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Review

Diverse pathogenetic roles of SOX genes in acute myeloid leukaemia and their therapeutic implications

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ABSTRACT

Acute myeloid leukaemia (AML) is a heterogeneous group of diseases with diverse pathogenetic pathways. When treated uniformly with conventional chemotherapy and allogeneic haematopoietic stem cell transplantation (HSCT), it showed variable clinical outcome and prognosis. Members of the SOX [Sry-related high-mobility group (HMG) box] gene family are involved in diverse embryonic and oncogenic processes. The roles of *SOX* genes in AML are not entirely clear but emerging evidence, including that arising from studies in solid-cancers, showed that *SOX* genes can function as tumour suppressors or oncogenes and may be involved in key pathogenetic pathways in AML involving *C/EBPα* mutations, activation of β-catenin/Wnt and Hedgehog pathways and aberrant *TP53* signals. Recent data based on genomics and proteomics have identified key interactions between *SOX* genes and partnering proteins of pathogenetic significance. The observations illustrated the principles and feasibilities of developing lead molecules of potential therapeutic values. Studying the diverse pathogenetic roles of *SOX* genes in AML may shed lights to the heterogeneity of AML and generate information that can be translated into novel therapeutic strategies.

1. Introduction

The SOX [Sry-related high-mobility group (HMG) box] gene family comprises more than 20 transcription factors (TF) sharing in common an HMG box domain with more than 60% homology to that in SRY (sex-determining region on the Y chromosome), the first member in the *SOX* family [1]. Nine groups of SOX proteins have been described (Group A, B1, B2, C-H) based on their sequence similarities in the HMG and other functional and structural domains, the position of HMG domains within the proteins and the length of the proteins [1] (Table 1). SOX proteins of the same group shared at least 70% identity of amino acid whereas those from different groups showed very little similarity outside their HMG domain. They are implicated in diverse processes during embryonic development [2], oncogenesis [3] and epigenetic reprogramming of stem cells [4]. Their pleiotropic functions, intricate regulatory and interactive networks and apparent redundancy among group members have made functional studies challenging. Features of each *SOX* gene family and their roles in oncogenesis have been reviewed recently [5,6]. However, most information reported in the literatures pertains to solid cancers and comprehensive review of *SOX* gene family in haematologic malignancies is lacking. In this article, the molecular structure, functions and regulations of *SOX* genes were reviewed. This was followed by an overview of acute myeloid leukaemia (AML), a disease in which treatment outcome has been unsatisfactory and its pathogenetic link to *SOX* genes was scarcely reported. Thereafter, *SOX* gene expression, their prognostic implications and potential pathogenetic roles in AML will be discussed. However, due to diversity of *SOX* genes and AML pathogeneses, discussion will be focused on key signaling pathways in AML where *SOX* genes have been reported. Finally, therapeutic potential of targeting *SOX* genes in AML as well as potential opportunities and challenges, will be described.

1.1. Molecular structure of SOX genes

The HMG domains in SOX proteins recognize a hexameric core DNA consensus sequence of WWCAAW (W = A/T) and bring SOX proteins to close interaction with the minor groove of DNA in cooperation with other partnering proteins and TF [3,4]. The interaction causes bending of DNA towards the major groove and induces changes in DNA structure conducive to transcription activation by specific SOX protein. The HMG box domains may also mediate transportation of SOX proteins across nuclear membrane. Most SOX proteins also contain functional and structural domains outside the HMG box at the carboxyl and amino terminal regions that collectively define the characteristics of individual *SOX* genes and their respective groups [3,4].

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Table 1
The *SOX* gene family and their roles in AML pathogeneses.

Groups	Members	Potential role(s) in AML [References]
A	Sry	
B1	SOX1, SOX2, SOX3	Sox2 downstream of Hedghog pathway [44,45]
B2	SOX14, SOX21	Enhanced β-catenin [24,34]
C	SOX4, SOX11, SOX12	Sox4 induced self-renewal of LSC in c/ebpα AML [36]; SOX4 stabilized TP53, implying tumour suppressor role [50]
D	SOX5, SOX6, SOX13	SOX6 stabilized TP53 [51]
E	SOX8, SOX9, SOX10	SOX9 transactivated p21WAF1/CIP1 [52]
F	SOX7, SOX17, SOX18	SOX7, SOX17 suppressed β-catenin [7,32,33]; SOX18 was downstream of Hedghog pathway [43]
G	SOX15	
H	SOX30	SOX30 stabilized TP53 [53]

1.2. Molecular functions of SOX genes

SOX family members show pleiotropic functions at different stages of embryonic development and oncogenesis [3,4]. They may form homodimers or heterodimers with partnering TF to induce specific transcription changes in a context dependent fashion. Specifically, *SOX* genes may direct the enhancer and/or repressor functions of the partnering TF by recruiting them to specific DNA sites. Furthermore, they may bind to target proteins at regions outside their HMG domain and these proteins may determine the physiological or pathogenetic roles of specific *SOX* genes.

Members of the *SOX* gene family have been shown to play distinct roles in oncogenesis [6]. For instance, *SOX2*, *SOX4*, *SOX9* and *SOX18* were highly expressed in various cancer types and were considered as oncogenes that promote cancer growth. On the other hand, *SOX6*, *SOX7* and *SOX17* were epigenetically silenced and played tumour suppressor role in oncogenesis. Other SOX genes e.g. *SOX10* could serve as both oncogene or tumour suppressor, depending on the specific cancer type. Information about the mechanism of action of *SOX* genes is clinically relevant, as aberrant regulation and defective function of *SOX* genes are associated with wide spectrum of developmental disorders and cancers.

1.3. Regulation of SOX gene expression

SOX gene expression was regulated by diverse mechanisms, depending on the specific *SOX* members and cell types involved. Aberrant regulation of *SOX* gene has been associated with oncogenesis. In particular, genomic amplifications of *SOX2* and *SOX18* have been reported during progression and recurrence in solid cancers [3] and might confer proliferative and survival advantage to cancer cells. Epigenetic regulation of *SOX* gene expression has also been reported in cancer initiation, including solid-cancers and AML. For example, *SOX7* and *SOX17* genes were known as tumour suppressors during oncogenesis and were epigenetically silenced by promoter CpG island methylation [7–9]. In mouse model, *Sox2* expression was repressed by histone H3 lysine 27 trimethylation (H3K27me3). The latter was reduced in tumour initiating cells in cutaneous squamous cell carcinoma [10], resulting in increased expression of oncogenic *Sox2* expression that plays a pivotal role in cancer initiation and growth. *SOX* expression could also be enhanced by upstream TF binding to *SOX* promoter. This has been demonstrated in mammary epithelial cells in which exogenous TGF-β induced *SOX* 4 expression [11]. Yes-associated protein 1 (YAP1) might interact with OCT4 and the YAP1-OCT4 complex has also been shown to induce *SOX2* expression by binding to its promoter [12]. *SOX* expression may also be regulated by microRNA, as recently reviewed [3]. In most cases, miRNAs suppressed oncogenic *SOX* expression, hence reduced cancer initiation, proliferation and migration. Epigenetic silencing of miRNAs in oncogenesis resulted in unopposed *SOX* gene expression and hence tumour growth. *SOX* genes may also undergo post-translational modification, including phosphorylation, acetylation, ubiquitination and SUMOylation [3]. Stabilization or activation of oncogenic *SOX* genes and degradation or inactivation of tumour suppressor *SOX* genes might play a role in oncogenesis.

1.4. Acute myeloid leukaemia

AML is one of the most lethal cancers worldwide [13]. It is a heterogeneous group of diseases with distinct clinicopathologic, cytogenetic and genetic characteristics sharing in common an abnormal increase in myeloblasts in blood and bone marrow (BM). Conventional chemotherapy and allogeneic haematopoietic stem cell transplantation (HSCT) are the mainstays of treatment but relapses are common and only 30–40% young patients can be cured [13,14]. The outcome of elderly or unfit patients who are ineligible for these treatments is dismal. In recent years, novel agents targeting specific gene mutations of *FLT3* (Fms-Like Tyrosine Kinase-3) [15], isocitrate dehydrogenase 1/2 (*IDH1/2*) [16,17] and inhibitors of BCL-2 [18] and sonic hedgehog pathways [19,20] have been approved for AML treatment. Identification of key pathogenetic pathways of AML will provide new targets for therapeutic intervention.

1.5. Expression of SOX genes in AML and their prognostications

Members of *SOX* gene family have shown differential expression in AML cell lines and primary samples [7]. The observations reflected distinct regulatory mechanisms of *SOX* gene expression and the unique pathogenetic role of *SOX* genes pertinent to specific AML subtypes. Expression of *SOX* genes could be silenced in AML, suggesting potential tumour suppressor roles, or enhanced, indicating their roles as oncogenes. For instance, expression of *SOX7*, *SOX17* and *SOX30* was shown to be epigenetically silenced across different AML subtypes and in myelodysplastic syndrome (MDS), a pre-leukemic state [21–23]. CpG islands could be identified in their promoters and their methylation accounted for the respective gene silencing. Epigenetic gene silencing of these *SOX* genes has been associated with inferior treatment outcome and survival in patients with MDS and AML. On the other hand, *SOX12* was shown to be highly expressed in AML compared with normal hematopoietic stem and progenitor cells and its knockdown was shown to reduce leukaemia cell proliferation and growth *in vivo* [24]. *SOX4* expression in AML was enhanced by long non-coding RNA (LncRNA) Casc 15 via transcription factor YY-1 and was associated with high relapse rate independent of age, presenting white cell counts, cytogenetics and molecular characteristics [25]. Expression of other *SOX* genes including that of *SOX2*, *SOX11* and *SOX18*, was associated with inferior disease-free and overall survivals in AML patients [26].

1.6. Pathogenetic role of SOX genes in AML

Comprehensive research of the role of *SOX* genes in cancers has been challenging due to their diverse expression profiles and regulatory mechanisms as aforementioned. Members of the *SOX* family can be tumour suppressors or oncogenes and they are involved in intricate signaling pathways in different cancer types [5,6]. As these pathways are also critical to the pathogenesis of AML, examination of *SOX* gene

functions may provide important insights to leukaemogenesis and development of novel therapeutic strategies. In the following paragraphs, these pathways will be described followed by the specific roles of *SOX* genes.

1.6.1. SOX and the β-catenin/Wnt pathway

The β-catenin/Wnt pathway plays an important role in the initiation and maintenance of leukaemia stem cells (LSC) in *de novo* AML and myeloblastic transformation of chronic myeloid leukaemia (CML) [27,28]. In the absence of Wnt ligands, β-catenin is degraded by a destruction complex comprising axin, adenomatosis polyposis coli (APC), glycogen synthase kinase-3 (GSK-3) and casein kinase 1 (CK1), whereby β-catenin is phosphorylated, ubiquitinated and degraded by proteosomes. Binding of Wnt ligands to their receptors, in association with their co-receptors LRP5/6, result in dissociation of destruction complex and free β-catenin will bind to T-cell factors/lymphoid enhancing factors (TCF/LEF) and activate expression of target genes. In mouse models, β-catenin stabilization has been demonstrated in AML subtypes that are associated with constitutively active tyrosine kinase and MLL rearrangement [29,30]. In human AML patients, β-catenin expression has been demonstrated in primary AML samples and correlated with inferior clinical outcome [31]. However, its association with specific AML subtypes has not been ascertained.

Different SOX proteins have been shown to activate or inhibit β-catenin/Wnt pathway. Proposed mechanisms include direct protein-protein interaction, binding of SOX proteins to Wnt target gene promoters, recruitment of co-repressors or co-activators and regulation of β-catenin stability [32]. While a complete review of the SOX-Wnt interaction is beyond the scope of this review, some aspects are relevant to AML pathogenesis. In particular, SOX7 and SOX17 have been shown to play tumour suppressor role in AML pathogenesis by binding β-catenin directly at the β-catenin binding site of the C-terminus, thereby interfering with its downstream signalling [7,32,33]. Epigenetic silencing of these *SOX* genes in AML resulted in unopposed β-catenin/Wnt pathway characteristics of leukaemogenesis. Hypomethylating agent induced *SOX7* expression by demethylating its GpG islands at promoter region, ameliorated β-catenin/Wnt pathway and abrogated leukaemogenesis in both *in vivo* and *in vitro* models [7]. On the other hand, *SOX4* and *SOX12* have been shown to enhance β-catenin/Wnt pathway and play an oncogenic role in solid cancers and AML. SOX4 protein has been shown to stabilize β-catenin by inducing casein kinase 2 (CK2) activity that protects β-catenin from proteosome degradation and activate transcription of *TCF4* in solid cancers [34]. *SOX12* expession was up-regulated in AML and knockdown of *SOX12* has been shown to ameliorate Wnt signaling and suppress leukaemia growth of AML cell lines [24] (Fig. 1A). The mechanism of SOX12 and β-catenin interaction is presently unclear and whether the similarity between SOX4 and SOX12 reflects a group effect of SOXC would have to be further investigated. The pathogenetic link between SOX and β-catenin/Wnt is clinically relevant. As genetic deletion and pharmacologic inhibition of β-catenin have been shown to ameliorate leukaemogenesis at the level of LSC, perturbing the interaction between SOX and β-catenin may disrupt β-catenin/Wnt signaling in AML [32], thereby providing an important molecular target for the development of novel therapeutic agents.

1.6.2. SOX and CEBPα mutant AML

The CCAAT-enhancer binding protein α (*C/EBPα*) is a leucine zipper transcription factor that is involved in myeloid development. It is the founder of the C/EBP family that comprises *C/EBPα*, *C/EBPβ*, *C/EBPδ*, *C/EBPε*, *C/EBPγ*, and *C/EBPζ*, in their order of discovery [35]. C/EBP members share a similar C-terminal domain for DNA binding and dimerization, but are different in the N-terminal domain [35]. *C/EBPα* resides in chromosome 19 and translation of C/EBPα proteins from 2 distinct AUG start sites generated the p42 and p30 isoforms. Among *C/EBPα* mutant AML, 30% involves frame-shift mutations of one allele, mostly in the N-terminal region. 70% involves mutations of both alleles in which frame-shift mutations in the N-terminal of one allele lead to increased expression of the p30 isoform and the C-terminal in-frame mutations in the other allele result in compromised DNA binding and homo-dimerization. AML carrying bi-allelic *CEBPα* mutations form a distinct category with unique gene expression profiles and good clinical response to conventional chemotherapy. In addition to being driver mutations in this AML subtype, deregulation of *C/EBPα* at both transcriptional, post-transcriptional and post-translational levels were shown to mediate leukaemogenesis in other AML [35].

SOX genes were identified as downstream targets of C/EBPα. Conditional knockout of *c/ebpa* in mice completely blocked neutrophil development at the common myeloid progenitor (CMP) stage [36]. Gene expression profiling of LSC from *c/ebpa* knockout mouse model of AML showed up-regulation of *Sox4* expression [36]. Furthermore, *Sox4* knockdown abrogated the proliferation and clonogenic activities of LSC and induced terminal myeloid differentiation. In the same study, overexpression of *Sox4* induced self-renewal and impaired differentiation of mouse haematopoietic stem and progenitors [36]. These observations underscored the key pathogenetic role of *Sox4* in *c/ebpa* deletion mouse model of AML. Mechanistically, c/ebpa has been shown to bind to *Sox4* promoter and repress its expression. Abrogation of c/ebpa function by gene deletion relieves *Sox4* promoter inhibition, resulting in its overexpression. Importantly, gene expression profiles of LSC in *Sox4* overexpression and biallelic *c/ebpa* mutant mouse models were clustered together and were distinct from other leukaemia subtypes. These observations supported the proposition that SOX4 being a direct mediator of leukemogenesis in biallelic *CEBPα* mutant AML [37]. Information arising from mouse models could be generalized as *SOX4* expression was also up-regulated in human AML with bi-allelic *CEBPα* mutations. As an oncogene, *Sox4* has been shown to expand cancer stem cell pools in mouse model and accentuate β-catenin/Wnt pathway via stabilization of β-catenin and activation of *Tcf4* transcription [38]. Intriguingly, *SOX4* has also been shown to serve as tumour suppressor in some solid cancers [38].

1.6.3. SOX and the Hedghog Pathway

The Hedghog pathway includes 3 ligands including sonic-, desert- and Indian Hedghogs and is highly conserved in vertebrates. The receptor, known as Patched, is a negative regulator and in the absence of ligand, it represses the translocation of signal transducer Smoothened to the plasma membrane. Upon binding of ligand, the inhibitory effects of Patched are relieved and Smoothened is translocated to the plasma membrane and becomes activated, thereby inducing activation of target gene transcription through GLI proteins [39] (Fig. 1B). Aberrant activation of Hedghog signaling has been reported in LSC [40]. Very recently, a Smoothened inhibitor Gladesgib in combination with low dose cytarabine was shown to improve overall survival of elderly patients with AML who are unfit for conventional chemotherapy, attesting to the clinical relevance of Hedghog pathway activation in AML [41,42]. However, biomarkers predictive of response to Gladesgib are lacking and the link between GLI and leukaemogenesis is unclear. In cervical carcinoma cell lines, GLI1 and GLI2 enhance the promoter and transcription of *SOX18* and inhibition of Smoothened and GLI1/2 down-regulated Hedghog activities and *SOX18* expression at transcript and protein levels, supporting the hypothesis that SOX18 being a downstream TF of Hedghog pathway [43]. In medulloblastoma model driven by activated SHH signals, *Sox2* was expessed in a rare population of cancer stem cells that were replicatively quiescent, slowly cycling, capable of generating tumours when transplanted into immunodeficient mice and were resistant to chemotherapy [44,45]. These observations suggested SOX2 could be a target for therapeutic intervention in cancers and its role in AML pathogenesis would have to be further evaluated.

1.6.4. SOX and TP53 signaling

AML carrying complex or monosomy karyotype (CK/MK) represents

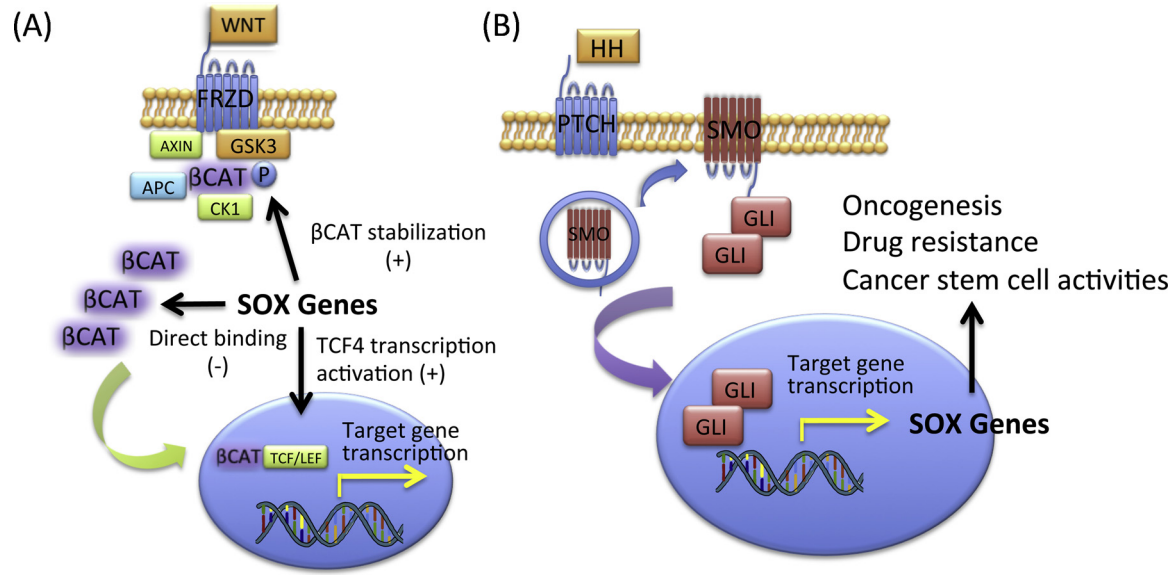

Fig. 1. Pathogenetic roles of SOX genes in aberrant β-Catenin/Wnt pathway (A) and Hedghog pathway (B) during leukaemogensis. (A) Members of SOX genes have been shown to ameliorate β-Catenin/Wnt pathway by direct binding to β-Catenin or activate it by β-Catenin stabilization of TCF4 transcription activation. FRZD: Frizzled; APC: Adenomatosis Polyposis Coli; CK1: Caesin Kinase 1; GSK3: Glycogen Synthase Kinase 3; βCAT: β-Catenin; TCF/LEF: T-Cell Factor/Lymphoid Enhancer Factor. (B) Members of the SOX genes have been shown to be direct target of GLI which is the effector transcription factor in Hedghog pathway. HH: Hedgehogs; PTCH: Patched; SMO: Smoothened.

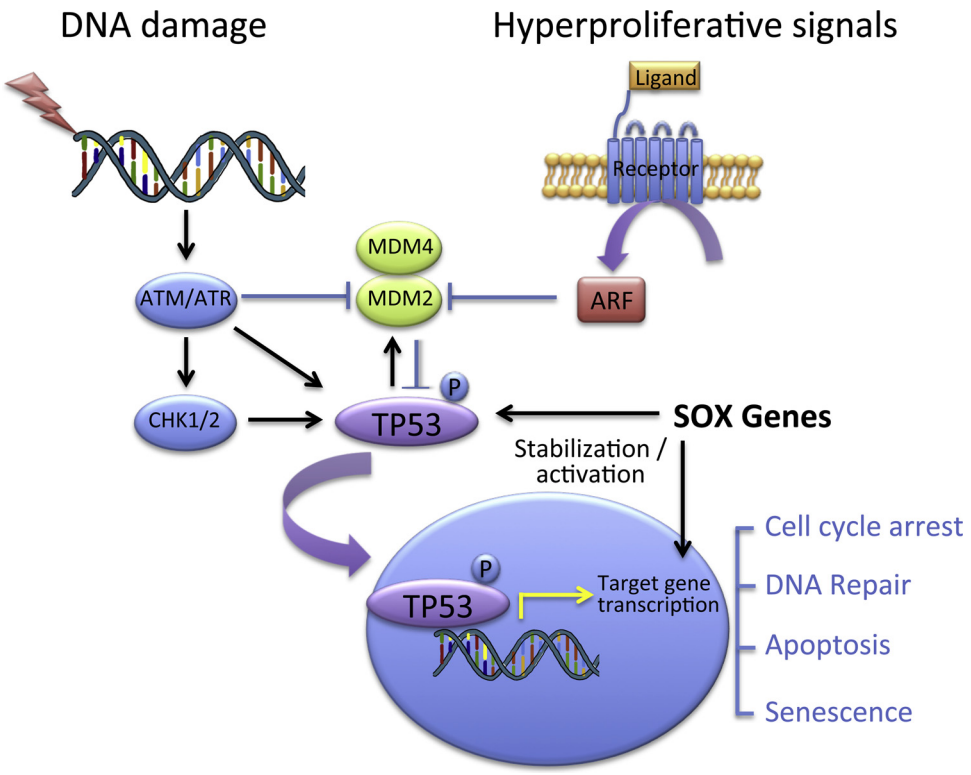

Fig. 2. Pathogenetic role of SOX genes in aberrant TP53 pathway. Members of the SOX genes have been shown to activate TP53 pathway by stabilization or activation of TP53 or its target gene transcription. ATM/ATR: Ataxia telangiectasia mutated (ATM) and ATM and RAD3-related (ATR); CHK: Checkpoint kinase; MDM: Mouse double minute 2 homolog.

one of the most difficult-to-treat subtypes. It is characterized by genomic and chromosomal instabilities [46]. Mutations of *TP53*, hitherto uncommon in other AML cytogenetic subtypes, are found in about 50% of cases and are associated with chemo-refractoriness and an extremely poor clinical outcome [47]. Dysfunctional TP53 signaling also occurs and is related to increased expression of MDM-2 that degrade TP53 [48,49]. There is an unmet clinical need to identify therapeutic targets that restore TP53 activities and signaling. *SOX* genes are known to involve in the regulation of *TP53* and defective SOX gene functions may result in defective TP53 signaling and present a molecular target for therapeutic intervention. In human cancer cell lines, *SOX4* expression was induced upon DNA damage and such response contributed to TP53 functions including cell cycle arrest, apoptosis, and tumorigenesis. SOX4 was shown to interact physically with and stabilize TP53 protein by inhibiting MDM2-mediated ubiquitination either directly or by acetylating TP53 [50] (Fig. 2). It is presently unclear if *SOX4* plays similar tumour suppressor role in AML and if so its roles are subtype specific as *SOX4* is oncogenic in other AML including those

with biallelic *CEBPα* mutations. *SOX6* [51], *SOX9* [52] and *SOX30* [53] are tumour suppressors and have been shown to bind and activate TP53 and its downstream targets including p21 and BCL-2 like protein 4 (BAX) in human cancers. Their potential tumour suppressor roles in AML would have to be further evaluated.

1.7. Therapeutic targets of SOX genes

Understanding the diverse pathogenetic roles of *SOX* genes has provided insights to the heterogeneity of AML and opportunities for therapeutic targeting. As different *SOX* genes may serve as tumour suppressors or oncogenes depending on the cellular context, both promotion of *SOX* expression or inhibition of SOX function may be relevant for therapeutic consideration.

The tumour suppressor roles of *SOX* genes in oncogenesis suggested their up-regulation may have therapeutic potential. Hypomethylating agent that demethylated CpG island of *SOX7* promoter has been shown to induce its gene and protein expression in AML [7]. While SOX7 down-regulated β-catenin signaling and in principle would suppress leukaemia growth, hypomethylating agents as monotherapy show only modest remission rate in the clinics and are not curative in most patients. Therefore, concurrent therapy on top of β-catenin modulation by *SOX7* expression is needed to eradicate leukaemia. On the other hand, the oncogenic roles of SOX genes open up the possibility of therapeutic targeting in cancer treatment. While targeting of TFs has been challenging and inhibition of their DNA binding lacks specificity, recent studies in search of small molecules targeting protein interaction of SOX have provided important leads for future evaluation [54]. Examination of protein-protein interactions involving SOX18 by genomics, proteomics and biophysics have identified small molecules that disrupted subets of SOX18-dependent interactions, leading to selective transcriptional blockade of SOX18 target genes [55]. Functionally, these molecules could perturb angiogenesis and cancer growth, providing important leads for future mechanistic and clinical trials. These observations proved the principle and feasibility of TF targeting and might provide a novel paradigm for the development of novel therapeutic agents that target key pathogenetic pathways in AML.

1.8. Challenges and opportunities of SOX targeting

The diverse pathogenetic pathways in AML and myriads of interacting partners of SOX proteins and transcriptional networks has posed both challenges and opportunities for the development of novel therapeutic targets. First, different *SOX* genes play redundant and compensatory roles in AML pathogenesis and targeting a particular *SOX* gene will unlikely eradicate AML. Second, a particular SOX protein may have distinct functions in different AML subtypes, depending on the specific driver events. This may hamper generalization of laboratory findings. Third, *SOX* genes have been shown to regulate normal stem cell function and the potential side effects of molecular targeting of SOX proteins and the related signaling pathways would have to be examined.

These limitations notwithstanding, investigation of SOX genes in AML pathogenesis may provide opportunities to improve treatment outcome in AML. For instance, understanding the pathogenetic mechanisms of *SOX* genes in specific AML subtypes may generate information about protein-protein interaction between SOX proteins and key leukemogenic signals and provide important leads for the development of novel targets for therapeutic intervention. Moreover, enhancing expression of tumour suppressor *SOX* genes by hypomethylating agents [7,8] might inhibit key pathogenetic signals in AML and provide the mechanistic basis for combination treatment. Finally, the pathogenetic roles of SOX genes in AML may become a point of reference for research in other haematologic maligancies in which the roles of SOX genes are currently unknown.

In conclusion, emerging evidence showed that *SOX* genes were involved in key pathogenetic pathways in AML. The diversity of SOX genes and AML pathogeneses have made laboratory research and their generalization challenging. Detailed mechanistic studies are needed to evaluate the pathogenetic roles of *SOX* genes in individual AML subtypes that may shed lights to personalized treatment of AML.

Declaration of competing interest

There is no conflict of interests to declare.

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