presence of cancer stem cells (CSCs) shape a tumor and crucially affect the progress of the disease, especially the response to therapeutic measures and the development of resistances to antitumoral compounds [75]. According to the CSC model, a small population of highly treatment-resilient stem-like cells within the tumor bulk sustains the growth of a tumor and causes relapses after initially successful treatment [76]. Since CSC share the self-renewing capacity with normal stem cells and since SOX2 plays an important role in maintaining the stemness of pluripotent stem cells it is not surprising that many studies report about SOX2 being involved in regulating the stemness and self-renewal of CSC. Several groups were able to show that silencing SOX2 in GBM tumor-initiating cells drastically decreases their proliferative, migrative, invasive and tumorigenic potential while arresting the cells in the G0/G1 phase of the cell cycle underscoring the crucial role of SOX2 in GBM progression and recurrence [62,77–82]. In medulloblastoma Vanner and colleagues identified a SOX2-positive cell population that is quiescent and resistant to therapy. This cell population gives rise to rapidly cycling doublecortin-positive progenitors that in turn yield the tumor bulk of postmitotic cells. Interestingly, chemotherapeutic treatment leads to an accumulation of SOX2-positive cells which are responsible for relapse. Targeted removal of this population with mithramycin completely abolishes tumor growth [83]. In breast cancer, a SOX2-expressing stem cell population resists the treatment with the estrogen receptor antagonist tamoxifen. The size of this population and its resilience towards tamoxifen positively correlates with SOX2 expression. It could be shown that the resistance to tamoxifen is promoted via SOX2-mediated activation of Wnt signalling [84]. Das and colleagues were able to deplete the stem cell population in breast cancer by applying actinomycin D which specifically downregulates SOX2. This treatment completely abrogates the tumor-initiation capacity of breast cancer cells [85]. Gong and colleagues confirmed the importance of SOX2 for the functionality of breast CSC by identifying the transcriptional repressor GATA binding 1 as a suppressor of SOX2 expression that could abolish the CSC features of breast CSC and nullify their tumor initiation capacity [86]. Lundberg and colleagues could identify a SOX2-expressing population in colorectal cancer that is also positive for the stem cell markers CD24 and CD44 while showing reduced expression of the tissue-specific intestinal marker CDX2. Moreover, these cells are less proliferative and exhibit a spheroid growth pattern which are features of stem-like cells [87]. In lung squamous cell carcinoma (LSCC), SOX2 and the protein kinase Cι (PKCι) jointly induce and sustain a stem-like phenotype. Upon being phosphorylated by PKCι SOX2 can bind to the promoter of HHAT and promote its expression. HHAT on the other hand plays an important role in Hh ligand production. Thus, PKCι, SOX2 and HHAT enable cell-autonomous Hh signaling which results in the maintenance of a stem-like and tumorigenic phenotype [59]. Separating SOX2-positive from SOX2-negative cervical cancer cells revealed that SOX2 expression goes along with the expression of stemness markers and the capacity for self-renewal, differentiation and tumor formation [88]. In pancreatic cancer, SOX2 expression goes along with the expression of the pancreatic CSC markers ALDH1, ESA and CD44 and was found to be enriched in the CSC populations from patient samples. Knocking down SOX2 results in cell cycle arrest whereas overexpression of SOX2 promotes cell proliferation. Beyond that, SOX2 stimulates EMT by activating the transcription of Snail, Slug and Twist and downregulating E-cadherin and ZO-1 [89]. There are many more studies that report a relation between SOX2 expression and CSCs in other cancer entities, such as bladder cancer, different forms of lung cancer, melanoma, osteosarcoma, ovarian cancer, prostate cancer, pancreatic carcinoma and different variants of SCCs [[90–92,94–104][89]]. Remarkably, the majority of these studies show that SOX2 promotes CSC maintenance and therapy resistance indicating that SOX2 drives a fundamental mechanism of cancer progression beyond cell lineage of origin of a particular cancer.

4.3. SOX2-dependent clinical outcome and therapy resistance

As already mentioned in Section 4.2, SOX2 expression is aberrantly increased in many different cancer types and drives cancer progression. Hence, the level of SOX2 expression in a tumor represents a prognostic factor to determine the clinical outcome for a cancer patient (Table 1). Expectedly, a great number of studies correlates high SOX2 expression in different cancer types with a poor prognosis, among them breast,

oral/tongue, esophageal, lung, hepatocellular, colorectal, ovarian and prostate cancer as well as nasopharyngeal and sinonasal carcinoma [66,69,84,94,105–111]. Poor prognosis is usually associated with high migrative, invasive and consequently metastatic capacity of tumor cells. A prerequisite for acquiring these characteristics is EMT. Evidence for SOX2 promoting EMT in cancer cells has been found for laryngeal, esophageal, gastric, pancreatic, colorectal, lung, breast and prostate cancer [112–119]. A direct correlation between high SOX2 expression and increased invasive and metastatic capacity of tumor cells has been shown for colorectal and prostate cancer. Here, the amount of lymphatic and distant metastases is increased in tumors that express SOX2 [120,121]. In esophageal squamous cell carcinoma increased invasion, poor differentiation and incomplete surgical resection were linked to tumors with more than 50% of SOX2-expressing cells [106]. More examples of tumor types in which SOX2 expression correlates with increased migrative and invasive capacity comprise gastric, liver, prostate and laryngeal cancer [74,106,111,113,116,117,122]. Although these examples demonstrate that high SOX2 expression is very often linked to cancer progression, one must keep in mind that in the end not a single molecule but the interplay between a multitude of factors determines the course and severity of cancer. This is emphasized best by studies showing that in gastric and squamous cell lung cancer poor prognosis is not associated with high but with low SOX2 expression [74,123]. Interestingly, for ovarian cancer as well as head and neck squamous cell carcinoma some studies show that poor prognosis is linked to high SOX2 expression while others show the opposite [71,94,[105]125]. The development of resistances to established cancer therapeutics is closely linked to clinical prognosis and represents a massive problem that drastically limits the efficacy of the available therapeutic options. Many studies reported on the involvement of SOX2 in therapy resistance and demonstrated that it affects a wide range of molecular mechanism. The sensitivity of breast CSCS to paclitaxel was found to be dependent on the presence of SOX2. Knockdown of SOX2 increased chemosensitivity and reduced the invasion capacity of these cells [126]. Similarly, breast cancer cells with a stem cell-like phenotype are resistant to tamoxifen. This resistance can be abrogated by knocking down SOX2 [84]. Upregulation of SOX2 in breast cancer cells can be triggered by tumor-associated macrophages via EGFR and STAT3 activation resulting in chemoresistance [127]. In PC3 prostate cancer cells elevated SOX2 levels promote resistance towards paclitaxel via activating the PI3K/Akt pathway [128]. SOX2 was also linked to antiandrogen resistance in prostate cancer since knocking down SOX2 negates this resistance [129]. Ovarian cancer cell lines developed resistance to carboplatin, cisplatin and paclitaxel after ectopically overexpressing SOX2. On the other hand, knockdown of SOX2 in SOX2-positive ovarian cancer cells renders them sensitive to these compounds [104][]. Like in prostate cancer, resistance to paclitaxel in ovarian cancer has been shown to be promoted by SOX2 via the PI3K/Akt pathway [131]. In glioma chemoresistance was found to be mediated by upregulation of the ABCC3 and ABCC6 transporters [132] or via activation of the mTOR pathway [78]. SOX2 as a mediator of drug resistance was also confirmed for glioblastoma and medulloblastoma [83,133]. In gastric cancer chemoresistance to doxorubicin is reduced after knocking down SOX2. This results in increased apoptosis and reduced tumorigenicity [134]. High SOX2 expression is connected to gemcitabine resistance in pancreatic cancer. Here, SOX2 promotes the expression of the transcription factors GLI1 and GLI2 which in turn activate the transcription of CD24, a marker of tumor-initiating cells in pancreatic cancer [135]. Chen and colleagues discovered that the long non-coding RNA LBCS strongly suppresses the self-renewal, chemoresistance and tumor initiation capacity of bladder CSCs by preventing SOX2 transcription. Accordingly, low levels of LBCS correlate with a poor prognosis of bladder cancer patients [136]. Colorectal cancer patients with tumors expressing high amounts of SOX2 respond less to chemoradiotherapy and show higher relapse rates [106]. Similarly, patients with cervical SCC highly positive for SOX2 respond much less to radiotherapy than patients whose tumors express low levels of SOX2 [137]. In head and neck SCC chemoresistance is confered by SOX2-induced ABCG2 transporter expression. Knocking down SOX2 results in reduced ABCG2 expression and restored sensitivity to chemotherapy [94]. In lung cancer SOX2-expressing cells are resistant to paclitaxel and cisplatin [66]. Another study demonstrated that increased sensitivity to cisplatin can be achieved by treating lung cancer cells with rapamycin. Rapamycin inhibits the mTOR pathway and thereby blocks SOX2 expression [138]. Also in terms of targeted therapy, SOX2 expression was linked to resistance mechanisms. It was shown for NSCLC that SOX2 expression favors a CSC phenotype which is resistant to EGFR inhibitors [139]. Recently, our group succeeded in showing that SOX2 is upregulated via STAT3 in melanoma cells in response to BRAF inhibitor treatment. After that, SOX2 activates the transcription of CD24 which results in decreased activity of Src and STAT3 and eventually in increased resistance towards BRAF inhibitors [140].

5. Conclusions and future perspectives

SOX2 is absolutely essential for normal embryonic development and its absence results in early embryonic lethality. It is also well-known for being one of the members of the core-transcriptional network that guarantees the maintenance of stemness in pluripotent stem cells. Here, we summarized its role in cancer pathogenesis showing that SOX2 contributes to cancer progression and the emergence of therapy resistance in a plethora of different cancer types. SOX2 seems to trigger a fundamental mechanism that enables cancer cells to acquire a stem-like phenotype independent of the cell lineage of origin of a particular cancer. Since therapy resistance and clinical prognosis are closely related to the expression and activity of SOX2 it is of great importance to uncover the molecular network that is influenced and controlled by SOX2. Compounds that inhibit SOX2 or its downstream effectors might have the potential to be effective in the treatment of different types of cancer. On the other hand, SOX2 is still expressed in many tissues in the adult and it is likely that targeting SOX2 directly might cause severe, unwanted side effects that outweigh the merits of SOX2-specific cancer therapy. Future studies will shed light on molecular pathways and signaling cascades affected by SOX2 activity potentially discovering points of vantage for efficient new cancer therapies.

Declaration of Competing Interest

No potential conflicts of interest were disclosed

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