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Review Article

Paradoxical role of SOX2 in gastric cancer

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Abstract: Sox2 is a critical regulator of embryogenesis and necessary for cellular reprogramming. It also plays an important role in tissue homeostasis and regeneration, maintaining the population of undifferentiated adult stem cells. Like various developmental and stem cell genes, SOX2 is aberrantly expressed and amplified in several human cancers. Moreover, functional studies have shown that it regulates many biological processes including cell proliferation, apoptosis, self-renewal and invasion. While it is oncogenic in most cancers, SOX2 activity is controversial in gastric cancer, where it might behave as a tumor suppressor in some situations. In this review, we discuss its role in cancer biology, with particular attention to what is known about the involvement of SOX2 in gastric cancer biology.

Keywords: SOX2, gastric cancer, H. pylori, stem cells

Introduction

Studies on SOX proteins started with the discovery of the mammalian testis-determining factor *Sry*. This protein contains a high mobility group (HMG), which permits specific DNA binding [1]. Proteins carrying an HMG domain with 50% or higher amino acid similarity to that of Sry are called Sox proteins (from Sry-related HMG box). Therefore, SOX is a family of transcription factors characterized by containing a conserved HMG domain, which allows them to act as activators or suppressors of gene transcription. There are at least 20 members of this family in humans and mice, and based on their degree of HMG sequence identity, they are divided into 8 groups [2]. In general, members within a group have a sequence identity of more than 80% in their HMG domain and share other well-conserved regions. Additionally, they present overlapping expression patterns, share biochemical properties, and have redundant or synergistic functions [3]. In contrast, members from different groups usually have distinct functions. SOX proteins are essential developmental regulators with functions in sex determination, chondrogenesis, hematopoiesis, neural crest development and neurogenesis. Moreover, they are involved in the instruction of cell fate and stem cell maintenance during embryogenesis as well as in adult tissue homeostasis and regeneration [4]. In recent years, a growing body of evidence has emerged indicating the presence of SOX family gene dysfunction in several human diseases, including a variety of cancers. Most of these diseases originate in tissues where SOX family members are expressed during embryonic development, suggesting that they are involved in promoting and facilitating the development of disease.

SOX2

SOX2 belongs to the SOXB1 subgroup along with the closely related SOX1 and SOX3 genes. It is required for establishing embryonic stem cells and the maintenance of the early embryo [5]. It is also one of the factors necessary for reprogramming terminally differentiated cells into induced pluripotent stem cells [6]. Furthermore, Sox2 belongs to the core transcriptional circuitry found in the regulatory regions of many genes with embryonic stem cell-specific expression [7]. These findings demonstrate that Sox2 is a key factor in the control of embryonic stem cell fate and activity.

During development, Sox2 has additional functions emerging as a critical regulator of stem cell maintenance and cell fate decisions. Further, Sox2 plays a relevant role during adulthood controlling tissue homeostasis and regeneration. Its expression has been found to be elevated in various different populations of stem cells [8-11], and its presence at high levels can be used to identify quiescent stem cells and distinguish them from transient amplifying progenitors [12, 13]. In the central nervous system, it plays a particularly prominent role [14]. There, Sox2 expression is initiated concomitantly with the acquisition of neural progenitor identity, and high levels are indispensable for maintaining neural stem cell activity during embryogenesis and adult life [5, 15, 16]. Additionally, Sox2 becomes downregulated during differentiation, and as a consequence, it is not expressed in immature neurons. Consistent with this result, loss of the *Sox2* gene leads to premature neural stem cell differentiation [17], while overexpression of Sox2 maintains cells in a precursor state and prevents the expression of proneural genes. These activities make Sox2 fundamental for the control of stem cell fate.

During embryonic development, Sox2 is highly expressed in the developing foregut, where it plays an essential role in gastric patterning in a dose dependent manner [18]. In adulthood, Sox2 is expressed in the glandular epithelium of the stomach and genetic tracing experiments have demonstrated that *Sox2*$^+$ cells are capable of generating all cell types that give rise to gastric units. Moreover, ablation of these *Sox2*$^+$ cells leads to the disruption of the physiological renewal of the gastric epithelium, indicating an important role for Sox2 in gastric differentiation [11]. Moreover, Sox2$^+$ colocalizes with Troy$^+$ cells representing the population of gastric stem cells in the stomach body and antrum [19]. *In situ* analysis performed in chicken embryos showed that Sox2 regulates pepsinogen expression in the developing gut [20]. Likewise, it has been shown that Sox2 induces the expression of the pepsinogen A gene in human embryonic kidney-derived cells [21]. Subsequently, it has been suggested that Sox2 seems to be essential to maintain the differentiation of oxyntic and pyloric glands [22]. These activities make Sox2 fundamental for the control of adult stem cell fate and tissue maintenance, particularly in the brain but also in the gastrointestinal compartment.

SOX2 in disease

The pivotal role of SOX2 during embryogenesis and tissue homeostasis in adults makes plausible that its deregulation might be involved in different diseases. Indeed, *SOX2* heterozygous inactivating mutations are known to cause anophthalmia-esophageal-genital (AEG) syndrome [23, 24]. *SOX2* mutations have also been associated with anterior pituitary hypoplasia, hypogonadotropic hypogonadism, variable defects affecting the corpus callosum and mesial temporal structures, hypothalamic hamartoma, sensorineural hearing loss, and esophageal atresia [25]. Apart from these genetic mutations, the levels of Sox2 are altered with physiological aging. Specifically, Sox2 expression was observed to qualitatively decrease in several areas of the brain, including neural stem cells, in aged mice [26]. Conversely, its expression was found to be elevated in old neural stem cells *in vitro* and *in vivo* in a mouse model with delayed adult stem cell exhaustion, cognitive decline, and extended lifespan [27]. These data indicate that Sox2 decline correlates with neural stem cell aging and suggest that this decline might be responsible for brain disease in some situations. In line with this, it has already been postulated that SOX2 plays a role in Alzheimer's disease, the most common neurodegenerative disorder, where patients show a progressive loss of memory, cognitive function, and dementia [28]. However, so far, there are no functional or biological data to support this idea. In addition, future studies should explore the role of Sox2 in other aging-related diseases. In contrast, SOX2 deregulation has been observed in several types of tissue in cancer. Indeed, intensive work has been carried out to establish the expression and function of this master regulator of stem cell activity in this disease. The next part of the review consists of a summary of the influence of SOX2 in different types of cancer, and to conclude we present an overview of the impact of the protein on gastric adenocarcinoma in particular.

SOX2 in cancer

SOX2 deregulation occurs in several types of cancer, and, in most cases, the protein is aberrantly overexpressed and acts as an oncogene. Probably the best-established case is squamous cell carcinoma (SCC), in which genomic

Table 1. Oncogenic activity of SOX2

Cancer	Function	Mechanism	Reference
SCC	↑proliferation; ↑tumor formation; ↑self-renewal CSCs amplification (yes)	↑SOX2 → ↑STAT3	[29, 31, 32]
Glioblastoma	↑proliferation; ↑invasion; ↑migration; ↑tumor formation; ↑self-renewal CSCs; amplification (yes)	TGF-β pathway → SOX4 → ↑SOX2	[37, 44, 45, 46,]
Pituitary	↑proliferation; ↑tumor formation; ↑self-renewal	↑SOX2 → WNT/β-catenin pathway	[50, 51]

amplification of *SOX2* occurs in the esophagus and lung [29, 30] *SOX2* was identified as an SCC driver and oncogene with a major impact on global SCC transcriptome deregulation, thereby contributing to activate embryonic stem cell-like transcriptome phenotypes [29]. Further, studies with SOX2 gain-of-function mouse models demonstrated that Sox2 overexpression was oncogenic *in vivo* [31] and synergizes with inflammation-induced STAT3 activation to transform basal progenitors and initiate SCC in the esophagus [32]. Taken together, these data establish SOX2 as a key regulating transcription factor in lung and esophagus SCC, modulating both direct and indirect target genes involved in tumor progression. More recently, it has also been shown that SOX2 controls tumor initiation in skin SCC, although in this case, it is transcriptionally regulated and not linked to genomic amplification [33]. Notably, Sox2 was found to be the most elevated factor in a population of cancer stem cells (CSCs), and experiments with conditional deletion and lineage-tracing mouse models demonstrated that Sox2 regulates the function of CSCs, establishing a continuum between tumor initiation and progression in primary skin tumors [33, 34]. These effects are exerted through direct interaction with target genes controlling stemness, survival, proliferation, adhesion and invasion [33]. Overall, these data demonstrate that SOX2 plays several roles in cancer, from an oncogenic driver to a marker and regulator of tumor-initiating cells and CSCs.

SOX2 genomic amplification has also been described in human small cell lung cancers and glioblastoma. In these cases, genomic amplification leads to overexpression of SOX2 [35-38]. Moreover, it is overexpressed in other types of cancer including sarcomas [39], prostate cancer [40], breast cancer [41], and brain tumors [42], further indicating that the mechanism of *SOX2* activation in cancer is not exclusively associated with genomic amplification. A brief outline of the role of SOX2 in some of these types of cancer is included below and summarized in **Table 1**.

Several groups have observed aberrant expression of SOX2 in central nervous system tumors. In fact, glioblastoma, medulloblastoma, ependymoma and pontine gliomas express high levels of SOX2 [36, 37, 42, 43]. In glioblastoma, expression of SOX2 together with other stem cell markers identifies a subset of patients with poor clinical outcome [41]. In addition to genomic amplification, SOX2 is regulated by both epigenetic changes [36] and transcriptional regulation through Transforming Growth Factor-β (TGF-β) (45). Functionally, SOX2 is enriched in human-derived CSCs and its genetic inhibition causes depletion of self-renewal and tumor regression [44, 45]. It maintains CSC self-renewal by using the same molecular targets as normal neural stem cells, a fact which supports a hierarchical model of brain cancer controlled by SOX2 [43, 45]. Additionally, SOX2 is one of the transcription factors responsible for the reprogramming of glioblastoma cells into glioma stem cells (GSCs) [46], together demonstrating that SOX2 sustains stemness, maintenance of tumorigenicity and glioblastoma progression. In medulloblastoma, rare *Sox2*$^{+}$ cells are responsible for hierarchical growth and therapy resistance in the sonic hedgehog group [43]. These actions indicate that SOX2 can be considered a putative therapeutic target and highlight the relevance of identifying agents that could silence its expression [47]. Consistent with this idea, downregulation of *SOX2* conferred sensitivity to treatment with platelet-derived growth factor (PDGF) and insulin-like growth factor 1 receptor (IGFR1) inhibitors [48]. Moreover, vaccination with Sox2 peptides elicited a response that significantly delayed tumor development in mice [49], underscoring the feasibility of using SOX2 as a target in various therapeutic approaches for brain tumors.

In the pituitary gland, it has been shown that *Sox2* haploinsufficiency significantly decreases tumor formation in *p27*^{Kip} mutant mice [50]. On the other hand, genetic lineage tracing demonstrated that targeted expression of oncogenic β-catenin in *Sox2*$^{+}$ cells gives rise to pituitary

tumors. Surprisingly, the tumor mass is not derived from these *Sox2*$^{+}$ cells [51], showing that while these cells are the cell of origin of pituitary tumors, Sox2 plays different roles in the induction and maintenance of oncogenesis within different tissues.

SOX2 overexpression is detected in different types of breast cancer, and these elevated levels correlate with higher tumor grade, lymph node metastasis and poor clinical outcome [41, 52-54]. Moreover, SOX2 expression is enriched in breast CSCs, which are responsive to the Sox2 regulatory region 2 (SRR2) [55]. Enhanced expression of SOX2 induces proliferation *in vitro* and tumor initiation *in vivo* [54]. These functions are promoted by facilitating the G1/S transition and inducing *cyclinD1* gene upregulation, β-catenin acting as a transcription partner for SOX2 [52].

SOX2 is also overexpressed in prostate cancers and its levels are significantly higher in androgen-independent than in androgen-dependent human prostate cancer cells [56, 57]. Moreover, elevated SOX2 expression predicts cancer progression and lower patient survival in individuals with metastatic prostate cancer [58]. Functionally, SOX2 activity facilitates cell proliferation and evasion of apoptosis by activating the epidermal growth factor receptor/phosphatidylinositol 3-kinase/protein kinase B (EGFR/PI3K/PKB) pathway [56], but at the same time, SOX2 plays a critical role in EGFR-mediated self-renewal of prostate CSCs [59]. These data suggest that SOX2 promotes progression of prostate cancer and might serve as a useful therapeutic target for this type of neoplasia.

All these observations indicate that SOX2 protein can induce aberrant cell growth and tumorigenesis. In addition, SOX2 function in cancer has been associated with CSC activity and maintenance, and vice versa, a molecular characteristic of CSCs is their elevated expression of SOX2.

Gastric cancer

Gastric cancer is the second most common cause of cancer-related mortality in the world, and developing countries are the most affected [60]. It is preceded by a prolonged precancerous process. The first recognized histological change is active chronic inflammation associated with *Helicobacter pylori* (*H. pylori*) infection, which may persist as non-atrophic chronic gastritis, or advance to multifocal atrophic gastritis, the first real step in the precancerous cascade. The following step is intestinal metaplasia, which is considered a point of no return in gastric carcinogenesis. It represents a change from a gastric to an intestinal differentiation profile, and is the most common premalignant condition of the stomach. The next step is dysplasia, and the final stage is invasive carcinoma, which is associated with degradation of the intercellular matrix [61].

H. pylori is the main etiological agent of gastrointestinal infections in children and adults. The prevalence of infection varies considerably across geographical regions [62]. Natural acquisition of *H. pylori* infection mostly occurs during childhood. Once established, the bacterium persists within the gastric mucosa for life if left untreated [63]. *H. pylori* interacts with gastric epithelial cells and elicits a host inflammatory response that includes the infiltration of the mucosa by polymorphonuclear leukocytes, macrophages, and T- and B-lymphocytes. The inflammatory response has a slow onset and persists for a long period of time, becoming chronic [61]. The condition is persistent and, in most cases, the infection results in asymptomatic chronic active gastritis. H. *pylori* exhibits a high level of genetic diversity, and there are various virulence factors targeting different cellular proteins which modulate the host inflammatory response, and initiate distinct “hits” on the gastric mucosa. Cytotoxin-associated gene A (*cagA*) or vacuolating cytotoxin gene (*vacA*) are the major pathogenic *H. pylori* virulence factors [64].

Gastric cancer is a heterogeneous cancer, which may be classified into several distinct subtypes based on molecular and genetic mutations [65]. This heterogeneity is also observed at the cellular level. In particular, several studies support the existence of a subpopulation of cancer cells with stem cell characteristics [66]. It has been postulated that such cells are responsible for gastric cancer initiation, progression and metastasis. Evidence also backs the view that CSCs are the primary target of *H. pylori* infection. Specifically, it seems that *H. pylori* infection of gastric epithelial cells disrupts the epithelial apical junctional complex and induces the transition to a mesenchymal

Table 2. Tumor suppressor activity of SOX2 in gastric carcinogenesis

Type of study	Main Outcomes	Mechanism	Reference
In vitro (SOX2 overexpression)	↓proliferation; ↑cell-cycle arrest; ↑apoptosis	Cyclin D1 and pRb, ↓$p27^{Kip1}$	[72]
In vivo (74 primary gastric carcinoma)	↑*SOX2* methylation → ↓SOX2; SOX2 methylation was associated with shorter survival		
In vitro and *in vivo* (SOX2 overexpression)	↓proliferation; apoptosis; ↓invasion; ↓motility, ↓tumorigenesis in vivo	↓SOX2 → ↓PTEN/PKB	[75]
In vivo (755 stomach samples)	SOX2 is downregulated progressively during gastric carcinogenesis		
In vitro (*H. pylori* co-culture)	*H. pylori* → ↓SOX2	↓SOX2 → CDX2	[22]
In vitro (*H. pylori* co-culture) and *in vivo* (*H. pylori*-infected human gastric mucosa)	*H. pylori* → ↓SOX2 → may trigger Correa's cascade	IL4/STAT6 pathway →↓SOX2 → CDX2	
In vitro and in a mice model infected with *Helicobacter* spp	*H. pylori* upregulates the BMP pathway; and CDX2 and SOX2 are downstream targets of the BMP pathway in gastric carcinogenesis	BMP pathway → ↓SOX2 → CDX2	[82]

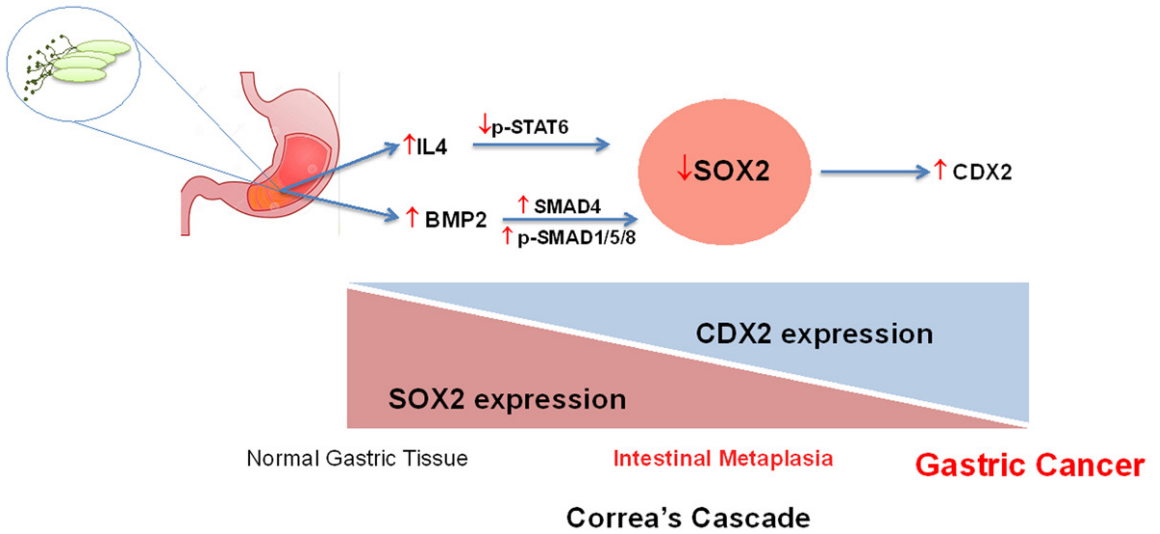

Figure 1. SOX2 activity in gastric carcinogenesis. The upstream epigenetic regulation of *SOX2*, and its downstream targets. SOX2 is frequently downregulated in gastric carcinogenesis, affecting a wide range of cellular processes including proliferation, apoptosis and metastasis.

phenotype [67], a process widely associated with cell plasticity and cancer [68]. Moreover, infection with *H. pylori* in gastric cancer cells promotes epithelial-mesenchymal transition-like changes, generating cells with stem cell properties [69]. There is also evidence that *H. pylori* establishes a symbiosis with gastric stem cells, promoting cancer progression [70]. Next, we will review what is known about the role of SOX2 in gastric cancer.

SOX2 in gastric cancer

As previously described, SOX2 deregulation occurs in cancer and, in the majority of the cases, it is overexpressed and acts as an oncogene. The exception is gastric cancer, in which SOX2 seems to act as a tumor suppressor (**Figure 1** and **Table 2**). Notably, several authors have observed that SOX2 is frequently downregulated in gastric cancer [71-76]. Furthermore, low SOX2 expression is associated with a short survival time [72], and poor prognosis [74]. In contrast, higher SOX2 levels are found among patients who have a better prognosis [74]. In a large set of patients, Wang and coworkers demonstrated that SOX2 expression is progressively reduced during gastric carcinogenesis, from healthy cells to invasive cancer cells, including a series of premalignant states, supporting the role of lower levels of SOX2 expression as a robust predictor of disease outcome [75]. Similarly, downregulation of SOX2 is linked to diffuse cancer, its expression being a good biomarker to discriminate between tumor (negative) and non-tumor (positive expression), and also to distinguish high/low grades of tumor malignancy [76]. The regulation of SOX2 expression in gastric cancer has been mostly associated with epigenetic changes. In particular, aberrant DNA methylation has been shown to be a key mechanism underlying SOX2 downregulation in a set of primary gastric carcinoma samples [72]. Besides promoter methylation, miR-126 overexpression also decreases SOX2 levels and therefore acts as a tumor suppressor [73] (**Figure 2**).

Recently, it has been shown that SOX2 has an important role in gastric differentiation [77]. It is known that during gastric carcinogenesis Caudal-related homeobox 2 (CDX2) is critical for intestinal differentiation driving the onset of intestinal metaplasia [78, 79]. Further, Camilo and coworkers showed that SOX2 is associated with gastric differentiation in incomplete intestinal metaplasia and is lost in the progression to dysplasia, whereas CDX2 is acquired de novo in intestinal metaplasia and maintained in dysplasia [77]. Based on these findings, the authors hypothesized that changes in the balance between gastric and intestinal differentiation programs might interfere with the progression of gastric carcinogenesis [77]. Notably,

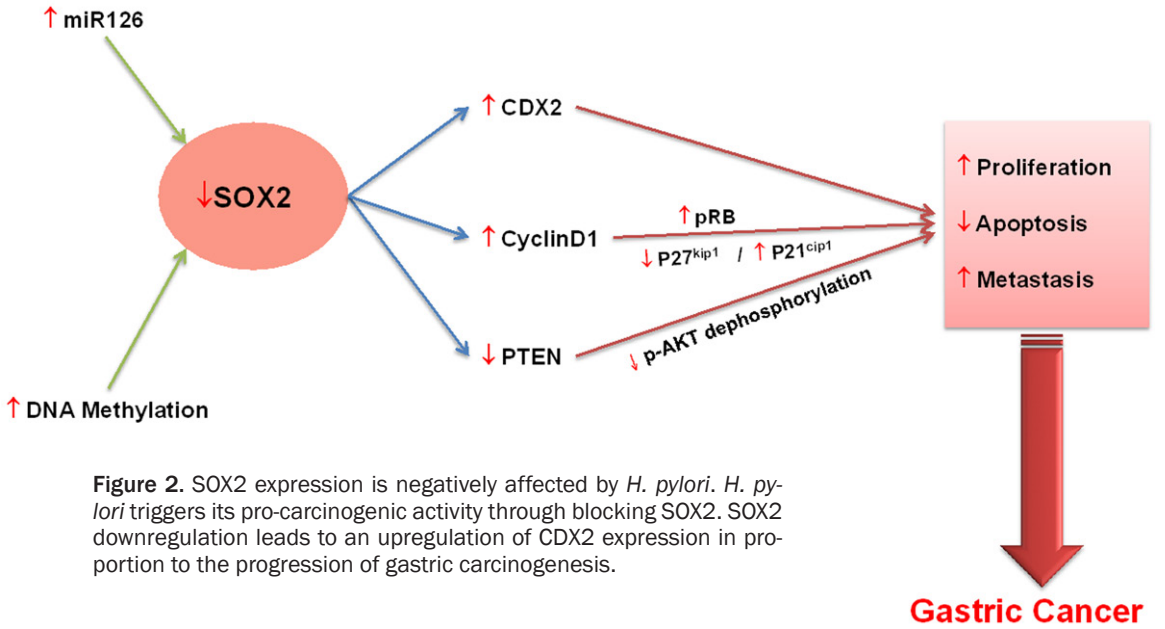

Figure 2. SOX2 expression is negatively affected by *H. pylori*. *H. pylori* triggers its pro-carcinogenic activity through blocking SOX2. SOX2 downregulation leads to an upregulation of CDX2 expression in proportion to the progression of gastric carcinogenesis.

SOX2 and CDX2 expression were found in about half of cases, but the interaction of these two transcription factors in gastric carcinogenesis remains to be investigated.

Functional characterization performed in gastric epithelial cell lines showed that SOX2 ectopic activation inhibits cell proliferation through G1 cell-cycle arrest, and induces apoptosis by decreasing cyclin D1 and phosphorylated Rb, and increasing $p27^{Kip1}$ protein levels [72]. Overall, the authors observed that SOX2 plays a critical role in gastric carcinogenesis, operating as a tumor suppressor through SOX2 downregulation. Similarly, Wang and coworkers verified that enhanced SOX2 expression inhibited proliferation, increased apoptosis, and reduced invasion and motility both *in vitro* and *in vivo* [75]. Mechanistically, SOX2 directly transactivated PTEN. Therefore, this SOX2-dependent PTEN upregulation may directly orchestrate downstream dephosphorylation of protein kinase B, affecting diverse cellular phenotypes such as survival, growth, proliferation, and migration [75] (**Figure 2**). These studies show that SOX2 plays important roles in inhibiting growth of gastric epithelial cells through cell-cycle arrest and apoptosis.

H. pylori infection is responsible for atrophic gastritis in both the antrum and body of the stomach [61], this type of gastritis being histopathologically characterized by loss of oxyntic and pyloric glands and leading to oxyntic and pyloric metaplasia [80]. SOX2 expression is negatively affected by *H. pylori* and this inhibition leads to an upregulation of CDX2 expression in proportion to the transdifferentiation into intestinal metaplasia in *H. pylori*-infected mucosa [22, 81]. Mechanistically, SOX2 is regulated by interleukin 4 through the Signal Transducer and Activator of Transcription 6 (STAT6) signaling pathway *in vitro*. Such regulation is suppressed by *H. pylori* [22]. These results suggest that downregulation of SOX2 in oxyntic and pyloric glands, by a Th1-dominant host immune response to this bacterial species, induces the transdifferentiation into intestinal metaplasia. Additionally, experiments *in vitro* and in a mice model infected with *Helicobacter* spp demonstrated that CDX2 and SOX2 are downstream targets of the bone morphogenetic protein pathway in gastric carcinogenesis. The authors showed that *H. pylori* upregulates this pathway through an increase in bone morphogenetic protein2 (BMP2), SMAD4 and pSMAD1/5/8 expression. Thus, SOX2 expression was downregulated by *H. pylori* and the BMP pathway [82]. From a mechanistic perspective, it was postulated that the activation of an intestinal differentiation program may occur concomitantly with the silencing of gastric differentiation, induced or controlled by SOX2 [82]. Another recent study identified that *H. pylori* might trigger its pro-carcinogenic activity through blocking SOX2 [75] (**Figure 2**).

However, other authors have verified that overexpression of SOX2 is associated with tumor invasion, lymph node metastasis and chemoresistance [83-86]. Tian and coworkers were able to show that SOX2 enhances the tumorigenicity and chemoresistance of cancer stem-like cells derived from gastric cancer, suggesting an oncogenic effect of SOX2 in the stomach [83]. In addition, it has been demonstrated that SOX2 overexpression is significantly correlated with lymph node metastasis and the stage of tumor invasion in gastric cancer, indicating that SOX2 might be a prognostic factor [84]. Hutz and coworkers showed that high levels of SOX2 are involved in gastric carcinogenesis by regulating the expression of genes associated with proliferation, apoptosis and cell cycle regulation, *in vitro* and *in vivo* [85]. Functionally, SOX2 suppression induced a decrease in cell proliferation which coincided with an increase in apoptosis in AZ-521 cells. Similarly, blocking of SOX2 in a xenograft mouse model resulted in reduced tumor growth [85]. Moreover, in human gastric tumor samples, SOX2 expression was observed in area with a high proliferation rate [85]. Recently, SOX2 overexpression was observed by other authors [86], a surge in the expression being attributed to *SOX2* locus copy number variation, and was related to the presence of regional lymph node metastases [86].

Concluding remarks

The outcome of SOX2 activation in cancer depends on the tumor origin and cellular context, likely reflecting its roles in different areas during development. In most types of cancer, the SOX2 protein can induce aberrant cell growth and tumorigenesis, whilst genetic inactivation impairs self-renewal and tumor growth. In addition, SOX2 functions in cancer are associated with CSCs, and vice versa, a molecular characteristic of CSCs is their elevated expression of SOX2. Therefore, it has been postulated that silencing SOX2 activity should be investigated as a novel therapeutic approach in various types of cancer, including brain, breast or skin. However, a note of caution needs to be sounded in the case of gastric cancer, in which it has been shown that, at least in a few subsets of samples, SOX2 levels are decreased and this low expression correlates with poor patient outcome. Moreover, functional studies have demonstrated that SOX2 might promote or inhibit tumor growth, likely depending on the cell type. *H. pylori* infection induces gastric cancer progression through an increase in both reactive oxygen species generation and mutation rate. As pointed out in this review, infection suppresses SOX2, which further supports the view that SOX2 plays a tumor suppressor role in gastric cancer. Future experiments with lineage tracing and gain- and loss-of-function mouse models are required to clarify the role of SOX2 in this particular type of cancer and deepen our understanding of *H. pylori*/SOX2-related molecular mechanisms in the context of CSCs and associated with gastric carcinogenesis.

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