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Review

Regulatory roles for SOX11 in development, stem cells and cancer

Siu Man Tsang, Erik Oliemuller, Beatrice A. Howard*

The Breast Cancer Now Toby Robins Research Centre, Division of Breast Cancer Research, The Institute of Cancer Research, London, UK

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ABSTRACT

The transcription factor SOX11 (SRY-related high-mobility-group (HMG) box 11), a member of the SOXC group, is expressed during embryogenesis but largely absent in most adult differentiated tissues. SOX11 regulates progenitor and stem cell behavior, and often acts together with the other two SOXC group members, SOX4 and SOX12, in regulating developmental processes, including neurogenesis and skeletogenesis. Dysregulation of SOX11 has been implicated in a number of diseases including, neurodevelopmental disorders and osteoarthritis, and a wide variety of cancers. Functions of SOX11 during both development and disease could be attributed to its context-dependent post-transcriptional modifications or interaction with other co-factors. We review the molecular and functional roles of SOX11 during development where similar processes appear to be deregulated in cancers.

1. Introduction

In this review, we confine our discussion to one of the three SOXC transcription factors, SOX11, an established regulator of embryonic development and cell fate determination. We review studies that show roles for SOX11 in regulating development of a variety of embryonic tissues and those that indicate SOX11 as a key regulator of progenitor/stem cells. We then discuss SOX11 function in disease pathogenesis, including Coffin-Siris Syndrome (CSS9), a rare congenital genetic disorder characterised by intellectual disability, and in inflammation, which underlines both osteoarthritis and cancer.

We highlight the SOX11-associated pathology of cancer, which results when SOX11 is activated during cancer initiation and/or progression. SOX11 has been described as a key oncogenic factor in mantle cell lymphoma (MCL) [1]. High levels of *SOX11* expression is associated with poor overall survival and increased formation of metastasis in breast cancer patients [2,3]. Expression of SOX11 in Estrogen Receptor negative (ER-), DCIS.com cells promote invasive transition *in vivo*, supporting a role for SOX11 in promoting progression of DCIS to invasive breast cancer [4]. Alterations in progenitor and stem cell homeostasis are associated with breast cancer [5,6]. Evidence is accumulating that SOX11 may promote cancer progression in a number of cancer types *via* deregulation of progenitor/stem cells [7].

Finally, we discuss mechanisms by which SOX11 expression is regulated at the transcriptional and post-translational level. Phosphorylation, DNA methylation and histone modification have been shown to regulate SOX11 expression and activity in different settings. Recent studies also suggest that miRNA and SOX11 expression are both dysregulated in inflammatory response and some cancers. Understanding the mechanisms of progenitor/stem cell and tissue remodelling dysregulation mediated by SOX11 in diseases, including cancer, will be crucial for developing effective therapies to treat them.

2. Molecular characteristics of SOX11

The family of SRY-related high-mobility group (HMG) box (SOX) transcription factors has 20 members in most vertebrates and is subdivided into eight groups (A–H) [8]. Members of the *SOX* gene family are characterised by the HMG domain that was first identified in SRY, the sex-determining gene on the Y chromosome. The human SOX11 gene is located at chromosome 2p25.2. SOX11 belongs to SOXC group of transcription factors, which also has two other members, SOX4 and SOX12, in most vertebrates [9,10]. SOXC proteins have a highly conserved HMG box DNA-binding domain in the N-terminal and a transactivation domain in the C-terminal region [9]. A recent study has demonstrated that the DNA-binding domain of SOX11 is highly similar with members of the SOXC group, as well as that of SOX2 [11]. All SOXs bind preferentially to the same core DNA motif TTGT [12], with a few variable flanking bases [12,13] conferring different binding efficiencies to DNA, which occur *via* the RPMNAFMVW SOX-HMG signature motif [14]. Each SOX protein has two different nuclear localisation signals and a leucine-rich nuclear export signal, which help to shuttle SOX proteins between the nucleus and cytoplasm [15]. In mice, stage-specific subcellular location of SOX11 has been reported during

* Corresponding author.
E-mail address: beatrice.howard@icr.ac.uk (B.A. Howard).

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neurogenesis [16]. Immunofluorescence staining detected SOX11 expression in the nuclei of the developing cortex at embryonic stage E15.5-stage, while at later stages SOX11 was detected in both nuclear and cytoplasmic compartments [16]. There is no evidence of splicing associated with mouse *Sox11* or human *SOX11 RNA* and hence only one isoform is present in both species [17]. A half-life of under two hours has been reported for both mouse and human SOX11 protein, which is typical for transcriptional regulators which are often rapidly turned over [18,19].

The three SOXC proteins transactivate and bind DNA with different efficiencies *in vitro* [9]. Reporter assays demonstrated that fusion of the GAL4 DNA-binding domain with SOX11 transactivation domain (TAD) have a stronger transactivation potential than the fusion of GAL4 with the SOX4 or SOX12 TAD, indicating that SOX11 is the more potent transactivator in the SOXC group. However, SOX11 does not bind to its known targets as well as the other two members; electrophoretic mobility shift assay showed that SOX11 does not bind to the DNA corresponding to SOXC binding sites of the Fibroblast Growth Factor 4 (*Fgf4)* or Tubulin Beta 3 Class III (*Tubb3)* promoter as efficiently when compared to SOX4 and SOX12 [9]. Results from *in vitro* studies indicate that the three SOXC proteins have distinct DNA-binding and transactivation capabilities for known target genes *in vivo*. A recent study suggested that SOX11 can initiate transcription events in closed chromatin and act as a pioneer factor [11]. SOX11 can use binding energy to initiate chromatin opening, and thereby facilitate nucleosome remodelling and subsequent transcription to enable gene expression from regions of the genome with closed chromatin [11]. SOX11 can bind to nucleosomal DNA, which facilitates detachment of terminal nucleosomal DNA from the histone octamer and leads to greater accessibility of terminal DNA for non-pioneer partner proteins [11].

2.1. Expression of Sox11 during mouse development

The three SOXC genes have overlapping expression patterns in the mouse embryo from embryonic day E10.5 to E18.5 [9]. SOXC genes are co-expressed in neural and mesenchymal cells with high levels in the developing nervous system including the brain, neural tube and in the peripheral nervous system such as retina, dorsal root ganglia, olfactory and cochlear epithelium [9]. Variable levels of SOXC genes are observed in other tissues, including the epithelium and the mesenchyme of lung, gut and pancreas at the same embryonic developmental stages [9]. Differential expression is also noted at certain sites. For example, *Sox4* and *Sox12*are expressed in the heart and the lungs from embryonic day E10.5 to E18.5, whereas *Sox11* is hardly detected at these sites [9]. Overall, both overlapping and differential expression pattern of SOXC genes were observed in different tissues, suggesting that SOXC genes can either function together or have distinct tissue-specific roles in embryonic development.

SOX11 is widely expressed during early embryogenesis. Immunohistochemical staining shows that SOX11 expression is detected in the cerebral cortex, kidney, lung, mammary gland and spinal cord of embryonic day E14 embryos (Fig. 1). However, *Sox11*expression is largely absent in the heart in the early post-gastrulation embryo [20], as well as, in most adult differentiated tissues [2]. *Sox11* is known to express at sites where inductive epithelial-mesenchymal interactions occur during embryogenesis, including the mammary buds [20]. A transcriptomic analysis of embryonic mouse mammary bud epithelial cells from E12.5 mammary organs compared with the postnatal mammary epithelial cells was carried out to identify embryonic mammary-specific factors. *Sox11* is one of the most highly expressed genes in the embryonic mammary epithelium during initial mammary organ formation [2]. *Sox11* is also a component of fetal mammary stem cell signatures defined from subpopulations of E18.5 mammary cells profiled in two other studies [21,22]. A small-scale single cell-RNA sequencing analysis of mammary epithelial cells from E14.5 embryos showed that most non-proliferating Lgr5+ cells express high levels of *Sox11*. Recently, an integrated analysis of single cell RNA and ATAC-sequencing data indicates that mammary progenitor/stem cells from embryonic day E18 mouse embryos also express high levels of *Sox11* [23]. It is not yet clear whether *Sox11* is a marker for multipotent embryonic mammary cells which are thought to exist predominantly during embryonic development, or whether *Sox11* is also expressed by lineage-restricted embryonic mammary cells that have recently been reported [24].

2.2. SOX11 regulation of development and progenitor cells

Sox11-deficient mice display severe developmental defects and die at birth [20]. Defects include anterior eye segment, craniofacial and skeletal malformations, asplenia, and hypoplasia of the lung, stomach, and pancreas, defective heart and outflow tract formation [20,25]. The affected tissues undergo extensive tissue interactions and remodelling during development, suggesting that *Sox11* could regulate inductive tissue remodelling [20]. *Sox4*-deficient mice die at embryonic day E14 and display a more severe heart outflow tract malformation [26]. Conditional mutagenesis, used to delete both *Sox4* and *Sox11* in the developing sympathetic nervous system, showed both genes are essential for cell proliferation and survival of developing sympathetic neurons, in addition to their role as differentiation factors in promoting pan-neuronal or noradrenergic sympathetic neurons [27]. Unlike *Sox4*-null or *Sox11*-null mice, *Sox12*-null mice appear normal and are viable [28]. However, the phenotypic defects appear more severe as the number of deleted SOXC alleles increases. Triple SOXC knockout mice display greater phenotypic severity compared to either $Sox4^{+/-}11^{+/-}$ or $Sox4^{-/-}11^{-/-}$ embryos [28]. Massive neural and mesenchymal progenitor cell death and developmental arrest at mid-gestation were observed in $Sox4^{-/-}11^{-/-}12^{-/-}$ embryos, indicating that SOXC genes are critical for the survival of the neural and mesenchymal progenitor cells, and that SOXC factors act in redundancy to fulfil essential roles during organogenesis. Neural and mesenchymal progenitor cells give rise to many cell lineages during organogenesis and have important roles in adult tissue homeostasis and repair. Further studies are needed to assign specific roles for SOX C genes in adult tissue homeostasis and repair, which could be extremely informative with respect to which specific cell types are involved in these processes, particularly if single cell methodologies are employed in the analyses.

SOX11 was identified as mesenchymal stem cell (MSC) characteristic gene [29] and a potential marker for early progenitor human mesenchymal stem cells (MSCs) [30]. Microarray assays showed a progressive reduction of *SOX11* mRNA levels during MSCs expansion, suggesting *SOX11* could be used as a marker as it distinguishes early progenitors from more mature MSCs [30]. Knockdown of *SOX11* in both studies using primary MSC and MSC lines leads to reduction in self-renewal capacity [29,30]. *SOX11*+/− heterozygous human embryonic stem (ES) cell lines have recently been generated by CRISPR/Cas9 genome engineering [31]. *SOX11* haploinsufficiency in ES cells impaired generation, proliferation and survival of neural progenitor cells. SOX11 can regulate human stem cells, but more in depth studies will be required to elucidate which effectors are enabled.

Studies using mouse models have shown SOXC proteins, including SOX11, can amplify canonical WNT signalling during skeletogenesis in mice, linking SOX11 with a key regulator of development, stem cells and cancer pathogenesis [32]. SOXC and canonical WNT signals act in synergy to stabilise β-catenin and in turn contribute to repression of SOX9 expression in the presumptive joint and perichondrium cells to ensure proper delineation and articulation of skeletal primordia [32]. In addition, SOXC proteins can also bind an upstream enhancer of *Wnt5a* and directly transactivate *Wnt5a*, a non-canonical WNT ligand, in chondrocytes and perichondrocytes to regulate skeletal growth. Deleting all three SOXC genes from limb bud skeletogenic mesenchyme or from chondrocytes perturbs the asymmetric distribution of non-canonical WNT/Planar cell polarity protein, VANGL2, that controls growth

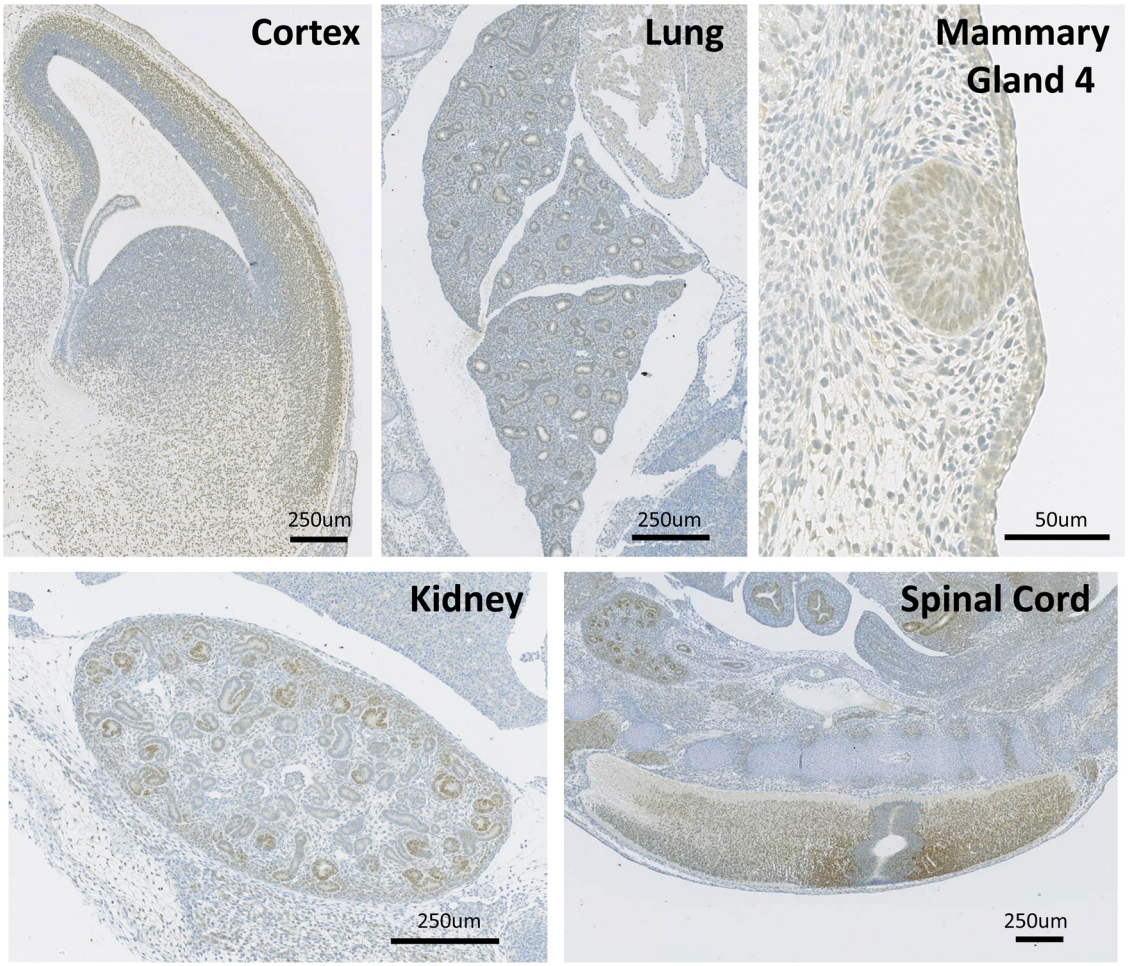

Fig. 1. SOX11 is widely expressed throughout embryonic day E14.5 mouse embryo, including the cerebral cortex, lung, mammary gland, kidney, and spinal cord.

plate chondrocyte alignment, proliferation and survival [25]. During kidney development, *Wnt4* is required for nephrogenesis [33]. Wilms' tumour 1 (WT1) and SOX11 interactions were found to regulate *Wnt4* promoter activity in an embryonic kidney mesenchyme-derived mouse cell line and in *Xenopus* pronephros, suggesting a role for SOX11 in regulating WNT4-mediated kidney development [34]. More recently, WNT7B has been shown to activate calcium-dependent NFATC1 signalling to induce *Sox11* transcription, which, in turn, regulates the self-renewal and osteogenesis of bone marrow-derived mesenchymal stem cells [35]. SOX11 is likely to act in concert with other SOXC group members and other signalling pathways, including WNT, to regulate progenitor cell fate and tissue remodelling [20]. Single cell genomic profiling of cells with conditional deletions of *Sox11* and other SOXC genes could expand our understanding of their impact on regulating particular progenitor cells types and major pathways that affect cell fate and development.

2.3. SOX11 role in developmental disorders

Human heterozygous missense mutations or deletions of *SOX11* are linked to intellectual disability phenotypes associated with Coffin-Siris Syndrome (CSS9) [36]][111]. CSS9 is a rare congenital multi-systemic genetic disorder characterised by variable levels of intellectual disability, such as developmental delay and/or learning difficulties, as well as other clinical manifestations, such as aplasia or hypoplasia of the distal phalanx or nail of the fifth digit, and coarse facial features [36]. Using morpholino oligonucleotide-mediated knockdown of *sox11* in either *Xenopus laevis* or *Danio rerio* significantly reduced head size, supporting associations of SOX11 mutations with microcephaly and brain abnormalities which have been reported in humans [36,37]. A milder form of Coffin-Siris Syndrome, CSS10, is associated with another SOXC group member, *SOX4*, resulting in similar clinical characteristics of *SOX11* mutations [38]. Missense variants of SOX11 and SOX4 were both located in the highly conserved HMG domain and in both genes these variants lacked transcriptional activity, as demonstrated by reporter assays [38]. Studies using a *SOX11*$^{+/-}$ heterozygous human embryonic stem cell (hESC) line showed *SOX11* haploinsufficiency led to impaired neuronal differentiation and survival [31]. It is possible that SOX11 may have gained specific functions in human development that the other two SOXC factors cannot compensate [31]. In mice, *Sox11* gene disruption has been reported to cause congenital anomalies of the kidney and urinary tract (CAKUT) [39]. Mutation analysis in a cohort of patients suffering from CAKUT identified a series of rare *SOX11* variants, one of which interferes with the transactivation capacity of the SOX11 protein [39]. These results show *SOX11* mutations can contribute to rare human congenital abnormalities and genetic diseases (Table 1).

2.4. SOX11 and cancer

Aberrant up-regulation of *SOX11* has been reported in a number of lymphoid and solid malignancies including malignant glioma [40], medulloblastoma [41], mantle cell lymphoma [42], subsets of Burkitt's lymphoma [43], ovarian cancer [44] and breast cancer [2] (Table 1). Global RNA expression profiling data from six different types of cancer was recently assessed by Principal component analysis to investigate

Table 1
Table summarising SOX11-associated pathological conditions.

Tissue	Disease or injury	Description
Brain	Coffin-Siris Syndrome (CSS9)	Human heterozygous missense mutations or deletions of *SOX11* [93].
	Malignant glioma and medulloblastoma	High expression of *SOX11* mRNA [40,41]
Bone	Osteoarthritis	SOX11 promotes induction of TNF-α [95] Pro-inflammatory cytokines stabilise SOX11 protein in human inflamed synovium and FLS from patients with arthritic disease [63].
	Bone marrow mesenchymal stem cells (BMSC)	WNT7B enhances self-renewal and osteogenic differentiation *via* SOX11 [35]. MiR-141 inhibits the proliferation of BMSC by targeting SOX11 [].
Female reproductive organs	Endometrial Cancer	*SOX11* promoter hypermethylation []. MiR-145 targets the *SOX11* 3'UTR to inhibit its expression and suppresses cancer growth [86].
	Breast cancer	SOX11 activates SLUG-induced EMT and suppresses *ESR1* expression [60]. SOX11 re-activated in mouse *Brca1-/-* tumours and human basal-like breast cancers [2]. High levels of *SOX11* expression is associated with poor overall survival and promotes invasive growth and ductal carcinoma *in situ* progression [4].
Kidney	Congenital abnormalities of the kidney and the urinary tract (CAKUT)	Identified rare SOX11 variants which interferes with its transactivation capacity [39]. Decreased expressions of Sox11 and FAK in alveolar epithelial and interstitial cells []. High expression of *SOX11* mRNA is associated with aggressive NELC [].
Lymphomas	Mantle cell lymphomas	CCND1 and STAT3 regulate SOX11 expression [54]. SOX11 increased B-cell receptor signalling [52]. SOX11 regulates MCL homing and invasion via regulation of CXCR4 and FAK expression [53].
Skin	Wound repair	SOX11 and SOX4 drive the reactivation of an embryonic gene program [65].
Spinal cord	Spinal cord injury	MicroRNA-204-5p targets *SOX11* to regulate the inflammatory response [90].

their biological relationships [45]. *SOX11* is a heavily weighted element of one principal component that distinguishes a number of cancers including breast cancer, colorectal cancer, lung adenocarcinoma, lung squamous carcinoma, glioblastoma, and ovarian cancer [45]. However, the prognostic relevance of *SOX11* expression in cancer appears to be cell-context dependent since it is found to be associated with both improved survival in ovarian [44] and gastric [46] and reduced survival in breast cancers [2,3]. Amplification and upregulated expression of *SOX11* has been reported in brain metastasis [47,48]. However, *SOX11* amplifications or mutations in primary cancers are not frequently observed [49,50].

SOX11 has been described as a key oncogenic factor in mantle cell lymphoma (MCL) [1]. Nuclear SOX11 is detected in the majority of MCL, B and T-lymphoblastic leukaemia or lymphoma, half of childhood Burkitt's lymphomas, and a small subset of hairy cell leukaemia [43]. SOX11 is considered as a reliable diagnostic marker for MCL since its nuclear localisation can distinguish it from other types of B-cell lymphomas [51]. SOX11 regulates a broad transcriptional program in MCL cell lines, including B-cell differentiation pathways and tumour–microenvironment interactions. In an immunocompetent transgenic model, overexpression of Sox11 in B cells using a specific IgH-E enhancer (Eμ-SOX11-EGFP) resulted in increased B-cell receptor signalling and oncogenic proliferation of B1a B-cells and MCL-like tumour development [52]. Single cell mass cytometry (CyTOF) analysis and flow cytometry showed that Eμ-SOX11-EGFP mice display increased frequency of CD19 + CD5 + CD23- B cells in the blood, spleens, lymph nodes and bone marrow [52]. Using a mouse xenograft model, Balsas et al. showed SOX11 regulates MCL homing and invasion through direct regulation of CXCR4 and FAK expression and PI3K/AKT and ERK1/2 signalling activation, suggesting crosstalk between the microenvironment and tumour cells can lead to a more aggressive phenotype [53].

Other studies have revealed potential mechanisms of aberrant SOX11 expression that are observed in some MCL [52]. In conventional MCL, *SOX11* expression may be regulated by a cell-cycle regulator cyclin D1 (CCND1). Overexpression of CCND1 in several human MCL cell lines showed that CCND1-mediated HDAC1 and HDAC2 sequestration from the *SOX11* promoter led to increases in both histone acetylation (H3K9/14Ac) and SOX11 expression. In the indolent non-nodal forms of MCL, which do not express SOX11, STAT3, a post-germinal center B-cell differentiation factor, is recruited to both the *SOX11* gene and enhancer loci and functions as a transcriptional repressor in several MCL lines to decrease *SOX11* expression [54]. Identifying the specific vulnerabilities of cancer cells such as understanding different aspects of SOX11 deregulation in MCL may provide new insights and therapeutic implications for MCL and other types of cancers where SOX11 expression is associated with poor outcome.

2.5. SOX11 and breast cancer

SOX11 is not detected in the normal mature postnatal breast, but is expressed in approximately 80% of human basal-like breast cancers (BLBC), a subtype which lacks Estrogen Receptor (ER), Progesterone Receptor (PR) and HER2 expression, and is associated with poor prognosis [2]. Inhibition of SOX11 by siRNA suppressed growth of several ER- BLBC cell lines, but had little effect on growth of several ER + cell lines [3]. *SOX11* inhibition led to reduced cell migration and invasion of BLBC cells lines grown in 2D. siRNA-mediated knockdown of *SOX11* in ER- MDA-MB-468 cells resulted in reduced expression of Forkhead Box C1 (FOXC1), Cyclin E1 (CCNE1), Keratin 14 (K14), Secreted Frizzled Related Protein 1 (SFRP1) and Melanoma-Derived Growth Regulatory Protein (MIA), all of which are PAM50 genes that are highly expressed in BLBC tumours, suggesting SOX11 modulates key elements of the basal-like subtype [3]. A significant association of SOX11 expression with ER- status was found in DCIS: high levels of SOX11 expression were detected in 59% of ER- ductal carcinoma *in situ* (DCIS) preinvasive lesions stained by IHC [4]. When SOX11 is constitutively expressed in ER- DCIS.com cells, which originate from the isogenic MCF10 breast cancer cell line progression series, a distinct type of breast cancer stem cell population (CD44 + /CD24-/ALDH +) was expanded *in vitro* [55]. High levels of aldehyde dehydrogenase (ALDH) activity are associated with increased tumorigenicity of breast cancer cells and a poor clinical outcome [56,57]. Intraductal xenografting model is used to mimic ductal carcinoma *in situ* (DCIS) to study *in situ* to invasive transition. Following injection of DCIS.com cells expressing SOX11 into the mammary duct, DCIS lesions formed and progressed more rapidly to an invasive stage compared to control cells [4]. Expression profiling of SOX11 + DCIS-like lesions and invasive mammary tumours identified a number of potential downstream effectors of SOX11 that are associated with developmental processes, including migration and extracellular matrix components that regulate cell adhesion [4]. Overall, high levels of *SOX11* expression is associated with poor overall survival and increased formation of metastasis in breast cancer patients [2,3]. SOX11 might serve as a marker for distinct types of breast cancers and its downstream effectors could be targets for the treatment of some basal-like breast cancers, a subtype with limited therapeutic options.

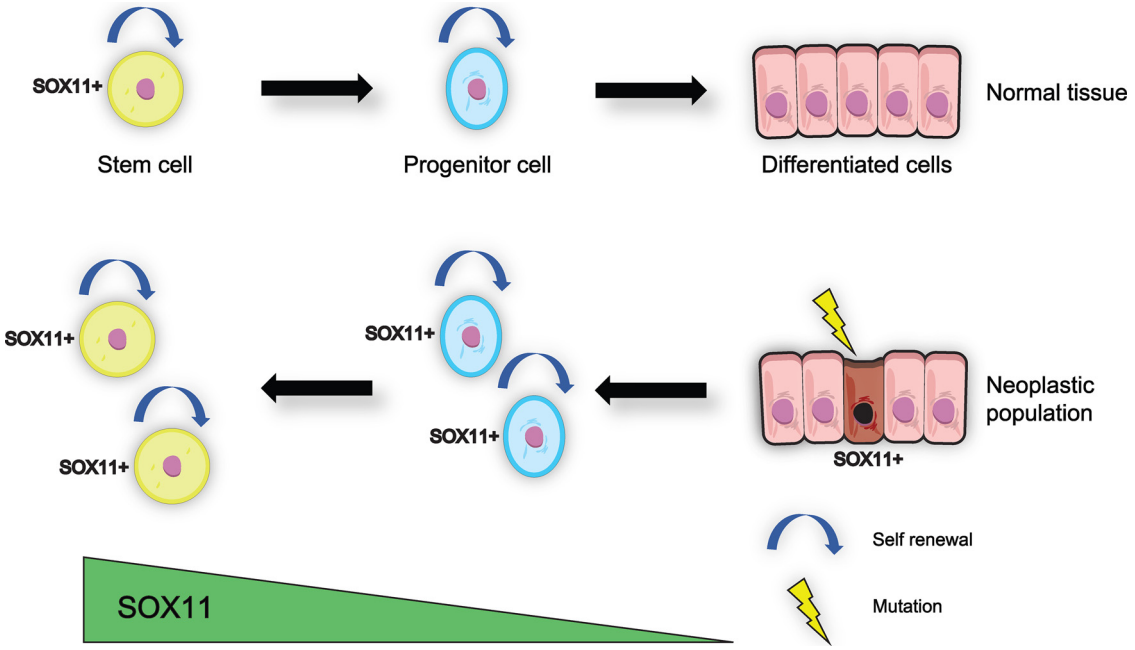

Fig. 2. Model showing how reactivation of *SOX11* in cancer cells could led to de-differentiation and re-acquisition of embryonic mammary stem-cell properties including quiescence, lack of differentiation marker expression, and multipotency.

SOX11 is expressed in a subset of *Brca1-/-* tumours from the BLG-Cre; BRCAfl/fl/p53+/- mice, which are used as a model for BLBC [2]. Nuclear SOX11 staining is observed at the tumour-invasion front at sites of active tissue remodelling in some *Brca1-/-* mouse mammary tumours, providing evidence that expression of SOX11 in tumours cells could lead to reactivation of embryonic developmental signals and activity [2] (Fig. 2). Links between embryogenesis and tumorigenesis have been widely noted [58]. For instance, epithelial to mesenchymal transition (EMT), a process commonly observed during tumorigenesis, has long been recognised as an essential embryonic process. Indirect evidences showed that *Sox11* is up-regulated throughout TGF-β and EGF-induced EMT of tubular epithelial cells to form fibroblasts [59], suggesting that SOX11 could be involved in EMT. A recent study indicates SOX11 can activate *SLUG* expression in endocrine resistant breast cancer cell lines by binding to its promoter, resulting in promotion of EMT and suppression of *ESR1* expression [60]. This study provides a potential mechanism underlying the lack of ER expression observed in SOX11+ breast cancers. Studies using patient samples will be needed to assess its clinical relevance since experiments were carried out only using tamoxifen-resistant MCF-7 cell lines. Further investigations of SOX11's role in regulating specific progenitor cell phenotypes may lead to ways of stratifying and targeting distinct BLBC subtypes.

2.6. SOX11 may mark distinct cancer types driven by stem cells

Emerging evidence indicated a subpopulation of cancer cells referred as cancer stem cell (CSCs) share similar characteristics with normal stem/progenitor cells such as self-renewal and differentiation capacities to drive tumour growth and heterogeneity [5,6,61]. A recent study based on single cell RNA sequencing of oligodendrogliomas supports the existence of a developmental hierarchy present in normal tissues is also seen in cancer [7]. Oligodendrogliomas was found to be differentiated along two specialised glial programs, and a rare subpopulation of undifferentiated cells was detected. This rare population has enriched proliferative potential and is associated with stem cell expression signatures, of which *SOX11* is a key element [7]. This genome-wide transcriptional signature of cancer stem/progenitor cells showed that CSCs are present in oligodendroglioma to drive proliferation and tumour growth.

Bhattaram et al. have recently proposed that SOXC proteins may control progenitor/stem cell fate and actions in many lineages using different mechanisms from other SOX proteins [62]. Instead of regulating cell type-specific genes like other SOX proteins, they hypothesise that SOXC proteins could control members of signalling pathways *i.e.* HIPPO and WNT that are universal to other cell types. This mode of action may contribute to the fundamental characteristic of progenitor/stem cells which are highly versatile in adjusting to extrinsic cues. This has obvious clinical relevance since it raises the possibility that progenitor/stem cells from diverse types of SOX11+ cancers might respond to similar therapies.

2.7. SOX11 and inflammation

SOX11 has been implicated in mediating arthritic progression in studies using mouse models of arthritis and patient samples. Synoviocytes are fibroblast-like cells that proliferate, show anchorage-independent growth, and secrete a variety of effector molecules that promote inflammation and joint destruction. During arthritic disease progression, synoviocytes become cancer-like with traits including increased cell survival and migration. Fibroblast-like synoviocytes (FLS) from adult mice were genetically modified so that they lacked expression of SOXC genes (*Sox12-/-*, with conditional inactivation of *Sox4* and *Sox11* from Prg4+ cells) [63]. SOXC gene inactivation led to a reduction in tumour necrosis factor (TNF) -induced synovial hyperplasia and joint degeneration compared to control mice (which express the three SOXC genes and TNFα) [63]. It was shown that pro-inflammatory cytokines, such as TNF and interleukins, IL-1α and IL-6, could stabilise the levels of SOX4/11 protein in human inflamed synovium and FLS from patients with arthritic disease to augment pathogenic traits during FLS transformation [63]. Another study showed that adenovirus-mediated expression of SOX11 in mouse femoral head cartilages resulted in destruction of the articular cartilage matrix which displayed increased levels of disintegrin-like and metallopeptidase thrombospondin type 5 (*Adamts5*) expression [64]. This is in line with higher levels of *SOX4* and *SOX11* mRNA expression detected in the deep cartilage zone at the most degenerated areas of osteoarthritic cartilage samples compared with non-osteoarthritic patient samples [64]. These studies showed that SOXC proteins are likely mediators of pro-inflammatory cytokines and

matrix metalloproteinases in arthritic diseases.

A recent study showed that SOX11 and SOX4 could promote the reactivation of an embryonic epidermal gene programme during wound repair in mice and lead to altered expression of cytoskeletal/extracellular matrix components and downregulation of differentiation markers [65]. The concept of cancer being viewed as a wound that does not heal has been promoted by Dvorak and still receives considerable attention [66]. This opens up therapeutic possibilities particularly for inflammation, an inevitable consequence of wound healing response, which is also associated with cancer progression [67–69]. It is plausible that SOX11 activates a core embryonic genetic program when expressed in adult epidermal-derived tissues and activates similar developmental pathways that lead to enhanced cell proliferation, migration and remodelling of extracellular matrix. The role of SOX11 in regulating wound healing, inflammation and cancer may have common underlying mechanisms and warrants further investigation given the association of SOX11 with all of these pathological states (Table 1).

2.8. SOX11 downstream targets

A growing number of downstream target genes of SOX11 have been identified based on overexpression or knockdown of *Sox11* and analysing the resulting changes in gene expression. Overexpression of SOX11 protein in human embryonic kidney (HEK293) cells and assessment of transcriptional changes by microarray analysis identified markers of neurogenesis and other genes that are also involved in neuropsychiatric disorders, including TEA Domain Transcription Factor 2 (*TEAD2)* and Tubulin Beta 3 Class III (*TUBB3)* [70]. Transcriptional profiling of *Sox11-/-* epidermis from embryonic day E16 mouse embryos detected downregulated expression of genes encoding markers of simple epithelium, including the cytokeratins, *K4*, *K8*, and *K19*, the tight junction protein, *Claudin3,* and upregulation of genes encoding peptidase inhibitors, IL-1 cytokine signals and oxidoreductase processes [71]. However, these studies do not provide information on whether SOX11 binds directly to regulatory sequences or indirectly through the activation of intermediate genes. Methods used in both studies could also lead to up- or downregulation of its target genes that are not usually activated under physiological conditions [72]. A more direct approach *i.e.* CHIP-seq was used to identify SOX11 binding targets in Granta-519 MCL cell line which showed SOX11 binds directly to WNT pathway members including SMAD3, TGFBR1 (Transforming growth factor, beta receptor 1), WNT4, NLK (Nemo-like kinase) and PRKACA (Protein Kinase A catalytic unit alpha) [73]. Additional studies will be required to fully delineate the significance of each interacting partner of SOX11, which could potentially help in the identification of therapeutic target to inhibit SOX11 activity in pathological conditions, including cancer.

2.9. Regulators of SOX11

DNA methylation alters chromatin structure and DNA accessibility and causes repression of tissue-specific genes [74]. An inverse correlation between *Sox11* DNA methylation and transcriptional activity of *Sox11* during mouse development has been reported [75,76]. *Sox11* DNA from brain, kidney and testis of fetal and neonatal mice were less methylated at the 5′UTR of *Sox11* and displayed a higher *Sox11* mRNA expression compared to adult stages, which were more methylated and expressed less *Sox11* [75]. *Sox11* is expressed throughout prenatal stages of mouse mammary gland development by embryonic mammary epithelial cells [77]. However, after birth, SOX11 is not expressed in mammary epithelial cells in either the mouse mammary gland or human breast [4,78,79]. This in line with its chromatin status, where *Sox11* is in an inaccessible state in postnatal mouse mammary epithelial cells [23]. These studies demonstrated that stage-specific chromatin accessibility is associated with transcriptional activities of *Sox11*.

Another major epigenetic mechanism is histone modification, which like DNA methylation can alter gene expression. *SOX11* expression could be activated by H3K9/14Ac and H3K4me3 bivalent histone marks in pluripotent embryonic cell line as well as some aggressive B-cell neoplasms [80]. On the other hand, repression of *SOX11* can be associated with H3K9me2 and H3K27me3 marks in adult stem cells, normal hematopoietic cells and other lymphoid neoplasms where SOX11 is not expressed [80]. In the developing mouse cerebral cortex, both LIM homeodomain transcription factor (LHX2), an upstream regulator of SOX11, and FEZ Family Zinc Finger 2 (FEZF2), are essential for the specification of sub-cerebral projection neurons [81]. Chromatin immunoprecipitation and mass spectrometry studies in cortex-specific *Lhx2* conditional mutant mice showed that LHX2 interacts with nucleosome remodelling and histone deacetylase (NuRD) complex of chromatin regulators to edit the chromatin status of its target genes and regulates their expression. The NuRD complex associates with the distal *Lhx2* occupancy sites and/or the transcription start sites (TSSs) of both *Fezf2* and *Sox11*, and erases the active histone marks at both the *Fezf2* and *Sox11* loci. In the absence of *Lhx2*, active histone marks are enriched, resulting in an increased expression of *Sox11* and *Fezf2* [81]. These studies suggest chromatin accessibility, as indicated by histone marks, is associated with *Sox11* expression status during neural development, in stem cells, as well as in lymphoid neoplasms.

Many human cancers display altered epigenetic patterns. Aberrant *SOX11* promoter methylation has been linked to most mature B-cell lymphomas, bladder cancer [82] and in nasopharyngeal carcinoma patients with lymph node metastasis [83]. In non-malignant mature B cells, including naive, germinal centre and memory B-cells, *SOX11* expression is highly repressed by H3K27me3 histone marks with a lower level of DNA methylation [84]. However, in solid tumours, cells have a more diverse methylation patterns, likely a reflection of an inter-tumour heterogeneity [84]. In breast cancer, a correlation between SOX11 methylation and ER-positive status has been reported [84]. SOX11 + DCIS shows a significant association with ER-negative status raising the possibility that in many ER + pre-invasive DCIS breast lesions, *SOX11* could be methylated and kept in a non-active state but this has not yet been investigated [4]. Furthermore, epigenetic drugs, including the histone deacetylase inhibitors, Vorinostat and Trichostatin A, are able to induce *SOX11* expression in unmethylated breast cancer and neuroblastoma cell lines, suggesting that histone acetylation could be an important mechanism for *SOX11* regulation in some cancers [84]. It is possible that epigenetic mechanisms involving aberrant permissive chromatin state could lead to re-activation of *SOX11* expression in MCL, breast cancer and other types of cancers.

MicroRNAs (miRs) are important post-transcriptional regulators during development. MicroRNAs are single-stranded, small non-coding RNAs, which bind to the 3′-untranslated regions (3′UTRs) of the target gene mRNAs. They can function as either oncogenic or tumor suppressor genes, depending on cancer type [85]. miR-223 − 3p, miR-145 and miR-211-5p have been identified as regulators of *SOX11* and target the 3′-untranslated regions (3′UTRs) of *SOX11* mRNAs to inhibit its expression [86–90]. In endometrial cancer, miR-145 can inhibit SOX11 protein expression which, in turn, suppresses migration and invasion and promotes cell apoptosis of ECC-1 endometrial cancer cells [86]. *SOX11* expression is inversely correlated with miR-223-3p mRNA levels in both ovarian cancer cell lines and in ovarian cancer tissue specimens from patients [87]. Expression of miR-223-3p mimic results in decreased SOX11 expression, and promoted proliferation, migration, and invasion of ovarian cancer cell lines *in vitro* and promoted tumor growth *in vivo* [87]. In another study, miR-223 mRNA was downregulated in purified CD19 + lymphocytes from mantle cell lymphoma (MCL) patients when compared to those obtained from healthy donors [88]. Lower levels of miR-223 mRNA is also associated with higher *SOX11* levels in clinical samples and correlates with high-risk clinical features and poorer survival of MCL patients [88]. Ectopic expression of miR-223 in a MCL cell line led to downregulation of SOX11 expression and decreased cell viability, proliferation and promotion of G0/G1

accumulation and cell apoptosis [88]. In human thyroid cancer (TC) cells, overexpression of miR-211-5p inhibited the expression of *SOX11* and suppressed the cell cycle, proliferation and invasion of TC cells and also inhibited tumour formation *in vivo* [91]. Compelling evidence shows miRNA and SOX11 expression are both dysregulated in some cancers, suggesting that miRNAs could be potential candidates for therapeutic intervention for some SOX11-driven cancers.

Inflammatory cytokines and *SOX11* expression were enhanced in plasma of patients with spinal cord injury (SCI) and from a mouse SCI model [90]. Lentivirus-mediated expression of microRNA-204-5p in mice with SCI led to reduction of *Sox11* expression and attenuated inflammatory response, which was assessed by both Toll-like receptor 4 (TLR4) and iNOS expression. Expression of high levels of *Sox11* after SCI, delivered to mice via tail vein injections of a plasmid construct expressing *Sox11*, could partially reduce the inhibitory effect of microRNA-204-5p on TLR4 and iNOS expression. These results suggest that microRNA-204-5p could inhibit the inflammatory response caused by SCI by targeting *Sox11* [90]. miRNAs and SOX11 appear to regulate inflammatory response in the SCI model and since microRNA-204-5P is conserved between vertebrate species, this axis might also provide therapeutic options for SOX11-driven inflammatory responses in humans. However, it has yet to demonstrate whether miRNAs and SOX11 act together as key regulators of inflammation in the context of the tumor microenvironment.

SOX11 can be post-translationally modified by phosphorylation. Using mass spectrometry and mutational analysis, ten serine residues have been identified in the SOX11 protein that can be phosphorylated [16]. Immunostaining for SOX11 in HEK293T cells transfected with wild type and mutated SOX11 showed that phosphorylation of the serine 30 residue promotes nuclear localisation of SOX11 *in vitro* [16]. However, nuclear localisation of SOX11 was insufficient to activate SOX11-dependent gene expression. The significance of phosphorylation-induced nuclear localisation of SOX11 is still unknown and other co-factors might be required for SOX11 to function in this context [16].

3. Concluding remarks

SOX11 regulates a number of similar cellular processes during both normal embryonic development and during tumourigenesis. SOX11's role as a potential biomarker for diagnosis and prognostic purposes is being assessed in a variety of cancers. Tumours co-opt normal developmental processes to facilitate cancer initiation, maintenance and progression. Expression of distinct organ-specific co-factors is likely to contribute to context-dependent roles for SOX11 in different types of cancers. It is possible that when expressed in postnatal tissues, SOX11, through its role as a pioneer factor, creates a permissive state to initiate transcription and, in turn, leads to reprogramming of cells to a more undifferentiated stem-like state. A challenge faced by cancer researchers will therefore be that SOX11 protein function may need to be assessed separately for different cell and tumour types. As single cell genomic, transcriptomic and proteomic technologies are more routinely used and more data accrues, this precise functional assessment of SOX11 should become feasible in both normal and cancerous tissues.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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