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New insights into KLFs and SOXs in cancer pathogenesis, stemness, and therapy

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Abstract

Despite the development of cancer therapies, the success of most treatments has been impeded by drug resistance. The crucial role of tumor cell plasticity has emerged recently in cancer progression, cancer stemness and eventually drug resistance. Cell plasticity drives tumor cells to reversibly convert their cell identity, analogous to differentiation and dedifferentiation, to adapt to drug treatment. This phenotypical switch is driven by alteration of the transcriptome. Several pluripotent factors from the KLF and SOX families are closely associated with cancer pathogenesis and have been revealed to regulate tumor cell plasticity. In this review, we particularly summarize recent studies about KLF4, KLF5 and SOX factors in cancer development and evolution, focusing on their roles in cancer initiation, invasion, tumor hierarchy and heterogeneity, and lineage plasticity. In addition, we discuss the various regulation of these transcription factors and related cutting-edge drug development approaches that could be used to drug “undruggable” transcription factors, such as PROTAC and PPI targeting, for targeted cancer therapy. Advanced knowledge could pave the way for the development of novel drugs that target transcriptional regulation and could improve the outcome of cancer therapy.

Keywords

KLF4; KLF5; SOXs; pathogenesis; stemness; carcinogenesis and therapy

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Conflicts of Interest Statement

The authors declare that there are no conflicts of interest.

Introduction

Cancer cells almost invariably evolve resistance, leading to cancer recurrence, metastasis, and eventually patient mortality [1,2]. Historically, most studies focus on genetic drivers of drug resistance, that enable cancer cells to bypass the targeted pathway and then develop new therapies to overcome the resistance correspondingly [3]. But cancer cells can gain resistance to new treatments by similar mechanisms. More and more studies, especially data from single-cell profiling, show that non-mutational mechanisms, such as cell lineage plasticity, serve as key drivers for drug resistance in various cancers [1,2,4,5]. Cell plasticity enables cancer cells with a single genotype to switch between different phenotypic states (or cell identities) in response to external stimuli, including stresses in the adverse tumor microenvironment and anti-cancer drug treatments to survive and thrive (Fig. 1). Such a phenotypic switch can be reversible, as is demonstrated by the loss of resistance when cultured in the absence of the drug. Indeed, the subpopulation of cancer cells adapted to the treatment can serve as a reservoir to proliferate and gain stochastic mutations. Eventually, those cancer cells with genetic mutations that confer better resistance to the treatment will survive as the set of fittest clones under drug selection. Besides drug resistance, cancer cell plasticity also facilitates malignant progression, which requires phenotypic switches such as the epithelial-to-mesenchymal transition (EMT) for migration and mesenchymal-to-epithelial transition (MET) for colony formation [6]. In the context of cancer stem cell (CSC) theory, cancer cell plasticity can also be interpreted as the capacity of a differentiated cancer cell to revert to a stem cell-like state [2,7].

Transcription factors (TFs) are crucial in reprogramming cancer cells to control these phenotypic switches. Transcription factors bind to specific DNA sequences in the genome, and coordinate gene expression in response to signaling [8]. Transcription factors are the fundamental players in determining cell lineage during the development of multicellular organisms by decoding the same genetic code differentially. Furthermore, TFs are also essential for cell survival as they work as endpoints of cellular signaling pathways to coordinate the rapid transcriptional response to internal and external stimuli. Given their central regulatory role in biology, TFs are critical players in many diseases, including cancers [9–12]. It is hypothesized that dysregulated transcription leads to the fundamental features of cancer. Consistently, cancer cells have gene expression profiles distinct from their normal tissue of origin, and these gene expression profiles change during different stages of cancer development [13–18], highlighting the crucial roles of transcription factors. Furthermore, gene expression profiles can predict clinical outcomes of many cancers [19–22], indicating the critical roles of transcription factors in cancer prognosis.

Given their central regulatory roles in cancers, TFs represent potential therapeutic targets [9–12]. The therapeutical potential of modulating TF action has been well demonstrated by hormone therapies that target nuclear hormone receptors, a subtype of transcription factor, in cancer treatments. Anti-estrogen and anti-androgen compounds, such as tamoxifen, bicalutamide, and enzalutamide have been in clinical use to treat breast cancer and prostate cancer, respectively, for many years [23,24]. Despite the great potential of targeting transcription factors for cancer treatment, transcription factors (other than nuclear receptors with ligands) have been considered undruggable due to the lack of enzymatic sites

or ligand binding pockets to develop small-molecule inhibitors or activators. However, new technologies, such as proteolysis-targeting chimeras (PROTACs) for targeted protein degradation and structure-based protein-protein interaction inhibitors, have made targeting transcription factors for cancer treatment into viable options [12,25]. In this review, we focus on the roles of several pluripotent transcription factors, KLF4, KLF5, SOX2, SOX4, and SOX9 in cancer progression, metastasis, stemness, stress response, and drug resistance, as well as their regulation to explore the potential and possible strategies of targeting these transcription factors in cancer treatment.

KLFs and SOXs in pluripotency

Human Krüppel-like factors (KLFs) are a family of DNA-binding transcription factors with 17 members, that is highly conserved among mammals from humans to mouse [26]. Structurally, all members of the KLF family have a highly conserved triple C2H2 zinc-finger DNA-binding domain at the carboxyl terminus regions [26]. Each zinc finger recognizes three base pairs in the DNA sequence, and thus KLFs can interact with nine base pairs in total. The N-terminus of KLFs, where an activation or repression domain is typically located, is highly divergent [26]. SRY-related high-mobility-group box (SOX) family is another group of transcriptional factors with over 20 members in vertebrates. SOX factors are defined by a highly conserved DNA-binding high-mobility group (HMG) domain homologous to the HMG domain of sex determining region Y protein (SRY) [27]. KLFs and SOXs play essential roles during development. They work as transcription factors to mediate responses to external and internal stimuli and regulate many cellular processes, including proliferation, apoptosis, differentiation, and migration [26,28,29]. Several members from the two families, especially KLF4, KLF5, SOX2, SOX4, and SOX9, are expressed in stem cells and function as pluripotent factors to regulate cell lineage and stemness (Fig. 2).

KLF2, 4, and 5 are co-expressed in ESCs to maintain pluripotency and their combined knockdown leads to robust differentiation of ESCs [30,31]. The expression of KLF4 and KLF5 is induced through the LIF/STAT3 pathway, which is required to sustain pluripotency [32–34]. KLF4 and KLF5 activation leads to the expression of NANOG, SOX2, and OCT4 [35,36], while OCT4 further activates KLF2 [34] and reinforces SOX2 expression [37]. These downstream targets of KLF4 and KLF5: NANOG, SOX2, and OCT4, play a critical role in maintaining the pluripotency of embryonic stem cells [38]. SOX2, OCT4 and KLF4 are three of the four OSKM factors for induced pluripotent cells(iPSCs) [39,40]. The other OSKM factor is c-MYC, which promotes iPSCs but is strictly dispensable [41].

In addition, KLF4 and KLF5 also play a critical role in adult stem cells. Both KLF4 and KLF5 are highly expressed in the intestinal tract [42,43]. KLF4 modulates the intestinal stem cells marked by BMI1. In $BMI1^{+}$ stem cells, KLF4 inhibits proliferation to maintain homeostasis under normal conditions while promoting the regenerative response upon ionizing radiation injury [44]. KLF5 is required to maintain intestinal stem cells. Conditional knockout of KLF5 suppresses the proliferation and survival of mouse intestinal stem cells and completely prevents the tumorigenesis induced by β-catenin [45]. KLF5 also regulates the maintenance and differentiation of basal progenitors in prostate development [46]. This differential regulation is mediated by the posttranslational regulation of KLF5: acetylated

KLF5 is required to maintain basal progenitors while deacetylated KLF5 promotes basal-to-luminal differentiation partially through activating Notch signaling [46].

SOX factors also play critical roles in development and tissue homeostasis through maintenance of stem and progenitor cells. Besides the well documented role of SOX2 in induction of pluripotent stem cells [39], SOX2 and SOX9 play key roles in neuronal development and maintenance of neural progenitor cells [47]. SOX9 also is critical for maintenance of adult stem and progenitor cells in the intestine and hair follicles [48], and is essential for normal development of the pancreas [49] and mammary gland [50]. In addition to SOX9, SOX4 is also critical for development of the pancreas [51] and breast [52]. In fetal mammary stem cells, SOX4 inhibits differentiation by maintaining expression of a stem cell gene expression program [52]. SOX4 is essential to development of many tissues including neural crest [47], heart [53], B cells [54], and skeleton [55]. In adult stem cells, SOX4 is essential for stem cell reactivation in response to wounding of the skin [56].

KLFs and SOXs in cancer

Along with their roles in development, many studies have suggested that KLF4, KLF5, SOX2, SOX4 and SOX9 are associated with cancer stemness, progression, metastasis, drug resistance, and prognosis [28,57–65] (Fig. 4). Dysregulated KLF4 and KLF5 have been found in multiple cancer types including breast cancer, lung cancer, pancreatic cancer, prostate cancer, colon cancer, and stomach cancer [57]. SOX2, SOX4, and SOX9 also have increased expression in a wide variety of tumors [58–65].

Cancer pathogenesis

KLF4 and KLF5 exert contrasting effects on cell proliferation in many instances; while KLF4 is an inhibitor of cell growth, KLF5 stimulates proliferation [66] (Fig. 3). KLF4 inhibits cell proliferation by regulating the transcription of cell cycle genes. KLF4 transactivates the expression of cyclin-dependent kinase inhibitor 1B (CDKN1B, also known as p27 or Kip1) and cyclin-dependent kinase inhibitor 1A (CDKN1A, also known as p21 or Cip1) [67–70], and down-regulates cyclin D1 [68,69,71]. These actions of KLF4 lead to cell cycle arrest at the G1-S checkpoint. KLF4 generally plays a tumor-suppressive role in various cancers by inhibiting cell proliferation. In primary hepatocellular carcinoma, KLF4 has been demonstrated to suppress oncogenic TGF-β signaling by transactivating Smad7 and loss of KLF4 could lead to the activation of TGF-β signaling and tumor promotion [72]. In non-small cell lung cancer cells, KLF4 can also inhibit tumor cell proliferation by suppressing TGF-β1 mediated ERK/JNK/NF-κB signaling pathways [73].The absence or reduced expression of KLF4 has been found in a variety of cancers, including bladder cancer [74], pancreatic carcinoma [67,69], lung carcinoma [68], medulloblastomas [75], cervical carcinoma [70], colon cancer [76,77], hepatocellular carcinoma [78], and neuroblastoma [79]. However, KLF4 also plays an oncogenic role in breast cancer [80] and squamous cell carcinomas [81]. KLF4 overexpression was detected in about 70% of primary human breast cancer [80]. Ductal carcinoma in situ also exhibits similar KLF4 expression, suggesting that KLF4 overexpression may be an early event in breast carcinogenesis [80]. In addition, KLF4 shows stage-specific effects in some cancer types, such as esophageal squamous

cell carcinogenesis (ESCC). The downregulation of KLF4 in early-stage ESCC, is required for esophageal tumorigenesis while in later stages, the expression of KLF4 is restored to promote tumor invasion and metastasis [82]. The contrasting roles of KLF4 in cancer cell proliferation can be partially explained through CDKN1A inactivation [81], the oncogenic RAS^{V12} mutation, or cyclin-D1 overexpression (a common target of KLF4 and RAS) [83]. KLF5 can also partially contribute to this switch as the oncogenic RAS^{V12} induces the expression of KLF5, which stimulates the proliferation of colorectal cancers [84]. In addition, KLF4α, an alternatively spliced isoform of KLF4 that is upregulated in pancreatic cancer, suppresses the expression of CDKN1A and CDKN1B to promote the cell cycle and enhance cancer progression [85].

In contrast to KLF4, KLF5 is generally pro-proliferative in normal cells [26]. KLF5 promotes cell proliferation by accelerating the transition of G1/S and G2/M phases of the cell cycle. KLF5 transactivates the expression of cell cycle genes, such as cyclin D1 [86], cyclin B1, and Cdc2 [87], while repressing the expression of the cell cycle inhibitory proteins such as p27 and p15 [88]. KLF5 promotes the progression of various cancers, including pancreatic cancer, gastric cancer, and breast cancer by advancing the cell cycle through transcriptional regulation of cell cycle related genes [89–92].

However, KLF5 could be a potential tumor suppressor in other epithelial cancer types, such as prostate cancer and certain breast cancers. KLF5 deletion is frequently reported in breast [93] and prostate [94] cancers. KLF5 is frequently deleted or downregulated in prostate cancer and is associated with poor prognosis [89,95,96]. KLF5 knockdown increases prostate cancer cell proliferation in androgen receptor-positive cell models [97]. The context-dependent function of KLF5 in cancer progression could be partially determined by the status of p53, which is the most frequently inactivated tumor suppressor in cancers [98–100], and the switch of its transcriptional function by posttranslational modification [101–104]. In keratinocytes and ESCC cells, when p53 is wild-type, KLF5 is pro-proliferative. In addition, KLF5 and p53 work coordinately to induce the expression of BIRC5 (encoding survivin) and hypoxia-inducible factor (HIF1α), and therefore inhibit apoptosis [105]. However, when p53 is mutated, KLF5 becomes anti-proliferative through transactivating CDKN1A (p21) [98] and NOTCH1 [99], thus working as a potent tumor suppressor.

Recently, another KLF family member, KLF7, was found to play a oncogenic role in a variety of cancers, including pancreatic cancer [106], hepatocellular cancer [107], gastric cancer [108], endometrial cancer [109] and squamous carcinoma [110] and could be a potential therapeutic target. In high-grade serous ovarian cancer, KLF7 functions as an oncogene to promote tumor growth and serves as an unfavorable prognostic marker for overall survival in late-stage TCGA-OV and GSE26712 HGSOC cohorts. In addition, the downstream targets of KLF7 are involved in epithelial to mesenchymal transition, and the maintenance of pluripotency and self-renewal characteristics of cancer stem cells [111]. In pancreatic cancer, KLF7 promotes pancreatic cancer growth and metastasis by up-regulating ISG expression and maintaining Golgi complex integrity [106]. In hepatocellular cancer, the KLF7/VPS35 axis promoted HCC cell cycle progression by activating the Ccdc85c-medicated β-catenin pathway [107]. In gastric cancer, KLF7 promoted gastric carcinogenesis via upregulation of ANTXR cell adhesion molecule 1 (ANTXR1) [108].

The role of SOX factors in tumorigenesis and cancer progression has been the subject of several recent review articles [58–65]. SOX2, SOX4, and SOX9 are overexpressed in a wide variety of tumors, and SOX4 overexpression is associated with poor prognosis [112], metastasis [113], and EMT [114].

The roles of KLFs and SOXs in tumorigenesis have also been demonstrated in murine models. Generally, KLF4 deletion promotes tumorigenesis. Intestinal epithelium specific ablation in $KLF4^{Loxp/Loxp}$/ AAV7-Cre-mCherry mice are more susceptible to DNA damage and increased genomic instability when challenged with genotoxic stress like radiation, suggesting KLF4 knockout may create a tumor permissive environment and facilitate gastric tumorigenesis [115]. Li et al also showed that conditional deletion of KLF4 in villin-positive antral mucosa cells ($Villin\text{-}^{Cre(+)};Klf4^{(fl/fl)}$ mice) has greater chemical-induced gastric carcinogenesis and tumor promotion [116]. Similarly, Ghaleb et al. found that $Klf4^{\Delta/S}/Apc^{Min/+}$ mice with *in vivo* KLF4 deletion leads to increased colonic adenomas as compared to the WT $Klf4^{fl/fl}/Apc^{Min/+}$ mouse [117]. It has also been shown by adoptive transfer studies that KLF4 deletion in CCR2+ myeloid-derived suppressor cells results in decreased lung metastases when mice are inoculated with melanoma or breast cancer cells [118].

In contrast to KLF4, KLF5 deletion tends to inhibit tumorigenesis in mouse model studies. Heterozygous deletion of KLF5 can inhibit intestinal tumor formation [45,119]. In one mouse model, tamoxifen-induced KLF5 deletion in Lgr5(+) stem cells suppressed cell proliferation and prevented oncogenic transformation [45]. In breast cancer, mammary gland-specific KLF5 conditional knockout mice showed decreased breast epithelial cell proliferation, reduced mammary cell survival and inhibited PyMT-induced tumorigenesis [120].

SOX2 was also found to regulate gastric stem cell self-renewal and epithelial homeostasis. Loss of SOX2 in gastric cells promotes Wnt-driven tumorigenesis. Sarkar et al generated APC knockout (APC KO) and APC/SOX2 double-knockout (DKO) mice and found significant increase in the number of adenomas in tamoxifen treated DKO mice compared to APC KO mice [121].

Cancer cell metastasis is a prime example of tumor cell plasticity, and most tumor cells have inherent plasticity [122]. Tumor cells often undergo the epithelial–mesenchymal transition (EMT) for migration for cancer metastasis. EMT is typically characterized by downregulation of the cell adhesion molecule E-cadherin. Transcriptional regulators, such as SNAIL and SLUG, drive EMT by suppressing the expression of E-cadherin [123]. KLF4 also plays a multi-faceted role in tumor metastasis. Some reports indicate that KLF4 works as a stem cell factor to maintain stemness required to promote EMT, as the expression of KLF4 along with other stem cell factors is altered by different factors regulating EMT, including ZEB1,p53, NF-kB and ALDH1 [124–127]. KLF4 is required to promote migration and invasion of the breast cancer cell lines, MCF-7 and MDA-MB-231, via the Notch pathway [128]. Consistently, KLF4 also promotes mesenchymal properties in colorectal cancer stem cells by upregulating EMT factors, such as SNAIL via the TGF-β1/SMAD pathway [129]. However, in mouse and human prostate cancer cells, KLF4 works

with FOXA1, which directly inhibits the transcription of SLUG, the dominant regulator of TGF-β induced prostatic EMT [130]. In addition, KLF4 overexpression in 4T1 cells reduces the expression of SNAIL, a key mediator of EMT and metastasis in breast cancer [131].

Similar to KLF4, the role of KLF5 in metastasis also seems to be context-dependent. In some cases, KLF5 seems to promote metastasis. For example, KLF5 transactivates tumor necrosis factor-α (TNFα)-induced protein 2 (TNFAIP2), which in turn increases the activity of two GTPases: Rac1 and Cdc42, to change actin cytoskeleton and cell morphology, and thus promotes cell migration and invasion in breast cancer cells [132]. In agreement with this, KLF5 promotes cervical cancer proliferation, migration and invasion partly by transactivating tumor necrosis factor receptor superfamily member 11a (TNFRSF11a) [133]. KLF5 also promotes EMT in laryngeal carcinoma Hep-2 cells, where KLF5 knockdown increases E-cadherin, while decreasing N-cadherin, Vimentin, and the regulatory factors SNAIL and SLUG along with the attenuation of EMT [134]. In contrast, in the human non-small cell lung cancer (NSCLC) cell line, A549, KLF5 knock-down, decreases E-cadherin expression [135]. The function of KLF5 in EMT also seems to depend on the activity of p53, [98,99,105,136]. In the absence of p53, KLF5 inhibits EMT in liver cancer cells by suppressing ZEB2 protein expression via inducing miR-192 [136]. Reciprocally, in primary human keratinocytes harboring mutant p53, KLF5 depletion induces EMT as confirmed by the induction of SNAIL, TWIST, and the suppression of E-cadherin [99].

SOX4 is a master regulator of EMT [114] and regulates EMT in response to TGFβ signaling[137–140]. In gastric cancer cells, SOX4 promotes EMT by upregulating the expression of EMT transcription factors, including Twist1 and ZEB1 [138]. TGFβ signals can drive SOX4 to induce apoptosis, but KLF5 cooperates with SOX4 to prevent TGFβ-induced apoptosis [139] (Fig. 5). Both SOX4 and SOX9 have been shown to play critical roles in metastasis [113,137,141–144].

Cancer stem cells

In the cancer stem cell (CSC) theory, a subset of cells called CSCs are predisposed to drive self-renewal and differentiation to produce a diverse population of daughter cells [145]. Recently, pluripotency factors, including KLF4 and KLF5, have been rediscovered as the drivers of cancer stemness. KLF4 and KLF5 are preferentially expressed within cancer stem-like cells [146]. KLF4 is highly associated with the stemness of cancer cells. In both cancer cells and normal stem cells, KLF4 is required to maintain telomerase activity for the long-term proliferative potential of these cells through transactivating the expression of human telomerase reverse transcriptase (hTERT) [147]. In human osteosarcoma cells, KLF4 overexpression promotes tumorsphere formation, the transcription of stemness-associated genes, chemoresistance and distant metastasis [148]. KLF4 promotes stem cell-like characteristics partially by activating the p38 mitogen-activated protein kinase (MAPK) signaling pathway [148]. In breast cancer, KLF4 expression is increased selectively in the mammary cancer stem-like cells (MaCSCs) of cultured human triple-negative breast cancer (TNBC) cell lines, and the aldehyde dehydrogenase high MaCSCs derived from xenografted human mammary carcinomas [149]. In MaCSCs, KLF4 exerts pro-survival signaling by inhibiting pro-apoptotic signaling molecules like programmed cell death 4 (PDCD4) and

connexin 43 (CX43) through its downstream effector, microRNA-206 [149]. In addition, KLF4 promotes the transcription of ALDH1, which induces and functionally marks CSCs [150]. In colorectal cancer, KLF4 is enriched in $Lgr5^{+}CD44^{+}EpCAM^{+}$ cancer stem cells and required to maintain stemness via the TGF-β1 pathway [129]. In pancreatic acinar cells, KLF4 induces acinar-to-ductal cell reprogramming by inducing the ductal specific marker Krt19 expression and suppressing Amylase, Ptfa1, and CAII. In addition, KLF4 synergizes with K-Ras mutations to initiate the formation of premalignant pancreatic intraepithelial neoplasia (PanIN) [151]. Another study showed that KLF4 mediates pancreatic cancer cell stemness promoted by secreted mucin 5AC (MUC5AC) [152].

KLF5 has also been reported to promote stemness in various cancers, including lung cancer [153], hepatocellular carcinoma [154], and triple-negative breast cancer [155]. In lung cancer, KLF5 mediates cell stemness promoted by α-Catulin. Mechanistically, α-Catulin interacts with the C-terminal region of KLF5, and such an interaction inhibits WWP1-mediated KLF5 degradation and thus increases KLF5 protein levels [153]. KLF5 knockdown blocks α-Catulin-driven cancer stemness as measured by sphere formation, ALDH activity, and stemness factors OCT4 and NANOG [153]. In hepatocellular carcinoma, KLF5 overexpression enriches cancer stem-like cell populations, promotes colony-formation, and enhances drug resistance [154]. In triple-negative breast cancer (TNBC), KLF5 degradation that is triggered by metformin treatment reduces the percentage of stem cells marked with high ALDH activity [155]. Taken together, KLF4 and KLF5 could be potential therapeutic targets for cancer treatments to prevent cancer recurrence.

In breast cancer, a SOX2-SOX9 signaling axis is essential for maintenance of breast luminal progenitor cells, Wnt signaling, and expression of ALDH1A3 [156]. Consistent with these data, SOX2 and SOX9 were both top hits in a genome-wide CRISPR screen for genes essential for glioma stem cells [157]. Both SOX9 [158] and SOX4 [52] have been shown to be important in breast cancer stem cells [50]. In organoids derived from a PyMT genetic mouse model, SOX4 inhibits differentiation of breast cancer by reactivating a set of genes enriched in fetal mammary stem cells (fMaSC) [52]. In colorectal cancer, cells with high activity of the SOX2 promoter, indicated by Sox2 promoter dependent DsRed fluorescence, exhibit typical asymmetric cell division and high stem cell markers [159]. Consistently, SOX2 overexpression in colorectal cancer cells drives cancer stem characteristics [160]. In gastric cancer cells, SOX4 promotes cancer stemness through pluripotent factors SOX2 and OCT4 [138].

Drug resistance

Several studies have shown that conventional chemotherapy and ionizing radiation enhance the stemness of cancer cells and induce drug-resistant cancer stem cells (CSCs) [161–164]. This phenotypic switch is tightly interconnected with the concept of tumor cell plasticity and is associated with transcriptional reprogramming [2,7]. KLF4, KLF5, and SOX factors have been shown to modulate therapeutic responses in cancer.

In normal tissue, KLF4 and KLF5 function as stress response genes and are induced by various noxious stimuli to support cell survival. The expression of KLF4 is induced by shear stress [165] and pro-inflammatory stimuli [166] in endothelial cells. KLF4 can also

be induced by injury in normal adult vascular smooth muscle cells [28]. Like KLF4, KLF5 also protects cells from various external cellular stresses. Part of this function of KLF5 is achieved by modulating apoptosis signaling. In pulmonary artery smooth muscle cells, KLF5 upregulates survivin, which hyperpolarizes mitochondria membrane potential and inhibits apoptosis [167,168]. In contrast, KLF5 knockdown increases apoptosis coupled with activation of caspase-3 and pro-apoptotic Bad in neurons [169].

Consistent with their pro-survival roles in normal tissues, KLF4 and KLF5 also protect cancer cells from a variety of harmful stimuli, including various drug treatments. KLF4 and KLF5 proteins are upregulated in human breast cancer cells after treatment with the HER2/EGFR inhibitor lapatinib and induce the anti-apoptotic factor, myeloid cell leukemia 1 (MCL1), to mediate resistance to lapatinib [170] (Fig. 4). Consistently, in human breast cancer, KLF4 deficient cancer cells show poorer survival under different stresses, even though they proliferate faster [149,170].

Recent studies have pinpointed the role of KLF4 in regulating DNA damage response and DNA repair, resulting in maintaining genome stability [171–175]. Upon DNA damage, KLF4 is arginine methylated by PRMT5, whose methylation reduces its basal ubiquitination, thus stabilizing KLF4 [174]. DNA damage-induced upregulation of KLF4 causes cell cycle arrest by transactivation of the cell cycle inhibitor $p21^{Cip1/Waf1}$ that induces p53-dependent G1/S arrest [171–175], and suppressing the expression of cell cycle-promoting genes, including CCND1 (cyclin D1) [71] and CCNB1 (cyclin B1) [176]. In addition, KLF4 prevents chromosomal amplification following DNA damage by transcriptionally suppressing cyclin E expression [177]. In addition to regulating $p21^{Cip1/Waf1}$, another critical function for KLF4 is modulating cellular apoptosis by inhibiting the expression of pro-apoptotic Bax [173–175]. In addition to ubiquitination in response to DNA damage, KLF4 is PARylated by PARP1, facilitating KLF4 recruitment from the soluble nucleus to the chromatin and its transcriptional activity [175]. Moreover, recent bioinformatics analyses have unraveled the previous undocumented role for KLF4 in transcriptionally regulating BRCA1 and further governing homologous recombination (HR) DNA repair [175]. Taken together, the DNA damage-induced ubiquitination and PARylation of KLF4 promote cellular survival under the circumstance of genotoxic stress through arresting cell cycle progression and enhancing HR DNA repair by regulating BRCA1, resulting in the maintenance of genome stability.

KLF4 also mediates doxorubicin-induced drug resistance in cancer cells. In osteosarcoma, doxorubicin treatment induces the upregulation of KLF4 along with a stem-like phenotype, shown as the increased transcriptional level of stem cell-related markers (CD133, ABCG2, and ALDH1A1) and high metastatic capacity (Fig. 4). KLF4 depletion with siRNA blocks these doxorubicin-induced phenotypes, showing that KLF4 is required to stimulate the formation of CSCs in response to doxorubicin treatment [178]. Consistently, KLF4 depletion sensitizes breast cancer cells to chemotherapy agents such as doxorubicin and cisplatin [175].

KLF5 is frequently overexpressed in non-small cell lung cancer (NSCLC), and increased KLF5 prevents cells from undergoing apoptosis induced by hypoxia and cisplatin treatment

[179,180]. Consistently, high KLF5 expression is associated with a poor prognosis of NSCLC [179,180]. In NSCLC cells, KLF5 is upregulated by hypoxia. The increased KLF5 promotes the expression of hypoxia-inducible factor 1α (HIF-1α) and forms a complex with HIF-1α. The KLF5/HIF-1α complex upregulates cyclin B1 and survivin, while suppressing caspase-3 and therefore inhibiting apoptosis [179]. KLF5 can also protect cells from genotoxic stress by promoting DNA repair. In NSCLC, KLF5 affects the phosphorylation of H2AX at S139 to promote DNA repair after cisplatin treatment by regulating Chk1/Chk2 kinase levels [180]. In contrast, KLF5 knockdown attenuates the activation of checkpoint kinases Chk1 S345 and Chk2 T68, permitting cells with damaged DNA to enter mitosis and leading to mitotic catastrophe [180]. Thus, KLF5 promotes cell survival under stress by enhancing DNA repair and preventing cells with damaged DNA from entering mitosis.

Different treatments also modulate the expression of KLF5 to modulate therapeutic responses. KLF5 promotes resistance to endocrine therapy in advanced prostate cancer [181]. Endocrine therapy that inhibits the androgen receptor (AR) is frequently used in the treatment of recurrent prostate cancer but leads to the progression to castration-resistant prostate cancer (CRPC) in most cases. In these CRPC tumors, the expression of KLF5 is induced during endocrine therapy and works as an oncogene to promote cell migration and colony formation [181]. However, KLF5 is required to promote the sensitivity to docetaxel by inhibiting autophagy in prostate cancer cells and the expression of KLF5 is reduced by docetaxel treatment through the AMPK/mTOR/p70S6K signaling pathway [95]. Thus, the role of KLF5 in drug resistance could be treatment dependent. When targeting KLF5 for drug resistance the interaction of KLF5 with other therapies needs to be considered.

In nasopharyngeal carcinoma, loss of miR-34 can upregulate SOX4 and leads to cisplatin resistance [182]. SOX4 also mediates cisplatin resistance in non-small cell lung cancer cells [183,184], and 5-FU in colorectal cancer [185]. SOX9 also mediates cisplatin resistance in NSCLC via regulation of ALDH1A1 [186]. SOX9 can mediate resistance to tamoxifen in breast cancer [187], gefitinib in lung cancer [188], oxaliplatin in colon cancer 42[189], and temozolomide in glioblastoma [190]. SOX9 increases sorafenib resistance in liver cancer via upregulation of ABCG2 [191]. SOX2 mediates resistance to paclitaxel in melanoma via upregulation of ABCC1 [192]. Both SOX4 [193], SOX9 [194], and SOX2 [195] can promote resistance to T-cell mediated immune killing via multiple mechanisms.

The regulation of KLF4, KLF5 and SOXs

The expression of KLF4 can be regulated by epigenetic modifications and various signals. Reduced transcription of KLF4 due to hypermethylation of the KLF4 promoter region has been detected in primary lung carcinoma, cervical cancer, and medulloblastoma [68,75,196]. The expression of KLF4 is induced by the LIF/STAT3 pathway [32–34], RAS/RAF/MEK/ERK signaling [197], luteinizing hormone [198], shear stress [165] and proinflammatory stimuli [166]. Several microRNAs have been found to suppress the expression of KLF4 by directly targeting its 3’-untranslated region [199–203].

The protein level and transcription activity of KLF4 can be regulated by various post-translational modifications. Several E3 ligases, including VHL, the Cdh1 subunit of the

anaphase promoting complex (APC), the F-box proteins βTrCP, and Mule can mediate the ubiquitination of KLF4 for proteolytic degradation [77,174,204–210]. ATXN3, a deubiquitinating cysteine enzyme, deubiquitinates KLF4 in breast cancer [208]. In addition, methylation by PRMT5 stabilizes KLF4 in triple negative breast cancer (TNBC) [211]. The transcriptional activity of KLF4 is regulated by several posttranslational modifications, including acetylation, SUMOylation, PARylation, and phosphorylation. The p300/CBP complex acetylates KLF4 to promote the transactivation function of KLF4 [81,212,213], while HDAC2 promotes KLF4 deacetylation [213]. SUMOylation is required for KLF4 to inhibit cell proliferation [214,215] and inhibit its transactivation of NANOG, which mediates the induction of iPSCs [216]. Upon DNA damage, KLF4 is PARylated, which enhances its binding to the CDKN1A and Bax promoters, resulting in cell cycle arrest [175]. TGF-β1 Induces KLF4 phosphorylation through Smad and p38 MAPK pathways in vascular smooth muscle cells [217].

Focal amplification of super enhancers near KLF5 leads to KLF5 expression in squamous cell carcinomas [218]. Various signaling pathways also regulate the transcription of KLF5. The expression of KLF5 is inhibited by retinoic acid receptor signaling [219], and upregulated by androgen receptor signaling [91,220], progesterone [92], tumor necrosis factor (TNF)-α [133], oncogenic KRAS mutation ($KRAS^{V12G}$) [84], and by lysophosphatidic acid (LPA) [221] in different cancers. In addition, the expression of KLF5 can also be inhibited by multiple microRNAs, including miR-153 [222], miR-217 [223], miR-5195–3p [224], miR-590–5p [225], miR-145–5p [226] and miR-320 [227] in different cancers.

KLF5 is also regulated by various posttranslational modifications, including ubiquitination, SUMOylation, phosphorylation and acetylation. KLF5 can be ubiquitinated by several E3 ubiquitin ligases for proteasomal degradation, including FBW7 [218,228,229], WWP1 [153,230], EFP [231], and SMURF2 [232]. In addition, three deubiquitinases (DUBs), ubiquitin-specific protease 3 (USP3), BRCA1-associated protein 1 (BAP1), and ataxin-3 like (ATXN3L), can stabilize KLF5 via deubiquitination [233–235]. SUMOylation is required for the nuclear accumulation of KLF5 [236]. Furthermore, SUMOylation also switches the transcriptional activity of KLF5 by regulating its interaction with transcription corepressors and coactivators [101]. Phosphorylation affects the binding of KLF5 to various effector proteins and therefore regulates its stability and transcriptional activity [229,237,238]. Acetylation of KLF5 can switch the transcriptional regulation effect of KLF5. For example, in epithelial cells, TGF-β recruits acetylase p300 to acetylate KLF5 at Lys369 [102,103]. Such acetylation in KLF5 reverses its transcriptional suppression of p15 (CDKN2B) to activation. In contrast, KLF5 transcriptional activation of MYC changes to repression, thus reversing the proliferation-promoting ability of KLF5 [102,103]. In addition, acetylation of KLF5 at Lys 369 can be deacetylated by histone deacetylase 1/2 (HDAC1/2), and the deacetylation promotes KLF5 degradation [239].

SOX9 has been shown to be directly transactivated by YAP, mediating stem-like properties in esophageal cancer cells [240]. SOX2 can also be transcriptional induced by YAP through its interaction with OCT4 in non-small cell lung cancer (NSCLC) cells [241]. SOX proteins are also regulated post-transcriptionally by many miRNAs [60,62] and post-

translationally by multiple mechanisms [242]. Post-translational regulation of SOX proteins includes phosphorylation, acetylation, SUMOylation, methylation, and ubiquitylation and has been recently reviewed elsewhere [242]. SOX2 and SOX9 have been shown to undergo all of these modifications, whereas SOX4 PTMs are less well studied, and only acetylation of SOX4 has been demonstrated [243]. Acetylation of SOX factors promotes nuclear localization, methylation impacts pioneer factor activity, phosphorylation enables transcriptional activation, and SUMOylation reduces DNA binding activity [242].

In addition to the aforementioned regulations, the expression of KLF4, KLF5, SOX2, SOX4, SOX9 can be induced by hypoxia to promote cancer progression. Hypoxia is a common phenomenon in many solid tumors and strongly associated with metastasis, stemness, and drug resistance. The hypoxia-inducible factors (HIFs) are master regulators of hypoxia response through the transcriptional regulation of hypoxia associated genes [244]. Hypoxia promotes stemness of cancer cells through upregulating pluripotent factors, including KLF4 and SOX2 [245]. In glioblastoma, SOX2 and KLF4 are upregulated through HIF1α and HIF2α under hypoxia, contributing cancer stemness and chemotherapy resistance to temozolomide TMZ [246].

In human vascular smooth muscle cells, KLF4 is upregulated by HIF1α under hypoxia to mediate hypoxia-induced migration [247]. Interestingly, a KLF4 mutation, $KLF4^{K409Q}$, found in meningioma patient samples, potentiates hypoxia signaling by inhibiting oxygen dependent degradation of HIF-1α [248].

Hypoxia induces the expression of KLF5 in various cancer cells to promote cancer survival [179,249,250]. In non-small cell lung cancer (NSCLC) cells, KLF5 promotes hypoxia-induced survival and inhibits apoptosis by interacting with HIF-1α and mediating its upregulation under hypoxia [179]. In addition, KLF5 also mediates hypoxia-induced cisplatin resistance by promoting the HIF-1α-dependent glycolysis via the PI3K/Akt/mTOR pathway in NSCLC cells [250]. Consistently, KLF5 also transactivates HIF-1 in colon cancer cells [105]. The expression of KLF5 can be regulated by HIF-1α reciprocally. In pancreatic cancer cells, KLF5 coimmunoprecipitated with HIF-1α and HIF-1α knock down reduces KLF5 [249]. Recent studies indicated that SOX2 could be an important mediator of hypoxia induced stemness and metastasis. SOX2 expression can be induced by hypoxia through HIF-1α and HIF-2α in prostate cancer cells [251], endometrial cancer stem cells [252], glioblastoma cells [246] and epithelial ovarian cancer cells [253] to promote malignant progression. In human embryonic stem cells (hESC), HIF-2α binds directly to predicted hypoxic response elements (HREs) in the proximal promoter of SOX2 under hypoxia [254]. Meanwhile, SOX2 has also been reported to mediate the upregulation of HIF-1α in various cancers including breast cancer [255], esophageal squamous cell carcinoma (ESCC) [256] and gastric cancer [257], promoting cancer metastasis. For example, in breast cancer cells, hypoxia induced SOX2 upregulates the expression of HIF-1α by transactivating NEDD9 and therefore promotes hypoxia-induced breast cancer cell migration [255].

The expression of SOX4 can be upregulated by HIF-1α via a lncRNA, CASC15. In NSCLC, HIF-1α transactivates CASC15, and CASC15 subsequently promotes the expression of its

neighboring gene SOX4 [258]. The upregulation of SOX9 expression under hypoxia has been reported in various cancers, including ovarian cancer [259], colorectal cancer [260] and pancreatic cancer [261]. In ovarian cancer cell A2780, SOX9 promotes cell survival under hypoxia and depletion of HIF-2α abolishes the expression of SOX9 [259]. In colorectal cancer (CRC) cells, upregulated SOX9 under hypoxia promotes the EMT by stabilizing SNAIL via the transactivation of a deubiquitinating enzyme, ubiquitin-specific protease 47 (USP47) [260]. Interestingly, SOX9, induced by hypoxia in a nonmetastatic pancreatic cell line FG (LMET), becomes constitutively overexpressed in a corresponding metastatic derivate L3.6pl (HMET) cell line independently of hypoxia. In the metastatic cell line, SOX9 functions as an alternative transcription factor to induce the expression of hypoxia-associated genes independent of hypoxia to support growth, angiogenesis, and metastasis [261].

Targeting KLF4, KLF5, and SOXs in cancer treatment

Given their crucial roles in cancer pathogenesis, cancer cell stemness, and drug resistance, KLF4, KLF5 and SOXs are potential therapeutic targets. But for transcription factors without a ligand, direct targeting has been considered challenging. Thus, previous efforts have focused on targeting these transcription factors by modulating their upstream regulators, including transcription, mRNA stability, and protein degradation with small molecules.

In breast cancer cells, Kenpaullone inhibits the transcription of KLF4 [128]. Treatment with Kenpaullone suppresses cancer stem cell self-renewal and cell migration and sensitizes breast cancer cells and xenograft tumors to paclitaxel [150]. Application of PKA inhibitors, including H89 and 14–22 Amide (PKI), enhances the transcription of KLF4 expression [128,198]. Under these circumstances, when KLF4 works as a tumor suppressor, induction of KLF4 could have potential for cancer treatment. For example, APTO-253, initially discovered to be cytotoxic to human colon adenocarcinoma HT-29 cells, is a prominent inducer of KLF4 in various cancer cell lines. A Phase 1 study of APTO-253 in patients with advanced solid tumors showed stable disease for 3.6–8.4 months in 5 of 21 (24 %) patients, and APTO-253 toxicity was well tolerated in this clinical trial [262]. Three potential KLF5 inhibitors, wortmannin (a PI3K/AKT inhibitor), AG17, and AG879, were screened out from a library containing 1,280 biologically active compounds and found to be able to inhibit cell proliferation *in vitro* [263]. Mifepristone, a drug used for abortion, exerts its anti-tumor activity by inducing the expression miR-153 to down-regulate the expression of KLF5. Inhibition of KLF5 by mifepristone inhibits tumor growth of patient-derived xenografts, and reduces the population of CSCs [222]. Similarly, crocin also suppresses KLF5 expression via upregulation of a microRNA, miR-320, which mediates the inhibitory function of crocin on EMT, migration, and invasion of gastric cancer cells [227]. Short interfering RNA has also been applied to knock down KLF5. A “wrapsome” (WS) enveloped by a neutral lipid bilayer and hydrophilic polymers with siRNA targeting KLF5 and a cationic lipofection complex was used to transfect siRNA into tumors to knock down KLF5 and inhibit tumor angiogenesis *in vivo* [264].

Statins, the cholesterol-lowering agents, such as both simvastatin and atorvastatin, remarkably reduced the amount of KLF4 protein levels in osteosarcoma cells. The application of statins reduces CSC properties induced by doxorubicin treatment in osteosarcoma cells [178]. Similarly, curcumin, a natural compound with many anticancer properties, promotes the degradation of KLF5 by downregulating YAP/TAZ [265], which interacts with the PY motif of KLF5 and protects it from WWP1-mediated ubiquitination [266,267]. In addition, the degradation of KLF5 can be triggered by metformin, a first-line drug for type 2 diabetes mellitus. Metformin inhibits protein kinase A (PKA) activity, which in turn induces glycogen synthase kinase-3β (GSK3β)-mediated KLF5 phosphorylation and degradation [155]. Consistently, one of the direct target genes of KLF5, HNF4α, which is required for gastric cancer (GC) proliferation, is also downregulated by metformin treatment [268].

Targeting KLF4 could also modulate the efficacy of cancer immunotherapy as KLF4 is also implicated in the regulation of immunity. KLF4 was previously reported to be induced in response to proinflammatory signals, such as interferon-γ (IFN-γ), lipopolysaccharide (LPS) and tumor necrosis factor-α (TNF-α) to promote macrophage activation [269]. However, recent studies show that KLF4 plays an anti-inflammatory role through regulating macrophage polarization [270]. Macrophages are polarized into M1 or M2 states. M1 is considered pro-inflammatory and anti-tumorigenic and while M2 is anti-inflammatory and pro-tumorigenic. KLF4 suppresses inflammation by promoting M2 polarization macrophages while inhibiting M1 polarization [270]. Consistently, KLF4 deficient macrophages show increased expression of proinflammatory genes [270]. In cancer immunotherapy, a widely used immune checkpoint inhibitor, PD-L1 inhibitor, promotes polarization of macrophages to a proinflammation state partially by reducing the expression of KLF4 via upregulating the expression of KLF4-targeting miR-34a [271]. The high expression of KLF4 is also associated with an immunosuppressive tumor microenvironment in lung cancer [272]. In the Cancer Genome Atlas (TCGA)- lung adenocarcinoma (LUAD) cohort, KLF4 is significantly positively associated with the infiltration levels of immunosuppressive M2 macrophages [272]. In addition, a multikinase inhibitor, regorafenib, suppresses M2 polarization of macrophages and promotes CD8+ T cells partially by downregulating the transcription of KLF4, suggesting potential synergistic antitumor efficacy between KLF4 inactivation and cancer immunotherapy [273].

More recently, with the development of new technologies such as proteolysis-targeting chimeras (PROTACs) for degrading a protein of interest [274–276] and protein-protein interaction (PPI) inhibitors [277], targeting of TFs directly for cancer treatment may become a reality. Targeting TFs directly could provide a specific modulation of the transcriptional activity with fewer off-target effects and could reach the full therapeutic potential of TFs [10,12,23].

PROTACs degrade a protein of interest (POI) by hijacking the ubiquitin-proteasome system. A PROTAC is a bifunctional protein that contains the ligand of an E3 ligase and a molecule binding to POI. Therefore, it mediates the interaction of the POI with the E3 ligase, inducing its polyubiquitination, and finally promotes its degradation by the proteasomal machinery [278]. PROTAC-induced degradation offers a new strategy to target TFs with different

kinds of baits, including analogs of known ligands for nuclear receptors, double-strand nucleotides containing the binding motif of TFs, and small molecules designed based on the structure of TFs [278]. Substrates of PROTACs were initially applied to target two nuclear receptors: estrogen receptor (ER) and androgen (AR) receptor, which have been implicated in the progression of breast and prostate cancer. The ability to degrade the POI has been demonstrated *in vitro* and *ex vivo* when injected into cells [279]. Taking advantage of the DNA binding ability of TFs, the challenge of lacking a defined ligand-binding pocket in most TFs can be bypassed by using double stranded oligonucleotides as a bait to recruit TFs for degradation. Nevertheless, the specificity of this strategy, known as TF-PROTAC [275], still needs to be demonstrated. In TF-PROTAC, the ligand of an E3 ligase is directly connected with a double strand oligonucleotide containing the binding motif of a TF. This method was successfully applied to induce the degradation of NF-kB and E2F, inhibiting proliferation of Hela cells [275]. Recently a highly potent PROTAC, SD-36, that targets STAT-3, has been developed and shows high selectivity for STAT3 over other STAT family members [280,281]. SD-36 is a cell-permeable small-molecule inhibitor based on the structure of SH2 domain of STAT3 that has the drug delivery advantage of a small molecule that can directly get into cells without additional assistance. *In vivo* studies with mouse xenograft models have shown that SD-36 is well tolerated and induces durable tumor regression [281]. Similar strategies can be expanded to design PROTAC for each TF, including KLF4, KLF5, and SOXs when suitable baits are created or screened out from chemical libraries. The structure of the DNA binding domain of KLF4 is now available and can be used to design baits binding to this domain [282].

To regulate transcription, TFs need to interact with co-activators or co-repressors to recruit or block the transcription machinery. In addition, the transcriptional activity and stability of TFs can be modulated by different posttranslational modifications, which is also mediated through PPIs with corresponding enzymes [8]. These PPIs are potential sites for drug targeting. PPI interfaces have been previously considered impossible to block with small molecules [283]. However, with the development of unbiased high throughput drug screening, huge chemical libraries, and broad cell-based reporter assays, more potential chemicals that modulate targeted PPI have been identified [277,284]. When KLF5 works as a tumor suppressor, a compound that disrupts the PPI between KLF5 and its ubiquitin ligases, such as FBW7 and WWP1 [218,230], could have the potential to suppress cancer progression. PPI inhibitors that block interactions of SOX factors with co-activator complexes could also have wide applicability for cancer therapies.

Conclusion

Considering the crucial roles of KLF4, KLF5 and SOXs in cancer progression, metastasis, cancer stemness, and drug resistance, targeting them could exert a synergic effect, provide longer-lasting clinical responses, and lead to survival benefits, which could surpass that of targeting downstream effectors of these TFs. Recently, the potential of modulating transcription factors to reprogram cancer cells to inhibit cancer metastasis has been demonstrated in preclinical models. EMT-derived breast cancer cells were differentiated into post-mitotic adipocytes with a combination of a potent agonist of peroxisome proliferator-activated receptor γ (PPARγ) and MEK inhibitors, resulting in loss their invasiveness

[285]. In addition, significant progress in drug development has made targeting TFs from “undruggable” to reality [12]. In the future, new drugs targeting different TFs will fully exploit the power of transcription factors in reprogramming cancer cell plasticity. Reprogramming cancer cells by modulating sets of TFs with chemical cocktails that induce differentiation of cancer stem cells could hold significant promise for future cancer therapies.

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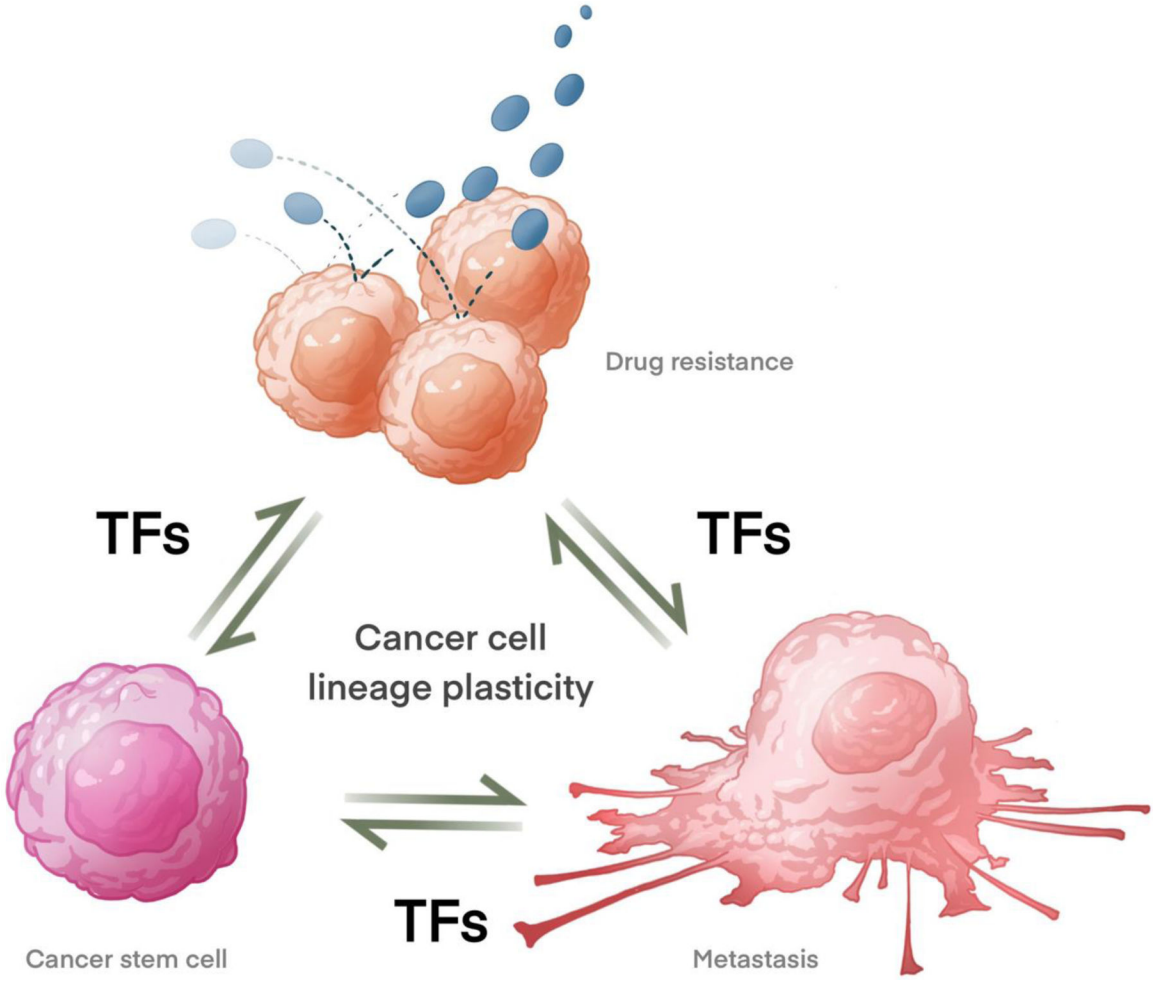

Figure 1. Transcription factors mediate cancer cell lineage plasticity, which enables the phenotypic switch of cancer cells and drives metastasis, stemness and drug resistance.

Resistant cancer cells surviving from anti-cancer treatment can undergo further transformation and leverage these malignant properties to promote cancer metastasis. TFs: transcription factors.

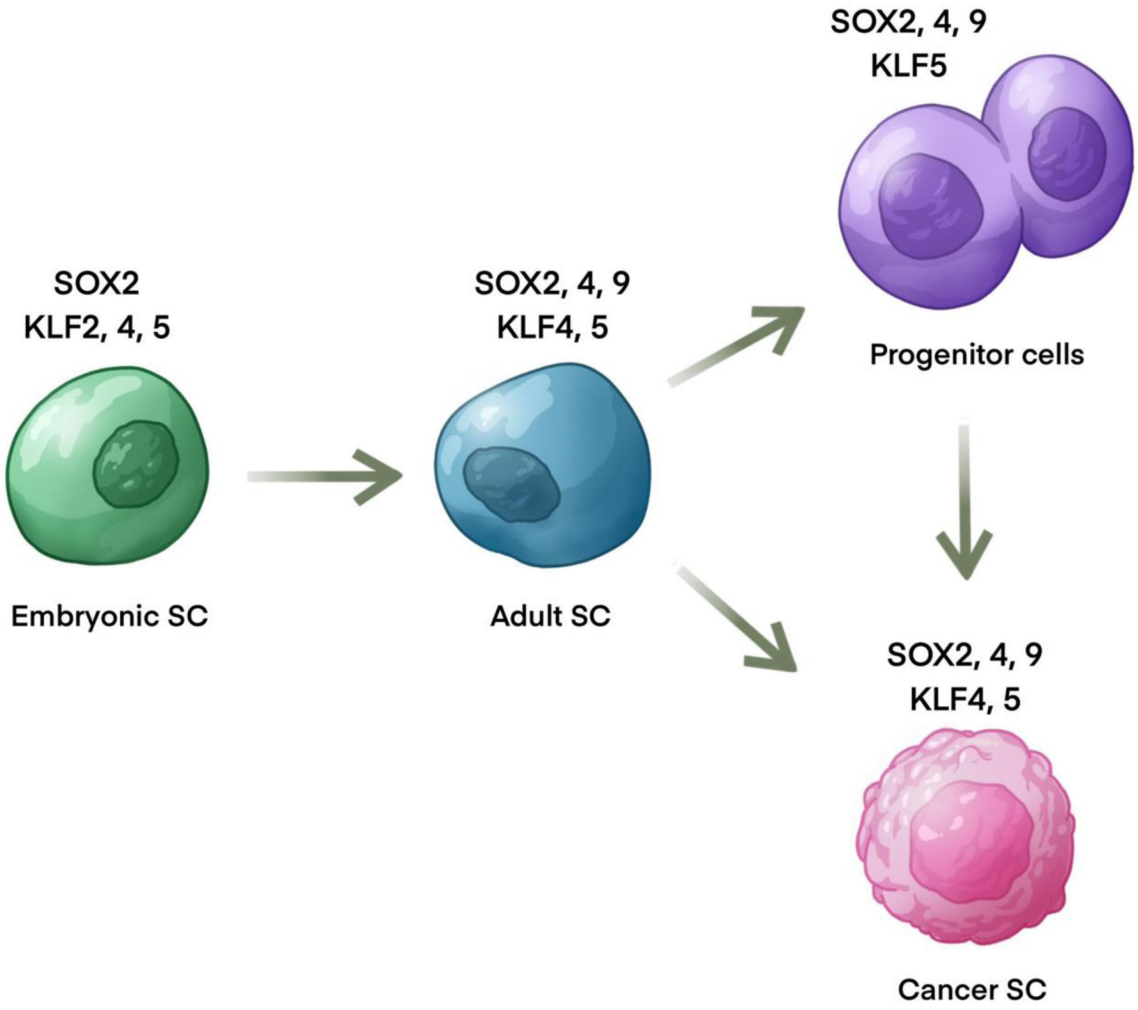

Figure 2.
Expression of SOX and KLF factors in stem and progenitor cells.

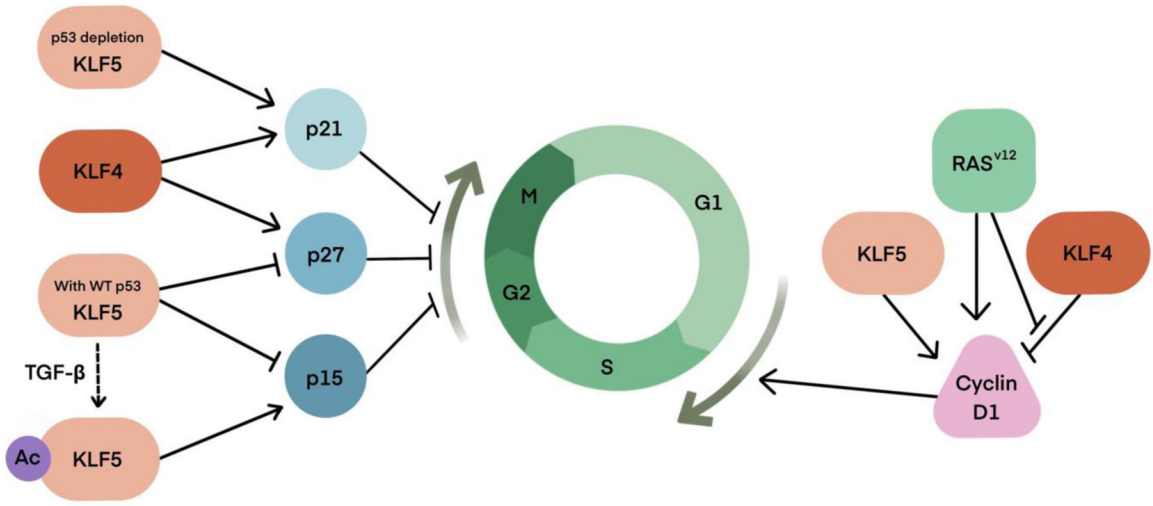

Figure 3. KLF4 and KLF5 regulate cell proliferation in a context dependent manner.

Generally, KLF4 inhibit cell cycle and KLF5 stimulates proliferation by regulating the transcription of cell cycle genes. But the cytostatic action of KLF4 can be neutralized by CDKN1A (p21) inactivation, the oncogenic RAS^{V12} mutation, or cyclin-D1 overexpression (a common target of KLF4 and RAS). The cell cycle regulation function of KLF5 can be switched by the status of p53, which is a frequently inactivated tumor suppressor in cancers and posttranslational modification, especially acetylation. When p53 is mutated or KLF5 is acetylated at Lys369, which can be triggered by the TGF-β signaling, KLF5 becomes anti-proliferative through transactivating CDKN1A (p21) or CDKN2B (p15), respectively.

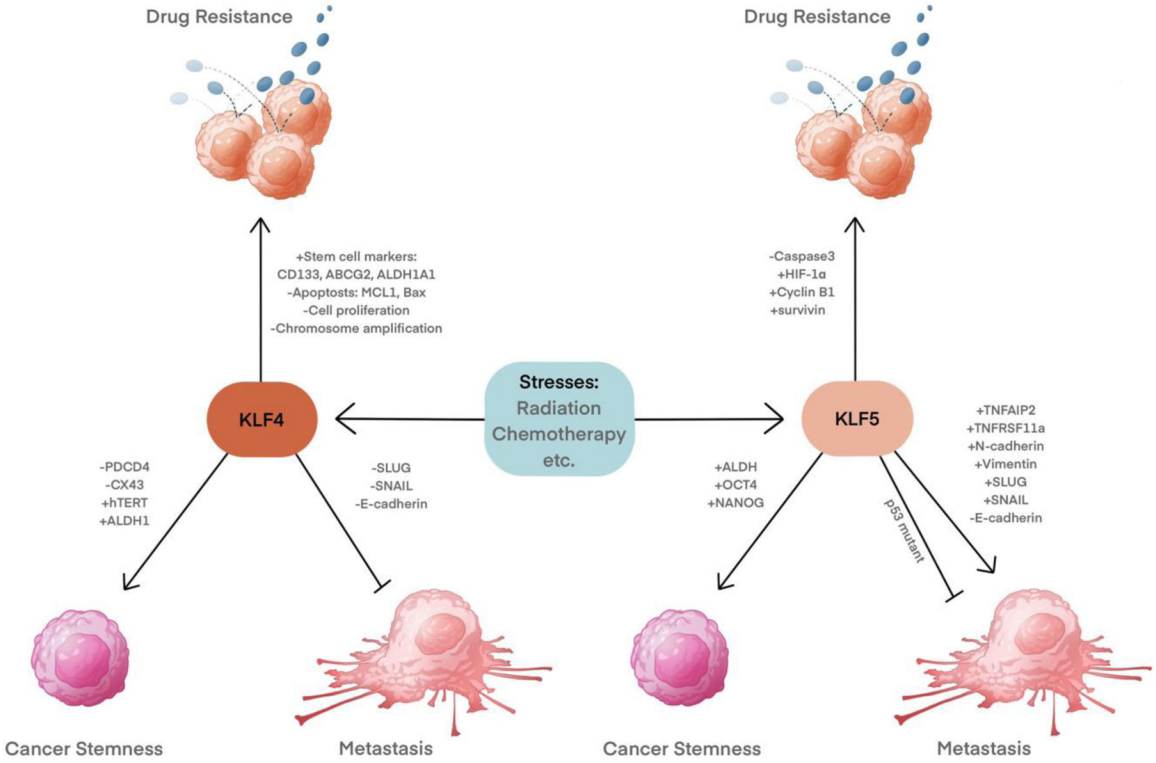

Figure 4.
KLF4 and KLF5 regulate metastasis, cancer stemness and drug resistance.

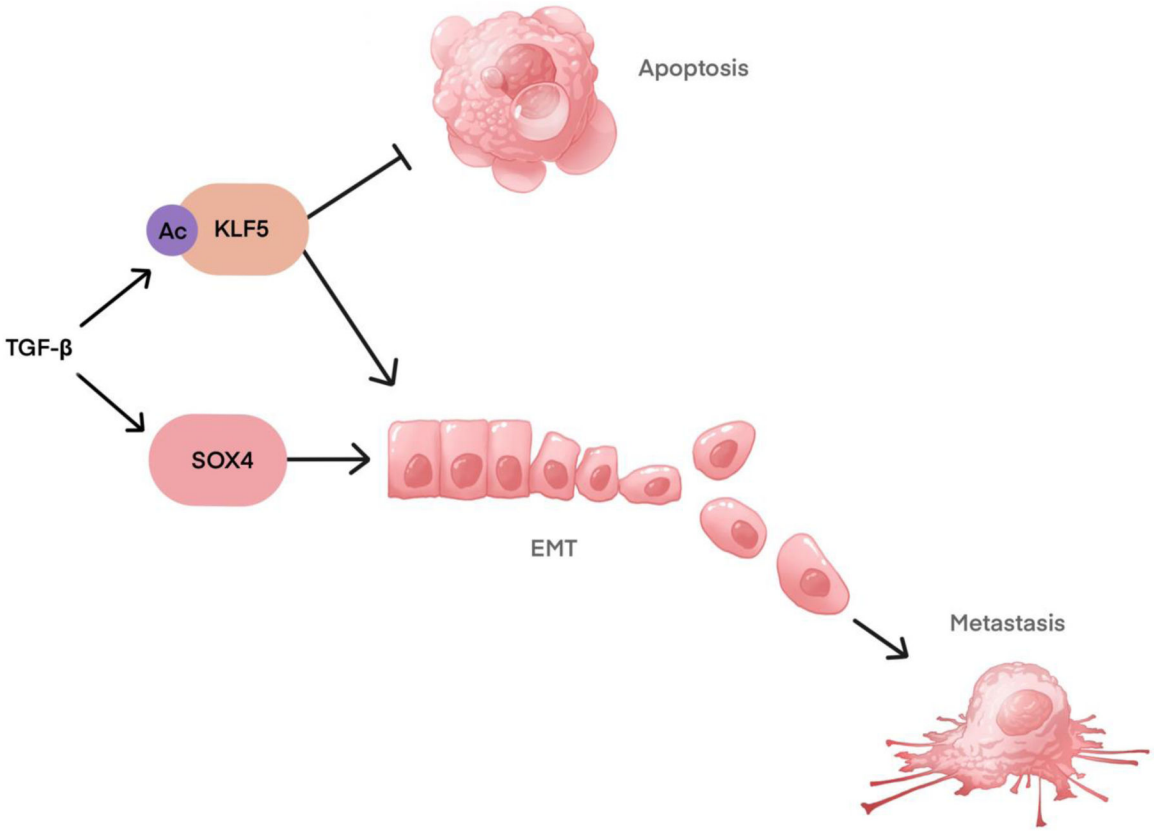

Figure 5.
Interaction of SOX4 and KLF5 with TGFβ in apoptosis, EMT, and metastasis.

Table 1.

The function of KLF4, KLF5, SOX2, SOX4 and SOX9 in cancers. "↑": upregulation;" ↓" : down regulation.

	Function	Mechanism
KLF4	Inhibit cell proliferation (by inducing cell cycle arrest at the G1-S checkpoint)	↑ CDKN1B (p27) [67–70] ↑ CDKN1A (p21) [67–70] ↓ cyclin D1 [68,69,71]
	Promote cell proliferation (KLF4α)	↓ CDKN1B (p27) ↓ CDKN1A (p21)
	Promote tumor metastasis	↑ Notch pathway [128]
	Inhibit tumor metastasis	↓ SLUG [130] ↓ SNAIL [131]
	Promote cancer stemness	↑ hTERT [147] ↑ stemness-associated genes [148] ↑ MAPK signaling pathway [148] ↓ pro-apoptotic signaling molecules PDCD4 & CX43 through microRNA-206 [149] ↑ ALDH1 [150] ↑ MUC5AC [152]
	Promote drug resistance	↑ MCL1 (anti-apoptotic factor) [170] ↓ pro-apoptotic Bax [173–175] ↑ BRCA1 for HR DNA repair [175] Induce cell cycle arrest: ↑ p21 [171–175] ↓ CCND1 [71] ↓ CCNB1 [176] Prevent chromosomal amplification: ↓ cyclin E [177]
KLF5	Promote cell proliferation (by accelerating the transition of G1/S and G2/M phases)	↑ cyclin D1 [86] ↑ cyclin B1 [87] ↑ Cdc2 [87] ↓ CDKN1B (p27) [88] ↓ p15 [88]
	Inhibit cell proliferation when p53 is mutated	↑ CDKN1A (p21) [98] ↑ NOTCH1 [99]
	Inhibit apoptosis	↑ BIRC5 (survivin) [105] ↑ HIF1α [105,179]
	Promote tumor metastasis	↑ TNFAIP2 [132] ↑ TNFRSF11a [133] ↓ E-cadherin [134] ↑ N-cadherin [134] ↑ Vimentin [134] ↑ SNAIL [134] ↑ SLUG [134]
	Inhibit tumor metastasis (in the absence of p53)	↑ E-cadherin [99,135] ↓ ZEB2 [136] ↓ SNAIL [99] ↓ TWIST [99]
	Promote cancer stemness	↑ α-Catulin [153]
	Promote drug resistance	Inhibit apoptosis: ↑ MCL1 (anti-apoptotic factor) [170] ↑ cyclin B1 [179] ↑ survivin [179] ↓ caspase-3 [179] Promote DNA repair: ↑ Chk1/Chk2 kinase levels [180]
SOX2	Paclitaxel resistance	↑ ABCC1 [192]
	Promote tumor metastasis	↑ HIF1α [255–257]
SOX4	Promote tumor metastasis	↑ Twist1 and ZEB1 [138]

	Function	Mechanism
	Promote cancer stemness	↑ SOX2 [138] ↑ OCT4 [138]
SOX9	Cisplatin resistance	↑ ALDH1A1 [186]
	Sorafenib resistance	↑ ABCG2 [191]

Table 2.

Drugs targeting KLF4 and KLF5

	Mechanism	Compounds
KLF4	Inhibit KLF4 transcription	Kenpaullone [128] Regorafenib [273]
	Enhance KLF4 transcription	PKA inhibitors: H89 and 14–22 Amide (PKI) [128,198] APTO-253 [262]
	Reduce KLF4 protein	Simvastatin and atorvastatin [178]
KLF5	Inhibit KLF5 transcription	Wortmannin (a PI3K/AKT inhibitor), AG17, and AG879 [263]
	Inhibit KLF5 expression via inducing miRNA targeting KLF5	Mifepristone [222] Crocin [227]
	Promotes KLF5 proteasome degradation	Curcumin [265] Metformin [155]