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Dysregulated FOXM1 signaling in the regulation of cancer stem cells

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ABSTRACT

Since the introduction of the cancer stem cell (CSC) paradigm, significant advances have been made in understanding the functional and biological plasticity of these elusive components in malignancies. Endowed with self-renewing abilities and multilineage differentiation potential, CSCs have emerged as cellular drivers of virtually all facets of tumor biology, including metastasis, tumor recurrence/relapse, and drug resistance. The functional and biological characteristics of CSCs, such as self-renewal, cell fate decisions, survival, proliferation, and differentiation are regulated by an array of extracellular factors, signaling pathways, and pluripotent transcriptional factors. Besides the well-characterized regulatory role of transcription factors OCT4, SOX2, NANOG, KLF4, and MYC in CSCs, evidence for the central role of Forkhead box transcription factor FOXM1 in the establishment, maintenance, and functions of CSCs is accumulating. Conventionally identified as a master regulator of the cell cycle, a comprehensive understanding of this molecule has revealed its multifarious oncogenic potential and uncovered its role in angiogenesis, invasion, migration, self-renewal, and drug resistance. This review compiles the large body of literature that has accumulated in recent years that provides evidence for the mechanisms by which FOXM1 expression promotes stemness in glioblastoma, breast, colon, ovarian, lung, hepatic, and pancreatic carcinomas. We have also compiled the data showing the association of stem cell mediators with FOXM1 using TCGA mRNA expression data. Further, the prognostic importance of FOXM1 and other stem cell markers is presented. The delineation of FOXM1-mediated regulation of CSCs can aid in the development of molecularly targeted pharmacological approaches directed at the selective eradication of CSCs in several human malignancies.

1. Introduction

There are more than 2500 proteins in humans thought to bind to chromatin to regulate replication, repair, unwinding, and transcription of DNA. A considerable number of these proteins (about 1500) function as transcription factors (TFs), characterized are proteins that bind to certain regulatory regions on the DNA helix to activate or inhibit transcription. The transcription process in all living beings leads to the fine and spatiotemporally controlled synthesis of ribonucleic acids and is initiated by extrinsic or intrinsic triggers through a signal transduction

Abbreviations: CSC, Cancer stem cell; TF, Transcription factor; Fox, Forkhead box; TNBC, Triple-negative breast cancer; BCSC, Breast cancer stem cell; BC, Breast cancer; CRC, Colorectal cancer; CCSC, Colorectal cancer stem cell; MnSOD, Manganese-dependent superoxide dismutase; MELK, Maternal embryonic leucine zipper kinase; EMT, Epithelial to mesenchymal transition; ESC, Embryonic stem cell; HCC, Hepatocellular carcinoma; ROS, Reactive oxygen species; LCSC, Liver cancer stem cell; HSC, Hepatic stellate cell; HGF, Hepatocyte growth factor; LGSOC, Low-grade serous ovarian carcinoma; HGSOC, High-grade serous ovarian carcinoma; OCSC, Ovarian cancer stem cell; ATRA, All-trans retinoic acid; OCSLC, Ovarian cancer stem-like cell; hCTR1, Human copper transporter 1; EOC, Epithelial ovarian cancer; NSCLC, Non-small cell lung cancer; SCLC, Small cell lung cancer; Lung CSC, Lung cancer stem cell; GBM, Glioblastoma; GSC, Glioma stem cell; PC, Pancreatic cancer; PCSC, Pancreatic cancer stem cell; PDAC, Pancreatic ductal adenocarcinoma; TAM, Tamoxifen; Hh, Hedgehog.

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system. The TFs are classified into families based on DNA-binding domain homologies [1].

One such family is the Forkhead box (Fox) proteins, which consist of a group of evolutionarily sustained TFs that are distinguished by a monomeric forkhead domain that binds to DNA with 100 amino acids [2]. The three-dimensional structure of the FOX domain comprises of two W1 and W2 loops (or wings) and three helices. Because of its butterfly-like look, the FOX domain is often described as a 'winged-helix' domain. FOX proteins are involved in a variety of cellular mechanisms including proliferation, metabolism, apoptosis, migration, invasion, and survival [3–5]. In the human genome, 50 FOX genes are classified into 19 subfamilies (A–S). The FOXM subfamily has only one member, FOXM1 [6] that has three identified functional protein domains: (1) an N-terminal negative regulatory domain (NRD), (2) a centrally positioned DBD, and (3) a C-terminal acidic TAD (Fig. 1) [7–10].

FOXM1 is expressed throughout the cell cycle, rising in late G1-phase, reaching its apex in S-phase, and remaining there in G2/M and late M-phase [10–12]. FOXM1 facilitates S phase entry by stimulating the transcription of genes that regulate the G1/S checkpoint (e.g., SKP2 and CKS1) [13]. Later, FOXM1 activates genes that control the G2/M checkpoint (e.g., PLK1, CDC25B, CCNB1, NEK2, and BIRC5), allowing cells to enter the M phase [13–15]. Eventually, FOXM1 facilitates chromosomal segregation and mitotic spindle assembly by stimulating genes such as AURKB, KIF20A, CENPA, CENPB, and CENPF [13–15]. As a consequence, FOXM1 plays a significant role in multiple key cell cycle phases.

FOXM1 is a legitimate TF that not only regulates spatiotemporal gene expression during embryonic and fetal development but also maintains adult tissue homeostasis and repair. A balanced transcriptional program through regulated FOXM1 expression is required for the growth and maturation of the embryo and fetus as well as homeostasis and repair of adult tissues. Contrarily, abnormal upregulation of FOXM1 possibly influences cell migration, angiogenesis, invasion, renewal of stem cells, cellular senescence, and DNA damage repair, ultimately contributing to the initiation, progression, angiogenesis, metastasis, and drug resistance of tumors [16–19].

Cancer stem cells (CSCs) are cancer cells that have the ability to self-renew and differentiate into a range of malignant cell types [20]. There are strong shreds of evidence that a subpopulation of cells within a tumor contains stem cell-like features, and these CSCs are responsible for tumor growth. There three main mechanisms that are involved in the generation of CSCs from mature cells are genomic instability, gene transfer, and alterations in the microenvironment [21,22]. These CSCs are critical for tumor growth and metastasis, as well as relapse and resistance to traditional treatments like chemotherapy and radiotherapy [23]. Such cells have an effective DNA repair system, increased cellular plasticity, activated survival pathways, apoptosis, avoidance of the immune system, and the ability to adjust to adverse microenvironments [24,25]. Expression profiling of CSCs in various solid and hematological malignancies has led to the identification of several biomarkers [26,27] which include cell surface-adhesion molecules, TFs, cytoprotective enzymes, and drug efflux pumps [28]. The most common CSC markers identified in various human malignancies are CD44, CD133, EpCaM, ALDH1A1, CD166, CD90, CD151, CD138, CD105, CD66c, CD49f, CD47, CD45, CD19, CD20, CD24, CD26, CD38, CD34, CD27, CD13, LGR5, SSEA-1, TRA-1–60, CD117/c-kit, and TNFRSF16 [29].

In addition to surface markers, there are intracellular biomarkers in CSCs that regulate pluripotency. A core network of TFs including OCT-3/4, SOX2, NANOG, KLF4, and c-MYC along with others regulate pluripotency in embryonic stem cells (ESC) and CSCs [30–32]. The TF SOX2 is one such intracellular biomarker that maintains the cell in an undifferentiated state [30]. SOX2 expression has been linked to progression as well as poor prognosis in stomach cancers [33,34]. OCT-3/4 is another intracellular biomarker that regulates pluripotency in stem cells and is upregulated in many malignancies [35].

Aberrant signaling pathways in addition to TFs including Wnt/ß-catenin, JAK/STAT, TGF-ß, Hedgehog/Notch, NF-κB, PI3K/AKT/mTOR, PPAR, and FGF also work intracellularly to regulate pluripotency [36]. To regulate CSC growth, these signaling pathways comprise of interwoven networks of signaling mediators, rather than a single regulator [37]. FOXM1 is a master regulator of cell cycle function. The dysregulated expression of FOXM1 has been linked with tumorigenesis of many human malignancies (Fig. 2). With regards to stemness, recently it was shown that FOXM1 is involved in the regulation of pluripotent stem cell markers like OCT4 and NANOG [38]. During differentiation, the decline in FOXM1 expression was found to precede the decline in the expression of stem cell markers. Interestingly, gene silencing of FOXM1 was shown to reduce the expression of OCT4 and NANOG, implying the direct involvement of FOXM1 in the regulation of the OCT4 promoter. On the other hand, overexpression of FOXM1 alone was shown to reactivate the expression of OCT4, NANOG, and SOX2 in differentiated cells. These findings underscore the regulatory role of FOXM1 in stem cell pluripotency and maintenance [38] In this review, we describe the role of dysregulated FOXM1 signaling in CSCs of different tumor lineages.

1.1. Mechanism of FOXM1 mediated regulation of CSCs

The main role of FOXM1 is to contribute to stemness in several malignancies. It regulates number, maintenance, renewal, and tumorigenicity of CSCs through cross-talk with various pathways (Table 1). FOXM1 increases the DNA repair by increasing the expression of genes

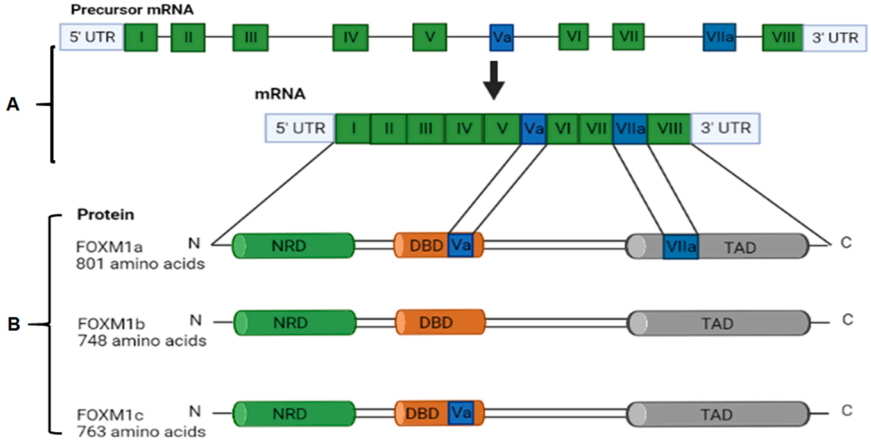

Fig. 1. FOXM1 isoforms and its various domains: (**A**) FOXM1 precursor mRNA followed by mRNA with exons only **(B)** protein structure showing major protein domains: N-terminal repressor domain (NRD); DNA binding domain (DBD); and Transactivation domain (TAD).

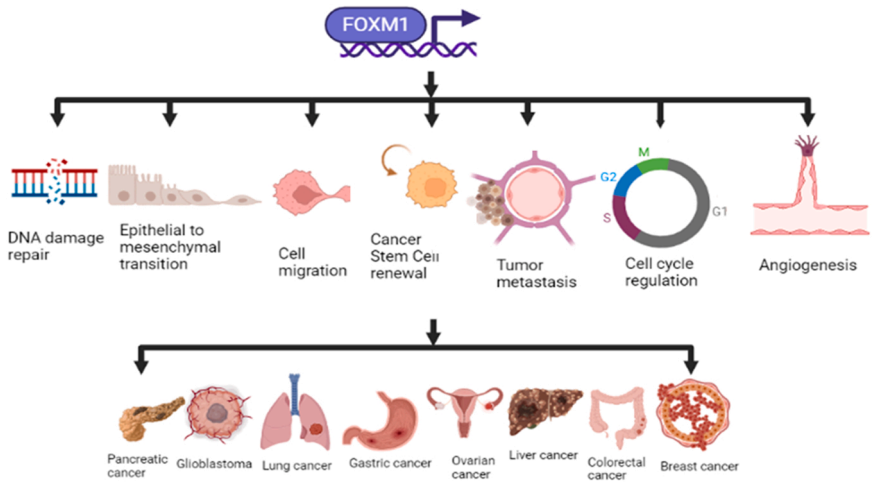

Fig. 2. Role of FOXM1 in oncogenesis. FOXM1 regulates key processes involved in tumor initiation, progression, cancer stem cell renewal and drug resistance of various human malignancies.

Table 1
Regulatory role of FOXM1 in stemness in various tumors.

Tumor Type	Regulation Of CSCs	Signaling Pathway	Clinical Implications	Ref.
Breast cancer	Stemness	β-catenin pathway	Potential therapeutic target	[66]
	Driver of CSC phenotype	Wnt signaling		[67]
	Maintenance of stemness	MAPK-ERK pathway and the PI3K-mTOR pathway		[68]
	Regulation of BCSC properties	DNMT1/FOXO3a/FOXM1/SOX2 pathway		[69]
	Stemness	Hippo pathway		[71]
	Self-renewal of BCSCs	PI3K-AKT, ATM/p53-E2F and p38-MAPK-MK2 signaling cascades		[73]
	Stemness and drug resistance	AKT/mTOR pathway		[75]
	Induction of stem cell markers	Hedgehog signaling		[77]
	Stemness	MELK signaling pathways		[78]
Colorectal cancer	Maintenance of Colon CSCs	Mitochondrial oxidative phosphorylation		[97, 98]
Hepatocellular carcinoma	Stimulates expression of stemness genes Bmi1, NANOG, and cMyc	–		[108]
	Supports survival of CD90 + , CD44 + , and CD133 +CD44 + HCC cells	MnSOD-mediated regulation of ROS		[108]
	Stemness acquisition and maintenance of liver CSCs	DNMT1/miR-34a/FOXM1 signaling axis		[110]
Ovarian cancer	Promotes stemness in cisplatin-resistant ovarian cancer cells	FOXM1/β-catenin pathway		[138]
Gastric cancer	CSC survival and proliferation	PI3K-AKT signaling pathway		[153]
	Metastasis of CSCs	Twist1/N-cadherin expression and EMT induction		[154]
Lung cancer	CD44-induced metastasis in CD133 + CD44 + LCSCs	wnt/β-catenin pathway		[160]
	Migration and invasion of lung CSCs	snail, slug and twist-induced EMT		[160]
	Migration of cells	TGF-β1-ERK- induced EMT through increased vimentin expression		[162]
	Maintenance of CSCs	AKT signaling pathway		[163]
Glioblastoma	Stemness and tumorigenicity	FOXM1 and Wnt/β-catenin signaling pathway		[174]
	Proliferation of glioma stem cells	MELK-FOXM1 signaling pathway		[173]
	Proliferation of glioma stem cells	MELK-c-JUN-FOXM1 signaling pathway		[78]
	Stemness and radio resistance	FOXM1-SOX2 signaling pathway		[175]
	Self-renewal and tumorigenicity	FOXM1-STAT3- β-catenin signaling pathway		[48]
Pancreatic cancer	Cell stemness, invasion, and metastasis	FOXM1-VDR- β-catenin signaling pathway		[181]
	Stemness	FOXM1-SOX2 signaling pathway		[176]
	Drug resistance, invasion, and metastasis	FOXM1-EMT		[180]

involved in it. It not only increases the expression of driver genes for CSC's phenotype and maintains the stemness through Wnt signaling, MAPK-ERK pathway and the PI3K-mTOR pathway, but also plays role in self- renewal (Fig. 3). Cell proliferation, migration, metastasis, drug resistance and radioresistance, increased energy demand through mitochondrial oxidative phosphorylation, evasion of apoptosis, angiogenesis, and epithelial-to-mesenchymal transition (EMT) are other mechanisms that are regulated by FOXM1 in CSCs.

The tumor microenvironment (TME), which consists of cellular and non-cellular elements, is the cellular setting in which tumor cells reside. The cellular components include several kinds of stromal cells and immune cells while non-cellular components include extracellular components such as hormones, growth factors, cytokines and extracellular matrix. The TME offers favourable conditions for tumor cells to grow, evade host immune monitoring, and resist anticancer medication [39]. The CSC microenvironment, also known as the CSC niche, is a unique milieu that is vital for the maintenance of CSCs and can control their properties through cell-to-cell interaction and secreted proteins. The role of FOXM1-regulated CSCs in the TME, and metabolic reprogramming is emerging. The CSC transcriptome contains significant expression of iron regulation, which mediates interaction with the TME. Despite the iron-mediated regulation of transferrin receptor (TFR) and

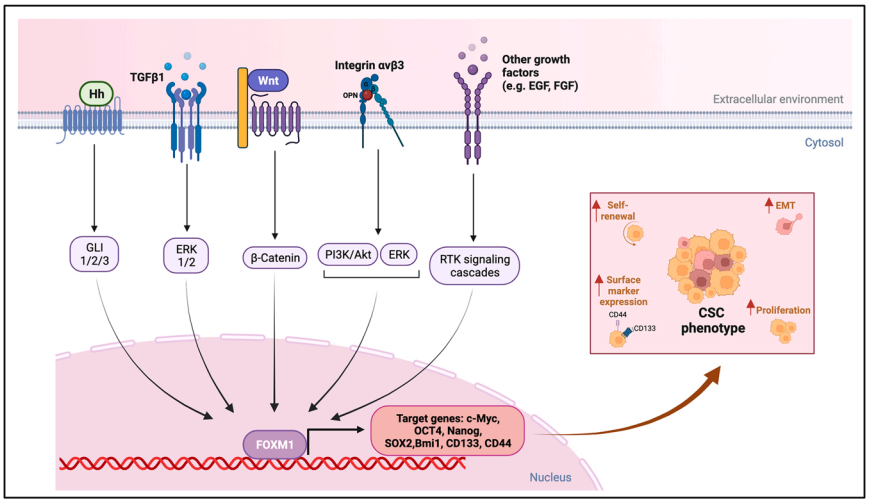

Fig. 3. Signaling pathways involved in FOXM1-mediated regulation of CSC phenotype. Various upstream regulators including growth factors and RTK signaling cascades involved in the regulation of FOXM1 are depicted. FOXM1 interacts with various signaling pathways, including SHH, PI3K/AKT, Wnt, TGFβ, and integrin αvβ3/Akt/Erk pathways. The cross-talk between FOXM1 and the signaling pathways triggers EMT and CSC-like properties, accelerating the progression of various cancers.

ferritin (FTH1 and FTL) genes , their expression have also been found to be stimulated by microenvironmental factors such as nitric oxide (NO) [40,41], cytokines, NF-κB [42–44], and TGF-β [45–47]. The most prominent mechanisms impacted by ferritin depletion are STAT3 phosphorylation and FOXM1 signaling. The significance of FOXM1--STAT3 signaling pathway has recently been strengthened in GBM, whereby FOXM1 was found necessary for the activation of STAT3 promoting CSC self-renewal and tumorigenicity [48].

In order to produce a pro-tumorigenic response in the face of development and maintenance of malignant properties, cancer cells have the capacity to modify their metabolism by increasing the absorption and use of carbohydrates, lipids, and proteins. This process is known as metabolic reprogramming [49]. It has recently been demonstrated that blocking the metabolic enzyme O-GlcNAc transferase (OGT) reduces the proliferation of cancer cells. This could be as a result of OGT's participation in posttranslational alterations of well-known cancer cell proliferation regulators like MYC, FOXM1, and EZH2 [50]. OGT activates well-known oncogenes such c-MYC [51], NF-κB [52], YAP [53], and EZH2 [54] in cancer cells by glycosylating them. However, it is unclear what exactly characterizes cancer cells' dependence on OGT or whether it is determined by the tissue type. It is interesting to note that OGT overexpression expression enhances the Yamanaka factors' (c-Myc, Oct4, Sox2, and Klf4) [55] ability to reprogram mouse embryonic fibroblasts. Although this has not been formally explored, it is feasible that enhanced OGT activity, as seen in malignancies, may encourage the development of the stem cell-like state through Yamanaka factors.

By reprogramming the methylome and shifting its composition towards the cancer cells, a study showed that aberrant overexpression of FOXM1 via HELLS and two DNA methyltransferases (DNMT1 and DNMT3B) "brainwash" healthy cells [56]. The genes C6orf136, MGAT1, NDUFA10, and PAFAH1B3, which were hypermethylated, and SPCS1, FLNA, CHPF, and GLT8D1, which were hypomethylated, were all shown to be FOXM1-induced differentially methylated genes [56]. The putative mitochondrial metabolism-related functions of C6orf136, NDUFA10, and GLT8D1 may point to a potential involvement for FOXM1 in metabolic reprogramming in cancer cells [57].

2. Dysregulated FOXM1 signaling in cancer stem cells

2.1. Breast cancer

Breast cancer (BCa) has become a major health concern for women in recent years, evident from the dramatic rise in incidence and mortality. 19.29 million new cancer cases were estimated by the International Agency for Research on Cancer across the globe in 2020, with 2.26 million BCa cases representing around 11.7% of all cancer cases [58].

On both the biological and clinical level, BCa is regarded as a complex disease. It is made up of five unique subtypes: luminal A, luminal B, basal-like, normal breast-like, and HER-2 enriched [59–62]. On a molecular level, BCa tumors exhibit disruption of a multitude of cell growth and proliferation pathways, including the MAPK, RB/E2F, P13K/AKT/mTOR, and TP53. These pathways are molecular systems that are controlled by a variety of genes. The oncogenes c-MYC, HER2, and RAS; the tumor suppressor genes TP53, RB, and PTEN; the genes for cell cyclin D1 and E; and the BCa susceptibility genes BRCA1 and BRCA2 are all altered in BCa, resulting in abnormal cell proliferation and growth of BCa cells [63].

Triple-negative breast cancer (TNBC) is an aggressive form of cancer and is therapeutically challenging. Chemoresistance is often developed in TNBC, which causes relapse and metastasis. Stemness and DNA damage repair are involved in chemoresistance. A large number of CSCs are found in TNBCs [64]. 85% of TNBCs have overexpression of FOXM1 with an oncogenic role. Integrin β1 has been found to be overexpressed in invasive BCa and is linked with adverse outcomes in TNBC. In TNBC cells, FOXM1 regulates the expression of the integrin β1 gene by directly binding to its promoter to control transcription as well as the activity of focal adhesion kinase (FAK) [65]. Frizzled 5 (FZD5) expression is elevated in TNBC and is related to adverse outcomes. FZD5 is involved in stemness, survival, DNA damage repair, DNA replication, and cell G1/S transition in TNBC. FOXM1 plays a role in FZD5 signaling by acting as a downstream effector and promoting transcription of BRCA1 and BIRC5. Wnt7B, which is a ligand for FZD5, is also involved in FZD5 signaling and found to play a role in stemness, DNA damage repair, and cell proliferation [66]. In the same line, AMP-response element-binding (CREB) binding protein (CREBBP or CBP) has been suggested to play a role in CSC biology. The gene expression in TNBC is driven by the CBP/ß-catenin/FOXM1 transcriptional complex and is linked with high numbers of CSCs, therapeutic resistance, and poor prognosis [67]. This complex may provide molecular targets for personalized treatment [67]. Another study that investigated the maintenance of CSCs in TNBC found amplification/overexpression of cadherins (CDHs) 2, 4, 6, and 17 in 47% of TNBC while downregulation/mutation of E-cadherin (CDH1) in 10% of TNBC. The changes in CDH2/4/6/17 were tightly linked with high levels of many TFs such as FOXM1, MCM2, WWTR1, SNAI1, and SOX9 which are related to stemness [68]. Cross-talk between CDH2/4/6/17 and stem cell-related TFs may have implications for personalized treatment in TNBC [68].

The DNMT1/FOXO3a/FOXM1/SOX2 pathway has been found to regulate BCSC properties, suggesting them as potential therapeutic targets. FOXM1/SOX2 signaling is required for tumorigenicity and

maintenance of BCSCs. FOXO3a inhibits FOXM1/SOX2 signaling and consequently suppresses BCSCs. In BCa, DNMT1-mediated hypermethylation of the promoter has been found to downregulate FOXO3a . The expression of FOXO3a and FOXM1/SOX2/DNMT1 were found to be inversely correlated. Poor prognosis was predicted with loss of FOXO3a or elevation of FOXM1, SOX2, and DNMT1 [69]. By elevating the transcriptional activity of YAP1, disruption of the Hippo pathway can increase tumor growth, including BCa metastasis [70]. Elevation of YAP1 expression, mediated by FOXM1, has been found to promote clonal formation, and enhance cell proliferation and migration capacity in BCa. The interaction between FOXM1 and Hippo pathway has also been found to regulate stemness in BCa . OCT4 and NANOG transcription levels were lowered by the YAP1-TEAD binding inhibitor Verteporfin, but OCT4 and NANOG transcription levels were increased by the Hippo pathway activator XMU-MP-1 [71]. Another study investigating the relationship between FOXM1 and 14–3–3ζ in tamoxifen (TAM) resistance in BCa indicated that FOXM1 is a downstream effector of 14–3–3ζ signaling, which is elevated in more aggressive tumors. FOXM1

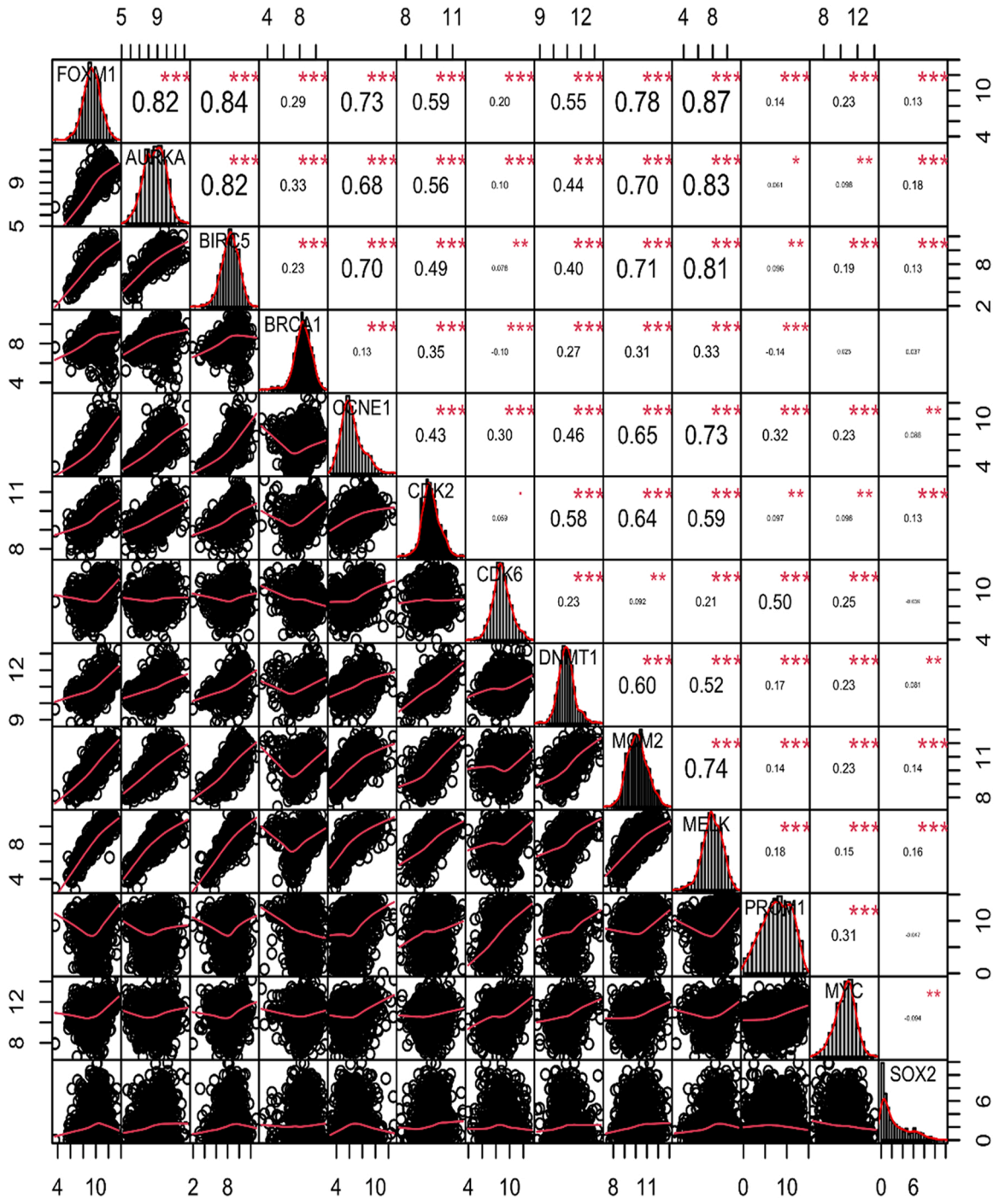

Fig. 4. Pearson correlation analysis of *FOXM1* with other stem cell markers. Log2 expression values of *FOXM1* and other genes were downloaded using TCGA data from LinkedOmics database (http://linkedomics.org). Correlation and statistical p values were computed using R package PerformanceAnalytics. Only genes showing statistical significant ($p < 0.05$) correlation are displayed. Upper diagonal shows correlation values as numbers and p values as stars with correlation significance levels annotated by the number of stars (*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$). The bottom diagonal represents the scatterplot of each pairwise correlation. X and Y-axis of each box are the log2 expression values of genes (Breast cancer - n = 1093)

binds at the transcription start site of genes which play a role in regulating the cell cycle, maintaining stem cell attributes, invasion, and metastasis, all of which contribute to adverse outcomes in ERα-positive patients that are treated with TAM [72].

Furthermore, other studies have also shown that FOXM1 induces and enhances stemness in BCa. Aurora kinase A (AURKA) plays a key role in BCSCs. FOXM1 has been reported to recruit nuclear AURKA to transactivate its target genes in a kinase-independent manner. Furthermore, FOXM1 and AURKA enhance the BCSC phenotype by participating in a tightly-connected positive feedback loop. A strong and significant correlation has been identified between the expression of both genes in samples of BCa patients [73]. One of the causes of the therapeutic resistance in BCa is the heterogeneity, that results from stemness. Growth differentiation factor-15 (GDF-15) has been reported to cause therapeutic resistance and stemness in BCa. The serum level of GDF-15 has been found significantly elevated in BCa patients [74]. The gene expression levels of GDF-15 as well as of OCT4, SOX2, and FOXM1 were found to be high in BCa tissue in comparison to nearby normal tissue. The expression of these genes as well as of p-AKT was high in MDA-MB-231 cells in comparison to MCF-7 cells. ABCC5, OCT4, SOX2, and FOXM1 were all found to be substantially linked with tissue GDF-15 [75]. Knockdown of GDF-15 abolished the expression of p-AKT, FOXM1, OCT4, SOX2, and ABCC5 while treatment with recombinant GDF-15 reversed it [75]. Further, Hedgehog signaling is abnormally activated in many cancers, including BCa, and stimulates GLI family members via Smoothened [76]. GLI regulates the transcription of GLI1, PTCH1, PTCH2, HHIP1, MYCN, CCND1, CCND2, BCL2, CFLAR, FOXF1, FOXL1, PRDM1 (BLIMP1), JAG2, GREM1, and Follistatin. Cellular proliferation is induced by Hedgehog signals by activation of N-Myc, Cyclin D/E, and FOXM1. The stem cell markers such as BMI1, LGR5, CD44, and CD133 are also induced by Hedgehog signals [77]. Maternal Embryonic Leucine Zipper Kinase (MELK), involved in CSC biology, has also been reported to be overexpressed in many cancers, including breast, colon, pancreas, ovaries, brain, and prostate. Both in vitro and in vivo, knockdown of MELK by RNA interference or depletion by small molecule inhibitors has been shown to induce apoptosis of CSCs originating from glioblastoma multiforme and BCa. MELK has been shown to directly bind to and activate cancer-causing TFs c-JUN and FOXM1 [78].

Dinaciclib, a CDK1/2/5/9 inhibitor, is being tested in clinical studies for a variety of cancers, including BCa. A study showed that Dinaciclib's therapeutic targets include FOXM1 as well as the Hedgehog signaling pathway, suggestive of its capacity to decrease BCa stemness [79].

In summary, FOXM1 regulates the expression of different BCSC markers, which was also confirmed through the correlation analysis of FOXM1 using The Cancer Genome Atlas (TCGA) data of breast carcinoma (Fig. 4). High expressions of most of the significantly associated markers were also found to be associated with poor overall survival (Supplementary Fig. 1).

Altogether, FOXM1 plays a role in inducing stemness in BCa and contributes to different outcomes such as cancer progression, cell survival, DNA damage repair, DNA replication, and cell G1/S transition, clonal formation, cell proliferation, and migration capacity, therapeutic resistance, and poor prognosis.

2.2. Colorectal cancer

Colorectal cancer (CRC) is the third most frequent cancer in men and the second most frequent cancer in women, with an estimated 1.9 million new cancer cases and 0.9 million mortalities in 2020 [80]. The incidence of CRC has risen over the years. It accounts for approximately 10% of all cancers and is the second leading cause of cancer mortality [81,82]. As a result, CRC is a major public health concern linked to significant morbidity, fatalities, and healthcare consumption, as well as rising medical costs [81,82].

CRC is a heterogeneous disorder marked by a variety of molecular changes, including the dysregulation of signaling pathways, resulting in tumor initiation, development, and metastasis [83]. CRC tumors exhibit considerable inter- and intratumor heterogeneity accounting for their complex molecular biology, which influences tumor response to therapy and patient survival [84]. At least three key molecular pathways are involved in CRC. The first involves chromosome instability (CIN), which affects 85 percent of sporadic CRC (sCRC), and is characterized by chromosomal structural and number abnormalities, widespread loss of heterozygozygosity (LOH) at tumor suppressor loci, gain and loss of chromosomal sections, and chromosomal rearrangements that result in gene copy number variations [85]. These mutations impair certain oncogenes or tumor suppressor genes which control cellular proliferation and the cell cycle and are important in the initiation and progression of CRC [86]. Another key pathway critical in CRC is microsatellite instability (MSI), which is produced by mutations in DNA mismatch repair (MMR) genes during DNA recombination, replication, and damage. As a result, it's frequently linked to genetic hypermutability [87]. The third key route to CRC is the CpG island methylator phenotype (CIMP), which can be divided into two types: $CIMP^{high}$ tumors characterized by mutations in BRAF, MLH1 methylation, and silencing of MGMT or CDKN2A and $CIMP^{low}$ tumors characterized by mutations in KRAS [87].

When an intestinal stem cell (ISC) goes rogue, it becomes a CSC, which causes CRC [88–92]. CSCs play an important role in tumor formation and growth, treatment resistance, relapse, and invasion in colorectal cancer [93,94]. Because of their vast proliferative abilities, colorectal cancer stem cells (CCSCs) can produce widespread metastatic tumors [95]. Certain cell signal transduction pathways that play a role in CRC cell viability, proliferation, and self-renewal such as NF-κB, Hedgehog, Notch, Wnt/-catenin, JAK/STAT, PI3K/AKT/mTOR, PPAR, and TGF-β/SMAD pathways have been found to be disrupted in CCSCs [96].

Colon CSCs use oxidative phosphorylation (OXPHOS) in the mitochondria to make ATP. Colon CSCs are maintained by the FOXM1/PRDX3 mitochondrial pathway in which FOXM1 induces peroxiredoxin 3 (PRDX3) to perpetuate the function of mitochondria. To sustain the stemness of colon CSCs, FOXM1 also induces the expression of CD133 (PROM1/prominin 1). FOXM1, PRDX3, and CD133 could be used as targets to selectively eliminate CCSCs, thereby addressing the therapeutic challenges posed by colon cancer [97,98]. Similarly, the EGFR--RAS-FOXM1-β-catenin signaling axis has been described to have a role in the biology of CSCs in CRC. The combinatorial treatment of CRC cells with celecoxib and cetuximab triggered cell death. This therapy was found to inhibit EGFR signaling and alter the location of β-catenin in the cell. The knockout of FOXM1 further intensified the inhibition. The adjunctive use of celecoxib and cetuximab lowered the interaction of β-catenin/FOXM1 reducing the CSCs in CRC. In human colorectal adenocarcinomas, FOXM1 immunodetection in the nuclei of tumor cells was found to be substantially linked to patient response to cetuximab, suggesting it may be used as a predictive biomarker [99]. Anti-EGFR/VEGF targeted therapies initially work well in several patients with metastatic colorectal cancer (mCRC), however, resistance develops after some time. A study explored the effect of targeting EGFR/VEGF and cyclooxygenase-2 (COX-2) in CRC cells to find out if it enhances the treatment by using AEE788 (dual tyrosine kinase inhibitor) and celecoxib against EGFR/VEGFR and COX-2, respectively. The adjunctive use of the two drugs augmented the effect of each other by blocking the EGFR/VEGFR signaling axis. The accumulation of β-catenin in the nucleus of tumor cells was also prevented. The FOXM1 protein expression was not only downregulated but also its interaction with β-catenin was impaired. The subpopulation of CSC decreased due to the downregulation of stem cell markers OCT4, NANOG, SOX2, and SNAI1 in cancer cells [100]. Another study utilized the Connectivity Map (CMap) approach to identify agents that selectively target CCSCs. In both parent HCT-15 and HT-29 human CRC lines, as well as EMT and chemoresistant clones produced from them, thiostrepton (a thiazole antibiotic in top candidates) could preferentially trigger apoptosis in CCSC subpopulations. The authors also looked into its impact on the ability of the

abovementioned CRC lines to produce spheres and colonies. The reduced expression of several modulators of cell phenotype was linked to the suppression of sphere and colony formation in vitro. Both CD44 (+) HCT-15 and HT-29 cells were eliminated more effectively with the conjunction of thiostrepton and oxaliplatin than with either treatment alone. In CRC lines, FOXM1was discovered to be a crucial positive regulator of stemness and the principal target of thiostrepton [101]. During the development of stem cells, the Hedgehog gene family plays an important role. Cellular proliferation is activated by the initiation of the GLI1 proto-oncogene. In addition to the promotion of carcinogenesis in the airway and pancreatic epithelia, Sonic Hedgehog (SHh) is also expressed in colonic stem cells. In human colonic adenocarcinomas and a CRC cell line, elevated expression of SHh mRNA has been indicated with a concomitant hike of GLI1 and FOXM1 mRNA expression. This indicates a possible function of the Hh pathway in colorectal carcinogenesis and may be targeted to overcome therapeutic challenges in CRC [102].

2.3. Hepatocellular carcinoma

Over the past decade, significant advances in molecular profiling techniques have improved our understanding of critical multifaceted molecular events driving hepatocarcinogenesis while, at the same time, unraveling hepatocellular carcinoma (HCC) complexity. In particular, it has unveiled the pronounced inter and intratumor heterogeneity of HCC tumors, primarily emanating from stochastic molecular alterations (defined by the traditional clonal evolution model) and varied etiologies [103]. In the last ten years, significant evidence has accumulated in favor of the hierarchic (CSC) model in installing intratumor heterogeneity in clonally-derived HCC tumors. The existence of the CSC has been validated in a subset of certain self-renewing stem cell marker-positive cells within the hierarchically-organized liver tumors; however, the existence and role of stem cells in the liver are in itself debatable [104–106]. Nevertheless, substantial progress has been made in the isolation of liver CSCs (LCSCs) and in delineating their role in tumor initiation, generation of metastasis, and local recurrence. These traits are particularly relevant for an aggressive therapy-resistant tumor entity like HCC, targeting which may bring a paradigm shift in the landscape of HCC management.

Currently, LCSC fractions are enriched from liver tumors based on their antigenic (i.e., positivity for CD133, CD90, and EpCAM) or functional (surrogate) properties (i.e., self-renewal, pluripotency, asymmetric division, anchorage-independent growth, and chemoresistance) [107]. Owing to the molecular complexity of CSCs, however, the exact regulation of LCSCs within hepatic tumors remains poorly understood. Emerging evidence generated by using different model systems has led to the identification of key intrinsic and extrinsic factors in regulating the stemness of cancerous liver cells [105]. Various genetic and epigenetic alterations as well as the tumor microenvironment-derived physical and cellular elements have been identified that essentially regulate the LCSC fate, survival, and properties during hepatocarcinogenesis [105]. In addition, a multitude of signaling cues have been deciphered that support the stemness phenotypes of LCSCs, including Wnt/β-catenin, MAPK, NF-κB, Hippo, IL-6/STAT3, and Notch signaling [105]. Amongst these, Wnt/β-catenin and autocrine IL-6/STAT3 signaling pathways are ascribed to key regulatory tasks in LCSC biology. Supporting this notion, FOXM1, the downstream effector of Wnt signaling activated in H-ras12V-driven HCC, has been demonstrated to regulate the expression of CD44 and EpCAM in HCC cells derived from Ras-induced mouse liver tumors [108]. Specifically, FOXM1 was shown to associate with the putative binding sites in the CD44 promoter and thus stimulate its expression. Beyond the cell surface markers, FOXM1 was found to stimulate the expression of the stemness genes BMI1, NANOG, and c-MYC in HCC cells. Of note, FOXM1 supported the survival of CD90 + , CD44 +, and CD133 +CD44 + cells in HCC through antioxidant gene, manganese-dependent superoxide dismutase (MnSOD)-mediated regulation of ROS. Indirect evidence of the role of FOXM1 in fostering liver cancer stemness has also been provided. Accordingly, an independent study reported the overexpression of MELK, a recurrence-related oncogenic kinase, in HCC cells and decoded its potential association with the stemness properties of CD44 +CD133 + cells [109]. Stable silencing of MELK inhibited the stemness of HCC cells, corroborating the functional role of MELK in the stemness property of HCC cells. In particular, MELK was determined to cooperate with the FOXM1/β-catenin signaling pathway to regulate the stemness features of LCSCs. A strong correlation was also seen between MELK and FOXM1 in TCGA HCC patients, and high expression of these genes was found to be associated with poor prognosis (Fig. 4A and Supplementary Figure 2). Given the implication of CD44 +CD133 + stem cell-like HCC cells in the hematogenous metastasis of liver cancers and the tight association of MELK overexpression with early HCC recurrence and poor survival, MELK-based targeted therapy could be a promising treatment option for patients with advanced HCC. Recently, Cao et al. [110] uncovered the FOXM1-related regulatory events that are upstream of stemness acquisition and maintenance of LCSCs. The team demonstrated that promoter hypermethylation-induced transcriptional silencing of tumor suppressor miR-34a by DNMT1 promotes stemness features (sphere formation and in vivo tumorigenicity) in liver cancer cells via FOXM1 upregulation. This study identified FOXM1 as a direct miR-34a target and determined the functional significance of the DNMT1/miR-34a/FOXM1 signaling axis in hepatic cancer progression. A significant correlation was seen between DNMT1 and FOXM1 in TCGA and high expression of DNMT1 correlated with poor patient prognosis (Fig. 5A and Supplementary Figure 2). Previous research has unveiled the association of the putative miR34a/FOXM1/c-MYC signaling network with poor prognosis in HCC patients [111], highlighting the prognostic significance of the co-expressed gene set of FOXM1 (apart from overexpressed FOXM1 [112]) in HCC patients. A recent report presented an in vitro evidence on the ability of novel synthetic genistein (GEN) analog 7-difluoromethoxyl-5,4′-di-n-octyl genistein (DFOG) to disrupt the cross-talk between hepatic stellate cells (HSCs) and LCSLCs, and abrogate HSC activation as well as stellate cell-induced stem-like characteristics in liver cancer cells by downregulating FOXM1 expression and reducing hepatocyte growth factor (HGF) secretion in HSCs [113]. Furthermore, one of the studies established the involvement of FOXM1 in inducing stemness properties in human HCC cells by using siRNA and siomycin A, a proteasome inhibitor regulating FOXM1 transcriptional activity [114].

From the clinical perspective, several studies have elucidated and identified a positive association of FOXM1 overexpression with adverse clinical outcomes in HCC [114–116]. Hyperactive FOXM1 is a common hallmark of HCC, with a direct link to aggressive clinicopathological features [114]. The functional role of FOXM1 in LCSCs and hepatic tumor biology has favored its consideration as a potential therapeutic target in HCC.

2.4. Ovarian cancer

Traditionally classified as a single entity, ovarian cancer is now considered a heterogeneous group of neoplasms, with distinct histological subtypes that differ in terms of molecular genetics, precursor lesions, pathogenesis, metastatic progression patterns, chemotherapeutic response, clinical course, and prognosis [117–120]. Recent efforts on integrating morphologic features with immune-molecular algorithms have led to a better definition of and high diagnostic precision for each histological subtype. Besides, large-scale molecular characterization studies have improved our understanding of the systemic nature of ovarian carcinoma and the underlying genomic complexity of ovarian tumors [120]. The expanding genomic landscape of ovarian cancer, built from the detailed mapping of genetic lesions, has led to the identification of peculiar genomic alterations and genetic evolution associated with different tumor histotypes [BRAF and KRAS mutations with

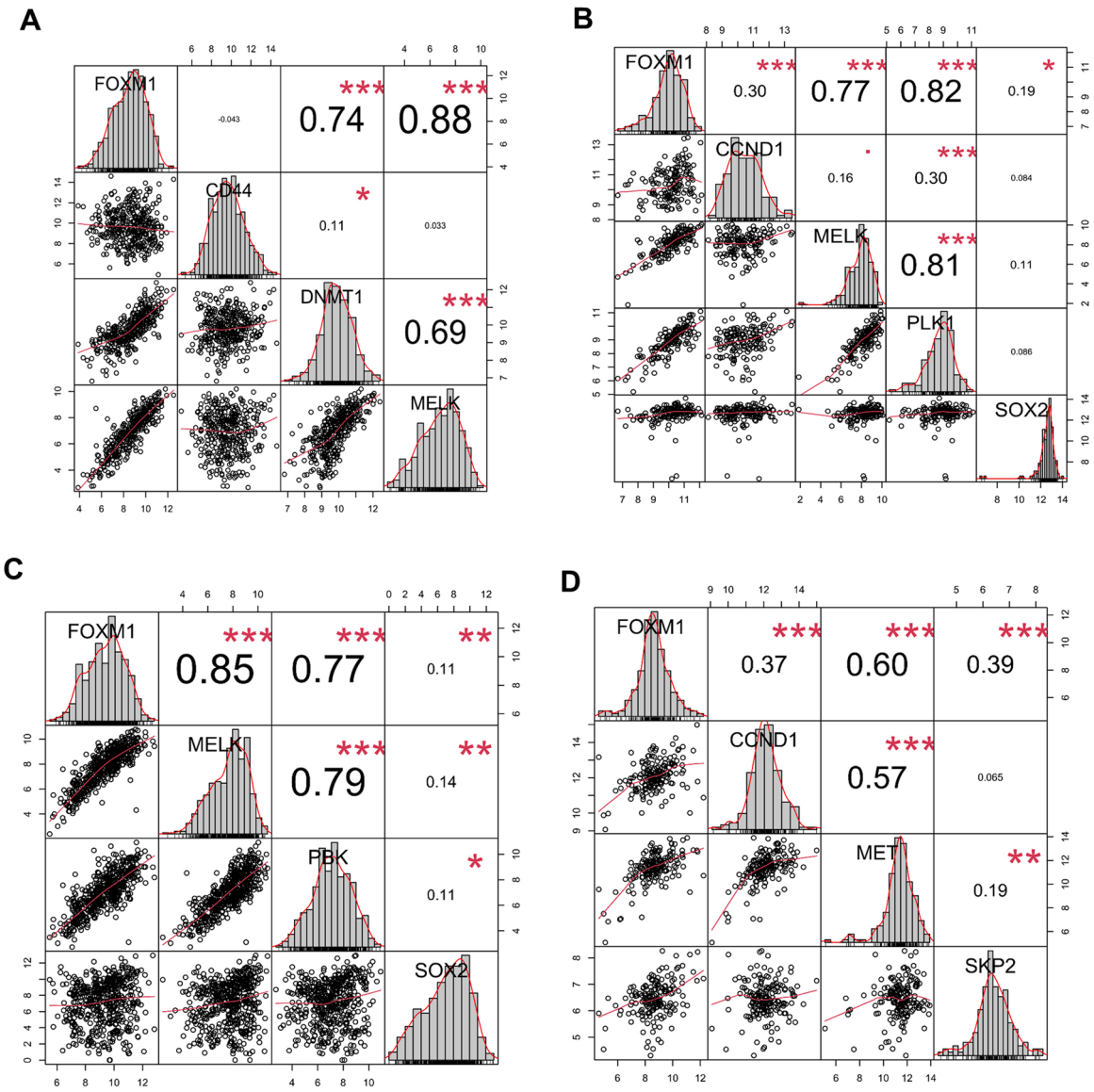

Fig. 5. Pearson correlation analysis of *FOXM1* with other stem cell markers. Log2 expression values of *FOXM1* and other genes were downloaded using TCGA data from LinkedOmics database (http://linkedomics.org). Correlation and statistical p values were computed using R package PerformanceAnalytics. Only genes showing statistical significant ($p < 0.05$) correlation are displayed. Upper diagonal shows correlation values as numbers and p values as stars with correlation significance levels annotated by the number of stars (*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$). The bottom diagonal represents the scatterplot of each pairwise correlation. X and Y-axis of each box are the log2 expression values of genes. (A) Hepatocellular carcinoma - n = 371 (B) Glioblastoma - n = 153 (C) Lung adenocarcinoma - n = 515 (D) Pancreatic cancer - n = 178.

genomic (chromosomal) stability of low-grade serous ovarian carcinoma (LGSOC) vs. TP53 and BRCA mutations with striking instability of high-grade serous ovarian carcinoma (HGSOC)] [117,121]. Regardless of the empirical molecular and morphologic evidence that has ushered a paradigm shift in the pathogenesis of ovarian cancer [122], the conclusions underlying its true picture have not been obtained yet.

Based on the biological features and clinical progression, ovarian cancer is an archetypal CSC-driven disease. Since the first in vivo indication of ovarian CSCs (OCSCs) in 2005 [123], numerous studies have isolated them from ovarian cancer patients (mainly peritoneal ascites), mouse models as well as ovarian cancer cell lines. In the last decade, emerging clinical evidence has established the association of OCSCs with poor survival outcomes. Specifically, several groups have acknowledged the correlation between the higher frequency of OCSCs and the higher likelihood of tumor recurrence with a lower chemotherapeutic response rate and shorter progression-free survival [124–126]. Besides clinical implications, compelling studies have delineated the complex biology of OCSCs and validated their tumorigenic, pro-metastatic [127], and chemoresistant properties [128]. In this process, several signal transduction pathways have been uncovered with a key role in stemness features such as self-renewal, as well as in tumor initiation and chemoresistance. These include the classical Wnt/β-catenin, Notch, IL-6/JAK/STAT3, Hedgehog, NF-κB, and PI3K/AKT pathways [36,129] as well as other potential pathways such as TLR2-MyD88-NF-κB [130], HMGA1 [131], PKCι/Ect2/ERK [132], YAP/TEAD [133], hypoxia-Notch1-SOX2 [134].

In ovarian cancer, a linear relationship between ALDH1 expression, chemoresistance [135], stemness, and tumorigenicity [136] has been established. Given the concordance in the expression of FOXM1, Notch1, and ALDH1 in ovarian cancer cells, ALDH1 has been shown to regulate the stemness and tumorigenic potential through the downstream FOXM1/Notch1 signaling [136]. In light of these findings, all-trans retinoic acid (ATRA), an active metabolite of Vitamin A, was shown to entail stemness by targeting ALDH1, reducing the oncogenic potential of

stem-like ALDH1-abundant cells, and inhibiting the self-renewal-related ALDH1/FOXM1/Notch1 pathway in ovarian cancer cells [136]. Similar to the inhibitory effect of DFOG in LCSCs, the GEN derivative has also been shown to preferentially inhibit proliferation, self-renewal capacity, and expression of CSC markers (CD133, CD44, and ALDH1) in the ovarian cancer stem-like cells (OCSLCs) derived from the SKOV3 human ovarian cancer cell line [137]. The DFOG-mediated inhibition was attributed, in part, to the inactivation of FOXM1, an observation deduced from the enhanced self-renewal of OCSLCs following forced overexpression of FOXM1. A potential mechanistic link between FOXM1, chemoresistance, EMT phenotype, and stemness in ovarian cancer has also been discovered [138]. Using in vitro models of resistance to the anticancer drugs paclitaxel and cisplatin, FOXM1 was shown to confer cisplatin resistance and subsequent stemness in ovarian cancer cells. FOXM1 hyperactivity in the cisplatin-resistant ovarian cancer cell line A2780CP70 was demonstrated to enhance the sphere formation ability in comparison to the A2780 parental line. The FOXM1-mediated activity of β-catenin, as well as the impaired human copper transporter 1 (hCTR1)-mediated cellular uptake of cisplatin, were primarily responsible for the bestowal of the resistant and stem cell phenotypes. Indeed, cisplatin/thiostrepton, a FOXM1 inhibitor, suppressed the expression of stem cell markers, sensitized cells to cisplatin, and abrogated the growth of subcutaneous mouse ovarian tumors [138].

More than 85% of ovarian cancer cases have been reported to be enriched in FOXM1 and the associated oncogenic transcriptional signature. Activation of the FOXM1 TF network is frequently detected in epithelial ovarian cancers (EOCs; 87%), especially those exhibiting high-grade serous pathophysiology [139,140]. In fact, FOXM1 is one of the key alterations in HGSOCs (84%), second only to the ubiquitous TP53 mutation [141]. In the clinical setting, multivariate analysis has indicated the prognostic significance of FOXM1 positivity with progression-free survival and overall survival as well as its association with lymph node metastasis in patients with EOC [142]. In non-serous EOC, the expression pattern and functional contribution of FOXM1 remain elusive, although a report has established a significant association of FOXM1 upregulation with chemotherapy resistance and adverse prognosis [143].

2.5. Gastric cancer

Gastric cancer is the third leading cause of cancer-related deaths after lung and colorectal cancer [144,145]. Although the incidence and mortality rate of gastric cancer has been reduced over the past five decades, it is still diagnosed in more than 1 million people each year worldwide [144]. In 2018, gastric cancer was the fifth most diagnosed cancer and was responsible for 1 in every 12 deaths [144,145]. Compelling evidence has demonstrated that gastric cancer gains stemness through the formation of CSCs that make up a subpopulation of cells in the tumor and play a major role in cancer initiation and progression. These cells present distinct cell surface markers, that include EpCAM, CD44, ALDH1, CD133, and LGR5 [146]. In addition to surface markers, certain TFs are also abnormally expressed in CSCs such as NANOG, SOX2, and OCT4. The aberrated activation of TFs prevents differentiation of the CSCs, suggesting that abnormal activation of TFs is linked with CSC formation [147]. FOXM1 is overexpressed in many cancers and is responsible for cancer initiation, progression, and metastasis [148]. The overexpression of FOXM1 in gastric cancer is found to be associated with advanced stage, lymph node metastasis, and poor tumor differentiation [149].

EMT is an important characteristic of CSCs. Mesenchymal cells exhibit self-renewal properties, a characteristic feature of CSCs [150]. Studies have shown a negative association between FOXM1 and the epithelial cell marker, E-cadherin. Tissues that exhibit high FOXM1 expression were found to be negative for E-cadherin [149]. Moreover, induction of FOXM1 in gastric epithelial cells is also associated with a reduction in E-cadherin expression and increased mesenchymal cell markers such as vimentin, ZEB1, and ZEB2. As a result, transfection of normal gastric epithelial cells with FOXM1 conferred them with invasive, migratory, and proliferative potentials [151]. This suggests that forced overexpression of FOXM1 in normal gastric epithelial cell lines induces an EMT phenotype [151]. Additionaly, knockdown of FOXM1 also resulted in a change in the cell morphology, making it appear like an epithelial cobblestone. The reduced expression of FOXM1 downregulated the expression of vimentin. These findings demonstrate that FOXM1 plays a major role in tumor cell aggressiveness by conferring an EMT phenotype in gastric cancer cells [151].

The activation of EMT initiates metastasis, which makes cancer cells more invasive and migratory [152]. The knockdown of FOXM1 in gastric cancer cell lines reduced cell survival and invasiveness, while the overexpression of FOXM1 correlated with enhanced proliferation and migration.

The low expression of FOXM1 in gastric cancer cells decreased the expression of certain genes that play a significant role in conferring CSC properties, such as cyclin D1, CD44, NF-κB P65 subunit, VEGF, Hes1, and EpCAM [151]. Additionally, FOXM1 plays a crucial role in the maintenance of gastric CSCs, evident from the finding that inhibition of EpCAM+ /CD44 + gastric CSCs by curcumin causes reduced expression of FOXM1. Moreover, FOXM1 is also correlated with the AKT signaling pathway for the survival of gastric CSCs. The downregulation of FOXM1 and p-AKT resulted in apoptosis and reduced proliferation in gastric CSCs which demonstrate that FOXM1, along with AKT supports the survival of gastric CSCs [153].

The importance of FOXM1 in gastric CSCs has also been substantiated by the finding that the FOXM1 exhibits upregulated expression in sphere-forming cells of gastric cancer as compared to parental cells. Similarly, the inhibition of CSC biomarkers is accompanied by the decreased expression of FOXM1 [154]. Additionally, the anti-cancer drug DFOG inhibited cell invasion, migration, and self-renewal and also downregulated ALDH1, CD133, and CD44. It also reversed the EMT phenotype and reduced the expression of Twist1 by modulating FOXM1 signaling [154]. The knockdown of FOXM1 reduces the sphere formation of gastric cancer stem-like cells, increases the expression of E-cadherin, and reduces N-cadherin and Twist1 expression [154].

2.6. Lung cancer

Lung cancer is a major health issue and a leading cause of death in the United States. It is a highly heterogeneous cancer and can form at different locations in the bronchial tree. Therefore, it shows different symptoms depending on its anatomical location. Moreover, many patients presenting with lung cancer show advanced-stage disease (stage III or IV) [155]. A large number (80%) of lung cancer cases are non-small cell lung cancer (NSCLC) whereas small-cell lung cancer (SCLC) accounts for 15% of lung cancer cases. SCLC is a lethal subtype of lung cancer with a 5-year survival rate of less than 7% [156]. The resistance to chemotherapy and radiotherapy and relapse have been a major hinderance in lung cancer treatment. The resistance is mainly acquired by the CSCs, which enable the growth of malignant cell population [157]. Several cell signaling pathways are abnormally activated in these cells, such as Wnt, Hedgehog (Hh), PI3K/AKT/mTOR, Notch, NF-κB, JAK-STAT, TGF/SMAD, and PPAR [158]. In addition to these pathways, FOXM1 also plays a major role in lung CSCs where it regulates self-renewal, migration, invasion, and metastasis.

Studies have revealed that CD133, CD44, and CD24 are the main CSC-specific surface markers in solid tumors [159]. The CD133 + CD44 + lung cancer stem cell-like cells (lung CSCs) exhibit high expression of the major proteins involved in the Wnt/β-catenin pathway and the downstream FOXM1. CD44 has been found to induce metastasis in CD133 + CD44 + lung CSCs through Wnt/β-catenin and FOXM1. Therefore, FOXM1 is involved in metastasis of CD133 + CD44 + lung CSCs [160]. The association of FOXM1 with migration and invasion is evident from the finding that knocking down

FOXM1 in CD133+ CD44+ lung CSCs reduced their ability to migrate and invade, whereas overexpression of FOXM1 increased migration and invasion. In addition, the knockdown of FOXM1 in CD133 + CD44 + lung CSCs also reduced mesenchymal-specific TFs such as SNAI1, Snail2, and Twist. This indicates that FOXM1 induces EMT and therefore is involved in the migration and invasion of the lung CSCs [160]. FOXM1 regulates Twist expression in CD133 + CD44 + lung CSCs by directly binding to the promoter of Twist [160].

The inhibition of FOXM1 in the lung CSCs is associated with reduced sphere formation and cancer stemness marker genes [161]. FOXM1 is overexpressed in the spheroids derived from the NSCLC cell line H460 and has been associated with the overexpression of MnSOD. The increased expression of FOXM1 in the H460 cell line has been found to correlate with the higher expression of CD44, CD133, ALDH1, OCT4, SOX2, and BMI1. Moreover, the knockdown of FOXM1 also reduces the self-renewal capability of the lung CSCs [161]. These findings demonstrate that inhibition of oncogenic FOXM1 is a novel strategy to treat NSCLC.

FOXM1 is also known to induce EMT in NSCLC cells [162] in addition to TGF-β1 . The introduction of TGF-β1 in NSCLC cells was shown to increase the expression of FOXM1, which eventually enhanced the expression of the mesenchymal marker, vimentin, and reduced epithelial marker, E-cadherin. The importance of FOXM1 in the induction of EMT in NSCLC cells is also evidenced by the finding that knockdown of FOXM1 by siRNA resulted in decreased expression of vimentin and enhanced E-cadherin expression. Moreover, knockdown of FOXM1 also decreased the migration of the cells even in the presence of TGF-β1. TGF-β1 induced phosphorylation of ERK in a panel of NSCLC cells, and the phosphorylation of ERK is associated with FOXM1 expression. The inhibition of the ERK pathway through its inhibitor U0126 upregulated E-cadherin and downregulated vimentin in the presence of TGF-β1. Moreover, inhibition of the ERK pathway also inhibited FOXM1 in NSCLC cells and eventually reduced the migratory ability of the cells. These findings highlight the ERK signaling pathway interacts with FOXM1 for TGF-β1-induced EMT in NSCLC cells [162].

MELK has been reported to maintain CSCs in SCLC. The inhibition of MELK in SCLC is associated with downregulation of FOXM1 and AKT which eventually induces apoptotic cell death [163]. This was also confirmed by a strong correlation between MELK and FOXM1 in lung carcinoma patients as derived from the TCGA data (Fig. 5C). High expression of MELK is associated with a poor prognosis of lung cancer patients (Supplementary Figure 3). Additionally, T-lymphokine-activated killer cell-originated protein kinase (TOPK) has also been reported to maintain CSCs and the inhibition of TOPK in SCLC is associated with downregulated expression of FOXM1 [164].

The role of FOXM1in the lung CSCs has been further indicated by a study where the knockdown of FOXM1 enhanced the inhibitory effect of genistein on lung CSCs [165]. Genistein exhibits anti-cancer properties , attributed to its capacity to inhibit sphere formation and reduce the expression of BMI1, NANOG, CD133, and CD44 in lung CSCs. The overexpression of FOXM1 antagonizes the anti-cancer effects of genistein [165].

2.7. Glioblastoma

The most frequently identified brain tumor is glioblastoma (GBM) with a high rate of recurrence and a poor prognosis. It accounts for 82% of all malignant glioma cases [166]. GBMs are generally found in the brain, but they can also be found in the brain stem, cerebellum, and spinal cord. Because the tumor is densely packed with blood vessels, it grows quickly and easily penetrates the surrounding normal brain tissue, making complete surgical excision difficult. Recurrence is also typically seen after surgery [167]. GBMs occur more frequently in men than in women, and in Caucasians than in other ethnic groups. It mainly affects the elderly, however, it can also be noticed as early as childhood [168].

GBMs are classified as primary, or de novo, when they develop without a known precursor, or secondary when a low-grade tumor develops into a GBM over time. The majority of GBMs are primary, and patients with primary GBMs are older and have a worse prognosis than those with secondary GBMs [169]. Several genetic and environmental factors have been investigated in glioblastoma multiforme, but no risk factor accounting for a large proportion of GBM has been discovered so far.

The genetic and epigenetic mutations in GBM must be found and categorized to understand the tumor behavior and therapy resistance throughout the clinical course [170]. Despite substantial advancements in neurosurgical procedures as well as the development of innovative chemotherapies and aggressive multimodal treatments, overall prognosis of glioma patients remains poor. Translational and biological research have shown that high rates of recurrence are mostly caused by gliomas with poorly defined margins, invasion potential, and uncontrolled proliferation. [171]. GBM is made up of a variety of tumor cell types, including glioma stem-like cells (GSCs) with stem-like characteristics. According to mounting data, GSC characteristics may play a role in GBM treatment resistance. Increasing evidence suggests that GSCs may contribute to GBM treatment resistance [171].

FOXM1 plays an important role in the aggressive phenotype behavior of GBM via enhancing invasion, angiogenesis, and EMT [172]. Vascular endothelial growth factor (VEGF), matrix metalloproteinase-2 (MMP-2), and β-catenin are downstream targets that enhance the CSC self-renewal by causing nuclear localization and transcriptional activity through direct binding to β-catenin [173]. Studies have shown that FOXM1 is a key component of the Wnt/β-catenin signaling pathway and is involved in the maintenance of stemness and tumorigenesis in GSCs. It was found that FOXM1-β-catenin interaction increased β-catenin transcriptional activity and the expression of Wnt target genes such as Axin2, c-MYC, and cyclin D1 [174]. Kaushal Joshi et al. [173] demonstrated that oncoprotein FOXM1 is phosphorylated and activated after forming a protein complex with the mitotic kinase MELK, increasing the expression of mitotic regulatory genes in GSCs. Researchers also found out that MELK-driven FOXM1 activation in GSCs is dependent on the kinase PLK1 [173]. According to the study by Ranjit Ganguly and his colleagues, treatment with siomycin A, a thiazole antibiotic and a FOXM1 inhibitor, drastically suppressed the expression of FOXM1 and MELK, implying that siomycin A treatment impairs MELK-driven FOXM1 transcriptional activity and thus abrogates cancer-specific MELK signaling in GSCs [78]. In another study, researchers discovered that inhibiting FOXM1 or β-catenin in GSCs inhibited their self-renewal and tumor-initiation abilities. . Additionally, constitutively active β-catenin partially reversed the inhibitory effect of FOXM1 knockdown on GSC tumorigenicity. [174]. In another study, FOXM1 was found to support stem cell processes via transcriptional upregulation of SOX2, and the FOXM1-SOX2 signaling axis was shown to affect GBM cell radioresistance [175]. TCGA data also revealed a strong correlation of FOXM1 with MELK, PLK1, and SOX2 gene expression in GBM patients suggesting co-expression of these genes with FOXM1 (Fig. 5B). A report by Gong et al. [48] showed that FOXM1 is necessary for GSC self-renewal and tumorigenicity, and it promotes STAT3 activation by boosting β-catenin binding to the STAT3 promoter [48]. Downregulation of FOXM1 and its downstream targets, in combination with treatment of GBM with traditional chemotherapeutic drugs, might be a method for improved glioma therapy.

2.8. Pancreatic cancer

Pancreatic cancer (PC) is defined as a carcinoma that arises from pancreatic duct cells. Due to the concealment of early indications and the lack of effective therapies throughout later stages, pancreatic ductal carcinoma is one of the deadliest human malignant tumors, with a high fatality rate [176]. Pancreatic cancer is becoming more common every year, especially in developed nations [177]. PC accounts for 3.2% of new

cancer diagnoses and 7.9% of all cancer-related fatalities [178]. White individuals are more impacted than people of other races, and the rate of incidence grows with age for both genders. Surgery, chemotherapy, radiation therapy, and combination therapies have failed as viable treatment options. One of the key reasons for this is the presence of CSCs in pancreatic tumors, which correlates to pancreatic cancer's early dissemination and resistance to chemotherapeutic drugs [177]. In PC cells, CSC cell surface markers such as CD44, CD24, CD133, CXCR4, c-Met, and EpCAM have been well studied [178,179]. When compared to other surface markers, CD133 + cells have a greater percentage of tumorigenic and metastatic potential [180]. Notch, PI3K/ AKT, NF-κB, Hedgehog (Hh), Wnt/β-catenin, JAK/STAT3, and PTEN signaling pathways are all involved in the regulation of pancreatic CSCs (PCSCs) [178].

In pancreatic cancer cells, FOXM1 is involved in self-renewal, carcinogenesis, and metastasis [177]. FOXM1 interacts with various signaling pathways involved in stemness and maintenance of PCSCs, including Hh, Notch, BMI1, PI3K/AKT, and Wnt pathways. Additionally, FOXM1 is a critical promoter of carcinogenesis, acting as an activator of pancreatic ductal adenocarcinoma (PDAC) development through interactions with pancreatic intraepithelial neoplasia (PanIN) and PCSC signaling pathways [177].

FOXM1 and the Vitamin D receptor (VDR) interact with β-catenin to control cellular processes and activate VDR signaling, which inhibits FOXM1 and its downstream target genes like Cyclin D1, CD44, SKP2, c-MYC, and c-Met. The levels and distribution of FOXM1 and β-catenin in PCSCs were similarly changed by VDR activation, resulting in lower nuclear FOXM1 and β-catenin expression [181]. Another study showed that enhanced expression of ZEB1, ZEB2, Snail2, and vimentin, as well as CSC surface markers CD44 and EpCAM, is induced by the overexpression of FOXM1 [180]. This was further supported by a strong positive correlation between MET expression with FOXM1 and SKP2 in pancreatic cancer patients from TCGA (Fig. 5D). High expression of these genes was associated with poor overall survival of PC patients (Supplementary Figure 4). These findings suggest that inhibition of FOXM1 represents a therapeutic strategy for treating PC. Furthermore, the dysregulated FOXM1 pathways can be targeted to treat several malignancies resulting from CSCs (Table 1).

It is noteworthy that despite the experimental data, clinical evidence supporting the contribution of FOXM1 to cancer progression and stemness is very scarce. Informed by the in vitro and in vivo evidence on the association of FOXM1 with stemness properties, Luo et al. [182] recently established a strong correlation between FOXM1 and the expression of characteristic stem cell markers NANOG, SOX2 and OCT4 in nasopharyngeal carcinoma (NPC) biopsy samples. The team also determined the involvement of FOXM1 with stem cell-related clinicopathological factors such as advanced tumor stage (T4), tumor recurrence, and distant metastasis. This study corroborates the findings that acquisition of the CSC phenotype and FOXM1 overexpression are highly interrelated and contribute to tumor recurrence and poor prognosis. However, well-designed clinical studies to comprehensively assess the association between FOXM1 expression and CSC phenotype/-related clinicopathological parameters are urgently needed.

3. Conclusion and future prospects

Stem cells play a crucial role in cancer initiation, progression, invasion, metastasis, and therapeutic resistance in breast, colorectal, ovarian, gastric, lung, pancreatic cancer, hepatocellular carcinoma, and glioblastoma, amongst several other malignancies. The pathways operating in the CSCs in these malignancies are almost similar: efflux of therapeutic drugs outside cells to reduce exposure, bringing cells to a quiescent state to escape drugs that target actively dividing cells, the complicated interplay of pathways, dynamic transcriptional profile, and the plasticity in metabolic machinery that cause heterogeneity and resistance to therapy. FOXM1, known as the master regulator of the cell cycle, has been found to be overexpressed in many malignancies. It is a key component of various signaling pathways operating in CSCs. From the clinical perspective, several studies have elucidated and identified a positive association between FOXM1 overexpression and adverse clinical outcomes. The transcriptional network associated with FOXM1 regulates many processes: stemness (tumorigenicity, number, maintenance, and renewal of CSCs), survival, DNA damage repair, DNA replication, and cell G1/S transition, cell cycle, cell proliferation, clonal formation, migration capacity, invasion and metastasis, tumor initiation and progression, therapeutic resistance, and poor prognosis. Cumulatively, the functional role of FOXM1 in tumor biology has favored its consideration as a potential therapeutic target. Targeting FOXM1 in CSCs may bring a paradigm shift in the landscape of cancer management and provide a viable treatment strategy.

In the light of mounting data, it is evident that FOXM1 and its mediators have the potential to be exploited as biomarkers. Some mediators of FOXM1 have been found associated with adverse outcomes, and therapeutic resistance, while others have been proposed for personalized treatment. Further longitudinal studies are required to find if these mediators can be materialized for prognostic, diagnostic, and therapeutic purposes. Extensive studies on the transcriptional network and pathways associated with FOXM1 that operate in the CSCs can not only illuminate the mechanisms in cancer but also potentially lead to the discovery of therapeutic targets.

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CRediT authorship contribution statement

GS: Conceptualization, Writing – review & editing. **TM**: TCGA data mining, writing, and preparing illustrations. **KP**: Writing, preparing illustrations, table preparation, reviewing, and editing. **SA** and **SK**: Writing and table preparation. **AA**: Conceptualization, Writing – review & editing. **SU**: Conceptualization, Supervision, and Writing – review & editing.

Conflict of interest

The authors declare no conflict of interest.

Data Availability

No data was used for the research described in the article.

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Appendix A. Supporting information

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