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Minireview

SOX genes as prognostic markers and potential therapeutic targets in cancer

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Summary. Human *SOX* genes (SRY-related HMG-box genes) represent a family of transcription factors with essential roles in various developmental processes. They control stem cell pluripotency maintenance, cell fate determination and cell differentiation. In the past decade, the focus on *SOX* genes research changed from their roles in development to their functions in disease, particularly cancer. The growing amount of data has shown *SOX* genes to be amplified in various types of cancer. SOX proteins are involved in cancer cell functions through modulations of signaling pathways and protein-protein interactions. In this paper, we review the roles of *SOX* genes in glioblastoma, nonseminoma testicular germ cell tumors (TGCT) and cervical carcinoma, focusing on our recent findings about the roles of *SOX1*, *SOX2*, *SOX14* and *SOX18* in these cancer types. We also evaluate the potential use of these genes as diagnostic markers, indicators of metastasis and targets in new therapeutic approaches.

Keywords: cervical carcinoma, glioblastoma, nonseminoma TGCT, *SOX* genes.

SOX genes basics

The SOX protein family includes more than 20 members in humans and mice (Schepers et al. 2002), divided into 8 groups (A-H) (Schepers et al. 2002). This classification is based on the homology in their unique DNA binding domain, the HMG (high mobility group) box, as well as their structural and functional characteristics. SOX proteins within the same group have high sequence homology, not only within the HMG domain (more than 80%) but also in the surrounding N- and C-terminal domains (Wegner 2010).

High structural conservation and overlapping expression profiles are responsible for synergistic or redundant functions of members within the same group. Despite recognizing similar DNA binding consensus sequences, SOX proteins belonging to different groups acquire diverse functions due to an altered affinity for consensus site flanking regions (Wegner 2010). They are also subjected to various posttranslational modifications and establish many protein-protein interactions such as homo- and heterodimerization among SOX proteins and other factors (Wegner 2010). These characteristics enable SOX proteins to secure various roles in basic biological processes (Wegner 2010). The fact that SOX proteins are regulators of stem cell pluripotency maintenance, cell differentiation and cell fate determination makes them essential factors in human development. They play many important roles in neurogenesis, sex determination, chondrogenesis, hematopoiesis, homeostasis and regeneration (reviewed in Sarkar and Hochedlinger 2013). The growing amount of data has revealed aberrant functions of *SOX* genes in various human pathologies, including cancers (Sarkar and Hochedlinger 2013). In the context of cancer biology, many findings support the involvement of different *SOX* genes in cancer development, and the *SOX* groups that have been most extensively studied in human malignancies are *SOXB1*, *SOXC*, *SOXE* and *SOXF* (Thu et al. 2014).

In this review, we summarize the role of SOX proteins in glioblastoma, cervical carcinoma and nonseminoma TGCT with specific emphasis on our study of selected members of the SOXB (SOX1, SOX2 and SOX14) and SOXF (SOX18) groups.

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SOXB group

Based on sequence similarity structure and functional studies, the *SOXB* group is divided into two subgroups, *SOXB1*, which includes *SOX1*, *SOX2*, and *SOX3*, and *SOXB2*, comprising *SOX14* and *SOX21* (Schepers et al. 2002). Both groups are implicated in the maintenance of neural stem cells and in neural differentiation (Pevny and Placzek 2005). Due to the high sequence conservation, SOXB1 proteins have very similar biological activities and exhibit functional redundancy in regions where they show overlapping expression patterns, such as neural progenitors (Pevny and Placzek 2005). Their function is context-dependent or cell-type-specific due to complex interplay with other transcription factors. During the early stages of CNS development, it was proposed that vertebrate SOXB2 transcription factors target the same genes as SOXB1 activators, but with the opposite effect (Uchikawa et al. 1999).

It is well established that members of the *SOXB* group influence oncogenesis and the malignant properties of various cancers (Acloque et al. 2011; Thu et al. 2014). Moreover, *SOXB* genes (except for *SOX14*) may serve as serological markers for small cell lung carcinoma (Gure et al. 2000).

SOXF group

The SOXF group consists of SOX7, SOX17 and SOX18 transcription factors that play important roles in vascular development and postnatal neovascularization (Matsui et al. 2006; Cermenati et al. 2008). Mutations in these genes are associated with aberrant vascular conditions in humans. Dominant and recessive mutations of *SOX18* have been found to underlie the human hereditary syndrome hypotrichosis-lymphedema-telangiectasia (Irrthum et al. 2003). In the last decade, several publications analyzed both *SOXF* expression in various carcinomas and their function *in vitro* and *in vivo*. *SOX7* and *SOX17* are mostly recognized as tumor suppressors and their downregulation in various carcinomas is correlated with poor prognosis (Tang et al. 2014; Liu et al. 2016; Zhang et al. 2016b). On the other hand, elevated *SOX18* expression has been detected in various carcinomas and also correlated with poor prognosis (Pula et al. 2013; Jethon et al. 2015)

SOX genes in glioblastoma

Glioblastoma multiforme (GBM) is the most common, aggressive and malignant adult brain tumor with an associated median survival of 15 months (Ostrom et al. 2014). This type of tumor comprises a morphologically, phenotypically and genetically heterogeneous population of cells composed of tumor and tumor-stem cells. Glioma stem cells (GSCs) represent a subpopulation of cells driving tumor propagation and growth (Suva et al. 2014). It was demonstrated that these cells are required for GBM occurrence, development, progression, metastasis, high recurrence rate, drug- and radio- resistance (Yang et al. 2015).

Several *SOX* members are involved in glioblastoma development, including *SOX2, SOX4*, *SOX9* and *SOX10*, while *SOX11* and *SOX21* have been shown to act as tumor suppressors in this tumor type (de la Rocha et al. 2014). The oncogenic activity and clinical relevance of *SOX2* is well established and most of its roles are linked to GSC regulation (reviewed in de la Rocha et al. 2014). In contrast, the function of *SOX1* and *SOX3* in GBM is almost unknown. Microarray analysis in *SOX2* knockdown glioma cells identified *SOX1* as one of the genes whose expression was altered (Fang et al. 2011). Moreover, literature data identified SOX1 as a substitute of SOX2 in the transcription factor cocktail that is required for the full reprogramming of GBM cells. This replacement led to *in vitro* reprogramming of glioblastoma cells, but could not initiate tumors *in vivo* (Suva et al. 2014). Taken together, these findings lead to the hypothesis that *SOX1* might have a role in glioblastoma.

To investigate this hypothesis, we started with an analysis of *SOX1* expression in glioblastoma tissue samples and found that *SOX1* is overexpressed in a subset of glioblastoma human biopsies when compared to healthy human brain tissue. We found that its high levels of expression are associated with shorter overall patient survival (Garcia et al. 2017). These data support the clinicopathological and prognostic significance of *SOX1* expression, and, to our knowledge, this is the first evidence of a high *SOX1* expression level being a negative prognostic biomarker in cancer.

Furthermore, we found that *SOX1* expression is highly elevated in the pool of patient-derived GSCs, as well as in de-differentiated stem cells derived from conventional glioblastoma cell lines (Garcia et al. 2017). The knockdown of *SOX1* in GSCs decreased their proliferation, viability, self-renewal activity and differentiation capacity *in vitro*, and delayed the formation of tumors when the cells were xenotransplanted into the brain of nude mice (Garcia et al. 2017). On the other hand, overexpression of *SOX1* promoted the self-renewal and proliferation of GSCs (Garcia et al. 2017). These results indicate that *SOX1* expression is necessary for GSC maintenance, most likely through the regulation of the interplay between proliferation, self-renewal and differentiation.

Previously, it was demonstrated that SOX1 acts as a tumor suppressor through interaction with β-catenin, and the consequent inhibition of the Wnt signaling pathway (Tsao et al. 2012; Lin et al. 2013; Guan et al. 2014). Interestingly, these oncogenic properties of SOX1 in glioblastoma that we identified seem to be independent of the Wnt/β-catenin signaling pathway since the downregulation of *SOX1* did not affect the expression of β-catenin and its downstream target, c-myc (Garcia et al. 2017).

Bearing in mind our results, we propose that *SOX1* is one of the central players driving glioblastoma cell hetero-

geneity and plasticity, and that it could serve as a prognostic and therapeutic target in glioblastoma.

SOX genes in nonseminoma TGCT (testicular germ cell tumors)

Testicular germ cell tumors (TGCTs) are classified into two groups: seminomas and nonseminomas. The latter category comprises embryonal carcinoma, yolk sac tumor, immature or mature teratoma, choriocarcinoma and other rare trophoblastic tumors (Nonaka 2009).

Adequate treatment and prognosis in TGCTs is highly dependent on the precise diagnostic distinction of seminoma and nonseminoma germ cell tumors. Recent data suggest that the use of SOX proteins in immunohistochemical applications can be a useful diagnostic marker in TGCT (Nonaka 2009).

SOX2 has been reported in the literature as a diagnostic marker for embryonal carcinoma (Nonaka 2009). Previous studies have shown that SOX2 was expressed in pure embryonal carcinomas, in the embryonal carcinoma component of mixed germ cell tumors and in intratubular embryonal carcinoma (Nonaka 2009). Since SOX2 expression in seminoma tumors was not reported, SOX2 is a useful discriminatory marker between embryonal carcinoma and seminoma tumors. It is interesting that another SOX protein, SOX17, is exclusively expressed in seminoma, which makes these two genes valuable markers in TGCT diagnostics (Nonaka 2009).

Embryonal carcinoma (EC) cells are the undifferentiated and pluripotent component of nonseminoma TGCTs. The NT2/D1 cell line is one of the several well-established human TGCT cell lines that retains the pathogenomic and cellular features of this malignancy (Andrews 1998; Burger et al. 1998).

This model system was used in our study of the interplay between *SOXB1* and the WNT signaling pathway, and the implications of these interactions on the pathogenesis of this malignancy. It is well known that aberrant activation of Wnt signaling is associated with the onset of cancer. Using well-known inhibitors and activators of Wnt signaling, we investigated changes in *SOXB1* genes expression in NT2/D1 cells after altering Wnt activity. Our results demonstrated that activation of the Wnt signaling pathway led to increased expression of *SOX2* and *SOX3* genes (Mojsin et al. 2014; Mojsin et al. 2015). In line with this result, inhibition of the Wnt signaling pathway downregulated master factors of pluripotency, including *SOX2*, in NT2/D1 cells. The observed inhibition of pluripotency may be the mechanism underlying the antitumor and antimetastatic effects of Wnt inhibition in NT2/D1 cells (Mojsin et al. 2014).

We also demonstrated that there is a negative feedback loop between SOX2 protein and the central signaling molecule in the canonical Wnt pathway, β-catenin in NT2/D1 cells. Since β-catenin and SOX2 have been linked to self-renewal and pluripotency, this result might have implications for future research on the maintenance of the stemness and cell commitment of cancer stem cells (Mojsin et al. 2015).

A growing body of data supports our finding and suggests that SOX proteins act as feedback regulators of the Wnt signaling pathway (reviewed in Kormish et al. 2010). In cancer, SOX factors may influence tumorigenesis by modulating β-catenin activity and the expression of oncogenic Wnt target genes. For example, overexpression of SOX7 or SOX17 in human colon cancer cell lines suppresses β-catenin activity, reduces cyclin-D1 expression, consequently repressing proliferation (Kormish et al. 2010). Also, SOX2 is frequently upregulated in aggressive human breast carcinomas where it promotes β-catenin-stimulated proliferation (Kormish et al. 2010).

Literature data suggest that SOX2 has great potential as a clinical biomarker for various cancer types. However, SOX2 is not a good candidate for direct therapeutic targeting. Due to its importance in transcriptional regulation, direct interference with SOX2 expression may have severe side effects. Accordingly, targeting signaling cascades upstream and downstream of SOX2 may be a promising direction in the search for a therapeutic approach based on SOX2 inhibition (reviewed in Weina and Utikal 2014).

SOX genes in cervical carcinoma

According to World Health Organization, cervical carcinoma is the fourth most common cancer affecting women worldwide, at the same time being the fourth most common cause of cancer death. Although the etiology of most cervical cancers is related to human papilloma virus (HPV) infection, the viral infection is not sufficient for cervical cancerogenesis and tumor progression (Lorincz et al. 1987). The molecular mechanisms involved in malignant transformation and progression have been well documented in numerous studies of the genetic and epigenetic landscape of cervical carcinoma (Atkin and Baker 1997; Lai et al. 2008). The *SOX* family emerged as a new, but rapidly growing field of research interest, since recent data revealed its role in the pathogenesis of this malignancy.

Genome-wide differential analysis of the methylation status of cervical cancer revealed that *SOX1* is frequently methylated in invasive cervical squamous cell carcinomas (Lai et al. 2008). Also, *SOX14* is one of four hypermethylated markers with high sensitivity for both adenocarcinoma and squamous-cell cervical carcinoma, while it is unmethylated in normal tissue (Wang et al. 2016a). However, data regarding its function in cervical carcinoma are rather conflicting. In general, the role of *SOX14* in various carcinomas, including cervical, is mainly correlated with its downregulation, indicating its tumor suppressive role (Wang et al. 2016a). However, there are data showing that SOX14 can promote the proliferation and invasion capacity of cervical cancer

cells by activating the Wnt/β-catenin pathway (Li et al. 2015). Our findings are consistent with the suggestion that it acts primarily as a tumor suppressor, since we showed that the *SOX14* promoter region is hypermethylated in cervical carcinoma cell lines, leading to its almost undetectable expression level (unpublished data). Also, our previous work analyzed the functional crosstalk between members of the *SOXB1* and *SOXB2* subgroups in cervical cancer cells (Popovic et al. 2014). In particular, we investigated whether *SOX14* interferes with the expression of other *SOXB* members and demonstrated that *SOX14* overexpression downregulates the SOX1 protein level in cervical carcinoma cell lines, with no effect on other *SOXB* members (Popovic et al. 2014). Since *SOX1* is considered a tumor suppressor (Tsao et al. 2012; Lin et al. 2013), the molecular mechanisms involved in the regulation of its expression that rely on *SOX14* gain additional significance and need to be further investigated.

Changes in the activity of various signaling pathways are being recognized as important oncogenic switches in many epithelial tumors. Several studies reported on the correlation between Hedgehog (HH) pathway activity and its role in cervical carcinogenesis (Xuan et al. 2006; Bohr Mordhorst et al. 2014). Our findings link the regulation of *SOX18* transcription with HH signaling in cervical carcinoma cell lines (Petrovic et al. 2015). We identified *SOX18* as a novel, direct target of GLI1/2 transcription factors that act as final effectors of canonical HH signaling. Moreover, HH pathway inhibitors reduced SOX18 expression, thus opening the possibility to alter *SOX18* expression. Although *SOX18* was recognized as a potential target in antiangiogenic tumor therapy, it is well known that the targeting of transcription factors for therapeutic application can be challenging. We presented the first data showing that *SOX18* expression could be targeted by using well-known pharmaceutical inhibitors.

There are some conflicting data regarding the role of *SOX18* in the regulation of cancer cell proliferation. While some groups have presented data showing that the silencing of *SOX18* suppresses the proliferation of hepatocellular, breast and pancreatic carcinoma cells *in vitro* (Wang et al. 2015; Wang et al. 2016b; Zhang et al. 2016a), others have shown that there is no effect on cell proliferation (Pula et al. 2013). Our research on cervical carcinoma cell lines showed that overexpression of either wild type *SOX18* or its dominant-negative counterpart, used for suppression of its function, does not change cellular proliferation or viability in *in vitro* assays. This was accompanied by unchanged cyclin D1 expression. On the other hand, all available data, together with our findings, agree that SOX18 is involved in the regulation of carcinoma cell migration. By applying various methodologies, we showed that SOX18 is able to promote both migration and invasion of cervical carcinoma cells *in vitro*. Also, our results imply that SOX18 does not only increase cell motility, but also alters the mode of cell migration, switching a cell's motility mode from cohesive to single cell motility (Petrovic et al. 2015). Changes in the mode of cell motility affect metastasis. It was shown that single cell motility increases the ability of cells to enter into the bloodstream, while cohesive motility reduces cell entrance into the bloodstream but allows lymphatic spread (Giampieri et al. 2009). Our findings indicate that SOX18 could promote blood-borne metastasis.

The identification of novel potential targets in carcinoma cells could provide many opportunities for developing novel therapeutic strategies for cancer. Evidence shows that the targeting of transcription factors for therapeutic applications can be difficult. Possible strategies designed to overcome these obstacles are discussed below.

SOX transcription factors as potential targets in anticancer therapies

Pharmacological targeting of transcription factors can be achieved through several different approaches, including modulation of their own expression either directly or indirectly, inhibition of their binding to cognate DNA sites and disruption of their interactions with other partner proteins (reviewed in Fontaine et al. 2015). Since the SOX family of proteins comprises transcription factors with important roles in development and cancerogenesis, they represent attractive targets for pharmacological manipulation in anticancer therapy. When designing SOX inhibitors against specific domains, researchers should consider that oncogenic activity of SOX transcription factors can be achieved via either their transactivation ability or interactions with their protein partners (Castillo and Sanchez-Cespedes 2012). Also, one of the major obstacles that should be taken into account is the functional redundancy between different SOX family members.

Two recent advances in targeting SOX2 and SOX18 showed great potential and addressed questions about this therapeutic approach. Narasimhan et al. identified Dawson polyoxometalates (POMs) as compounds that potently inhibited the DNA binding activity of the SOX2 HMG domain, but displayed low selectivity against other transcription factor families (FOXA1, REST and AP2) and were never tested in any *in vitro* or *in vivo* functional assays (Narasimhan et al. 2011, 2014). Nevertheless, the strategy of inhibiting transcription factor activity by POMs is promising, since these potent inhibitors are easily chemically modified so that the systematic testing of differently conjugated POMs may in future result in higher target selectivity.

In order to develop effective SOX18 inhibitors, functional redundancy among SOXF proteins and their different protein partners has to be taken into consideration. With this in mind, Overman et al. used a combination of genomic, proteomic and biophysical methods to discover a set of SOX18 protein-protein interactions and specifically targeted these interactions with the natural small molecule inhibitor Sm4 (Overman et al. 2017). They showed that

Sm4 selectively targeted SOX18-mediated transcription *in vitro* and interfered with SoxF-mediated vascular formation *in vivo*. Most importantly, this inhibitor increased survival in a mouse pre-clinical model of breast cancer by reducing tumor-induced neovascularization and metastatic spread (Overman et al. 2017).

In conclusion, pharmacological manipulation of SOX transcription factors in anticancer therapy shows great potential, with currently the most promising approach being the targeting of protein-protein interactions. In particular, one of the greatest challenges will be the designing and optimization of small molecule inhibitors that will be able to simultaneously inhibit interactions with a subset of selected protein partners, leading to the selective transcriptional blockade of a specific subset of target genes.

To achieve the proper suppression of tumor onset and progression, comprehensive research into the molecular mechanisms in which *SOX* genes participate is essential. Further work will help in delineating how and to what extent *SOX* genes can contribute to better diagnosis, prognosis and new therapeutic approaches in cancer treatment.

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