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Review

The role of SOX family members in solid tumours and metastasis

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ABSTRACT

Cancer is a heavy burden for humans across the world with high morbidity and mortality. Transcription factors including sex determining region Y (SRY)-related high-mobility group (HMG) box (SOX) proteins are thought to be involved in the regulation of specific biological processes. The deregulation of gene expression programs can lead to cancer development. Here, we review the role of the SOX family in breast cancer, prostate cancer, renal cell carcinoma, thyroid cancer, brain tumours, gastrointestinal and lung tumours as well as the entailing therapeutic implications. The SOX family consists of more than 20 members that mediate DNA binding by the HMG domain and have regulatory functions in development, cell-fate decision, and differentiation. SOX2, SOX4, SOX5, SOX8, SOX9, and SOX18 are up-regulated in different cancer types and have been found to be associated with poor prognosis, while the up-regulation of SOX11 and SOX30 appears to be favourable for the outcome in other cancer types. SOX2, SOX4, SOX5 and other SOX members are involved in tumorigenesis, e.g. SOX2 is markedly up-regulated in chemotherapy resistant cells. The SoxF family (SOX7, SOX17, SOX18) plays an important role in angio- and lymphangiogenesis, with SOX18 seemingly being an attractive target for anti-angiogenic therapy and the treatment of metastatic disease in cancer. In summary, SOX transcription factors play an important role in cancer progression, including tumorigenesis, changes in the tumour microenvironment, and metastasis. Certain SOX proteins are potential molecular markers for cancer prognosis and putative potential therapeutic targets, but further investigations are required to understand their physiological functions.

1. Introduction

Today, the second leading cause of death worldwide is cancer. It is responsible for an estimated 9.6 million deaths, according to the WHO Global Cancer Observatory (GLOBOCAN) data published in 2018 [1]. Tumorigenesis is caused by increased genetic and epigenetic alterations that ultimately convert healthy cells into cancer cells, which are characterised by uncontrolled proliferation, elevated survival, unlimited replicative potential and elevated angiogenesis behaviour, as well as an activated invasion potential and metastasis [2]. Therefore, it is necessary to support cancer research and identify disease causes and new strategies for the prevention, diagnosis, treatment and cure of different types of cancer. Despite knowledge of well-known mechanisms and pathways contributing to disease progression in various cancer types, curing this disease remains a difficult challenge.

Various factors involved in developmental processes are also key players in tumorigenesis. Many of them were initially identified as proto-oncogenes, with important roles in development. Examples of these factors include genes encoding secreted proteins, such as platelet-derived growth factors [3], the insulin-like growth factor axis [4], transmembrane proteins like RET and NTRK1 [5], sex hormones, products of suppressor genes, transcription factors of the SMAD family [6] and the forkhead/winged helix-box transcription factor (Fox) family [7], signal transduction pathways such as the hedgehog (SHH) [8], Wnt [9] and Notch [10] pathways, as well as viruses like the human papilloma virus, Epstein-Barr virus, Hepatitis B and C viruses and others.

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An important group of transcription factors involved in tumorigenesis and cancer is the SOX family. It comprises a number of transcriptional regulators that mediate DNA binding via a highly conserved high-mobility group (HMG) domain. These SOX transcription factors critically control cell fate and differentiation in cancer. Several SOX factors are involved in progression and metastasis.

In this review, we provide an overview of the SOX family and discuss the role of these transcription factors in tumorigenesis and metastasis, as well as recent advances in our understanding of the role of *SOX* genes in cancer. We will focus on the importance of SOX transcription factors for the tumour microenvironment, and provide current knowledge about the meaning and function of the SOX family of transcription factors in breast, prostate, renal cell, thyroid, gastrointestinal and lung cancers, as well as brain and skin tumours. These tumour types were selected because of their high incidence and mortality [1]. In addition, we will discuss the suitability of members of the SOX family as future drug targets in some cancer types.

2. Human SOX protein family, groups and domain structures

The sex-determining region on the Y chromosome-related high mobility group box (SOX) transcription factor family contains more than 20 members in vertebrates, which are classified into eight groups, denoted SoxA to SoxH (Fig. 1) [11–13]. This cluster of genes, which originates through a series of evolutionary processes, including duplication and divergence [13,14], was identified almost a quarter of a century ago. Since then, a substantial number of discoveries have documented their fundamental and dynamic function during embryonic development and disease, including the molecular basis for the genome engagement (comprehensively reviewed in two recent papers by She & Wang [12] and Hou et al. [15]).

SOX genes are defined as those that contain the evolutionarily conserved high-mobility group (HMG) box from a gene involved in sex determination called *SRY*, which resides on the Y chromosome. The abbreviation SOX stands for SRY-related HMG box. For vigorous shuttling between the nucleoplasm and cytoplasm, the HMG box contains two autonomous nuclear localisation signals (NLSs) [16] and one leucine-rich nuclear export signal (NES) [17]. This arrangement ensures diverse subcellular allocation of SOX transcription factor proteins during development [18]. The dynamic molecular mechanisms involved in nucleocytoplasmic shuttling have recently been reviewed [12]. The HMG box consists of a 79 amino acid-long DNA-binding motif, which facilitates binding to DNA through the consensus site (A/T)(A/T)CAA(A/T) (Fig. 1) [19]. SOX proteins bind to DNA with different levels of efficacy and have an unusually low affinity for DNA [19].

SOX transcription factor proteins play a crucial role in development. They bind to the minor groove of DNA and are involved in a number of important processes, including development of the retina, central nervous system and cardiovascular system, as well as chondrocyte differentiation and primary sex determination [12]. To ensure the fulfilment of these complex processes, SOX proteins are controlled through numerous genetic pathways, which are essentially facilitated by three features: (i) the tissue-specific and timely regulation of expression levels, (ii) regulation of post-translational modifications of SOX proteins, and (iii) regulated recruitment of partner proteins. The first feature guarantees exact timing within each of the major developmental stages [20]. Modulation of SOX protein expression is facilitated by microRNAs (*e.g.* miR-124, 145, 200 and 500 family members [20,21]). Feature two governs the alteration of SOX protein function by controlling transactivation and transrepression properties (Fig. 1) [22]. The post-translational modifications involve phosphorylation, acetylation, methylation, sumoylation and glycosylation (discussed further below) [12,20]. As SOX proteins function together with interaction partners to elicit their action, the last feature impacts the selection of specific binding sites in target genes by the SOX-partner complex. This also includes activation and repression activities [20].

SRY, which was the founding member of the SOX protein family [23], is the only member of the SoxA group [24]. Despite the fundamental role of SRY on sex determination, there is sparse information about the sequences surrounding the HMG box.

The SoxB group has been divided into the SoxB1 and SoxB2 subgroups, which harbour transcription activators and inhibitors, respectively [13,25]. SoxB1 factors, which include SOX1, SOX2 and SOX3, share a high degree of sequence similarity, both within and outside the HMG box. As a consequence, SoxB1 members have almost equal biological activities and display strong functional redundancy, *e.g.* in neural stem/progenitor cells in the development of the central nervous system [25]. SOX14 and SOX21 belong to the SoxB2 subgroup. SoxB1 and SoxB2 share a group B homology domain (a short, basic amino acid sequence adjacent to the HMG box). Unlike SoxB1, members of the SoxB2 subgroup harbour a C-terminal transrepression domain instead of a transactivation domain (Fig. 1).

The SoxC group is comprised of the SOX4, SOX11 and SOX12 members. They share a well-conserved C-terminal region with a 33-residue transactivating domain that forms specific helical conformations, which has various transactivation proficiencies [26]. The SoxD group, which includes SOX5, SOX6 and SOX13, all share a relatively

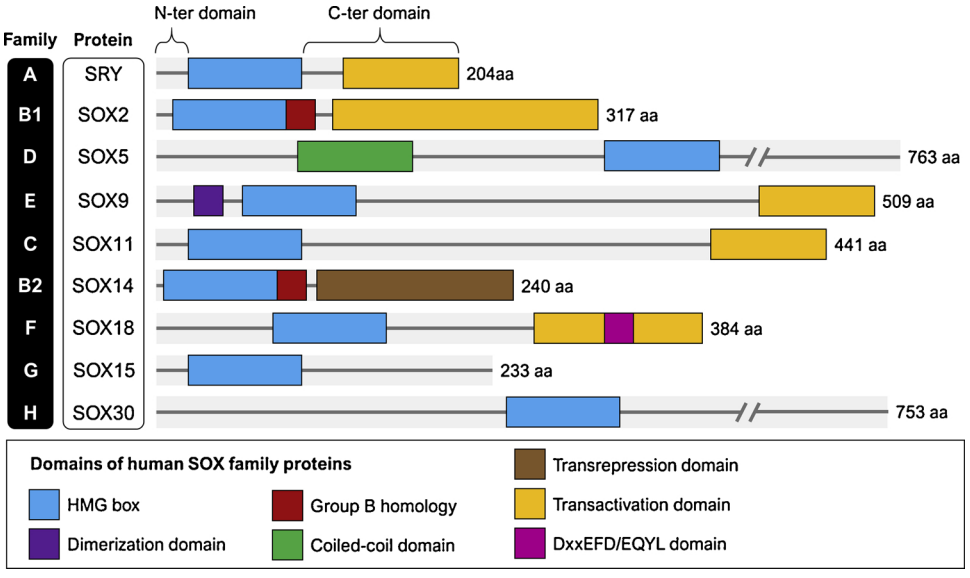

Fig. 1. Graphic depiction of domain structures of the human SOX protein family. Based on gene organisation and function in widespread developmental progressions, protein structure and phylogenetic analysis, the human SOX family of transcription factors has been subdivided into eight groups (SoxA through SoxH) [11,13]. The highly conserved and characteristic HMG box is specified alongside other functional domains, including the transactivation domain. Groups and representative protein members are indicated to the left. N-terminal (N-ter) and C-terminal (C-ter) domains of *SRY* are depicted at the top. The sizes in amino acids (aa) of the various SOX proteins are shown to the right. Domains of SOX family proteins are shown in the box.

extensive and evolutionarily conserved domain located in the N-terminal region of the involved proteins. It consists of various stretches of residues, forming two coiled-coil domains, a leucine zipper and a glutamine-rich motif. This enables SoxD members to form stable homo- or heterodimers, thereby enhancing DNA-binding via the HMG box [27].

SOX8, SOX9 and SOX10 are the three SoxE factors, all containing a distinct dimerisation domain located proximally to the HMG box [28]. This domain is required for chondrogenesis, but not for sex determination. In addition, the SoxE members have a unique transactivation domain [28]. SoxF proteins, including SOX7, SOX17 and SOX18, are characterised by a distinct C-terminal transactivation domain. Unlike other SOX protein containing a transactivation domain, the SoxF members also contain a short amino acid motif (DXXEFD/EQYL) inside the transactivation domain mediating β-catenin interactions (Fig. 1), and consequently, the regulation and coordination of processes like gene transcription. Because SoxF proteins have a fundamental role in vasculogenesis, cardiogenesis and lymphangiogenesis, gene variations figure significantly in the aetiology of human vascular disease [29].

SOX15 (also known as SOX20) is the only member of the SoxG group and shares the closest identity to members of the SoxB1 group. Even though the role of SOX15 in cell biology and development is relatively understudied compared to other SOX family members, a recent study has identified this factor as a potential tumour suppressor gene in pancreatic ductal adenocarcinoma (PDAC) [30]. The SoxH group forms a new group of SOX transcription factor proteins. Interestingly, the only identified member, SOX30, does not shown any apparent homology outside the HMG box to other SOX groups [31].

Evidently, SOX transcription factor proteins initiate fundamental functions during healthy development. In addition to these roles in development, SOX proteins also have a significant impact on muscle regeneration and notably, in tumorigenesis [12]. Accordingly, members of the SOX family may act as tumour suppressor genes, oncogenes or both, depending on the cellular environment, and can be stimulated or incapacitated through diverse genetic and epigenetic mechanisms, including DNA methylation, DNA copy number alterations and abnormal miRNA expression [30,32–34]. Hence, the misregulation (either up- or down-regulation) of SOX proteins may result in the progression of cancer. However, it is important to stress that the transcription factor function of SOX proteins may not overlap in development and cancer. In tumorigenesis, SOX transcription factors may thus activate unwanted targets which are not triggered under healthy conditions [35,36]. Another striking finding is that the up-regulation of a specific SOX transcription factor results in tumorigenesis in *e.g.* the CNS, whereas down-regulation of the same SOX protein results in lung cancer. In the following two chapters, the role of SOX transcription factors in tumorigenesis and the tumour microenvironment will be described.

3. SOX transcription factors and tumorigenesis

Coding for transcription factors with DNA binding domains, *SOX* genes control cell differentiation, organogenesis and many other developmental processes. In healthy organisms, their expression and silencing are tightly regulated. In tumours, however, *SOX* genes are frequently deregulated [37,38]. Tumorigenic deregulation occurs on transcriptional, translational and posttranslational levels. However, studies on different members of the *SOX* gene family revealed member-specific mechanisms of action [39]. Fig. 2 summarises the involvement of SOX proteins in different tumours in the human body.

Regarding the involvement of SOX family members in tumorigenesis (Table 1, Fig. 3), SOX2 is the most thoroughly investigated transcription factor. In healthy organisms, it plays a role in stem cell regulation during embryogenesis, as well as during adult tissue regeneration [39,40]. Together with Oct4 and NANOP, SOX2 regulates pluripotency and the self-renewal of stem cells, affecting promoters of a high number of other genes [41]. It also has an influence on proliferation and apoptosis, as well as on the migration and adhesion of cells [42].

The overexpression of SOX2 is frequently observed when the growth and propagation of tumours are investigated by clinical and experimental methods. For example, SOX2 overexpression correlates with the tumorigenicity of glioma cells *in vitro* and *in vivo* [43,44]. A similar correlation was observed in clinical specimens of ovarian carcinomas and head and neck squamous cell carcinomas [45,46]. If the overexpression of SOX2 is inhibited in these cells, proliferation and expansion of whole tumours may be reduced [47,48]. In the case of melanoma-initiating cells, the activation of *SOX2* expression by HH-GLI signalling even supports self-renewal and tumorigenicity [49].

SOX2 overexpression can be initiated by various mechanisms. The enhancement of transcription is caused by amplification of the *SOX2* gene. This was observed when SOX2 induced squamous cell carcinomas in multiple tissues, including the lung and oesophagus [39,50–52]. Furthermore, DNA hypomethylation has been cited as a cause of SOX2 overexpression in human gliomas [53]. In addition, growth factors and other members of the *SOX* gene family may cause the enhanced transcription of *SOX2*. For example, IL-4 enhances tumour aggressiveness in various human carcinoma cells via the induction of SOX2 expression [54], and IL-22 promotes colorectal cancer causing SOX2 overexpression via STAT3 [55]. SOX4 transfers TGF-β signals to promote SOX2 expression; this mechanism is active in various types of cancer, including gastric cancer and gliomas [56,57].

At a translational level, alterations to the number of distinct miRNAs have an influence on SOX2 overexpression. For instance, miRNA-145 and miRNA-34 appear to keep SOX2 expression at normal levels. If these types of miRNA are down-regulated, SOX2 expression is enhanced and the development of laryngeal squamous cell carcinomas [58] or osteosarcomas is promoted [59]. Furthermore, miRNA-1181 was found to directly suppress SOX2 expression, inhibiting stem cell-like phenotypes in pancreatic cancer [60]. At the post-translational level, a balance between methylation and phosphorylation determines the stability and degradation of SOX2 [61].

Another SOX family member promoting tumorigenesis is SOX9 (Fig. 3). A recent overview of clinical studies comparing the overall survival of patients suffering from solid tumours with the overexpression of SOX9 pointed to a clear promotion of tumour growth by SOX9 [62]. *in vitro* studies showed that the overexpression of SOX9 is critical for the tumorigenicity of pancreatic cells [63], hepatocarcinoma stem cells [64,65], oesophageal squamous cell carcinoma cells [66] and osteosarcoma tissue [67], while the enhancement of SOX9 expression decreases tumorigenicity of melanoma cells [68]. SOX9 forms group E of the Sox family, together with SOX8 and SOX10. Their common characteristic is a DNA-dependent dimerisation domain [69]. In melanoma, SOX9 and SOX10 regulate each other [70]. A special effect of SOX9 overexpression appears to relate to the weakening of tight junctions. This hypothesis was concluded from the observation that the overexpression of SOX9 in liver and lung tumours was accompanied by the repression of E-cadherin (CDH1) [71,72], which is consistent with our findings that SoxE members were found in thyroid cancer cells, but not in breast cancer cells when human thyroid and breast cancer cells were exposed to real and simulated microgravity [73,74].

A stay in orbit provides altered gravity conditions which are not achievable on Earth. Gravity is the most familiar force in our life. It is rarely considered as an experimental parameter in biological studies. In space, this force is reduced, resulting in microgravity. Microgravity simulation can be achieved by using the rotating wall vessel, 2D or 3D clinostat, random positioning machine and magnetic levitation [75,76]. These microgravity conditions are used to examine changes in cell growth and the function of different benign cell types and cancer cells. Researchers have demonstrated that exposure to microgravity influences biological processes which are relevant in cancer research. In space and under simulated microgravity, cells assemble into 3D multicellular spheroids and reveal an altered growth behaviour and function [77–79]. In addition, they show an altered cell shape, gene expression, protein synthesis and secretion, as well as changes in cell

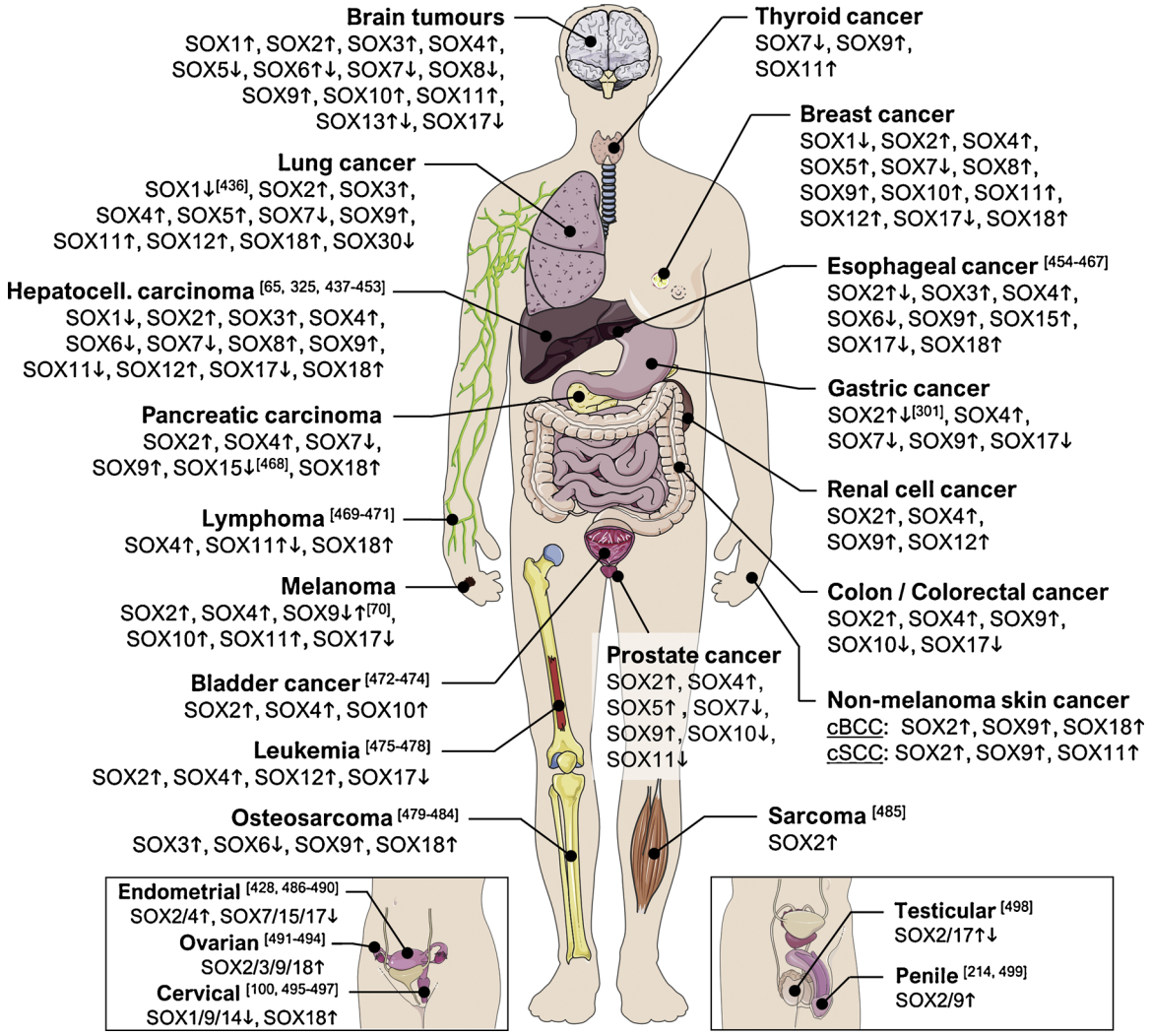

Fig. 2. Overview of SOX involvement in different tumours in the human body. Arrows indicate regulations in the respective tumour cells. To offer a complete overview, regulation of SOX factors in further tumour types were added as well as supplementary literature for the tumours described in this review (lung cancer [436], hepatocellular carcinoma [65,325,437–453], oesophageal cancer [454–467], pancreatic carcinoma [468], lymphoma [469–471], melanoma [70], bladder cancer [472–474], leukemia [475–478], osteosarcoma [479–484], sarcoma [485], endometrial cancer [428,486–490], ovarian cancer [491–494], cervical cancer [100,495–497], testicular cancer [498], and penile cancer [214,499]). Parts of the figure were drawn by using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).

signalling and cytoskeletal organisation [75]. The synthesis of a large number of proteins is modified when cancer cells are exposed to microgravity [73,80,81]. With the help of gravitational biology, it is possible to detect new proteins in organ tissues and changes in the rate of production and secretion [81]. Using microgravity as a new technology, it is possible to clarify pathways involved in the spread and progression of cancer, as well as angiogenesis. Microgravity-based investigations are useful to improve our knowledge in cancer biology and in the search for new target proteins, thus supporting the development of new anticancer technologies and therapeutic strategies [82,83]. In order to address cancer growth and regulation, further controlled studies conducted in microgravity are necessary.

In thyroid cancer cells, we observed that SOX transcription factors were only detected when the cells had been exposed to simulated microgravity [74]. Furthermore, if thyroid cancer cells remained adherent under simulated microgravity, the intracellular accumulation of SoxE members was twice as high as if they formed spheroids. Interestingly, CDH1 was detected in breast cancer cells, but not in thyroid cancer cells, after 3 days of exposure to simulated microgravity. This finding is in accordance with the above-mentioned inhibition of *CDH1* expression by SOX9 [71,72,84]. We also detected SOX11 in a thyroid cancer cell population that was exposed to simulated microgravity, but which did not form spheroids, because a prolonged pre-incubation phase caused high cell density [74]. In this population, members of the SoxE group were detectable, but accumulated to a lesser degree, while the amount of PTK2 was higher than in the cell population which formed spheroids and was exposed to simulated microgravity. Other studies have reported that SOX11 reduces *SOX9* expression [85], but favours the expression of PTK2, which plays a significant role in cell adhesion to the extracellular matrix (Fig. 3) [86]. Comparing knowledge of the activities of SOX9 and SOX11 with the findings in our microgravity research suggests an involvement of these SOX members in the adaptation of cancer cells to microgravity and confirms the link between microgravity and cancer research (Fig. 4). Human cervical carcinoma CaSki cells flown on the Chinese Shenzhou-IV space mission revealed changes in morphology and proliferation [87]. The authors measured a 3-fold change in the gene expression of *SOX4* in space-flown samples compared to controls. Control samples showed a low expression of *SOX4* [87]. SOX4 regulates epithelial-mesenchymal transition (EMT) in normal and cancerous breast epithelial cells; SOX4 is also involved in cell survival *in vitro* and for primary tumour growth and metastasis *in vivo* [88]. Therefore, the up-regulation of SOX4 in microgravity is an

Table 1
SOX family members as potential biomarkers and their effects in different tumour types.

SOX family	SOX member	Tumour	Described effects	References
SoxA	*SRY* gene	ND	ND	
SoxB1	SOX1	Breast cancer	Reduction of cell proliferation and invasion *in vitro;* apoptosis; suppression of the Wnt/β-catenin pathway	[134]
		CNS tumours	SOX1 promotes self-renewal, proliferation, apparently independent of Wnt/β-catenin signalling	[227]
	SOX2	Breast cancer	Angiogenesis; metastasis; down-regulation of mTOR signalling; activation of NF-κB-CCL1; and Wnt/β-catenin signalling	[142–147]
		Prostate cancer	Proliferation and invasion; regulation of store-operated Ca^{2+} channels; up-regulation of neural CAMs, neurotrophins, angiogenic and lymphangiogenic factors	[200–202]
		CNS tumours	Prognostic marker of glial lineages; self-renewal; neurosphere formation; regulation of key genes and pathways involved in malignancy and stemness; over 280 associated proteins in medulloblastoma; connected to TGF-β signalling	[57,118,230,243,244]
		Gastrointestinal tumours	Inconsistent reports about promotion and suppression of gastric cancer; stemness, drug resistance and metastasis in colon cancer; stemness in colorectal cancer; marker of pancreatic cancer, reduction of E-cadherin	[107,299,300,301,311–313,321,333]
		Lung cancer	Proliferation, EMT, migration, and invasion; regulation of c-myc, Wnt1, Wnt2, NOTCH1, and apoptosis; key factor in the FGFR1-ERK1/2-SOX2 axis; involved in the development of chemoresistance	[39,341–347,359]
		Renal cell Carcinoma	Prognostic marker; associated with poor prognosis	[215]
		Skin cancer	Acquisition of an aggressive oxidative tumour phenotype with enhanced drug resistance and metastatic ability; oxidative cancer metabolism; *in vivo* growth of cBCC cells after hedgehog-EGFR activation; cSCC growth via Nrp1/VEGF-signalling	[386,387,404]
	SOX3	CNS tumours	Proliferation, viability, migration and invasion capabilities through enhanced HH signalling and/or by suppressed autophagy	[248]
SoxB2	SOX14	ND	ND	
	SOX21	CNS tumours	Tumour suppressor; inhibition of SOX2 by complexation; apoptosis; initiation of aberrant differentiation	[99,229,250]
SoxC	SOX4	Breast cancer	Induction of EMT and progression; activation of TGF-β signalling; promotion of PI3K/Akt signalling	[91,159]
		Prostate cancer	Induction of EMT; targeting of 23 transcription factors (e.g. MLL, FOXA1, ZNF281 and NKX3-1)	[203,204]
		Renal cell Carcinoma	TGF-β-induced EMT; proliferation, migration and invasion	[211,212]
		CNS tumours	Potential tumour suppressor; induction of G0/G1 cell cycle arrest through Akt-p53 axis; influence on canonical and non-canonical TGF-β signalling; Oct4-SOX4 complexes cooperatively activate the enhancer activity of *SOX2*	[88,253,256]
		Gastrointestinal tumours	Survival of colon cancer via Cyr-61; growth promotion of pancreatic cancer	[318,337]
		Lung cancer	Proliferation, migration, invasion, metastasis; integral regulator of tumour malignancy	[362–364]
		Skin cancer	Promotion of melanoma cell migration; activation of the NF-κB signalling pathway	[390]
	SOX11	Breast cancer	Regulation of cell proliferation, migration, invasion	[161,164]
		Prostate cancer	Tumour suppressor; suppression of migration and invasion	[207]
		Thyroid cancer	Proliferation, migration, invasion in PTC	[220]
		CNS tumours	Potential tumour suppressor; inhibition of PLAGL1; overexpressed in malignant gliomas	[261,263]
		Lung cancer	Poor prognosis in large cell neuroendocrine carcinomas and NSCLC	[366]
		Skin cancer	Prognostic marker; presence of SOX11 protein was positively related to the proliferation index	[389]
	SOX12	Breast cancer	Promotion of growth, migration and invasion	[165]
		Renal cell Carcinoma	Prognostic marker	[215]
		Lung cancer	Proliferation; metastasis; increase of EMT (Twist1, E-cadherin), apoptosis (Bcl-2, Bax), invasion (MMP9) and cell growth (PCNA, Cyclin E)	[367]
SoxD	SOX5	Breast cancer	EMT; cell proliferation, migration and invasion	[166]
		Prostate cancer	TGF-β-induced EMT; metastasis; control of Twist1 expression	[208]
		CNS tumours	Potential tumour suppressor; suppression of PDGFB; regulation of $p27^{Kip1}$ in a $p19^{Arf}$-dependent manner, leading to acute cellular senescence	[266]
		Lung cancer	Induction of progression and metastasis via EMT; interaction with YAP1	[114,368]
	SOX6	CNS tumours	Aberrant expression in GBM; cytotoxic T-lymphocyte-induced anti-tumour activity in mice reported	[270,271]
	SOX13	CNS tumours	Increased in oligodendroglioma, either up- or down-regulated in astrocytomas and mainly down-regulated in GBM	[265]

(*continued on next page*)

Table 1 (*continued*)

SOX family	SOX member	Tumour	Described effects	References
SoxE	SOX8	Breast cancer	Marker for triple-negative breast cancer	[170]
		CNS tumours	Levels helpful for predicting the differentiation status of glioma subtypes	[265]
	SOX9	Breast cancer	Translocated in the cytoplasm; promotion of growth; proliferation, migration and invasion; metastasis; regulation of Wnt/β-catenin signalling	[175,179,181]
		Prostate cancer	Prognostic marker	[205]
		Renal cell Carcinoma	Proliferation, invasion	[213]
		Thyroid cancer	EMT; proliferation, invasion; activation of Wnt/β-catenin signalling	[84]
		CNS tumours	Poor prognosis; proliferation; stemness; triggers *LGR5* expression	[273,274,279]
		Gastrointestinal tumours	Metastasis via induction of S100-P in colon cancer; growth and progression of colorectal cancer, SOX9, β-catenin and PPARγ expression levels are deregulated; induction of claudin-7	[315,316,327,328]
		Lung cancer	TGF-β secreted by TAMs promotes *SOX9* via the C-jun/SMAD3 pathway, thereby promoting tumour metastasis; proliferation, migration and invasion; correlation with MALAT1 transcription	[115,369,371,372]
		Skin cancer	Proliferation of keratinocytes; metastasis of melanoma cells; Sox9 is required for BCC formation in a Wnt/β-catenin-dependent manner; induced by UVB in keratinocytes; activation of SHH and Wnt/β-catenin signalling in SCC development	[388,401,405–407,408]
	SOX10	Breast cancer	Myoepithelial differentiation; control of growth and invasion; induction of nestin	[187,188,189]
		CNS tumours	Glial diversification	[292]
		Gastrointestinal tumours	Tumour suppressor; inhibition of metastasis of digestive cancers by suppressing the Wnt/beta-catenin pathway	[319]
		Skin cancer	Promotion of melanoma cell proliferation, SOX10 regulated tumour growth and chemotherapy resistance of melanoma in vitro and in vivo.	[384]
SoxF	SOX7	Breast cancer	Inhibition of proliferation, migration, invasion	[190]
		Prostate cancer	Prognostic marker	[205]
		Gastrointestinal tumours	Tumour suppressor; inhibition of tumorigenesis and progression	[306]
		Lung cancer	Tumour suppressor; suppression of TGF-β1-induced invasion and adhesion	[373]
	SOX17	Breast cancer	*SOX17* promoter methylation involved in progression, prognostic biomarker, canonical Wnt antagonist	[192,193]
		Thyroid cancer	Tumour suppressor; inhibition of Wnt/β-catenin signalling	[219]
		CNS tumours	Tumour suppressor; epigenetic silencing of Wnt antagonists leads to up-regulation of Wnt/β-catenin signalling in gliomas	[297]
		Gastrointestinal tumours	Tumour suppressor; mice producing enhanced levels of SOX17 are more resistant to gastric cancer; down-regulation of Sox17 contributes to malignant progression through promotion of Wnt activity; SOX17 is a negative modulator of canonical Wnt signalling in CRC	[307,332]
		Skin cancer	Tumour suppressor; decrease correlates with melanoma progression; unfavourable survival; prognostic factor	[385]
	SOX18	Breast cancer	Tumour angiogenesis, poor outcome	[127]
		Lung cancer	Cytoplasmic Correlation with poor outcome	[375]
		Skin cancer	SCC and BCC development	[402]
SoxG	SOX15	Gastrointestinal tumours	Potential tumour suppressor of the Wnt/β-catenin signalling pathway in pancreatic ductal adenocarcinoma	[30]
SoxH	SOX30	Lung cancer	Tumour suppressor; inhibition of proliferation, migration, invasion, tumour growth and metastasis; it promotes apoptosis by transcriptional activating p53; increases the expression of desmosomal genes (*DSP*, *JUP*, *DSC3*); with Wnt-signalling	[378–380]

ND, not determined.

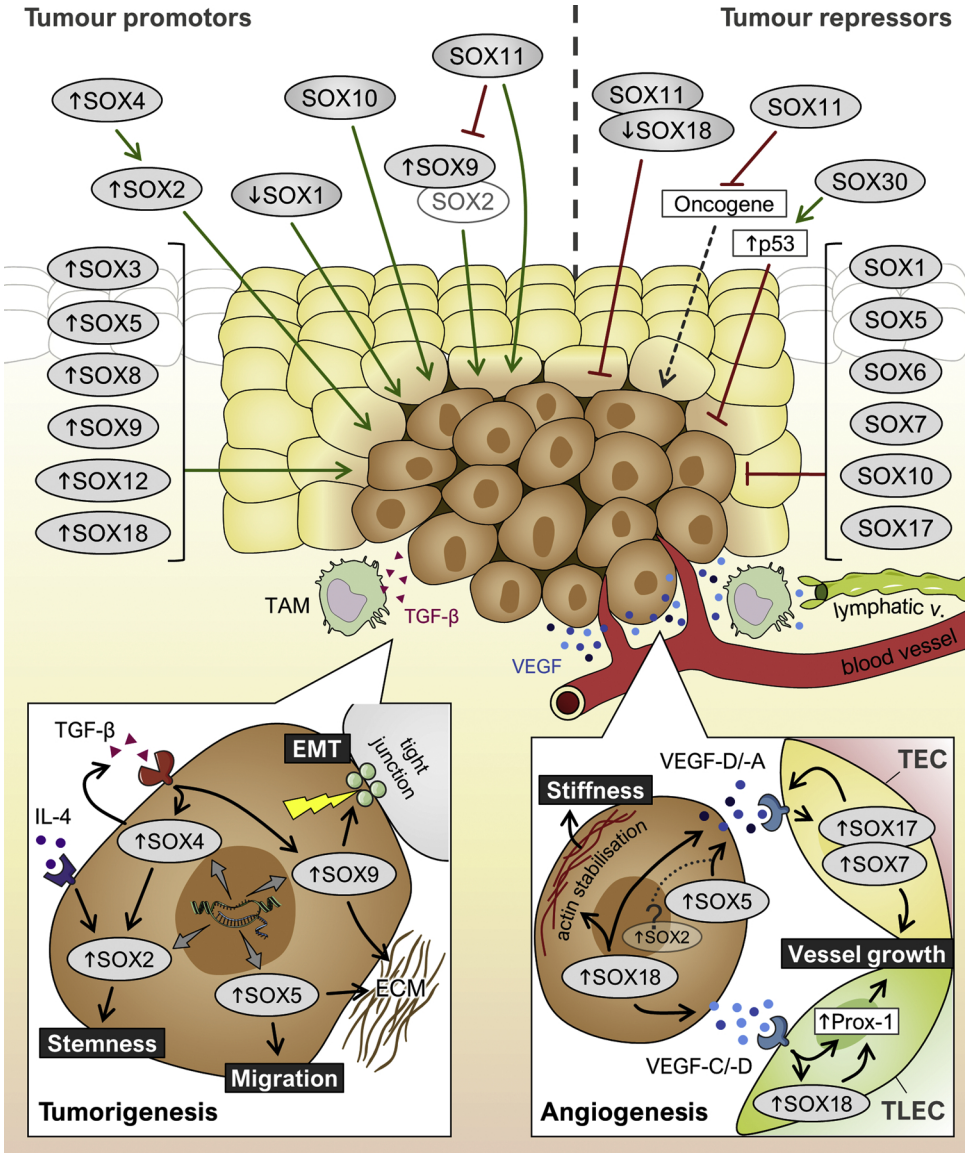

Fig. 3. Influence of SOX factors on tumour development. Dependent on cell and cancer type, SOX proteins can act as tumour promotors or tumour repressors. The large image displays different possibilities how single SOX proteins can contribute to tumorigenesis. The small image sections show in general how the SOX factors are involved in cell signalling resulting in tumorigenesis and angiogenesis. Abbreviated cell types: TAM, tumour-associated macrophage; TEC, tumour-associated endothelial cell; TLEC, tumour-associated lymphatic endothelial cell. Parts of the figure were drawn by using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).

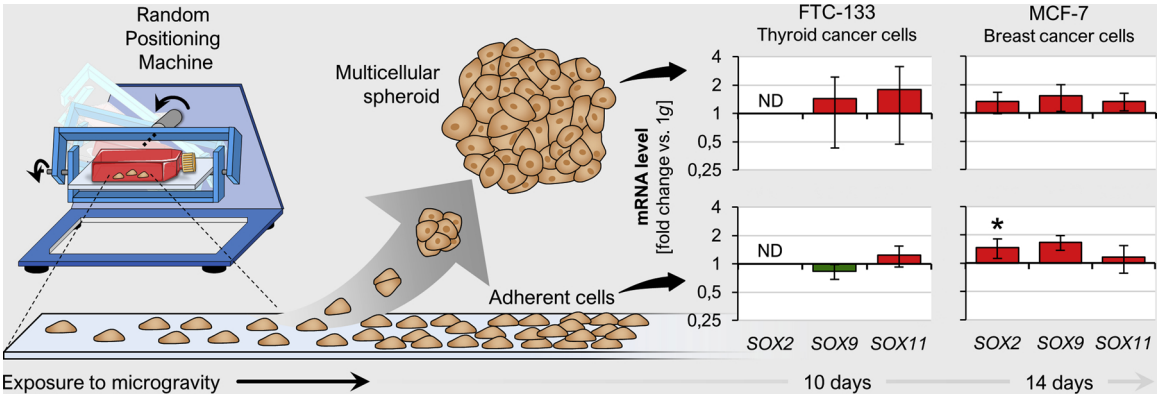

Fig. 4. SOX in microgravity-based tumour spheroid formation. FTC-133 follicular thyroid cancer cells and MCF-7 breast cancer cells were cultured on an RPM for 10 days (FTC-133) or 14 days (MCF-7). Some of the cells stayed adherent, others grew in form of multicellular spheroids (MCS) mimicking small metastases. Both populations were harvested and analysed separately and compared to a control group cultured under normal gravity conditions. The mRNA levels of *SOX2*, *SOX5*, *SOX6*, *SOX7*, *SOX9* and *SOX11* were determined by quantitative RT-PCR. The plots display fold changes of gene expression in adherent cells (lower panels) and MCS (upper panels). *SOX5*, *SOX6* and *SOX7* expression were below the lower quantification limit in both cell lines. All values are given as mean ± standard deviation. * $p < 0.05$ vs. control (Mann Whitney U test). ND, not detectable.

interesting finding with respect to changes in growth and proliferation. Further studies will determine the role of SOX transcription factors in microgravity.

Investigations into the tumorigenicity of other members of the *SOX* gene family are ongoing. So far, mainly clinical observations have been described in the literature. These studies suggest that some members have tumour-promoting activities, while others exert a tumour-suppressing activity (Fig. 3). *SOX4* is overexpressed in several human cancers, including prostate and pancreatic carcinomas, bladder cancer and triple-negative breast cancer [89–91]. An overexpression of *SOX4* may be caused by gene amplification [92] or by the down-regulation of miRNA-138 [93], while miR-129-3p decreases SOX4 [94]. As mentioned above, SOX4 influences the expression of SOX2 [56,57]. In addition, SOX3 overexpression plays a role in hepatocellular carcinomas [95] and might be critically involved in the pathogenesis of choriocarcinoma [96]. In contrast, SOX6 is a tumour suppressor. When it is down-regulated by Netrin-1 or miRNA-208, the aggressiveness of the affected tumours increases [97,98]. SOX5 and SOX6 together block the tumorigenic capacity of brain tumour stem cells [99]. SOX1 and SOX7 also appear to have tumour suppressive activities [100,101].

Further work is required to further elucidate the causative roles that various members of the SOX family play in tumour development. Emphasis may be placed on the mechanisms of deregulation of *SOX* gene expression and SOX factor production, aiming to identify the possibility of counteracting a malignant over- or under-expression of SOX members that is important in a specific tumour cell type. In this context, the development of animal models like knock-out or transgenic mice could be helpful.

4. The importance of SOX for the tumour microenvironment

Tumour biology is influenced not only by tumour cells, but also by the surrounding tumour microenvironment (TME). The TME is defined as the cellular environment in which the tumour is situated, grows and expands. The TME is comprised of nourishing blood vessels, lymph vessels, endothelial cells, fibroblasts, lymphocytes, immune cells, signalling factors and the extracellular matrix. There is a permanent interaction between the tumour and its TME. Tumour cells release extracellular factors like vascular endothelial growth factor, promoting tumour angiogenesis, or molecules inducing peripheral immune tolerance. In addition, immune cells in the TME and pro-inflammatory cytokines are drivers of tumorigenesis [102]. Moreover, SOX2 is known to be involved in metastasis and in recruiting tumour-associated macrophages of the M2 phenotype to the TME in breast cancer [103].

Cancer recurrence and metastasis can occur when a group of stem cells is dormant. Dormant cancer cells remain in a quiescent state for many years as single cells, which are resistant to chemotherapy, targeting the proliferating cell population [104]. Recurrences after decades of remission are problematic in breast cancer. Knowledge of the dormant tumour cell microenvironment is important for finding new targeted therapies that can remove resistant tumour cells. Approaches to mimic the breast cancer cell microenvironment were undertaken [105]. Carboplatin-resistant (treated) MDA-MB-231 (highly invasive, basal-like) and T47D (low-invasive, luminal) breast cancer cells showed an increase in Bcl-2, Oct-4 and SOX2, suggesting protection from apoptosis and an increase in stem-like markers [105].

Pancreatic stellate cells (PSCs) grow in the TME of pancreatic tumours and influence their growth and progression. PSC-released factors trigger the generation of hepatocyte growth factor (HGF) as well as the maintenance of cancer stem cells (CSCs). In Panc-1 pancreatic cancer cells, activation of its cognate receptor c-MET (tyrosine-protein kinase Met or hepatocyte growth factor receptor) by paracrine HGF resulted in yes-associated protein (YAP) nuclear translocation and hypoxia-inducible factor 1-alpha (HIF-1α) stabilisation. The next step is the increased expression of the CSC pluripotency markers NANOG, Oct-4 and SOX2 and an elevated spheroid formation [106]. In one study, SOX2 reprogramming in pancreatic cancer cells elevated cancer cell proliferation and contributed to stemness and dedifferentiation [107]. Transcription factors like SOX2 are involved in the dedifferentiation and reprogramming processes in healthy tissues. When glioma, lung cancer and hepatoma cells were studied under hypoxic conditions, SOX2, amongst others, was highly expressed and three-dimensional (3D) spheroid formation was found [108].

The signal transducer and activator of transcription-3 (STAT3) signalling pathway is involved in inflammation and also contributes to the maintenance of embryonic stem cell (ESC) pluripotency. STAT3 was overexpressed in gastric cancer stem-like cells (GCSLCs), while *SOX2* was up-regulated in spheroids of MKN-45 gastric cancer cells. The elevated level of *SOX2* in GCSCs could be a key factor for *STAT3* overexpression [109].

It has been shown that aberrant SOX5 expression is a key player in the progression of melanoma, colorectal cancer, lymphoma and hepatocellular carcinoma [110–113]. It remains unclear whether SOX5 drives the malignant potential in non-small cell lung cancer (NSCLC), and a regulatory mechanism for SOX5 needs to be elucidated. A recent study demonstrated that SOX5 promotes the invasion and migration of NSCLC cells; SOX5 acts as an oncogenic factor by interacting with YAP1 in NSCLC cells [114].

Tumour-associated macrophages (TAMs) also affect the TME and promote progression and metastasis in NSCLC. TAMs secrete TGF-β, which further increases SOX9 expression and promotes epithelial-mesenchymal transition (EMT) and disease progression. TGF-β released by TAMs has been shown to induce *SOX9* expression via the C-jun/SMAD3 pathway and, consequently, promotes metastasis [115].

In summary, little is known about the role of the SOX family in the cross-talk with the TME. SOX2, SOX5 and SOX9 are expressed in different cancer types and are often involved in increased growth, metastasis, drug resistance and poor survival. Their interaction with the TME has been demonstrated, but further studies are necessary.

5. Regulation of the expression of SOX family genes

Some SOX genes display a tightly regulated spatio-temporal expression pattern [116], whereas others show more complex expression patterns, demonstrating that they play an important role in tissue or organ development [117]. SOX expression is regulated differently in various settings through a complex network of transcriptional and post-transcriptional mechanisms [12,118]. Even though it is rather elusive how SOX-proteins are regulated, it is well documented that such processes involve the acetylation of nucleosomal histones, other transcription factors, signalling pathways, and miRNAs.

Acetylation of nucleosomal histones activates transcription through remodelling of the chromatin structure. In the case of SOX2, it has been shown that its regulation is influenced by PAX6, cell-cycle regulators (like E2F3a), the cyclin-dependent kinase inhibitor P21, and other SOX transcription factors (like SOX4) via the TGF-β signalling pathway [118]. Besides the TGF-β signalling pathway, SOX2 expression has also been shown to be activated through the Wnt, FGFR and SHH signalling pathways. Regulation of the expression of SOX2 and its downstream target genes by these signalling pathways has been recently reviewed by Mansouri and colleagues [118].

A number of studies have advocated that SOX proteins, including SOX2, can interact with beta-catenin and TCF (T-cell factor) transcription factors, thereby modulating Wnt signalling in both development and disease. Even though the exact mechanism by which the different SOX proteins regulate β-catenin/TCF activity are poorly understood, evidence suggests that SOX proteins in general repress Wnt transcriptional responses. However, some SOX proteins (e.g. SOX4, SOX5 and SOX11) seem to enhance Wnt-regulated gene expression [119].

Wnt signalling can be repressed by SOX factors stimulating proteasome-mediated β-catenin degradation [119]. The differential recruitment of transcriptional co-activators or co-repressors is another mechanism by which SOX proteins can either enhance or repress Wnt-target gene transcription. In addition to SOX proteins modulating Wnt activity, Wnt signalling seems to regulate SOX gene expression. Hence, these reciprocal interactions result in regulatory feedback loops that have the ability to fine-tune cellular responses following Wnt signalling [119].

Last, the regulation of SOX2 expression also occurs at the post-transcriptional level by miRNAs. The function of miRNAs, which comprise a class of small noncoding RNAs, is to fine tune the regulation of specific mRNAs. For SOX2, several miRNAs (e.g. members of the miR-200 family and miR-9) have been reported to maintain its level at a specific dose [118]. This is important for maintaining stemness or inducing differentiation. Similarly, some miRNAs targeting *SOX2* mRNA might possess the ability to either suppress the expression of oncogenes or suppress the expression of tumour suppressor genes. In this way, miRNAs facilitate the regulation of SOX2 in transformed tissues [118].

A growing body of evidence has also demonstrated post-translational modification as an important tool for the regulation of SOX proteins [12,118]. These modifications include ubiquitination, phosphorylation, sumoylation, acetylation, glycosylation, and methylation. The acetylation of lysine residues located in the DNA-binding domain of SOX2 influences the nucleoplasmic shuttling thereby inhibiting its transcriptional activity [120]. Similarly, the phosphorylation of SOX2 at specific serine residues stimulates the sumoylation of SOX2, which inhibits its ability to interact with DNA [121,122]. In contrast, the phosphorylation of SOX2 at threonine-118 has a stabilising effect on SOX2 [61]. The ubiquitination of SOX2, and its subsequent degradation, is induced by the methylation of SOX2 at lysine-119, thus inhibiting its transcriptional activity [61]. The glycosylation of specific residues in SOX2 suggest that this modification directly regulates core components of the pluripotency network [123]. Even though these post-translational modifications seem to be important in the regulation of SOX proteins, their biological significance during development and disease remains to be confirmed.

In the case of SOX2, Chen and co-workers [124] demonstrated that this factor binds β-catenin and promotes cell proliferation by transcriptionally activating the Wnt target Cyclin D1 gene in breast cancer cells. Kormish and colleagues [119] also showed that SOX17 binds β-catenin via its C-terminal region. Interestingly, another member of the SoxF family, SOX18, has been implicated in angiogenesis during wound healing and tissue repair, but not in the maintenance of endothelial cells in undamaged tissue. The function of the SoxF family transcription factors in cancer is largely unclear. SOX7 and SOX17 induced the VEGFR-2 expression in angiogenic vessels, suggesting a positive feedback loop between VEGF signalling and SoxF. SOX18 probably exerts its function by stimulating Flk1 (Fig. 3) [125,126]. In addition, in breast cancer specimens (invasive ductal breast cancer cases), the gene expression level of *SOX18* correlated with *VEGFD*, which indicates the role of SOX18 in the lymphangiogenesis process [127]. There is also evidence that SOX17 regulates tumour angiogenesis [128]. SOX17 was identified as a regulator of VEGFR-2 expression in tumour endothelial cells (tECs). Yang et al. [128] used *in vivo* mouse models (Lewis lung carcinoma (LCC tumours) and B16F10 melanoma tumours) and measured a strong and specific expression of *SOX17* in tECs. *SOX17* deletion inhibited tumour angiogenesis and normalised tumour vessels. Therefore, SOX17 inhibition is an interesting approach to combine vessel blocking and vessel normalisation. Future studies investigating the interaction of SOX18 with VEGF signalling in cancer are necessary, as this warrants extensive research.

6. The role of SOX in different types of cancer

This chapter summarises the current knowledge of the meaning and function of SOX family transcription factors in selected cancer types according to the incidence and mortality estimated by the GLOBOCAN database [1].

6.1. Breast cancer

According to the latest GLOBOCAN statistics, breast cancer is the most common invasive cancer in women and, after lung cancer, the second leading cause of cancer deaths worldwide [1]. The high mortality rate is directly related to its ability to readily metastasise. Breast cancer is not a single disease, but is composed of multiple subtypes with distinct morphologies, treatability and clinical outcome [129]. Predominantly based on the expression of classical immunohistochemistry (IHC) markers, including oestrogen receptor (ER), progesterone receptor (PR), androgen receptor (AR), human epidermal growth factor receptor 2 (HER2/ERBB2) and protein Ki-67 (KI67), seven molecular subtypes can be distinguished at present [130–133]: Luminal A ($ER^+/PR^+/AR^+/HER2^-/KI67^-$), luminal B ($ER^+/PR^+/AR^+/HER2^-/KI67^+$), HER2 enriched ($ER^-/PR^-/HER2^+$), molecular apocrine ($ER^-/PR^-/AR^+/HER2^+/KI67^+$), basal-like/triple-negative ($ER^-/PR^-/AR^-/HER2^-$), normal breast-like ($ER^+/PR^+/HER2^-/KI67^-$) and claudin-low ($ER^-/PR^-/HER2^-$).

SoxB1 group. SOX1 acts as a tumour suppressor and was found to be down-regulated in both breast cancer tissues and cell lines [134]. Song et al. [134] reported that *SOX1* overexpression reduced cell proliferation and invasion *in vitro* and promoted apoptosis. Inside the cells, SOX1 suppresses the Wnt/β-catenin pathway and inhibits the expression of β-catenin, cyclin D1 and c-myc [134]. SOX2 expression, which indicates a highly malignant tumour, cancer cell “stemness” and an increased risk of recurrence [135], regulates the invasiveness of breast cancer cells dependent on Twist1 and its own transcriptional status [136]. SOX2 is frequently up-regulated in aggressive human breast carcinomas [124,137]. It plays a role in early breast carcinogenesis, where it promotes β-catenin-stimulated proliferation [119,138]. The mechanisms of SOX2 regulation are still not clear. *SOX2* promoter-positive cells show a high sphere formation activity and have a unique stemness-related mRNA profile [139]. Furthermore, annulling gravity may trigger *SOX2* transcription in adherent MCF-7 cells *in vitro* (Fig. 4). It has been proposed that a multi-exon lncRNA (SOX2 overlapping transcript, SOX2-OT) may play a key role in the induction and/or maintenance of *SOX2* expression in breast cancer [140,141]. High *SOX2* expression results in the down-regulation of mTOR signalling [142], the activation of NFκB-CCL1 signalling for T_{reg} recruitment [143] and may improve metastatic potential [144,145] by promoting EMT through Wnt/β-catenin signalling [146]. In addition, SOX2-driven angiogenesis facilitates lymph node metastasis [147]. SOX2 is able to activate the expression of oncogenic lncRNA PVT1 [148]. A side effect of the SOX2-dependent activation of Wnt signalling could be the development of tamoxifen resistance in breast cancer [149]. SOX2 expression (correlated to CK5/6, EGFR and vimentin immunoreactivity) may play an important role in the biology of basal-like breast carcinomas by inducing a less differentiated tumour phenotype [150]. miR-590-5p was reported to down-regulate SOX2 protein expression [151]. The down-regulation of SOX2 expression resulted in decreased tumour cell proliferation and reduced colony formation *in vitro* [152,153]. shRNA-mediated knockdown of SOX2 decreased miR-181a-5p and miR-30e-5p levels and inhibited cell expansion and migration [154]. The induced expression of an artificial transcription factor down-regulating *SOX2* in a mouse model inhibited cancer growth *in vivo* (Table 2) [152]. Mouse models provided further evidence that leptin and its receptor LEPR could be necessary for the survival of breast cancer stem cells via the induction of *SOX2* expression [155].

SoxC group. SOX4 contributes to the metastatic spread of breast cancer [156]. The transcription factor is expressed in both normal breast cells and in breast cancer cells, but was found to be abnormally overexpressed in triple-negative breast cancer [91]. Kuipers et al. [157]

Table 2
SOX family members as potential targets for cancer treatments. Overview of studies targeting different SOX factors to regulate tumour growth.

Tumour	SoxB1			B2	SoxC			SoxD		SoxD		SoxF		
	SOX1	SOX2	SOX3	SOX21	SOX4	SOX11	SOX12	SOX5	SOX6	SOX9	SOX10	SOX7	SOX17	SOX18
Breast cancer	▲ [134]	▼ [153] □ [152] ■ [151] ■ [154] ✚ [153]			■ [160]	■ [164]	□ [165]	■ [166] ■ [167]		■ [21] ■ [182] ● [183]				■ [197] ● [196]
Prostate cancer Renal cell carcinoma					▲ [203] □ [212] ■ [210] ■ [211]			□ [208]		□ [209] ■ [213]				
Thyroid cancer						■ [220]				□ [84]				
CNS tumours	▲ [227] □ [227] ■ [228]	□ [242] ■ [239] ■ [247] ● [231] ✚ [240] ✚ [241]	▲ [237] □ [237]	▲ [250] □ [99]	● [257]	▲ [261] ▼ [261] ● [264]		□ [99] ■ [267] ■ [268]	□ [99] ▲ [271]	■ [274] ■ [281] ■ [282] ■ [283] ■ [284] ■ [285] ■ [286] * [287] ● [281]				
Gastro-intenstinal tumours		■ [321] ■ [323] ■ [324] ■ [334]											□ [307] ■ [307]	
Lung cancer					■ [361]		■ [367]	□ [368]		■ [371] ■ [372]		■ [373] ■ [374]		■ [376] ■ [377]
Skin tumours		□ [409]						■ [391]			▲ [384] ▲ [410] □ [384]		▼ [385]	

▲ overexpression; ▼ downregulation; □ suppression/knockdown; ■ RNAi (miRNA/siRNA/shRNA); * posttranslational, SOX stability; ● proteins, peptides, small molecules; ✚ pharmaceutical substances.

reported that SOX4 is sensitive to cellular tension. Expression seems to be inversely regulated by cytoskeletal tension and matrix rigidity [157] and can be increased by progestins [158]. SOX4 triggers the expression of EMT inducers and, additionally, activates the TGF-β pathway, which also contributes to EMT [91]. *In silico* analyses by Mehta et al. [159] identified *SOX4* amplification as a modulator of PI3K/Akt signalling. *in vitro* studies confirmed the role of SOX4 in regulating Akt phosphorylation [159]. SOX4-directed siRNAs were shown to induce apoptosis in the two breast cancer lines MCF-7 and BT474 [160]. High *SOX11* expression in breast cancer is directly correlated with poor clinical outcome [161]. An investigation by Liu et al. [162] of 116 cases of breast cancer, showed nuclear SOX11 in 36% and cytoplasmic SOX11 in 45% of breast cancer samples. SOX11 is thought to contribute to the progression of ductal carcinoma to invasive breast cancer *in situ* [163] and seems to be a critical regulator of cell proliferation, migration, invasion, gene-expression signatures and survival in basal-like breast cancer [161,164], the most aggressive form of breast cancer. SOX11 was the only transcription factor required for growth of basal-like breast cancer, but not for the growth of non-basal-like breast cancer cells [161]. In this way, SOX11 could be a potential target for the treatment of this cancer type. The first experiments with *SOX11* silencing in breast cancer cells led to an increased level of cleaved caspase-3 [164], suggesting a more rapid apoptosis after SOX11 knockdown. Ding et al. [165] provided the first evidence of *SOX12* overexpression in breast cancer tissues. Functional analyses confirmed its role in promoting the growth, migration and invasion of breast cancer cells and hinted at SOX12 involvement in the tumorigenesis and progression of breast cancer [165]. The knockdown of *SOX12* inhibited the proliferation of breast cancer cells *in vitro* and the growth of xenograft tumours *in vivo*. These cells showed cell cycle arrest and decreased levels of proliferating cell nuclear antigen (PCNA), CDK2 and cyclin D1 [165].

SoxD group. Oestrogen-responsive *SOX5* is overexpressed in highly invasive breast cancer cell lines, such as MDA-MB-435 and MDA-MB-231 [166]. SOX5 suppression by RNAi was shown to inhibit cell proliferation, and the migration and invasion of breast cancer cells *in vitro*. Furthermore, the knockdown of *SOX5* inhibited EMT by the up-regulation of E-cadherin and down-regulation of N-cadherin, vimentin and fibronectin [166]. By the transactivation of Twist1, a master regulator of invasiveness, SOX5 may play an important role in the regulation of breast cancer progression [166]. In addition, miR-146a-5p inhibits the proliferation and metastasis of triple-negative breast cancer cells by regulating SOX5 [167].

SoxE group. Members of the SoxE group (*SOX8*, *SOX9* and *SOX10*) are expressed in triple-negative breast cancer and are useful markers for this subtype [168–171]. For instance, SOX8 is used as a signature of basal-like immune-suppressed triple-negative breast cancer [172]; however, the contribution of *SOX8* expression in breast cancer initiation and progression is still unknown. Nevertheless, a comprehensive bioinformatics analysis of gene expression profiles revealed that the amplification of *SOX8* significantly shortens the survival of patients [170]. SOX9, a key regulator of mammary gland development [173], is up-regulated in breast cancer. Very high levels correlate with positive stem cell status [174] and poor prognosis. SOX9 regulates the Wnt/β-catenin pathway [175] and contributes to the induction and maintenance of the tumour-initiating capacity [176]. It has a key role in the metastasis of triple-negative and $HER2^+$ breast cancer, but was also found in $ER\alpha^+$ breast cancers where expression increases with cancer progression [177]. *SOX9* amplification is thought to be a potential mechanism of resistance to therapy [178]. Localisation is differentially regulated in normal and breast cancer cells. Normally localised in the nucleus, SOX9 was found in the cytoplasm of 25–30% of invasive ductal carcinomas and lymph node metastases [179]. Whereas the nuclear

expression of *SOX9* during mammary morphogenesis sustains a controlled cell proliferation, the loss of this regulation through cytoplasmic compartmentalisation may promote breast cancer growth [180]. In any case, the accumulation of SOX9 in the cytoplasm is correlated with the enhanced proliferation, migration and invasion of breast cancer and a metastatic phenotype [179,181]. *SOX9* silencing, for example by using miR-133b [182] or miR-511 [21], and SOX9 targeting with promyelocytic leukaemia (PML) protein (Table 2) [183] showed reduced tumour formation capacity and less metastasis of breast cancer cells *in vivo* [21,184]. SOX10 contributes to mammary epithelial cell growth *in vitro* by the activation of Notch4 and PBP (peroxisome-proliferative-activated receptor-binding protein) [185]. Furthermore, it is expressed in several invasive breast carcinomas, with the claudin-low subtype showing the highest expression level [186]. SOX10 supports myoepithelial differentiation and thus, directly controls the growth and invasion of basal-like, unclassified triple-negative and metaplastic carcinomas [187,188]. In addition, SOX10-induced expression of nestin modulates stem cell properties of triple-negative breast cancer cells [189].

SoxF group. Immunohistochemical analyses of clinical material by Pula et al. [127] clearly identified an increased gene expression of the SoxF group (*SOX7*, *SOX17* and *SOX18*) in the vascular endothelial cells of invasive ductal carcinomas, confirming its role in tumour angiogenesis. Normal *SOX7* and *SOX17* expression levels seem to play an important role in suppressing breast carcinogenesis as well. Stovall et al. [190] reported the down-regulation of *SOX7* in breast cancer cell lines and tumours. Functional studies confirmed the tumour suppressive role of SOX7 in breast cancer, similar to other cancers. *SOX7* expression inhibits the proliferation, migration and invasion of breast cancer cells *in vitro* and tumour growth *in vivo* [190]. In breast cancer cell lines and tissues, Fu et al. [191] found a decrease of the canonical Wnt antagonist SOX17 at both the mRNA and protein levels. In addition, they reported that *SOX17* overexpression strongly suppressed cell growth *in vitro*. Since promoter methylation of *SOX17* was only found in cancer tissues and hypermethylation of the SOX17 promoter contributes to the aberrant activation of Wnt signalling in breast cancer, they concluded that epigenetic inactivation by promoter methylation may play an important role in breast cancer progression [192,193]. With the exception of a negligible expression in triple-negative breast cancer, different levels of the SOX18 protein were found in several cancer cell lines [127]. However, in MCF-7 cells, the transcription of *SOX18* is not affected by 17-beta-estradiol [194]. In contrast to *SOX7* and *SOX17*, the knockdown of *SOX18* was shown to inhibit the cell growth and invasion of breast cancer [195], making SOX18 a promising pharmacological drug target. Indeed, treatment with the SOX18 inhibitor Sm4 reduced tumour vascular density and metastatic spread in mice [196]. *in vitro* studies with the MCF-7 cell line by Young et al. [197] confirmed that the inhibition of SOX18 leads to the destabilisation of the actin cytoskeleton, resulting in a decreased capacity of these cells to migrate. Interestingly, increased *SOX18* expression in MCF-7 cells leads to the increased proliferation of and capillary formation by human umbilical vein endothelial cells (HUVECs) [127]. This underlines the key role of SOX18 in tumour angiogenesis and breast cancer progression.

Overall, in addition to their physiological role in embryonic mammary development, SOX proteins play an important and complex role in the genesis and progression of breast cancer. They can act as both tumour suppressors and transcription factors, promoting malignant characteristics, and are also useful as markers for certain types of breast cancers, such as triple-negative tumours. Although employing mostly *in vitro* approaches, the studies compiled here present strong indications that SOX proteins might be promising subjects for future targeted therapy approaches.

6.2. Prostate cancer

Adenocarcinomas are the most common types of prostate cancer, which is found on all continents and causes more than 300,000 deaths annually worldwide. It is the most commonly diagnosed cancer in males worldwide. Today, prostate cancer is the second leading cause of cancer death in men, as estimated by GLOBOCAN in 2018 [1].

SOX2 is weakly expressed in both benign and malignant prostate tissue [198]. However, SOX2 characterised potential cancer stem cells as a minor subgroup (< 10%) in CD44-positive prostate cancer [198]. In addition, SOX2 is detectable in castration-resistant prostate cancer metastasis samples [199]. SOX2 was expressed in the developing prostate and basal cells of benign prostatic hyperplasia (BPH), as well as prostatic neuroendocrine tumours [200]. SOX2 is also involved in tumour progression. Reduced SOX2 levels attenuated the proliferation and invasion and elevated the re-differentiation of cancer cells [200]. SOX2 promotes tumorigenesis and apoptosis in human prostate cancer and exerts a regulatory effect on the activity of store-operated Ca^{2+} channels [201]. Moreover, SOX2 up-regulated neural CAMs, neurotrophins and their receptors, angiogenic and lymphangiogenic factors. SOX2 is proposed to serve as a functional biomarker for lymph node metastasis of prostate cancer [202]. In addition, SOX2 is proposed as a useful target for prostate cancer therapy.

SOX4 is associated with tumour progression and poor clinical outcome in several cancers [203]. *SOX4* was enhanced in prostate cancer tissues and cell lines. Expression profiling of human prostate cancer and benign tissues revealed *SOX4* up-regulation in prostate tumour samples, which was correlated with a high Gleason score. The silencing of *SOX4* by small interfering RNAs (siRNAs) induced programmed cell death of prostate cancer cells, suggesting that SOX4 could also be a therapeutic target for prostate cancer [160]. Direct transcriptional targets of SOX4 include EGFR, HSP70, Tenascin C, Frizzled-5, Patched-1 and Delta-like 1 [204]. In addition, SOX4 targets 23 transcription factors; examples include MLL, FOXA1, ZNF281 and NKX3-1 [204]. The knockdown of SOX4 reduced proliferation and migration in DU145 prostate cancer cells, while SOX inhibition reversed EMT via the up-regulation of E-cadherin and the down-regulation of vimentin [203]. This study provided evidence that SOX4 could serve as a potential therapeutic target in prostate cancer.

Another study reported on the involvement of SOX7, SOX9 and SOX10 in the aggressive progression behaviour of prostate cancer [205]. The authors measured significantly decreased expression of *SOX7* and *SOX10* mRNAs, whereas *SOX9* gene expression was increased in PC with a higher Gleason score [205]. SOX7 and SOX9 are proposed as prognostic markers for patients with PC.

SOX11 has been recently recognised as a potential tumour suppressor that is down-regulated in prostate cancer [206]. SOX11 overexpression suppresses migration and invasion in prostate cancer cells *in vitro*. A further study investigated SOX11 promoter methylation in prostate adenocarcinoma by comparing it with benign prostatic hyperplasia (BPH). The detection rates of SOX11 promoter methylation were significantly higher in prostate cancer compared to BPH. SOX11 hypermethylation was associated with adverse clinicopathological characteristics of prostate cancer, including a significantly elevated prostate-specific antigen (PSA) level [207].

in vivo studies suggested the involvement of SOX5 in prostate cancer metastasis [208]. This modulates the TGF-β-induced epithelial mesenchymal transition by controlling Twist1 expression [208]. The knockdown of SOX5 in a xenograft mouse model inhibited the progression of prostate cancer (Table 2) [208]. The combined analysis of SOX5 expression and clinical data revealed that patients with high SOX5 expression showed the progression of metastasis, a lower progression-free survival and reduced survival in clinic databases [208].

The down-regulation of SOX9 reduced tumoursphere formation and the *in vivo* (mice) tumorigenicity in androgen-deficient hosts [209].

In summary, the current knowledge of SOX transcription factors shows their involvement in tumorigenesis and that their up-regulation is important for progression in prostate cancer. Further studies investigating the SoxF family in prostate cancer are necessary.

6.3. Renal cell carcinoma

Among all types of kidney cancers, renal cell carcinoma (RCC) is the most common form, accounting for about 90–95% of all cases. Histological subtypes of RCC include clear-cell RCC, papillary RCC, chromophobe RCC, collecting duct RCC, sarcomatoid RCC and unclassified RCC. According to the latest GLOBOCAN (2018), RCC will cause about 403,262 new cases (2.35%) and 175,098 deaths (1.97%) per year worldwide [1].

So far, few studies have been conducted to study the potential roles of SOX proteins in RCC. In a more indirect approach, Wu et al. [210] investigated the impact of microRNA-204 (miR-204) on human RCC cell lines 786-O and A498. They showed that the overexpression of miR-204 resulted in a significant decrease of cell viability, migration and invasion in both cell lines. Furthermore, Western blot and reporter-gene assays indicated that the microRNA directly suppresses *SOX4* expression. Therefore, the authors concluded that SOX4 is implicated in RCC cancer progression [210]. Similar findings have also been reported for miR-338-3p. The authors found that it was down-regulated in four RCC cell lines (786-O, ACHN, Caki-1 and Caki-2) and in frozen RCC tissue samples, and suppressed cell proliferation, colony formation, migration and invasion, as well as SOX4 gene and protein expression in 786-O and Caki-1 cells. Furthermore, *SOX4* expression was inversely correlated with miR-338-3p expression in RCC tissue, and SOX overexpression eventually reversed the effects of miR-338-3p in a co-expression experiment (Table 2) [211]. Targeting SOX4 directly, it was shown that its specific overexpression or knockdown in 786-O, A498, ACHN and SN12-PM6 RCC cell lines were directly correlated to an increase or decrease in cell migration and invasion, respectively. In addition, it was demonstrated that SOX4 promotes TGF-β-induced EMT. In accordance with earlier studies, the authors also found that SOX4 was significantly up-regulated in clinical RCC samples and suggested a central role of SOX4 in EMT and metastasis [212].

The next member of the SOX family that was implicated in RCC was SOX9. In a study very similar to [210] and [211], the authors found SOX9 to be a target of miR-138 in RCC cell lines 768-O, ACHN, A498, Caki-1 and OS-RC-2. They also demonstrated that this miRNA was down-regulated in both renal tumour tissue and RCC cell lines and was able to suppress viability, proliferation and migration, as well as SOX9 gene and protein expression. In addition, miR-138-independent SOX9 knockdown also resulted in an inhibition of RCC cell proliferation and invasion, indicating the involvement of SOX9 in RCC development and progression [213]. Employing immunohistochemical studies for SOX9 protein expression in RCC tissue microarrays, it was found that SOX9 expression was significantly elevated in RCC. Furthermore, the SOX9 expression level was positively correlated with advanced pathological grade and clinical stage and negatively correlated with survival. Based on these data, SOX9 is a suitable prognostic factor for RCC [214].

Lastly, in a retrospective study, data from a total of 505 patients suffering from clear-cell RCC obtained from The Cancer Genome Atlas (TCGA) RNAseq database were systematically analysed for SOX-family expression, as well as for characteristics such as age, gender, tumour grade, stage, disease-free-survival (DFS) and overall survival (OS). Furthermore, a cohort comprising 192 patients with clear-cell RCC who underwent nephrectomies at the Fudan University Shanghai Cancer Centre was used in parallel for validation via quantitative RT-PCR analysis. Statistical analyses revealed that SOX2 and SOX12 can serve as independent prognostic factors for OS [215]. Apart from these clinical data, no studies employing *in vivo* models have been conducted to date.

6.4. Thyroid cancer

Thyroid carcinomas (TC) are malignant tumours of the thyroid gland and are classified into several categories: first, differentiated (DTC), covering papillary (PTC), follicular (FTC) and Hürthle cell cancer; second, medullary (MTC); and third, anaplastic thyroid cancer (ATC). The American Cancer Society recently estimated that in the US in 2018, about 53,990 new cases of thyroid cancer (40,900 in women and 13,090 in men), as well as about 2060 deaths from thyroid cancer (1100 women and 960 men). The most common TC is PTC, making up 80–90% of all TC types [1].

The impact of SOX proteins in thyroid cancer is unclear. Only a few studies have addressed this topic so far. A role for thyrotropin has been discussed. It is known that thyrotropin, or thyroid-stimulating hormone (TSH), influences *SOX9* gene expression. Epiphysial cartilage and chondrocytes *in vitro* expressed functional TSH receptor at levels similar to those measured in the normal thyroid gland [216]. Furthermore, the application of TSH to cultured chondrocytes suppressed the expression of *SOX9* [216].

The stem cell marker SOX2 has been detected in cancer stem cell subpopulations in different cancer types. Recently, it was shown that the papillary thyroid cancer cell lines TPC1 and 8505C, as well as the anaplastic thyroid cancer cell lines Hth74 and SW1736, were SOX2-positive [217]. Therefore, we investigated the poorly-differentiated follicular thyroid cancer cell line FTC-133 under altered gravity conditions using quantitative RT-PCR. The FTC-133 cells were exposed for 10 days to simulated microgravity created by a Random Positioning Machine (RPM) (Fig. 4) [76]. Earlier studies of FTC-133 exposed to an RPM had shown that the cells grew adherently as a two-dimensional monolayer and in the form of three-dimensional multicellular spheroids floating in the supernatant [218]. The cell line did not express *SOX2*, but was positive for *SOX9* and *SOX11*. These data are shown in Fig. 4.

SOX9 is detectable in several cancer types and exhibits various roles. SOX9 was elevated in PTC tissues and cell lines. A SOX9 knockdown inhibited proliferation, invasion and the EMT process in PTC by suppressing the Wnt/β-catenin signalling process [84]. Moreover, the knockdown of SOX9 induced programmed cell death in PTC cells. Therefore, SOX9 may act as a new molecular target for the prevention and treatment of PTC.

SOX17 is a tumour suppressor gene that inhibits the canonical Wnt/β-catenin signalling pathway in cancer. Little is known about its function in thyroid cancer. Li et al. [219] showed that *SOX17* was often methylated in human PTC. The loss of SOX17 expression was induced by promoter region hypermethylation. SOX17 inhibited cellular proliferation. The methylation of SOX17 activated the Wnt signalling pathway in human thyroid cancer [219].

The overexpression miR-211-5p inhibits the proliferation, migration, and invasion of papillary thyroid cancer cells via the down-regulation of SOX11 (Table 2) [220]. The anti-tumour role of miR-211-5p was proven by an *in vivo* experiment. Therefore, targeting SOX11 might be a new interesting new idea.

The importance of SOX family members in thyroid cancer is still a complex and unexplored research area and is largely unknown. Therefore, research in the field of thyroid cancer should be performed. Especially investigating the role of SOX family members in particular, the SoxF group in radioactive iodine-refractory differentiated thyroid cancer is of high interest.

6.5. Tumours of the central nervous system (CNS)

CNS tumours are a heterogeneous group of neoplasms and, according to the GLOBOCAN statistics, are responsible for around 2.5% of

deaths caused by cancer worldwide [1]. Additionally, they constitute the largest group of solid paediatric tumours and cause the highest mortality rates in children [221]. Under most circumstances, "brain tumours" refer to gliomas, which are the most common malignant primary tumours in cerebral hemispheres of adults displaying histologic features of glial cells. According to the 2016 WHO classification, gliomas are no longer classified only by histopathological appearance, but also by molecular parameters, such as shared isocitrate dehydrogenase (IDH) genetic status [222]. The historically different categories based on tumour histology (astrocytoma, oligodendroglioma, ependymoma or mixed glioma) are now grouped together as "diffuse gliomas." Based on clinical and pathological criteria, diffuse gliomas are still graded into four classes of malignancy [222]. Glioblastomas (pre-2016: glioblastoma multiforme, GBM), one of the most aggressive and fatal cancers overall, belong to the grade IV class. Only 0.05–4.7% of patients suffering from glioblastoma survive 5 years after diagnosis [223]. Originally classified as a glioma, medulloblastoma is now referred to as primitive neuroectodermal tumour (PNET) [224]. It is the most frequent embryonal CNS tumour and the most common malignant brain tumour in children, accounting for 15–20% of all childhood brain tumours [225].

SoxB1 group. During development, members of the SoxB1 group play a role in the maintenance of neural stem cells [226], but are also overexpressed in CNS tumours. SOX1 overexpression was confirmed in a subset of glioblastomas, and high levels of SOX1 correlate with lower overall survival [227]. In addition, high *SOX1* expression in glioma stem cells (GSCs) is reported to slightly promote self-renewal and proliferation, apparently independent of Wnt/β-catenin signalling [227]. *SOX1* knockdown in GSCs resulted in decreased self-renewal and proliferative capability *in vitro*, as well as tumour initiation and progression *in vivo* [227]. The presence of a SOX1 overlapping transcript (SOX1-OT) in the neuroblastoma cell line SH-SY5Y suggests a possible role for SOX1-OT in regulating SOX1 expression, similar to SOX2 in breast cancer [228]. SOX2 is a marker for undifferentiated, proliferating cells and can be found in all types of gliomas (including different kinds of paediatric brain tumours), in glioma cell lines, tumour-associated glial host cells and in ependymoma [229–234], but only rarely in neuronal tumours [235]. In addition to amplification, *SOX2* expression is upregulated in most anaplastic areas of glioblastomas and oligodendrogliomas [232]. In medulloblastomas, it seems to be dependent on the tumour subgroup used for analyses (i.e. higher expression in the SHH group) [118,229,236,237]. Elevated SOX2 levels were found to be essential, although not sufficient, for maintaining the self-renewal of GSCs [53]. Thus, some authors claim that SOX2 may be a tumour marker of glial lineages rather than a universal stem cell marker in brain tumours [230]. Nevertheless, SOX2 regulates the expression of key genes and pathways involved in malignancy and stemness of medulloblastoma [118] and GBM cells, maintaining plasticity for bidirectional conversion between stem-like and differentiated states [238]. SOX2 levels, and thus higher stem cell gene expression profiles, correlate positively with the malignancy grade of brain tumours and with a poor clinical outcome in patients [118]. The siRNA-mediated downregulation of SOX2 impaired the proliferation of GSCs and tumour formation in vivo [239]. Pharmaceutical treatment with neriifolin or mithramycin also reduced *SOX2* expression and inhibited the growth of GBM cells *in vivo* (Table 2) [240,241]. Fang et al. [242] performed a genome-wide binding pattern analysis for SOX2 in GBM and found 4883 binding sites for SOX2. Furthermore, *SOX2* knockdown altered the expression of 105 precursor microRNAs and 489 genes that are involved in signal transduction and membrane reception, as well as kinases [242]. Cox et al. [243] investigated the SOX2 interactome in medulloblastoma cells and identified over 280 proteins that are associated with SOX2. In addition, they demonstrated that MSI2 and USP9X play key roles in the growth of medulloblastoma and glioblastoma cells [243]. Several studies confirmed the SOX2 contribution to self-renewal in glioma. Ge et al. [244] reported that *SOX2* overexpression in glioma cells increased the number and size of neurospheres. Furthermore, they found a correlation between SOX2 level and the eukaryotic initiation factor 4E (eIF4E): the down-regulation of eIF4E decreases the SOX2 protein level in GSCs, but not the mRNA level, indicating the translational activation of SOX2 [244]. The down-regulation of some upstream regulators of SOX2 such as Bmi1-GSK3β [245] or CDC20-APC [246], which drives invasiveness and self-renewal of glioblastoma stem-like cells, was reported to suppress SOX2 specifically and could reduce its tumorigenic role in glioma. The chromatin remodelling protein HMGA1 regulates *SOX2* promoter function through changes in the chromatin architecture in response to miR-296-5p [247]. Through SOX4 regulation, SOX2 is also connected to the TGF-β signalling pathway [57], further mentioned in the SoxD section below. Schmitz et al. [231] discovered an immunogenic HLA-A*0201-restricted T cell epitope derived from SOX2 that effectively activates tumour-directed cytotoxic T lymphocytes and that could be suitable for T cell-based immunotherapy of glioma patients. One study has examined the effects of SOX3 in glioma. Marjanovic Vicentic et al. [248] reported that the *SOX3* expression was elevated in primary GBM. *SOX3* overexpression increased proliferation, viability, migration and invasion capabilities through enhanced Hedgehog signalling and/or by suppressed autophagy in these cells [248]. The authors suggested that SOX3 is able to promote malignant behaviour in glioblastoma cells by maintaining GSCs in their undifferentiated state [248].

SoxB2 group. Closely related to SoxB1, the SoxB2 group takes part in neurogenesis by counteracting the activities of SoxB1 proteins [249]. Whereas SoxB1 proteins are predominantly transcriptional activators, SOX21 has repressor activity and can act as a tumour suppressor during gliomagenesis [99]. The induction of *SOX21* expression inhibits SOX2 by complexation and leads to apoptosis in glioma cells [229,250]. Furthermore, *SOX21* expression, and thus decreased SOX2/SOX21 ratio, reduced the stem-like features of glioma cells and initiated aberrant differentiation *in vivo*. The increased presence of SOX21 in tumour cells not only inhibited glioma progression, but also significantly reduced tumour size [250]. This indicated that the balance between SOX21 and SOX2 is a cellular switch between a stem-like state and differentiation.

SoxC group. This group plays a role in different brain tumours. *SOX4* and *SOX11* are strongly expressed in most classical tumours, but only weakly in desmoplastic medulloblastomas [251]. In the latter, SOX4 was identified as a marker for cell differentiation, as well as a prognostic marker for slightly better survival [252]. In glioblastoma, SOX4 and SOX11 may exhibit opposing activities [251,252]. Nevertheless, there are conflicting reports about SOX4 levels in this tumour type. In cell line models, SOX4 seems to behave as a tumour suppressor, whereas analyses with primary tumour samples offered a good prognosis with high *SOX4* expression. The tumour suppressing function was documented by Zhang et al. [253], who found that SOX4 induced a G0/G1 cell cycle arrest through the Akt-p53 axis and inhibited glioblastoma cell growth. In human glioblastoma tissues, *SOX4* is co-expressed with *SOX2* at high levels [254], contributing to EMT, experimental primary tumour growth and metastasis [88]. SOX4 was identified as an important SMAD3 co-factor, controlling the transcription of EMT-relevant genes (i.e. *EZH2*) [88], pro-metastatic genes (i.e. *TGFBI*) and modulating cellular response to TGF-β [36,255]. In tumour-initiating GSCs, Oct4-SOX4 complexes cooperatively activate the enhancer activity of the *SOX2* gene, leading to a consequent boost of SOX2 expression [256]. This contributes to the activation of both canonical and non-canonical TGF-β signalling and enhances tumour activity in GSCs by maintaining stemness [57]. In contrast, the inhibition of TGF-β-SOX4-SOX2 signalling decreases the tumorigenicity of GSCs by promoting differentiation [57]. Han et al. [257] found that *SOX4* transcription can

be inhibited by 'four and a half LIM domain protein 3' (FHL3), which is able to interact with the SMAD2/3 complex at the *SOX4* promoter region. The associated down-regulation of *SOX2* suppressed GSC tumour sphere formation and self-renewal *in vitro* and *in vivo* [257]. Furthermore, *SOX4* expression seems to be inducible by hypoxia [258]. SOX11 is required for both embryonic and adult neurogenesis [259], but its role in brain tumorigenesis is much less clear. The presence of SOX11 in gliomas was confirmed by DNA microarray analysis [254]. On the one hand, *SOX11* expression is seen as a favourable prognostic factor in glioblastomas [260], whereas transcriptional down-regulation is associated with a significant decrease in survival [261]. Hide et al. [261] reported that SOX11 may work as a tumour suppressor, preventing gliomagenesis by the inhibition of oncogenic pleiomorphic adenoma gene-like 1 (PLAGL1) expression. They found that *SOX11* overexpression in glioma-initiating cells decreased levels of PLAGL1 and thus blocked their tumorigenesis by inducing differentiation towards the direction of neurons [262]. On the other hand, transcription analysis by Weigle et al. [263] revealed a 5 to 600-fold overexpression of *SOX11* in malignant glioma samples. The authors suggested that, after down-regulation of SOX11 in the adult brain, its expression is reactivated during tumorigenesis. Schmitz et al. [264] identified the SOX11-derived peptide LLRRYNVAKV, which is specifically expressed on glioma cells. This peptide is able to induce tumour-reactive cytotoxic T cells and could be suitable for immunotherapy.

SoxD group. Compared with normal brain tissues, *SOX5* levels are lower in different glioma tissues [265] and cell lines [266]. As part of the SoxD group, SOX5 may act as a tumour suppressor, since the overexpression of *SOX5* was reported to inhibit cell proliferation in human glioma cell lines *in vivo* [266]. Furthermore, SOX5 can suppress platelet-derived growth factor B (PDGFB)-induced glioma development in mice by inducing the inhibition of cell proliferation and acute cellular senescence through the regulation of $p27^{Kip1}$ and Akt [266]. The functional knockout of three *SOX* genes (*SOX5*, *SOX6* and *SOX21*) significantly increased the capacity of stem cells inside the subventricular zone to form glioma-like tumours in an oncogene-driven murine brain tumour model [99]. Results by Kurtsdotter et al. [99] indicate that these three SOX proteins mediate an anti-tumorigenic response mechanism to oncogenic stimuli in brain stem cells. The oncogenic microRNAs miR-16 and miR-21 target SOX5 in glioblastoma cells and might affect its expression and downstream signalling [267,268]. SOX6 was found in glioma, medulloblastoma and neurocytoma [265]. Its expression level is down-regulated in GBM, elevated in oligodendroglioma and slightly up- or down-regulated in astrocytomas, compared to the normal adult brain [265]. Studies by Ueda et al. [269] reported that SOX6 is present in GBM, but only a few cells in glioblastomas are $SOX6^{+}$, indicating an aberrant expression in these cells [270]. Additionally, they found that one-third of the patients suffering from gliomas develop IgG antibodies against SOX6 [270]. Glioma-bearing mice treated by DNA-vaccination with plasmids encoding SOX6 had cytotoxic T-lymphocyte-induced anti-tumour activity and showed longer survival times compared to untreated mice [271]. Little is known about the role of SOX13 in brain tumorigenesis. Schlierf et al. [265] reported that, compared to SOX13 expression in the healthy adult brain, mRNA expression of *SOX13* is increased in oligodendroglioma, either up- or down-regulated in astrocytomas and mainly down-regulated in GBM.

SoxE group. There is sparse information about the involvement of SOX8 in brain tumorigenesis. In addition to immature glia in the developing cerebellum, SOX8 is found in medulloblastomas [272] and oligodendrogliomas and is enhanced in low-grade astrocytomas. In GBM, *SOX8* expression is lower than in the healthy adult brain [265]. SOX8 levels may be helpful for predicting the differentiation status of glioma subtypes [265]. *SOX9* is over-expressed in different paediatric and adult brain tumours [252,273]. This was confirmed in glioma tissues and the U251 cell line [274]. High grade neuroepithelial tumours (GBM, anaplastic oligodendroglioma and primitive neuroectodermal tumours) show a strong co-expression of *SOX9* and *SOX10* [275]. Additionally, SOX9, together with SOX2, seems to play essential roles in craniopharyngioma formation, as well as in maintaining the cerebral tumour environment [276]. The strong correlation between SOX2 and SOX9 expression identified an oncogenic axis that regulates stem cell properties and chemoresistance [43,277]. High SOX9 levels are accompanied by lower disease-free and overall survival rates [273]. Epidermal growth factor receptor variant III (EGFRvIII)-induced co-expression of *SOX9* and *FOXG1* initiates the activation of an oncogenic gene regulatory program in GBM cells [278]. Additionally, SOX9 triggers *LGR5* expression, which is required for the tumorigenicity of glioblastoma cells [279]. Forced expression of *SOX9* in neural stem cells promotes self-renewal, is associated with increased expression of *GLI2* and generates the increased penetrance of a Gli2-expressing tumour [280]. However, down-regulation of *SOX9* in glioma cells inhibits cell growth, induces cell arrest in the G2/M phase and enhances apoptosis [274]. Furthermore, a decrease of cyclin D1, cyclin-dependent kinase 4 (*CDK4*) expression and retinoblastoma protein (Rb) phosphorylation was reported with the down-regulation of *SOX9*, which also correlates with a reduced number of cells in the S phase [273]. *SOX9* knockdown impairs proliferation [281] and suppresses stem cell-like properties and glioma cell sphere formation. Thus, Wang et al. [277] suggested that SOX9 plays a key role in GSC self-renewal via PDK1 signalling. Several miRNAs (miR-30c [282], miR-101 [283], miR-105 [284], miR-145 [285] and miR-613 [286]), can act as tumour suppressors, directly targeting SOX9 and suppressing its oncogenic activity in glioma cells (Table 2). Additionally, the post-translational regulation of SOX9 stability through the GSK3-SOX9-FBW7 axis may be a promising approach for targeting SOX9 in CNS tumours [287]. SOX10, a marker of oligodendrocytes [288], is expressed in different types of human gliomas, except for medulloblastomas [289–291]. This factor alone is not sufficient to induce gliomagenesis in mice, but it may act synergistically with other oncogenes, such as PDGFB, in glioma development [290]. There is evidence that SOX10, together with nuclear factor IA (NFIA), orchestrates glial diversification, both during development and tumorigenesis [292]. Hypermethylation of the *SOX10* promoter was found to be associated with shorter survival [293].

SoxF group. SOX7 is able to inhibit glioblastoma cell proliferation, but is frequently down-regulated in glioma tissues and cell lines, partially due to oncogenic miRNA targeting. miR-24 and miR-616 are two up-regulated, known tumour promoters in these cells that are involved in SOX7 regulation and Wnt/β-catenin signalling [294,295]. Tumour endothelial cells in mice suffering from highly angiogenic high-grade glioma up-regulate SOX7 via an increase of VEGFR-2 to promote tumour angiogenesis [296]. The exact role of SOX17 in human CNS tumours has to be explored. Methylated SOX17 was found in anaplastic oligodendroglioma samples. Majchrzak-Celińska et al. [297] suggested that epigenetic silencing of this gene may contribute to an up-regulation of the Wnt/β-catenin pathway in gliomas. A deletion of SOX17 in tumour endothelial cells leads to an up-regulation of *SOX7* in these cells [296].

So far, 14 of the 20 known SOX proteins have been reported to be expressed in CNS tumours. Reflecting their physiological roles, they are able to control different key processes related to tumour biology. Of these, the SoxB1 family is the most thoroughly investigated to date, including the most *in vivo* studies and even pharmacological intervention experiments, making them, but also the other SOX members, interesting candidates in the search for new therapeutic targets. Furthermore, a better understanding of the mechanisms for how SOX factors induce and maintain cell stemness would open up new possibilities to convert malignant gliomas to less-malignant sub-types to facilitate treatment.

6.6. Gastrointestinal tumours

Types of gastrointestinal cancer include gastric cancer, colon cancer, colorectal cancer and pancreatic cancer. These organs are responsible for a large proportion of cancer and cancer deaths [298]. In each of these types of cancer, deregulation of distinct members of the SOX family has been detected. Depending on the individual situation, deregulation can mean that too much or too little of a SOX member's mRNA is expressed and protein produced.

Regarding the role of SOX2 in gastric cancer, current research results are inconsistent. There are studies suggesting that SOX2 promotes gastric cancer, since its inhibition reduces cell proliferation and migration but increases apoptosis [299]. Other studies point to the possibility that SOX2 suppresses gastric cancer development [300,301]. The difference could be explained as follows: promoters of different genes can be targeted in different situations [301]. The up-regulation of *SOX4*, *SOX9* or *SOX17* was frequently associated with a more severe case of gastric cancer [302–305], while SOX7 appears to have suppressive effects [306]. In contrast, another study on a mouse model reported that the down-regulation of *SOX17* contributes to the development of gastric cancer [307]. Therefore, future studies in this area should be performed. Interestingly, SOX11 inhibits cell migration in gastric cancer, but does not affect proliferation [308]. Its deregulation may be caused by aberrant DNA methylation [309].

In colon cancer, SOX2 has been intensively investigated. This transcription factor contributes to the reprogramming of differentiated human somatic cells into a pluripotent state [310]. Together with OCT3/4 and KLF4, it is capable of transducing colon cancer cells into colon cancer stem cells [311]. High levels of SOX2 induce drug resistance and metastasis [312,313]. In addition, SOX9 becomes overexpressed in colon carcinogenesis [314]. It promotes tumour metastasis via induction of the protein S100-P, which interacts with ezrin [315,316]. SOX4 appears to control colon cancer and survival via the Cyr-61 protein, which is involved in cell adhesion [317,318]. However, SOX10 has tumour suppressive effects and is inactivated when colon cancer develops [319]. Similarly, the down-regulation of SOX17 contributes to the malignant progression of colon cancer [307]. The inhibition of colon cancer cell metastasis is also associated with an up-regulation of SOX17 and CDH-1 expression, during which their promoters are hypomethylated [320]. Interestingly, a relationship between SOX7 and colon cancer could not be found in the literature.

Also, SOX2 has been most often described in research on colorectal cancer (CRC). It favours the stemness of CRC cells [321] and is involved in metastasis [322]. If its translation is inhibited by relevant miRNAs, such as miRNA-203 and miRNA-126, tumorigenicity is reduced (Table 2) [321,323]. However, there are other reports that indicate that miRNA-429 suppresses apoptosis by down-regulated SOX2 [324]. Very often, SOX9 expression facilitates tumour growth and progression, whereas its inactivation reduces tumorigenicity [325]. CRCs with high expression of SOX9 were associated with a low 5-year survival rate [326]. SOX9 tumorigenicity frequently coincides with β-catenin protein enhancement [327]. It has also been observed that a decrease of SOX9 activity induces claudin-7 overexpression with a loss of cell polarity [328]. Also, altered expression levels of SOX4 were detected in CRC specimens [329]. The expression of oncogenic SOX4 was inversely associated with that of miR-129-2-3p and miR-129-5p, but not with miR-129-1-3p [330]. Hypermethylation of the *SOX17* promoter leads to the silencing of this gene, which facilitates tumorigenesis in colorectal cancer [331]. While the above-mentioned Sox family members predominantly favour tumour development and expansion, SOX7 also has tumour suppression activity in CRC [332].

The role of SOX family members in pancreatic cancer has been less well investigated until now. Nevertheless, SOX2 is already recognised as being involved in maintaining the characteristics of pancreatic stem cells. Its overexpression is also a marker of pancreatic cancer [333]. When aberrantly expressed in pancreatic cancer, SOX2 leads to a loss of the tight junction proteins E-cadherin and ZO-1 and contributes to cell proliferation and dedifferentiation [107]. Pluripotency is reversed when SOX2 is down-regulated by enhanced miRNA-145 expression [334]. *in vivo*, the growth of tumour initiating pancreatic cells needs synergistic activation by SOX2 and SOX9 [335]. Activation of SOX9 is initiated by binding of the NF-κB subunit p65 protein to its promoter [336]. In addition, SOX4 supports tumour growth in pancreatic cancer [337], and SOX18 was expressed in all pancreatic cell lines investigated by Saitoh and Katoh [194]. As in other gastrointestinal cancers, SOX7 appears to suppress pancreatic cancer [338].

Taken together, several SOX family members have so far been reported to play a role in gastrointestinal cancer. SOX2, which under healthy conditions regulates stem cell pluripotency, has been investigated most thoroughly. In most, but not all cases, it was found to promote the development of tumours. Similar results were obtained for SOX9, the second most studied SOX member in gastrointestinal cancer. SOX7, and to some extent also SOX17, appears to have suppressive activity in this type of cancer.

As the knowledge about the roles of the various SOX family members in gastrointestinal tumours increases, it appears reasonable to target the effects of de-regulated SOX transcription factors. New animal models appear to be the first steps in this direction. For example, a SOX9-EGFP mouse model allows cells to be localised *in vivo* which exert enhanced SOX9 levels and live in colon tumours [339] or the breeding of transgenic mice which produce enhanced levels of SOX17 and are more resistant to gastric cancer [307].

6.7. Lung cancer

Lung cancer is the single most prevalent cancer worldwide, with an estimated 2,093,876 new cases and 1,761,007 deaths per year worldwide. There is a marked gender difference in both absolute and age-standardised incidence (1,368,524 and 31.5/100,000 for men vs. 725,352 and 14.6/100,000 for women, respectively), as well as absolute mortality (1,184,947 and 22.5/100 000 for men vs. 576,060 and 18.6/100,000 for women) [1]. Lung cancer is classified into non-small-cell lung carcinoma (NSCLC) and small-cell lung carcinoma (SCLC). NSCLC can be further subtyped into adenocarcinoma (accounting for about 40% of all lung carcinoma cases), squamous-cell carcinoma and large-cell carcinoma.

SoxB1 group. SOX2 was reported to be overexpressed in all types of lung cancers [340]. Several studies have pointed out that SOX2 regulates the expression of oncogenes such as c-myc, Wnt1, Wnt2, and NOTCH1 as well as apoptotic processes, and is thus driving the development and progression of lung cancer [39,341–345]. SOX2 is also involved in the development of chemoresistance in lung adenocarcinoma or SCLC cells, as shown by overexpression and knockout experiments [346,347]. SOX2 overexpression seems partly to be caused by gene amplification [348–350]. Interestingly, despite being a major factor in lung cancer development, high levels of SOX2 protein expression or gene amplification in the tumour were reported to be associated with improved overall survival [351–357]. However, in whole blood, high *SOX2* mRNA expression was a significant prognostic factor for poor OS [358]. In addition, it was shown that SOX2 is a key factor in the FGFR1-ERK1/2-SOX2 axis and can promote cell proliferation, EMT, migration, and invasion in *in vivo* models of FGFR1-amplified lung cancer [359].

SoxC group. Most findings of SOX4 function in lung carcinoma have been made indirectly by studying miRNAs or long noncoding RNAs (lncRNAs). It was shown in adenocarcinoma that the lncRNA CASC2

suppressed SOX4 expression, which lead to a mediation of EMT and metastasis [360]. While investigating the CCAT1/miR-130a-3p axis, it was also shown that CCAT1 lncRNA was up-regulated and miR-130a-3p was down-regulated in cisplatin-resistant NSCLC cells. Concurrently, SOX4 expression was also increased, and it was shown that miR-130a-3p directly suppresses SOX4. Lastly, SOX4 was able to reverse a CCAT1 knockout-induced decrease in cisplatin resistance, indicating that SOX4 is an important regulator of this treatment [361]. Furthermore, different miRNAs have been identified in NSCLC cells, which target SOX4 and suppress migration and invasion, as well as EMT, both *in vitro* and *in vivo* in clinical samples [362,363], providing further evidence of SOX4 as an integral regulator of tumour malignancy. These findings were supported by another study that employed a SOX4-specific knockdown via a short hairpin RNA (shRNA) in XWLC-05 cells, which led to an increase in apoptosis and a decrease in cell proliferation and metastasis in an *in vivo* analysis in nude mice [364]. In fact, in two independent studies, SOX4 proved to be a biomarker for the prognosis and identification of tumours. In NSCLC patients, SOX4 protein expression is positively correlated with clinical stage, T-, N- and M-classification, as well as with poor overall survival [365], while SOX4 and SOX11 expression was specifically elevated in different tumour types in an mRNA expression study in different lung neuroendocrine tumours. In addition, increased SOX11 expression correlated with poor prognosis in large cell neuroendocrine carcinomas and NSCLC [366]. Very similar observations were made for SOX12. It was found that the SOX12 expression was up-regulated in clinical lung cancer samples and was predictive of poor survival. This was confirmed in further *in vitro* studies, where it was shown that SOX12 knockdown led to reduced cell proliferation, migration and invasion, as well as to an increase in apoptosis and mediated genes and proteins involved in EMT (Twist1, E-cadherin), apoptosis (Bcl-2, Bax), invasion (MMP9) and cell growth (PCNA, Cyclin E) in SPC-A-1 and A549 cells (Table 2) [367].

SoxD group. SOX5 has been identified as a possible predictor of prognosis in lung adenocarcinoma. In a cohort of 90 patients, high SOX5 expression was correlated with poor prognosis. Further *in vitro* and *in vivo* zebrafish xenograft cancer model experiments, employing both knockdown and overexpression techniques, showed that SOX5 induces adenocarcinoma progression and metastasis via EMT [368]. Additional mechanistic investigations revealed that SOX5, which was shown to be preferentially expressed in cancer stem-like cells (CSLCs) of NSCLC, regulated self-renewal, migration and invasion via interaction with YAP1, a protein involved in the Hippo signalling pathway [114].

SoxE group. Increased SOX9 expression in clinical NSCLC samples at both the mRNA and protein level has been reported by different studies. Chen et al. [369] showed that the up-regulation of *SOX9* and metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) were correlated in NSCLC tissue and that SOX9 protein was more abundant in MALAT1 mRNA-rich regions. Combined, *SOX9* and MALAT1 expression were positively correlated with age, tumour size and TNM stage, and high levels were predictive of poorer overall survival (OS) [369]. Very similar results were found by Zhou et al. [370], who found elevated SOX9 gene and protein expression in SK-MES-1, NCI-H460, NCI-H358, NCI-H1650, NCI-H1975, NCI-H596 and lung cancer cell lines, as well as increased SOX9 protein expression in 142 paraffin-embedded clinical lung cancer samples. A retrospective statistical analysis revealed that SOX9 abundance significantly correlated with tumour stage and shorter overall survival [370]. In addition, it was reported that, high densities of tumour-associated macrophages (TAMs) were associated with a poor prognosis in NSCLC. Furthermore, TAM density and SOX9 expression are directly associated with each other. TAMs secrete TGF-β, which induces SOX9 expression and SOX9-mediated EMT via the C-jun/SMAD3 pathway [115]. The role of SOX9 as a regulator of NSCLC cell proliferation, migration and invasion has been further established by two miRNA studies, which showed that two different NSCLC tumour suppressing microRNAs directly targeted SOX9 (Table 2) [371,372].

SoxF group. SOX7 was found to be down-regulated and miR-9 to be up-regulated in NSCLC tissues and cell lines, and both were negatively correlated to each other. Both miR-9 knockdown and SOX7 overexpression in A549 and HCC827 cells can suppress TGF-β1-induced NSCLC cell invasion and adhesion. TGF-β1 induces miR-9 expression, which then directly interacts with the 3′-UTR of the *SOX7* transcript, suppressing SOX7 protein expression, which mediates cell invasion and adhesion [373]. A similar tumour suppressive role of SOX7 in NSCLC was reported by Wang et al. [374], who showed that miR-616 was increased in NSCLC tissues and cell lines and that its expression level was inversely correlated with overall and disease-free survival. Furthermore, SOX7 overexpression and knockdown experiments both *in vitro* and in *in vivo* nude mice models indicated that SOX7 was able to reverse the effects of differential miR-616 expression and that it was an miR-616 downstream target [374]. An increased cytoplasmic SOX18 protein expression was reported to be correlated with a poor outcome in a study of 198 NSCLC cases comprised of 94 adenocarcinomas, 89 squamous cell carcinomas and 15 large cell carcinomas (LCC), both for the whole cohort and for the adenocarcinoma subgroup alone. Interestingly, *SOX18* mRNA expression was significantly decreased in NSCLC tissue compared to healthy specimens, which might be explained by the hypermethylation of the *SOX18* promoter [375]. In addition, it was shown that *SOX18* expression was regulated by various miRNAs, such as miR-7a and miR-24-3p in lung squamous cell carcinoma [376] or miR-7a and miR-24-3p in lung adenocarcinoma (Table 2) [377].

SoxH group. SOX30 is a tumour suppressor, which acts as a transcription factor and binds directly to the *p53* promoter, thus activating p53 transcription, initiating apoptosis and suppressing tumour formation. In lung cancer cells, SOX30 is down-regulated due to hypermethylation of the *SOX30* gene [378]. Furthermore, SOX30 increases the expression of most desmosomal genes, most notably *DSP*, *JUP* and *DSC3*, in lung adenocarcinoma both *in vitro* and *in vivo*; these genes are required for SOX30 to exert its full inhibitory effect on cell proliferation, migration, invasion, tumour growth and metastasis [379]. Lastly, it was recently discovered that SOX30 interferes with Wnt-signalling, either by suppressing β-catenin transcription directly or by binding to β-catenin, blocking T-cell factor (TCF) [380]. Interestingly, SOX30 expression correlates with histological type, clinical stage and better prognosis and is an independent prognostic factor for OS in NSCLC patients in general. However, SOX30 is only a favourable and independent prognostic factor in the lung adenocarcinoma subtype, where the high expression of SOX30 represents a favourable and independent factor for the prognosis at clinical stage II, with positive lymph nodes or at histological grade 2 or 3, but not in squamous cell carcinoma patients [381].

The SOX family in lung cancer is already well investigated and the known molecular basis of tumour pathogenesis allows attempts for a targeted therapy, supporting the cure of patients. In particular, targeting SOX2 and SOX18 proteins seems to be a promising topic in future anticancer strategies.

6.8. Tumours of the skin

Melanoma. Melanoma is the fifth most common cancer overall and skin cancer-associated with the largest mortality [1]. Melanoma skin tumours consist of cells with rather heterogeneous features including neural crest-like characteristics. If they become metastatic, they will be deadly for a patient [382]. Neural crest cells are embryonic stem cells, from which a number of different adult types of cells including melanocytes are derived. For the maintenance of normal melanocytes, a defined level of SOX10 is required [383] together with the appropriate expression of some other SOX proteins. The up-regulation of *SOX10*

promotes melanoma cell proliferation [384], while a decrease of *SOX17* expression correlates with melanoma progression [385]. Also, SOX2 plays an important role in the natural function of melanocytes [386]. Increased *SOX2* expression enables oxidative cancer metabolism [387]. A high level of *SOX9* promotes the metastasis of melanoma cells [388] and increased quantities of *SOX11* are frequently found in malignant melanoma tissue [389]. In addition, SOX4 promotes melanoma cell migration [390]. However, when targeted by miR-30a-5p, it suppresses the proliferation and migration of melanoma cells (Table 2) [391]. In addition, miR-21a-5p regulates melanogenesis via SOX5 [392]. Interestingly, endovascular progenitors were not influenced by VEGF-A signalling, whereas endothelial-specific loss of RBPJ (direct interactor of SOX18) diminished the population and clearly inhibited metastasis in a melanoma mouse model [393].

Cutaneous Basal Cell Carcinoma (cBCC). Basal cell carcinoma is another subtype of skin cancer. It affects humans worldwide with currently rising incidence. Although death from this type of cancer is rare, it attracts attention, because the costs of diagnosis and treatment are substantial [394]. Its incidence very much depends on the region in which patients live; it is much higher in Australia than in Africa, and even within the United Kingdom, considerable differences were observed between the Southwest of England and London [395]. The cellular origin of this tumour is still under investigation [396]. It is known, however, that basal cell carcinomas express stem cell markers, including SOX2 [397,398] and that SOX9 expression is a general feature of cBCC [399]. SOX9, which is an important regulator of epidermal keratinocytes [400] appears to play a role from the earliest step of tumour formation [401]. According to Eberl et al. [335] both, SOX2 and SOX9 are required for the *in vivo* growth of cBCC cells after their synergistic activation by hedgehog-EGFR generated signals. In addition, it is suggested that SOX18 plays a role in the development of BBC [402].

Cutaneous Squamous Cell Carcinoma (cSCC). Squamous cell carcinoma is an epithelial malignancy and the second most common form of skin cancer worldwide [403]. It often occurs in areas exposed to UV radiation, such as the face, ears, and hands but can also appear in other organs covered with squamous epithelium. In contrast to normal skin epithelium, where SOX2 is not expressed, SOX2 marks tumour-initiating cells in cSCC and is required for cSCC growth in mice and humans enhancing Nrp1/VEGF-signalling [404]. Passeron et al. [405] demonstrated that UVB radiation induces the SOX9 expression in epidermal keratinocytes. SOX9 triggers cell proliferation, leading keratinocytes to cancer-prone status [406]. The putative upstream signals for SOX9 include Wnt/β-catenin- and SHH-pathways, which are involved in cSCC development [407,408]. *SOX11* is only found in embryonic epidermis, but its expression is reactivated in cSCC. Nguyen et al. hypothesise that overexpression of *SOX11* contributes to cSCC tumorigenesis through the up-regulation of Tcf3 (Grantome #1R21CA187368-01A1).

Until now, it was recognised that the deregulation of SOX2 and SOX9 is the major cause of genesis of skin cancer. In order to develop countermeasures, it appears necessary to further elucidate the mechanisms of this de-regulation *in vivo*. For this purpose, mouse models may be helpful. To date, mice were genetically engineered with inactivated SOX2, which provided information about the action of SOX2 in tumour development *in vivo* [409]. In addition, the investigation of transgenic mice predominantly expressing SOX10 pointed out that SOX10 is a promising target for the treatment of melanoma (Table 2) [410].

7. SOX and metastasis

Although most SOX proteins have been sporadically implicated in metastasis, there are a few members of the family that are of particular importance and interest.

The SoxF group, comprised of SOX7, SOX17 and SOX18, is not only expressed in different tumours, as described in more detail above, but is also involved in angiogenesis and lymphangiogenesis. During embryonal development, members of this group are transiently expressed in endothelial cells, and SOX18 activates PROX1, leading to the development of lymphatic vessels [197,411]. SOX7 and SOX17 seem to have redundant functions, as they are able to functionally substitute a dysfunctional SOX18 mutation both *in vitro* and *in vivo* [412]. Apart from their physiological role, angiogenesis and lymphangiogenesis also play a crucial role in metastasis. Vascular endothelial growth factor D (VEGF-D) is important in tumour growth and is involved in pathological neo-lymphangiogenesis [294,413–415]. Using single and double knockout studies in mice, Duong et al. [416] showed that VEGF-D needs to modulate the nuclear SOX18 concentration in endothelial cells for functional vessel development, and suggested that associated pathologies might be partially due to a disturbance of this regulatory mechanism.

8. SOX and therapeutic perspectives

In previous sections, the roles of different SOX transcription factors in tumorigenesis, the microenvironment, different cancer types and metastasis are described. To understand the role of the SOX proteins in these processes often requires molecular approaches resulting in overexpression and/or the down-regulation of SOX transcription factors in cancer cell lines, as well as testing the effect in xenograft tumours *in vivo* in mice. Together with the observations of particular overexpression/down-regulation of a certain member of the SOX family in human cancer subtypes (Table 1, Fig. 2), this information paves the way for the development of assays to use SOX proteins as molecular markers for cancer prognosis, as well as for targeting a particular SOX member.

8.1. SOX as tissue markers for cancer, metastasis and chemoresistance

Several of the SOX proteins have been examined in human cancer tissues and are potential molecular markers (Table 1). Thus, SOX2, SOX4, SOX5, SOX8, SOX9 and SOX18 are up-regulated in different forms of cancer and are associated with poor prognosis [34], although studies with large cohorts of patients are limited to a small portion of these proteins including SOX4 and SOX18 [127,375,417,418]. Thus, SOX18 appears to be a promising diagnostic and prognostic factor, since its protein expression levels are higher in NSCLC tissue [375] and are also suggested to be predictive of the response to platinum-based chemotherapy in ovarian cancer [127]. Additionally, the up-regulation of SOX11 and SOX30 appears to be favourable for the outcome of glioblastoma and lung adenocarcinoma stage II, respectively [260,381]. Additional studies will be required to validate the use of these SOX proteins for survival in cancer patients.

Neoplastic cells often have or develop resistance to cytotoxic drugs, which explains the low success rate of drug regimens in the treatment of certain types of cancer. The cancer stem cell model explains therapy resistance and tumour relapse by the presence of a defined subpopulation of cells within the tumour with stem cell-like properties that survive treatment and initiate tumour regrowth [419]. SOX2 is an important transcription factor in cancer stem cells [420]. A series of studies determined an important role for SOX2 in different types of cancer cells in developing resistance toward chemotherapy, radiotherapy and targeted therapy [421], which makes it an attractive target for cancer therapy, as further discussed below. In addition, the expression of certain proteins, including SOX2 and SOX9, in cancers resistant to therapy may help in selecting a treatment plan, whether it is the direct targeting of these proteins or no treatment at all. Moreover, cancer cell

types with up-regulation of these proteins can form the basis for the development of novel, specific treatments, or for monitoring the effects of drugs targeting other pathways.

8.2. Targeting SOX for treatment of cancer

The up-regulation of SOX2 plays an important role in the maintenance of the stem cell status. SOX2 is associated with cancer progression, as it promotes proliferation, migration and invasion of a series of different cancer cells (Table 1). Moreover, the down-regulation of SOX2 inhibits tumorigenesis in lung cancer cells, prostate cancer cells and Ewing´s sarcoma, and in a SOX2 conditional knockout mouse model, a lack of SOX2 can cause a dramatic decrease in the frequency and onset of tumours [422]. These findings make SOX2 an attractive target for cancer therapy. The role of SOX2 as an anticancer target was recently reviewed [421]. A major concern is that it is difficult to convert cell studies showing effects of siRNA to therapeutic effects in patients, and the authors propose targeting upstream or downstream regulator pathways of SOX2, such as targeting the SOX2/miR-181a-5p, miR-30e-5p/TUSC3 axis in breast cancer or the restoration of miR-126 in hepatocellular carcinoma [421]. However, the approach used in the development of a small molecule inhibitor of SOX18 (see below) shows that other strategies may be feasible. One main concern about the inhibition or disruption of SOX2 is the potential delay of or absent tissue regeneration after such a treatment, and further research should be conducted to elucidate whether this is a real threat for a strategy of targeting SOX2 in anticancer treatment.

In previous sections of this review, we have described how the disruption of the genes for or the down-regulation of SOX4, SOX5 and SOX9 inhibits tumour formation and in some cases metastasis, while the up-regulation of *SOX7* overexpression was found to inhibit tumour cell growth and migration (Table 2). The molecular approaches/strategies are similar to those applied for SOX2, but fewer experimental studies exist. Therefore, it would be relevant in further studies to address whether these SOX proteins are potential drug targets.

SOX18 and the other SoxF members (SOX7 and SOX17) are key regulators of endothelial cell differentiation and are involved in the formation of vasculature by the up-regulation of PROX-1 and positive feedback through VEGF-D [126], as well as in the development of lymphatic vessels [411]. The deletion of SoxF genes affects blood vascular integrity and lymphangiogenesis [197] and inhibits tumour growth and metastasis in mice [128,423]. Mice with the genetic disruption of SOX18 are protected from tumour metastasis, which established this protein as a molecular target [197]. Based on the crystal structure of the SOX18 DNA binding high-mobility group (HMG) box bound to a DNA element regulating *PROX1* transcription, five decoys based on modified *PROX1*-DNA were designed, and four were found to inhibit SOX18 activity in COS7 cells [424]. Therefore, SOX decoys were proposed as a potential strategy for inhibiting SOX18 activity to disrupt tumour-induced neo-lymphangiogenesis [424], but the approach has to be tested *in vivo*. In a melanoma mouse model, the conditional ablation of RBPJ, a direct protein interactor of SOX18, inhibited endovascular progenitor (EVP) cells and decreased metastases *in vivo*. These results provide a new idea for tumour therapy by targeting the EVP cells [424].

A small molecule inhibitor has also been developed for the inhibition of SOX18 activity. By investigating the protein interactions of SOX18 and studying the effect of small molecules in a high-throughput screen for potential SOX18 blockers, Overman and colleagues [196] discovered a natural product derived from the brown algae *Caulocystis cephalornithos*, Sm4. More importantly, the authors also found that Sm4 selectively targets SOX18-mediated transcription over other key endothelial transcription factors and SOX proteins, and Sm4 exhibited anti-tumour and anti-metastatic effects in a mouse model of breast cancer [196]. Further preclinical testing will be required to examine toxicology of the compound, especially the effect on the vascular system in animal models for cardiovascular disease to examine whether the drug worsens ischemic conditions by inhibiting the development of collateral vessels. Another issue that has been raised is that in breast cancer, surgery often leads to lymphangia-oedema, and that the inhibition of SOX18 may worsen this condition [425]. However, the approach used in the search for a small molecule inhibitor of SOX18 is promising and would be interesting to apply to other SOX proteins in the search for novel anticancer therapies.

9. Conclusions and perspective

The review of SOX transcription factors emphases their important impact in the development and progression of cancer, but the knowledge of the biological functions of the SOX family members is still marginal. Especially little is known about the biological importance of these transcription factors in thyroid, renal, and prostate cancer, and therefore knowledge about the importance of SOX family transcription factors and their function warrants further extensive research. In this review, we have summarised the existing knowledge about the biology and function of SOX family members in various cancer types (Table 3, Figs. 2 and 3).

SOX genes modulate the direct reprograming of human cells, thereby influencing tumorigenesis. SOX factors from the SoxB1, SoxE and SoxF groups show an overarching function in different cancer types. SOX2, which belongs to the SoxB1 subgroup, was intensively investigated and has demonstrated common effects on proliferation, survival and differentiation in cancer [426]. The expression of SOX2 has been investigated and a common finding is that this gene contributes to tumorigenesis and progression of breast cancer [124,137], prostate cancer [200], thyroid cancer [217], brain tumours [118], lung cancer [341–345], colorectal tumours [322] and skin tumours [200].

Furthermore, the SoxE family member SOX9 is involved in the progression of tumour disease and might serve as a prognostic factor and as a future target in breast cancer [174,175], renal cell cancer [214], prostate cancer [205], thyroid cancer [84], brain tumours [273], colorectal cancer [325], lung cancer [369], skin tumours [33], and other cancer types [33]. The dysregulation of the Hedgehog, Wnt, EGFR, and NOTCH1 pathways have been shown among others to transcriptionally induce SOX9 [427]. Novel specific SOX9 inhibitors or compounds that attenuate SOX9 expression in SOX9-driven tumours, dependent or independent of F-box and WD repeat domain-containing 7 (FBW7), are important for future personalised anticancer treatment strategies [427].

Tumour suppressing properties of SOX17 were found in breast cancer [192,193], small cell lung cancer [33], thyroid cancer [219] and others [428,429]. SOX17 is an important β-catenin inhibitor, and inhibitor of the Wnt signalling pathway [428]. The reduced expression of *SOX17* was closely associated with cancer progression and poor prognosis in breast cancer; therefore, the level of SOX17 may have a prognostic value and serve as a biomarker in breast cancer [191].

The *SOX18* gene promotes angiogenesis and is also involved in tumorigenesis [197]. The expression analysis in different cancer types revealed that *SOX18* is clearly up-regulated compared to normal tissue [430]. High levels of *SOX18* were found in pancreatic, stomach, liver, breast, lung, ovarian and cervical cancer [431]. The current literature suggests a key role for *SOX18* in the regulation of tumour angiogenesis and lymphangiogenesis [127,431]. However, there is no or only scarce information regarding SOX18 in thyroid cancer and prostate cancer [432]; therefore, it is important to study the function of SOX18 in these cancer types. Progressive radioactive iodine-refractory differentiated thyroid cancers are not remediable with conventional therapy and a

Table 3
Summary of the literature used in this review.

Outline	Literature	Summary / Highlights
1. Introduction	[1–10]	SOX factors are not only involved in developmental processes, but also key players in tumorigenesis, progression and metastasis of different cancer types.
2. Human SOX protein family, groups and domain structures	[11–36]	The SOX family contains more than 20 members, classified into eight groups, SoxA to SoxH (Fig. 1) [11,12,13]. The work as transcription factors binding DNA via the evolutionarily conserved HMG box [19].
3. SOX transcription factors and tumorigenesis	[37–101]	*SOX* genes are frequently deregulated in tumours [37,38], especially SOX2 [39,43,44,45,46,47,48,49,50,51,52,53,54,55] and SOX9 overexpression [62,63,64,65,66,67,68,69,70,71,72] are frequently observed. Clinical observations suggest that some members have tumour-promoting activities (SOX2, SOX3), while others exert a tumour-suppressing activity (SOX1, SOX5, SOX6, SOX7) [56,57,89,90,91,92,93,94,95,96,97,98,99,100,101].
4. The importance of SOX for the tumour microenvironment	[102–115]	Interactions with the tumour microenvironment were demonstrated for SOX2, SOX5 and SOX9, which were expressed in different cancer types. These factors are often involved in increased growth, metastasis, drug resistance and poor survival.
5. Regulation of the expression of SOX family genes	[12,61,116–128]	SOX2 regulation is influenced through the TGF-β, Wnt, FGFR and SHH signalling pathways [118]. Many SOX proteins (e.g. SOX2) interact with β-catenin and TCF and in this way they modulate Wnt signalling [119]. Studies suggested a positive feedback loop between VEGF signalling and the SoxF group [125,126]. SOX17 regulates tumour angiogenesis [128]. There are hints for a role of SOX18 in lymphangiogenesis [127]. The interaction of SOX18 with VEGF is still unclear.
6.The role of SOX in different types of cancer		
6.1 Breast cancer	[21,91,119,124,127,129–197]	SOX2 is able to activate the expression of PVT1 [148]. The SoxE group comprises useful markers for triple-negative breast cancer [167,168,169,170,171]. SOX18 plays a key role in tumour angiogenesis and breast cancer progression [127,195,196,197].
6.2 Prostate cancer	[160,198–209]	SOX2 could be a functional biomarker for lymph node metastasis [202]. SOX2 and SOX4 may be useful targets for prostate cancer therapy [202,203]. Further studies investigating the SoxF family in prostate cancer are necessary.
6.3 Renal cell carcinoma	[210–215]	SOX4 and SOX9 are implicated in cancer progression [210,213]. SOX4 plays a central role in EMT and metastasis. SOX9 is a suitable prognostic factor [214].
6.4 Thyroid cancer	[76,84,216–220]	The impact of SOX proteins in thyroid cancer is still largely unknown. Especially involvement of the SoxF group in radioactive iodine-refractory differentiated thyroid cancer is of high interest.
6.5 CNS tumours	[43,53,57,99,118,221–297]	14 SOX proteins were reported to be expressed in CNS tumours. Their levels often depend on the tumour type or the cells of origin. Pharmaceutical treatment with neriifolin or mithramycin reduced *SOX2* expression and inhibited the growth of glioma cells *in vivo* [240,241].
6.6 Gastrointestinal tumours	[107,194,298–339]	Several SOX family members have so far been detected to play a role in gastrointestinal cancer. In most cases, SOX2 was found to promote the development of tumours [107,299,321,322]. Similar results were obtained for SOX9 [314,315,316,325,326,327,328,335,336]. SOX7, and to some extent also SOX17, appears to have suppressive activity [307,320,331,332,338].
6.7 Lung cancer	[39,114,115,340–381]	SOX2 promotes cell proliferation, EMT, migration, and invasion [359]. SOX30 interferes with Wnt-signalling [380]. Targeting SOX2 and SOX18 proteins seems to be a promising topic in future anticancer strategies.

(*continued on next page*)

Table 3 (*continued*)

Outline	Literature	Summary / Highlights
6.8 Skin tumours	[335,382–410]	Deregulation of SOX2 and SOX9 is the major cause of genesis of skin cancer. SOX10 is a promising target of treating melanoma [410].
7.SOX and metastasis	[197,294,411–416]	The SoxF group is involved in angiogenesis and lymphangiogenesis. VEGF-D is important in tumour growth and is involved in pathological neo-lymphangiogenesis [294,413,414,415].
8.SOX and therapeutic perspectives		
8.1 SOX as tissue markers for cancer, metastasis and chemoresistance	[34,127,260,375,381,417–421]	SOX18 appears to be a promising diagnostic and prognostic factor [375,418]. SOX2 has an important role in developing resistance toward chemotherapy, radiotherapy and targeted therapy [421]. Expression of proteins such as SOX2 and SOX9 in cancers resistant to therapy may help to develop novel, specific treatments.
8.2 Targeting SOX for treatment of cancer	[126,128,196,197,411,421–425]	SoxF members are key regulators of endothelial cell differentiation and are involved in the formation of vasculature by up-regulation of PROX-1 and positive feedback through VEGF-D [126] A small molecule inhibitor has been developed for the inhibition of SOX18 activity [196].
9. Conclusions and Perspective	[33,84,118,124,127,137,174,175,191–193,196,197,200,205,214,217,219,273,322,325,341,342,343,344,345,369,424,426–435]	SoxB1, SoxE and SoxF family members show an overarching function in different cancer types. SOX2 contributes to tumorigenesis and progression. In addition, SOX9 is involved in progression and may serve as prognostic factor. Moreover, a reduced SOX17 expression is closely associated to tumour progression. SOX18 is an interesting target and can be addressed by the small molecule Sm4 [196].

promising therapeutic approach involves the use of multikinase inhibitors (MKIs) to inhibit angiogenesis [433,434]. MKIs like lenvatinib target VEGF-R1/-3, FGFR1-4, ret proto-oncogene (RET), and platelet-derived growth factor receptor-beta (PDGFRβ), thus inhibiting tumour neovascularisation [433]. SOX18 is expressed during the initial steps of tumour vascularisation; regulation of the expression of the VEGF receptor Flk-1 is an interesting target, as SOX18 regulates similar pathways to VEGF [431]. Recently, the small molecule Sm4 has been shown to target SOX18, while showing a marginal impact on SOX7 and SOX17 [196]. Sm4 displayed anti-tumour and anti-metastatic effects in a mouse model of breast cancer. Derived from the brown alga *Caulocystis cephalornithos*, Sm4 was identified by the Queensland-led collaboration in a high-throughput screen for potential SOX18 blockers [196,435]. Another approach involves using SOX decoys to inhibit SOX18 activity [424].

Other promising candidates are SOX11 and SOX30. Even though SOX11 appears to have a role in the development of different cancer types, the overexpression or inhibition of this protein may have an important contribution in future treatment regimens. As for SOX30, which stimulates the production of p53, therapies based on increasing SOX30 expression seem appealing.

Further work to study these compounds in different cancer types is necessary *in vitro*, *ex vivo* and *in vivo*. Studies with compounds or antibodies targeting Wnt-driven cancer like the inhibitor of porcupine (Wnt-specific acyltransferase) LGK974, the small peptide Foxy-5 mimicking the effects of Wnt-5a, or the human monoclonal antibody vantictumab (anti-FZD) together with SOX18 inhibitors or MKI in metastatic cancer may be of interest and might enhance the development of novel treatments for cancer.

Conflict of interest

None declared.

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