# F-box proteins in cancer stemness: An emerging prognostic and therapeutic target

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**Cancer is a complex heterogenic disease with significant therapeutic challenges. The presence of cancer stem cells (CSCs) in cancer tissue orchestrates tumor growth, progression, and metastasis, the tumor heterogeneity, disease relapse, and therapeutic resistance. Hence, it is imperative to explore how progenitor or cancer-initiating cells acquire stemness features and reprogram different biological mechanisms to maintain their sustained oncogenicity. Interestingly, deregulation of F-box proteins (FBPs) is crucial for cancer stemness features, including drug resistance and disease relapse. In this review, we highlight recent updates on the clinical significance of targeting FBPs in cancer therapy, with emphasis on eliminating CSCs and associated therapeutic challenges. Moreover, we also discuss novel strategies for the selective elimination of CSCs by targeting FBPs.**

**Keywords: F-box proteins and signaling; Cancer pathogenesis; Cancer stem cells; Stemness; Poor clinical outcomes**

## Introduction

Cancer is a complex heterogenic disease with serious health concerns related to morbidity and mortality. In addition, increased cancer incidence also results in significant healthcare costs. Not only are available therapies costly, but they are also associated with a range of adverse effects and degrees of effectiveness. In addition, disease relapse, poor survival, and drug resistance are also of major concerns of current therapeutic plans.

Much progress has been made in exploring underlying mechanisms, especially signaling pathways and regulatory proteins, in the disadvantages of anticancer drugs, such as resistance and disease relapse. Exploring the role of cancer stem-like cells or CSCs, which are integral not only in cancer initiation and progression, but also in failures of cancer therapeutics, has also become an important focus of research. Increasing evidence indicate that CSCs or quiescent cells are the minute populations of cells inside tumors that are capable of transforming into other cell types, causing recurrence, relapse, metastasis, and resistance to therapeutic agents.[1] Interestingly, these cells can transit from CSCs to differentiated cells and have distinct mesenchymal features of an epithelial-like state. This phenotypic interconversion, or plasticity, of CSCs, has an integral role in tumor complexity and therapeutic challenges.[2] However, there are also reports suggesting that CSCs constitute up to 25% of tumor cells.[3] There are also various theories of the origin of CSCs, such as epithelial to mesenchymal transition (EMT) or instant mutations resulting from genetic or environmental factors (Fig. 1), but no consensus has been reached. Recent work has also highlighted the clinical and therapeutic importance of CSCs, given their oncopathogenic potential.[4]

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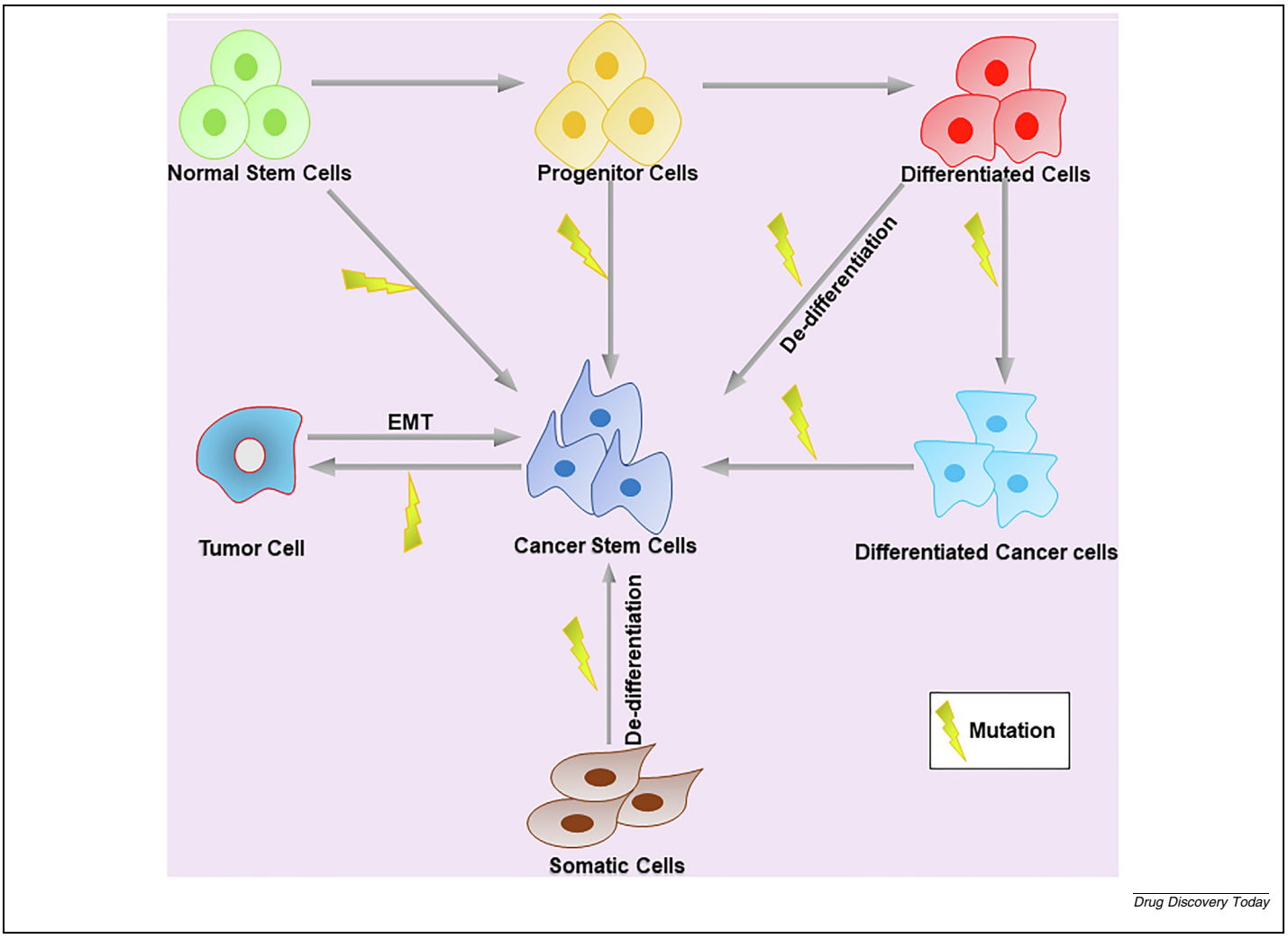


**FIGURE 1**
Overview of the origin of cancer stem cells (CSCs). There are different possible mechanisms related to CSC formation. For instance, mutation in the cells at the stage of different stages can result into the formation of CSCs. These cells can develop from a mutation in normal stem cells or in progenitor cells. Moreover, can also develop from a mutation affecting the differentiated cells which give rise to differentiated cancer cells that in turn can become CSCs. In addition, CSCs can develop from dedifferentiated somatic cells or from cancer cells that undergo epithelial to mesenchymal transition.

CSCs acquire stemness features and tumorigenic potential via deregulated signaling mechanisms, regulatory proteins, and noncoding (nc)RNAs. Indeed, cancer stemness has a significant role in the various hallmarks of tumorigenesis, including recurrence and drug resistance (Fig. 2). It is less clear how the tumor maintains the stemness features related to cancer pathogenesis and therapeutic failures. Hence, it is crucial to explore the underlying mechanisms of cancer stemness and to determine the regulatory moieties at the epigenetic, genetic, protein, and functional levels. In addition, deciphering how exogenous and endogenous factors converge toward stemness features is another important area of research. Thus, the past few decades have witnessed remarkable progress in exploring the role of regulatory proteins, and epigenetic and genetic factors in cancer stemness.

Deregulated signaling mechanisms and associated proteins are crucial players not only in cancer pathogenesis, but also in therapeutic adverse complications. Indeed, much progress has been made in understanding the crucial role of signaling pathways (Hippo, Wnt, Notch, Catenin, MAPK, m-TOR, PI3K/AKT, JAK/STAT, EGFR etc.) in cancer pathogenesis and acquisition of stemness characteristics.[5,6] In this review, we highlight recent updates on the clinical significance of targeting FBPs in cancer therapy, with emphasis on eliminating CSCs and associated therapeutic challenges.

## F-box proteins

Ubiquitylation, an important post-translational modification by the ubiquitin proteasomal system (UPS), has a major role in maintaining biological homeostasis by regulating proteins associated with cell cycle regulation, growth and survival, apoptosis, development, and stemness features, including EMT. Three major enzymatic reactions (mediated by ubiquitin-activating enzyme E1, ubiquitin-conjugating E2 enzyme, and ubiquitin-protein E3 ligase) are crucial steps in UPS-mediated biological functions. Notably, E3 ligases determine substrate recognition for ubiquitylation-associated degradation.[7] Ubiquitin ligases have integral roles, including substrate recruitment and ubiquitin transfer onto targets, and deregulated ubiquitin ligases are associated with cancer pathogenesis.[8] So far, more than 600 E3

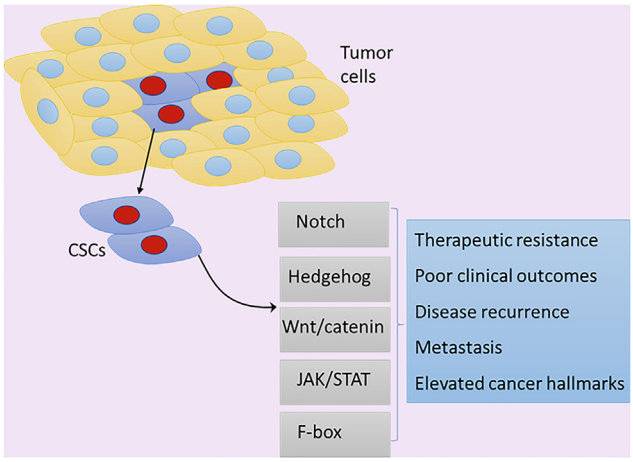


**FIGURE 2**
Cancer stem cell (CSC) function. A minority of CSCs in a bulk tumor perform a series of important functions to maintain stemness features and cancer pathogenesis. Different signaling pathways are often deregulated in CSCs and other cell types modulate the underlying mechanisms converging toward the development of cancer hallmarks, including stemness features.

ubiquitin ligases are known to be encoded by the human genome and, among these, the S-phase kinase associated protein 1 (SKP1)-cullin 1-F-box protein (SCF) E3 ligases are the largest (with eight members) and most widely studied category associated with protein homeostasis and in disease development. FBPs are the major target/substrate recognition components of SCF E3 ligase complexes in the UPS. There are 69 FBPs encoded by the human genome, which can be divided into three categories based on their specific substrate recognition domains: F-box and WD40 domain (FBXW) category, comprising 12 proteins (e.g., β-TRCP1, FBXW7, and β-TRCP2); the 21 F-box and Leu-rich repeat (FBXL) family members (e.g., SKP2) containing leucine-rich repeat domains; and 36 F-box only (FBXO) proteins with different domains, including zinc-finger, proline-rich domains, and Sec7.[9] These proteins regulate many biological processes, such as DNA replication, transcription, cell differentiation, and cell death, via ubiquitylation-mediated degradation of target proteins.[10] Accumulating results indicate the vital role of FBPs in the pathogenesis of different human diseases, including cancer, and, indeed, the deregulated expression of these proteins is often detected at preclinical and clinical levels.[7,10] Moreover, aberrant functioning of these proteins is a key determinant in challenges associated with cancer treatment.[11,12]

Various genetic, epigenetic, environmental chemicals, and drugs are putative factors associated with the expression and functioning of FBPs integral for normal homeostasis. Deregulated exposure or changes in these factors negatively affect FBP expression and cell signaling pathways associated with the activation, regulation, and reprogramming of metabolic and cellular physiological pathways, cancer resistance, stemness, and the tumor microenvironment (TME). In this line, various oxidative and proinflammatory mediators, among others, have a vital role in deregulated FBP signaling associated with cancer pathogenesis (Fig. 3).

## Cancer stemness and clinical challenges

Cancer stemness is a term used for the functional properties of CSCs, which include the ability to self-renew, maintenance of tumor heterogeneity, adaptative potential to survive under stress conditions, and activation of signaling mechanisms underlying therapeutic resistance, given that these cells manipulate or hijack genetic and epigenetic factors within tumors (Fig. 2). CSCs usually harbor mutations causing deregulation of the signaling pathways (e.g., Hippo, Wnt, Notch, Catenin, Stat3, Hedgehog, etc.) and transcription factors (e.g., SOX2, NANOG, and OCT4) converging on cancer stemness maintenance.[13] Significant research has focused on CSCs since their discovery in leukemic cells because of their strong association with disease pathogenesis and therapeutic challenges, such as recurrence and drug resistance. Moreover, CSCs have several characteristics, including intrinsic resistance to quiescence, higher expression of drug efflux mechanisms, survival proteins, DNA repair enzymes, and scavenging of reactive species. Overall, deregulated signaling mechanisms resulting from epigenetic and genetic changes are the central underlying mechanisms or modulators in the acquisition of cancer stemness features. For instance, development of tumor cell plasticity, transition of non-CSCs to CSCs, growth and maintenance of CSCs, including their oncogenicity, and clinical challenges are examples of stemness properties of CSCs resulting from a deregulated signaling network[13] (Fig. 3).

Recently, the therapeutic importance of targeting CSCs has been shown with reference to achieving prolonged disease-free survival and overall improved quality of life.[14] In addition, Schmidtova *et al.* demonstrated that targeting cancer stemness overcomes cisplatin resistance in ovarian cancer cells and abolished tumor recurrence.[15] Similarly, another investigation revealed the crucial role of signaling mechanisms in the stemness features of tumor cells and revealed that pan-EGFR inhibitors have the potential to selectively eradicate CSCs and might also enhance chemotherapeutic benefits in other cancer types.[15] Moreover, different pathophysiological phenomena, including inflammation and associated components, also modulate stemness features in tumor cells by regulating signaling moieties at both the epigenetic and genetic level. For instance, immune cells associated with stemness features pose a serious clinical challenge to immunotherapy and exclusion of these cells from the TME. Indeed, it was recently shown that cancer stemness features are highly correlated with immune cell exclusion, higher intratumoral heterogeneity, and compromised antitumor immune response in various cancer types.[16] In addition, upregulation of IL22RA1 in inflammatory immune cells or related signals correlated positively with cancer stemness and tumorigenicity in pancreatic cancer.[17] Hence, it is clear that CSCs are major pathological entities in cancer pathogenesis and therapeutic challenges. In this context, most major oncogenic signaling pathways trigger stemness of tumor cells, including MAPK and survival signals. Interestingly, stemness features also affect cell death processes, such as apoptosis and autophagy. In addition, it was recently demonstrated that CSCs abrogate signaling pathways converging toward cellular senescence, an antiproliferative mechanism resulting from upregulation of tumor suppressors, such as p53 and various CDK inhibitors (CKIs).[18]

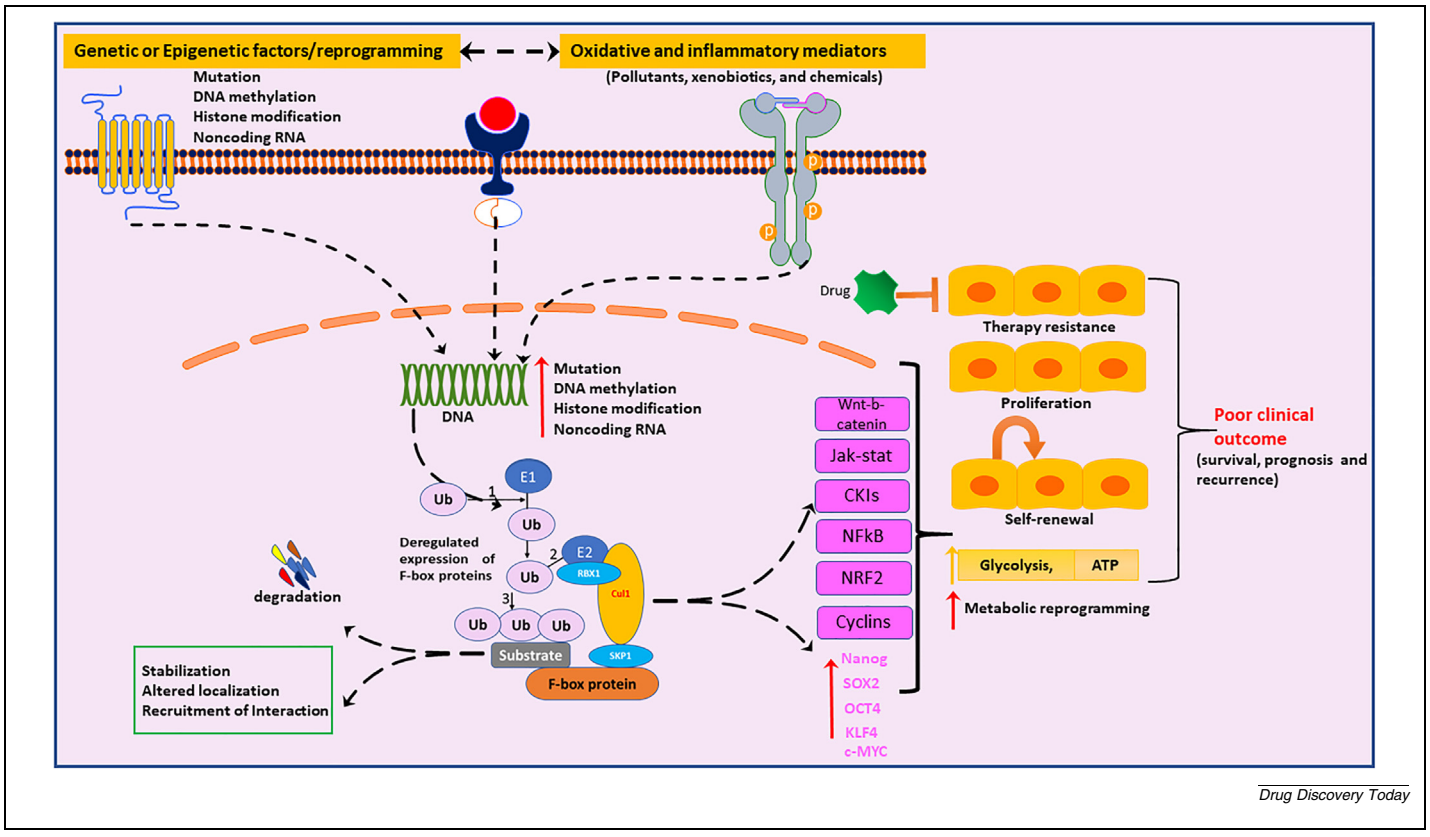


**FIGURE 3**

F-box proteins (FBPs) and cancer stemness features. Different factors, including genetic, intra- and intercellular signaling, epigenetic, environmental, chemical/drugs, and pollutants, can activate the expression of FBPs. Their activation results in substrate degradation or protein stabilization through post-translational modification. Under normal cellular physiological conditions, FBPs are vital in the regulation of numerous cellular functions, including stemness features and embryonic development. Sustained nonrepaired genetic/epigenetic changes or mutations ultimately lead to deregulation in the expression and functioning of FBPs. Deregulated FBPs have a central role in cancer pathogenesis and maintenance of stemness features by targeting various transcription factors (TFs) and signaling pathways.

## F-box proteins and cancer pathogenesis

There is ample scientific evidence exploring how deregulated signaling of FBPs (e.g., FBXW7, SKP2, and FBXW1/FBXW11) is crucial in cancer pathogenesis and therapeutic drawbacks via regulating proteins involved in cancer hallmarks[19,20] (Fig. 3). Interestingly, both the oncogenic and tumor suppressive natures of these proteins act as catalysts in carcinogenesis. Sun *et al.* showed that F-box only protein 22 (FBXO22) functions as both a tumor suppressor and an oncogene in breast tumorigenesis and metastasis. FBXO22 mediates inhibition of EMT, a crucial phenomenon of stemness, via targeting Snail and, thus, attenuates cancer pathogenesis.[21] In addition, dysregulation of F-box protein FBXW2 is associated with carcinogenesis (tumor migration, invasion, and metastasis) by targeting degradation of β-catenin, a pathway vital in stemness features, cell proliferation, and differentiation.[22] In clinical and nonclinical samples of hepatocellular carcinoma (HCC), the FBP FBXW10 promotes hepatocarcinogenesis in male patients and acts as independent risk factor and a potential prognostic marker for HCC.[23] Moreover, in patients with triple-negative breast cancer (TNBC), a differential correlation between FBXW7, ELF5, and the IFNGR1 signaling axis promotes the growth and metastasis of TNBC, which can be used for patient stratification and treatment strategies.[24] The deregulated NRf2-Kaep pathway has a major role in human cancer pathophysiology and poor clinical outcomes. Interestingly, FBXO22-mediated degradation of Bach1 is a crucial step in Nrf2-activated lung cancer metastasis.[25] Regulation of cell cycle-associated proteins, such as p27 and p21, is another striking feature of FBPs related to biological homeostasis. Indeed, dysregulated FBPs mediate the degradation of cell cycle regulatory proteins, which are central in carcinogenesis.[26] Considering the major role of FBPs in human cancer development and therapeutic drawbacks, research has focused on the identification of moieties regulating FBP expression and functioning and development of novel therapeutics. In addition to the genetic, epigenetic, and regulatory proteins, ncRNAs, such as miRNAs, long ncRNAs (lncRNAs), and circular RNAs (circRNAs), have been identified as regulators of the expression of FBPs in cancer.[27]

## F-box proteins and cancer stemness

FBPs have a major role in maintaining biological homeostasis by regulating proteins associated with cell cycle regulation, growth, and survival, development, and stemness features including EMT. Although much progress has been made in exploring the role of genetic and epigenetic changes affecting the expression and functioning of FBPs related to the pathogenesis of various

human diseases, including cancer, more research is required to result in improved therapeutic outcomes. Accumulating evidence shows that CSCs are crucial in cancer pathogenesis and clinical challenges; thus, thorough exploration is required of how major regulatory proteins of biological homeostasis are involved in CSC growth and survival. Here, we highlight recent advances in understanding how the dysregulated expression and functioning of FBPs modulate stemness features of CSCs (Fig. 3).

Yin *et al*. reported that FBXW2 has a crucial role in the expression of SOX2, an important stemness-associated transcription factor often dysregulated in human cancers, and further explored the vital role of the FBXW2–MSX2–SOX2 axis in regulation of cancer stemness and drug resistance.[28] Additionally, it has also been well elucidated that deregulated functioning of FBXL7 resulting from epigenetic changes has a crucial role in cancer pathogenesis and cancer stemness.[29]

Interestingly, to overcome resistance to apoptosis, it is important to explore the underlying mechanism associated with how CSCs evade cell death. Indeed, aberrant expression of FBXW7, a tumor suppressor often mutated in various human cancers, leads to cancer stemness and poor clinical outcomes. For instance, reduced FBXW7 expression has a crucial role in poor prognosis, survival, EMT, and chemoresistance in non-small-cell lung cancer (NSCLC), indicating its therapeutic importance.[30] Indeed, an increasing number of studies highlight the therapeutic importance of targeting the underlying regulatory mechanisms of cancer stemness, particularly the survival of CSCs. For example, it has been shown that FBXW7 is involved in protecting CSCs against cell death induced by anticancer agents.[31,32] Furthermore, by modulating the EMT-inducing transcription factor ZEB2, FBXW7 protects CSCs from anticancer drugs via modulating their stemness/dedifferentiation, chemoresistance, and cell migration. Hence, this axis uncovers a molecular pathway that governs the differential response of cancer cells toward chemotherapy and metastatic potential.[33] Therefore, FBXW7 has promising therapeutic importance because it targets cancer-initiating stem cells or malignant cells without affecting the growth and proliferation of normal stem cells. Somatic mutations affect the self-renewal and differentiation of cancer-initiating cells; for example, $FBXW7^{R465C}$ cancer somatic mutations, differentially affect CSCs and normal stem cells by regulating distinct thresholds of c-Myc expression between normal and malignant stem cells.[34] The clinical importance of FBXW7, a tumor suppressor, has also been explored because it has an integral role in DNA repair and maintaining genomic stability by promoting ATM-dependent phosphorylation and retention at damage sites, XRCC4 ubiquitination, and activation of nonhomologous end-joining (NHEJ),[35] and most human cancers harbor FBXW7 WD40 mutations that distort DNA repair mechanisms, resulting in genomic instability and tumorigenesis.[35] Moreover, aberrant functioning of FBXW7 resulting from mutation causes genomic instability, hematopoietic stem cell dysfunctions, and tumorigenesis by targeting cyclin E.[36] Furthermore, FBXW7 mutational status in human cancer cells respond differentially to pharmacological inhibitors/drugs, suggesting mutational status as a genetic biomarker in predicting drug sensitivity.[37] Although FBXW7 normally functions as a tumor suppressor, two mutations (D510E and D527G) in FBXW7 from adult patients with T cell leukemia have been shown to have oncogenic potential; thus, FBXW7 can also act as an oncogene associated with leukemia pathogenesis, including cancer stemness.[38]

FBXW7 acts as a key regulator of stemness features and functioning, given that its inactivation leads to aberrant proliferation and growth of stem or progenitor cells. In addition, inactivation of FBXW7 can lead to the regeneration of various pancreatic cell types (α, δ, and β cells) by reprogramming pancreatic ductal cells via stabilizing Ngn3, a key regulator of endocrine cell differentiation.[39]

Furthermore, aberrant expression of SOX9, a master regulator of stemness programming, development, and proliferation, is often detected in patients with cancer and is associated with poor prognosis and therapeutic outcomes. Interestingly, the tumor suppressor FBW7 regulates expression of SOX9 via ubiquitination and proteasomal degradation. However, in malignancies, distorted FBW7 expression resulting from genetic or epigenic changes results in SOX9 overexpression, and this is associated with metastasis and poor clinical outcomes.[40]

FBPs are a major regulator of nuclear factor erythroid-2-related factor 2 (NRF2), a key redox-sensitive transcription factor often overexpressed in cancer and CSCs, triggering their survival against cancer therapeutics.[41,42] The lncRNA SLC7A11-AS1 regulates stemness features, including anticancer drug resistance, via blocking FBP β-TRCP1-mediated ubiquitinated proteasomal degradation of NRF2, which ultimately results into low intracellular reactive oxygen species (ROS), favoring CSC stemness.[41]

SKP2 is another important FBP crucial for biological homeostasis; it is usually deregulated in human malignancies and orchestrates disease pathogenesis and clinical challenges, including cancer stemness.[43] Indeed, SKP2 regulates not only the stemness of CSCs, but also the proliferation of trophoblast stem cells, thereby having a pivotal role in placental development.[44] Furthermore, a recent investigation revealed that SKP2 is the central player in Mint3-regulated malignant features of pancreatic cancer, such as EMT, stemness features, and anticancer drugs (paclitaxel and gemcitabine) resistance.[45] Dysregulated SKP2 expression might also be involved in stemness features of, and is directly associated with, advanced clinical stages of synovial sarcoma.[46] Moreover, SKP2-induced p27 degradation promotes cancer stemness in osteosarcoma, a highly aggressive malignancy, highlighting the SKP2–P27 axis as a putative target for CSCs.[47] Interestingly, not only genetic but also pharmacological targeting of SKP2 attenuates stemness features and cancer pathogenesis, indicating its clinical importance.[43]

The molecular mechanisms underlying how CSCs switch to quiescence during treatment are a major research focus. FBPs (SKP2 and FBXW7) regulate the stem cell switch between quiescence and active mitotic division in lung adenocarcinoma, suggesting them as potential therapeutic targets.[48] In addition, elevated expression of SKP2 in patients with prostate cancer as well as in cell lines is central to the acquisition of cancer stemness phenotypes.[49] Strikingly, SKP2-induced stemness acquisitions through Twist stabilization are a major driving force in clinical challenges associated with castration-resistant prostate cancer (CRPC), suggesting Skp2 as a promising therapeutic target

for CRPC.[50] Moreover, SKP2 has a major role in regulating hematopoietic stem cell quiescence, pool size, and self-renewal, and has been shown to have therapeutic importance for BM transplantation and stem cell treatment.[51] In addition, cyclin-dependent kinase subunit 1 (CKS1), a rate-limiting component of the SKP2 ubiquitin ligase complex, maintains the growth and proliferation of normal and malignant hematopoietic stem cell self-renewal and quiescence via targeting SCFSkp2/Cks1.[52] Although EMT causes cancer stemness, there are also well-differentiated non-EMT cancer cells with tumorigenic potential and deregulated FBXO11 has been shown to selectively trigger the tumorigenicity of non-EMT-like clones via the p53/p21 pathway.[53]

FBXO9 is an integral regulator of CSCs features in patients with acute myeloid leukemia (AML). Indeed, ablating FBXO9 reversed oncogenic features, including tumor aggressiveness, and also enhanced sensitization to anticancer drugs.[54] Moreover, FBXL10 (KDM2B) with multifunctional domains, including JmjC domain and a CxxC zing finger, regulates stem cell self-renewal, somatic cell reprogramming and senescence, and tumorigenesis. Interestingly, it also induces negative regulation of cell proliferation via ubiquitylation and degradation of c-Fos protein and cancers with deregulated KDM2B because of mutations that inhibit c-Fos degradation, resulting in stemness and pathogenesis.[54] Hematopoietic stem cells with increased FBXL10 expression are associated with leukemia pathogenesis, affecting metabolic activation and Nsg2 expression and, thus, could be novel therapeutic targets.[55]

BXL5, a FBP with oncogenic potential, regulates stemness features, including therapeutic resistance, and, thus, could be a therapeutic target for CSCs in human cancers.[56] Furthermore, FBXO32 regulates Krüppel-like factor 4 (KLF4, GKLF) a zinc-finger transcription factor that controls myriad biological functions, including apoptosis, cell cycle, stemness features, cell fate decision, and cancer pathogenesis.[57] Indeed, upregulated KLF4 expression resulting from genetic and epigenetic ablation of FBXO32 promotes cancer pathogenesis and stemness.[58] Melanoma, a cancer with huge socioeconomic burden, and NRAS-mutant melanoma have poor prognosis and low survival rates. It was recently shown that FBXO42 is involved in NRAS-mutant melanoma-acquired resistance to the MEK1/2 inhibitor trametinib. Hence, the identification of genetic and epigenetic changes could improve the overall outcomes of patients with cancer.[59] Given the universal role of FBPs in biological homeostasis and disease pathogenesis, it was recently shown that FBXO11 enhances cancer progression, stemness, and epidermal development by targeting the increased ubiquitination of the Snail family of transcription factors.[60]

## F-box proteins: Promising targets to alleviate cancer stemness and to improve prognosis and clinical outcomes

Decades of research and clinical trials have demonstrated the critical role of FBPs in cancer pathogenesis, therapeutic challenges, and poor clinical outcomes. Protumorigenic (oncogenic) and antitumorigenic (suppressive) features of FBPs reflect their importance in cancer development, physiology, and homeostasis. Furthermore, increasing research on FBPs in human diseases and therapy also indicates the therapeutic importance of FBPs. For example, deregulated expression of FBPs is one a key determinant in disease pathogenesis and associated challenges, including poor prognosis and drug resistance.[61,62]

Thus, work is in progress to develop effective cancer drugs. For example, SKP2-targeted drugs might have major role in management of T cell acute lymphoblastic leukemia.[63] An array of studies (preclinical and clinical) reflects the therapeutic importance of FBPs (Table 1).

Accumulating evidence indicates the role of other FBP family members in poor prognosis and survival of patients with cancer by modulating stemness signaling mechanisms among others (Table 1).[28,30–32,34,36,40,43–50,55,58,64–85] Similarly, deregulated FBXO21 expression correlates with poor prognosis of patients with cancer via impacting EMT, which is often associated with cancer stemness and therapeutic failures.[86] Aberrant expression of FBXO11, a crucial cell cycle regulator targeting Bcl-6 and p53, in human renal cell carcinoma is associated with cancer metastasis and poor prognosis.[87] FBXO31 dysregulation resulting from epigenetic and genetic changes is associated with a higher malignant phenotype, poorer prognosis, and resistance in human cancers.[88] Similarly, clinicopathological features and therapeutic outcomes of patients with ovarian cancer are closely associated with deregulated FBXL20 expression, implying its prognostic and therapeutic potential.[89]

Interestingly, ncRNA, which constitutes a major portion of human genome, regulates underlying mechanisms of cancer pathogenesis, stemness, and therapeutic challenges, including poor prognosis and survival through FBPs. For instance, aberrant expression of miR-210 causes poor prognosis and survival in patients with cancer; it was recently shown that the miR-210/FBXO31 axis acts as an important therapeutic and prognostic target for esophageal squamous cell carcinoma.[90] In addition, deregulated expression of the lncRNA CASC2 through miR-367 and FBXW7 mediates cancer pathogenesis and therapeutic challenges by modulating EMT and, thus, is crucial as a clinicopathological feature of human neoplasm and can be a novel target for cancer treatment.[91] FBPs are also important in challenges associated with cancer chemotherapeutics, including poor survival and prognosis. Indeed, FBXW7 deregulation led to poor survival, cancer stemness, progression, and drug resistance via targeting NOTCH1 and leukemia sequence 1 (MCL1) in cholangiocarcinoma.[92]

## Concluding remarks and future directions

Overall, despite significant advances, the search for specific CSC markers and the integral signaling pathways underlying growth and stemness of CSCs is ongoing. Accumulating evidence suggests that FBPs, including FBXW7 and SKP2, are integral players in the development of cancer stemness features by modulating underlying mechanisms related to cancer hallmarks and reprogramming. Here, we have reviewed the potential of FBPs in regulating stemness features associated with biological homeostasis, cancer pathogenesis, and therapeutic challenges. In addition, recent developments have further explored the clinicopathological importance of FBPs in human disease and ther-

**TABLE 1**

**Title.**

| F-box proteins | Cancer type | Underlying stemness mechanisms and clinical values | Refs |
|---|---|---|---|
| FBXW7 | Colorectal cancer | miR-92a-3p regulates cancer pathogenesis and stemness features by targeting FBXW7 | 64 |
| | | FBXW7 deregulation promotes EMT, cancer stemness features, and drug resistance; mTOR inhibition attenuates its expression; thus, FBXW7–mTOR axis could be of major clinical importance | 65 |
| | | Deregulated expression has integral role in acquisition of cancer stemness features, including drug resistance, via targeting c-Myc | 31 |
| | Lung adenocarcinoma, NSCLC | Deregulated expression of FBXW7 and SKP2 have crucial roles in drug resistance by inducing stem cell switch between quiescence and proliferative stages by modulation of c-MYC and upregulation of p27 | 48 |
| | | Upregulate stemness features; have major role in maintenance of quiescence in gefitinib-resistant lung CSCs by modulating c-MYC | 32 |
| | | FBXW7 is crucial in oncogenic roles of miR-36,7 such as cancer stemness and drug resistance, via signaling modulation; predominately associated with stemness | 66 |
| | | FBXW7 mediates NSCLC pathogenesis by promoting cancer stemness by targeting EMT | 30 |
| | Cholangiocarcinoma | Essential role in cancer stemness features, including EMT and metastasis, by targeting several regulatory proteins | 67 |
| | | BXW7 regulates CSC self-renewal and differentiation degradation of MYC of spermatogonial stem cells | 68 |
| | T cell acute lymphoblastic leukemia | Aberrant expression of BXW7 because of mutations specifically bolster cancer-initiating cell activity in collaboration with Notch1 oncogenes but spare normal hematopoietic stem cell function by targeting MYC | 34 |
| | Glioma | Has important role in marinating diverse stem-like cell hierarchy that increases tumor aggressiveness and therapeutic resistance in association with Numb | 69 |
| | Prostate cancer | Vital in Guttiferone K-induced anticancer potential in prostate cancer via c-MYC degradation | 70 |
| | Lymphoid neoplasia | Dysregulated FBW7-mediated control of cyclin E is crucial in hematopoietic stem cell dysfunction and chromosomal instability associated with cancer pathogenesis | 36 |
| | Medulloblastoma | GSK3/FBW7-dependent activation of SOX9 promotes cancer pathogenesis and stemness features by targeting PI3K/AKT/mTOR pathway | 40 |
| FBXO11 | Breast cancer | Regulates EMT and metastasis. Hence, FBXO11 can act as metastasis inhibitor by suppressing cancer stemness | 71 |
| FBXL14 | Head and neck cancer | Crucial role in induced ubiquitinated degradation of Twist1; attenuates cancer pathogenesis and stemness features | 72 |
| | Glioblastoma multiforme (GBM) | Dysregulation in balance of USP13-mediated deubiquitination and FBXL14-induced ubiquitination of c-Myc has crucial role in GBM stem cell phenotype and tumorigenic potential; represents a therapeutic target and prognostic marker | 73 |
| FBX8 | Colorectal and liver cancer | Promotes stemness markers in liver metastatic dormancy of colorectal cancer; has potential as novel therapeutic strategies for metastasis | 74 |
| | Hepatocellular carcinoma | Crucial role in Nanog-associated cancer stemness features, including drug resistance | 75 |
| FBXL12 | | FBXL12 has a key role in regulation of ALDH3, a hallmark of normal stem cells (embryonic and adult tissue) and CSCs; is essential for their maintenance | 76 |
| βTrCP | | Crucial for proteasomal degradation of FAP4, a basic helix-loop-helix transcription factor regulating various genes related to stemness, and EMT in cancer | 77 |
| | Pancreatic ductal adenocarcinoma (PDA) | Upregulates cancer stemness features in PDA by associating with proteins, including SOX9, by modulating GLI1, β-catenin, and the anti-apoptotic factor MCL1; could be a major therapeutic strategies for cancer therapy | 78 |
| FBXW2 | | Regulates cancer stemness features and drug resistance by modulating SOX2, a transcription factor that controls expression of genes associated with stemness maintenance, growth, and survival; hence, FBXW2 targeting by therapeutic agents (e.g., MLN4924) would be of major clinical importance | 28 |
| SKP2 | | Has major role in stemness of various organs and developmental stages, such as placenta and trophoblast stem cells, by targeting p57 | 44 |
| | Prostate cancer | Has major role in EMT phenotypes, cancer stemness in prostate cancer patients via modulating expression of different genes | 49 |
| | Breast cancer | Deregulated p97/VCP play major role in cancer stemness and pathogenicity by upregulating CSC regulators such as MYC and SKP2, in addition to SOX2 and OCT4 | 79 |
| | NSCLC | Abnormal Skp2 expression promotes cancer pathogenesis and stemness via upregulating iPSC (induced pluripotent stem cell) and transcription factors (OCT4, SOX2, KLF4, and C-MYC) | 80 |
| | Synovial sarcoma | Associated with poor prognosis, promotes cancer stemness features and tumorigenesis by targeting p27 and Twist1 | 46 |
| | Castration-resistant prostate cancer (CRPC) | Has integral role in the progression and therapeutic resistance by maintaining stemness features through Twist stabilization | 50 |
| | Osteosarcoma | Orchestrates cancer stemness features and pathogenesis via targeting various proteins including p27 | 47 |
| | Nasopharyngeal carcinoma | Deregulated Skp2 has critical role in maintaining stemness features associated with poor clinical outcomes and prognosis | 81,82 |

(continued on next page)

**TABLE 1 (*CONTINUED*)**

| F-box proteins | Cancer type | Underlying stemness mechanisms and clinical values | Refs |
|---|---|---|---|
| | Pancreatic cancer | Integral for Mint3 induced cancer pathogenesis, stemness features, drug resistance, and poor prognosis | 45 |
| | Glioma | Has vital role glioma stemness via targeting regulatory genes and hence Skp2 could be a promising therapeutic target to improve the prognosis and survival | 83 |
| FBXL5 | | Regulates cellular iron homeostasis in maintenance and function of hematopoietic stem cells by modulating iron regulatory protein 2 (IRP2); hence, has potential clinical importance in human hematopoietic disease | 84 |
| FBXO32 | Breast cancer | Attenuates cancer stemness and pathogenesis by targeting post-translational modification of KLF4; thus, has both diagnostic and prognostic clinical importance | 58 |
| RBX2 | Leukemia | Downregulating RBX2 attenuates stemness features of embryonic stem cells and induces sensitization toward anticancer drugs by modulating associated signaling pathways | 85 |
| Fbxl10 | Leukemia | Hematopoietic stem cells with aberrant expression of Fbxl10 promote development of leukemia and stemness features by targeting metabolic and differentiation | 55 |



apy. Interestingly, the modulation of FBP expression and functioning because of genetic and epigenetic changes are the crucial determinants of cancer pathogenesis and stemness. Furthermore, deregulated expression of FBPs because of mutagenic and non-mutagenic changes modulates several underlying signaling mechanisms converging toward the cancer stemness features, including drug resistance, poor prognosis, and survival. Thus, FBPs exhibit great therapeutic importance with reference to targeting CSCs, disease-free survival, and better prognosis.

Moreover, additional preclinical and multicentric clinical studies are needed to better explore the clinical importance of targeting FBPs. Furthermore, it is also vital to understand the correlation between epigenetic and genetic oncogenic factors and status of stemness-regulatory FBPs to better understand and classify high-risk FBPs to achieve better prognostic and clinical outcomes. Developing novel models to identify and explore the underlying role of crucial FBPs in the dynamics and diverse functioning of CSCs would be an important step to identify and target deregulated FBPs regulating CSCs associated with tumor pathogenesis, including heterogeneity and resistance.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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