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Mini-review

Regulation of F-box proteins by noncoding RNAs in human cancers

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ABSTRACT

F-box proteins (FBPs) are proteins containing an F-box domain and are one of three subunits in SKP1–Cullin1–F-box protein (SCF) E3 ligase complexes. Accumulated evidence has shown that FBP regulates tumorigenesis and the progression of human cancer via ubiquitination and degradation of downstream substrates, which can be oncoproteins or tumor suppressors. Emerging evidence has revealed that noncoding RNAs (ncRNAs) govern the expression of FBP in human cancers. Specifically, microRNAs (miRNAs), long ncRNAs (lncRNAs), and circular RNAs (circRNAs) have been shown to govern FBP expression in malignancies. Therefore, in this review article, we discuss how miRNAs target FBPs and participate in tumorigenesis and tumor progression. Moreover, we briefly highlight the role of lncRNAs and circRNAs in the regulation of FBPs in cancer. Therefore, targeting ncRNAs could be a novel approach to regulate FBPs for anticancer therapy.

1. Introduction

The ubiquitin proteolysis system (UPS) and autophagic lysosome pathway are the two main pathways regulating protein degradation in cells [1,2]. The UPS mainly consists of a three-step enzymatic cascade (E1, E2, and E3) [3]. This reaction contains two well-defined steps that are involved in UPS-targeted protein degradation [4]. First, ubiquitins are activated and combined with the ubiquitin-activating enzyme E1, which requires an ATP. Then, the activated ubiquitins are transferred to the target protein via ubiquitin-conjugating enzyme E2. The ubiquitin-protein ligase E3 serves as a docking protein because it can bind to substrates and E2, leading to ubiquitin transfer [5,6]. Second, recognition and degradation of substrates containing polyubiquitin chains is conducted by the 26S proteasome [6,7]. E3 enzymes specifically recognize substrates of ubiquitination and subsequent degradation [8]. The human genome encodes more than 600 ubiquitinated E3 ligases. Many ubiquitinated ligases have been correlated with tumor occurrence and malignant phenotypes [9]. E3 enzymes are mainly categorized into two major types: one type of E3 ligase includes the Cullin-really interesting new gene (RING) domain, and the other E3 enzymes contain homologs of the E6-associated protein C-terminus (HECT) domain. The Cullin-RING ligase (CRL) includes SCF-type ligases that consist of Skp1, Cul1, Rbx1, and an FBP [10].

It has been verified that 69 FBPs are present in the human genome [3]. FBP contains two domains: a C-terminal domain that binds to specific targets [11], and an F-box motif that selectively binds to their cognate substrates [12]. The 69 FBPs are divided into three subclasses according to the specific domains: 10 FBXW proteins, 22 FBXL proteins, and 37 FBXO proteins containing WD40 repeat domains, leucine-rich repeat domains, and other motifs, respectively [13,14]. The FBP family regulates the level of its downstream targets, which could be oncoproteins or tumor suppressors, leading to the regulation of tumorigenesis and cancer progression [15,16]. Recently, emerging evidence has revealed that noncoding RNAs (ncRNAs) could govern FBPs expression in human cancer. Therefore, we will discuss how ncRNAs target FBPs and participate in tumorigenesis and tumor progression. Moreover, we will highlight that targeting ncRNAs could be a novel strategy for fighting cancer via the regulation of FBPs.

1.1. FBP is regulated by ncRNAs

More than 90% of human genome sequences can be transcribed, but only a few transcripts can be used as messenger RNA (mRNA) to encode proteins. Most transcripts are ncRNAs with little or no protein coding

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Table 1
MiRNAs-regulated F-box protein expression and their impacts on cancer.

F-box protein	MiRNAs	Cancer types	FBP Functions
FBXW7	miR-27a	BC, CRC, ccRCC	Tumor suppressor
	miR-27b	HCC	Tumor suppressor
	miR-27a-3p	ESCC	Tumor suppressor
	miR-770	HCC	Tumor suppressor
	miR-182, miR-367, miR-503	NSCLC, CRC	Tumor suppressor
	miR-223	PDAC, NSCLC, GC, CRC, T-ALL	Tumor suppressor
	miR-223–3p	TGCT, GC, ESCC.	Tumor suppressor
	miR-363	GC	Tumor suppressor
	miR-25	GC, NSCLC, PSCNC, ESCC	Tumor suppressor
	miR-92a	GC, CC, HCC, OS	Tumor suppressor
	miR-92b-3p	CRC	Tumor suppressor
	miR-194	BC	Tumor suppressor
	miR-155–3p	HCC	Tumor suppressor
	miR-32	MM	Tumor suppressor
	miR-24	TSCC	Tumor suppressor
FBXW8	miR-3160–5p	PrC	Tumor promoter
	miR-218	CHC	Tumor promoter
β-TrCP	miR-183	LE	Tumor promoter
	miR-BART 10–3p	NPC	Tumor suppressor
	miR-10b-5p	MM	Tumor promoter
	miR-135b	LC, HCC	Tumor suppressor
	miR-920	HCC	Tumor promoter
FBXW11	miR-182	PC, HNSCC	Tumor suppressor
	miR-106b-25	NSCLC	Tumor suppressor
Skp2	miR-340	NSCLC, HCC	Tumor promoter
	miR-30 family	LC	Tumor promoter
	miR-1236–3p	BLC	Tumor promoter
	miR-186	ESCC	Tumor promoter
	miR-508–5p	GC	Tumor promoter
	miR-1297	NSCLC	Tumor promoter
	miR-339	LC	Tumor promoter
	miR-30a-5p	OC	Tumor promoter
	miR-21–5p, miR-26–5p, miR-30–5p	BC	Tumor promoter
FBXL2	miR-346	HCC	Tumor suppressor
FBXL3	miR-181d	CRC	Tumor suppressor
	miR-4735–3p	NSCLC	Tumor suppressor
FBXL5	miR-20	CC	Tumor suppressor
	miR-1306–3p	HCC	Tumor suppressor
FBXL10	miR-146b	OC	Tumor suppressor
FBXL20	miR-3151	CN-AML	Tumor suppressor
FBXO8	miR-223	CRC	Tumor suppressor
FBXO11	miR-26a	HCC	Tumor promoter
	miR-621	BC	Tumor promoter
	miR-21	ME, PrC, GB	Tumor suppressor
FBXO31	miR-93, miR-106a	BC	Tumor suppressor
	miR-210	BC	Tumor suppressor
	miR-20a, miR-17	GC	Tumor suppressor
	miR-29c	ESCC	Tumor suppressor

BC: breast cancer; BLC: bladder cancer; ccRCC: clear cell renal cell carcinoma; CHC: choriocarcinoma; CN-AML: cytogenetically normal acute myeloid leukemia; CC: cervical cancer; CRC: colorectal cancer; ESCC: esophageal squamous cell carcinoma; GB: glioblastoma; GC: gastric cancer; HCC: hepatocellular carcinoma; HNSCC: head and neck squamous cell carcinoma; LC: lung cancer; LE: Leukemia; ME: melanoma; MM: multiple myeloma; NPC: nasopharyngeal carcinoma; NSCLC: non-small cell lung cancer; OS: osteosarcoma; OC: ovarian cancer; PC: pancreatic cancer; PDAC: pancreatic ductal adenocarcinoma; PrC: prostate cancer; TGCT: testicular germ cell tumors; T-ALL: T-cell acute lymphoblastic leukemia; TSCC: tongue squamous cell carcinoma.

ability. According to the lengths of nucleotides, ncRNAs can be divided into short ncRNAs (sncRNA, 17–30 bp), mid-size ncRNAs (mncRNA, 31–200 bp), and long ncRNAs (lncRNA, > 200 bp) [17]. Among them, lncRNA, microRNA (miRNA) and circular RNA (circRNA) are research hotspots [18,19]. MiRNAs are type of ncRNAs with approximately 22 nucleotides that governs gene expression at the post-transcriptional level and participates in cancer development and progression [20–22]. In recent years, multiple studies have shown that lncRNA is involved in regulating proteins at the transcriptional, post-transcriptional and epigenetic levels, thus affecting a variety of biological processes, such as cell growth, apoptosis, motility and angiogenesis [23,24]. The 3′ and 5′ ends of circRNA join together covalently and form a loop [25]. Increasing data have unraveled that circRNA is critical in controlling gene expression in cancer because it serves as sequestration or sponge in miRNA expression [26]. CircRNA could be an essential regulator in several human diseases, including Alzheimer, atherosclerotic vascular disease, and cancers [27–29]. In summary, ncRNAs are involved in cancer development and progression through targeting FBPs. Thus, we will describe how different FBPs are regulated by various ncRNAs (Table 1).

1.2. MiRNAs regulate FBPs in cancer

Evidence has indicated that FBPs are regulated by miRNAs in human cancers. Thus, in the following section, we summarize which miRNAs target FBPs in tumorigenesis. It should be noted that one miRNA can target multiple FBPs, and one FBP can be regulated by several miRNAs.

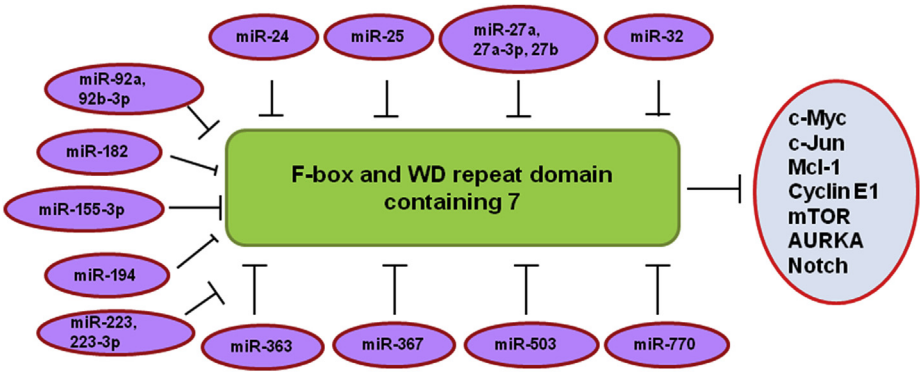

Fig. 1. FBXW7 expression is regulated by multiple miRNAs. Oncogenic miRNAs promote tumorigenesis and tumor progression by suppressing tumor suppressor FBXW7 expression in a variety of human cancers. FBXW7 promotes the degradation of its substrates, includng c-Myc, c-Jun, Mcl-1, cyclin E1, mTOR, AURKA, and Notch.

1.3. The FBXW family

1.3.1. Tumor suppressor FBXW7

It has been validated that the F-box and WD repeat domain containing 7 (FBXW7), which is also known as Sel10, hCDC4 and hAgo, is a tumor suppressor [30]. FBXW7 exerts its antitumor activity by targeting its downstream genes [31]. FBXW7 is also involved in the regulation of epithelial to mesenchymal transition (EMT) and cancer stem cells [32,33]. A study has described that FBXW7 is expressed at lower levels in tumor tissues and is associated with the overall survival rate in breast cancer patients [34]. In addition, miR-27a is overexpressed in breast cancer tissues and promotes cell migration via induction of EMT. Moreover, miR-27a downregulates FBXW7, resulting in EMT and increased migration in breast cancer cells [34]. This study revealed that FBXW7 is a direct target of miR-27a in breast cancer [34]. Similarly, another study identified that miR-27a directly targets FBXW7 in clear cell renal cell carcinoma (ccRCC) [35]. Specifically, that study found that cholesterol increases cell motility via regulation of the KLF5 (Krueppel-like factor 5)/miR-27a/Fbxw7 axis in ccRCC [35]. One group also showed that miR-27a enhances cell growth by targeting FBXW7 in colorectal cancer [36]. MiR-27b is overexpressed in human hepatocellular carcinoma (HCC) patients and targets FBXW7, suggesting that it plays an oncogenic role in HCC via inhibition of FBXW7 [37]. MiR-27a-3p promotes cell proliferation via suppression of FBXW7 in esophageal cancer cells [38]. Moreover, miR-770 has been reported to inhibit the expression of FBXW7 in HCC, leading to HCC development [39].

MiR-182 and miR-367 promote cell proliferation by suppressing FBXW7 in non-small cell lung cancer (NSCLC) [40–42]. Another study reported that miR-182 and miR-503 cooperatively inhibit the expression of FBXW7, causing adenocarcinoma transformed from colon adenoma [43]. It has been unveiled that oncogenic miR-223 promotes cell growth, migration, and invasion in pancreatic ductal adenocarcinoma (PDAC) by directly targeting FBXW7 and subsequently increasing heterogeneous nuclear ribonucleoprotein K (hnRNPK) [44]. The hnRNPK downregulation reduces miR-223 levels in PDAC cells, indicating a miR-223/FBXW7/hnRNPK feedback cascade in PDAC [44]. Similarly, miR-223–3p promotes cell growth and inhibits cell apoptotic death via suppression of FBXW7 in human testicular germ cell tumors (TGCT), esophageal squamous cell carcinoma, and gastric cancer [45–47]. Additionally, miR-223 is involved in erlotinib resistance via downregulation of FBXW7 in NSCLC [48]. Moreover, Akt and Notch signaling pathways increase the expression of miR-223 in NSCLC [48]. Consistently, miR-223 enhances doxorubicin resistance by regulating EMT due to direct targeting of FBXW7 in colorectal cancer cells [49]. Furthermore, miR-223 increases cisplatin resistance by governing the cell cycle by targeting FBXW7 in gastric cancer cells [50]. MiR-223 promotes chemoresistance to trastuzumab via inhibition of FBXW7 in gastric cancer cells [51]. Notch/nuclear factor-kappa B (NF-κB)-mediated miR-223 overexpression promotes the development of T-cell acute lymphoblastic leukemia (T-ALL), and decreases γ-secretase inhibitor (GSI) sensitivity via suppression of FBXW7 [52]. Moreover, the oncogenic transcription factor T-ALL protein 1 (TAL1)/stem cell leukemia (SCL) upregulates miR-223 expression and inhibits FBXW7, leading to the malignant phenotype of T-ALL [53].

Oncogenic miR-363 enhances cell proliferation and chemoresistance through suppression of FBXW7 in human gastric cancer [54]. In addition, miR-25 inhibits cell apoptosis and increases cell viability via suppression of FBXW7 and subsequent upregulation of cyclin E1, Myc and aurora kinase A (AURKA) in gastric cancer, NSCLC, and prostatic small cell neuroendocrine carcinoma [55–58]. Moreover, another group revealed that miR-25 promotes cell invasion and metastasis via inhibition of FBXW7 in esophageal squamous cell carcinoma (ESCC) [59]. Notably, miR-92a has been identified to inhibit the expression of FBXW7 in gastric cancer, cervical cancer, and HCC, leading to increased cell proliferation and invasion [60–62]. Similarly, miR-92a promotes tumor growth by inhibiting FBXW7 in osteosarcoma [63]. Strikingly, miR-92b-3p inhibits FBXW7 expression, which promotes cell proliferation, motility and invasion in colorectal carcinoma [64]. It has been proposed that miR-194 accelerates the proliferation of breast cancer cells through targeting FBXW7 [65]. Oncogenic miR-155–3p has also been found to promote HCC formation via suppression of FBXW7 [66]. One group observed an increase in miR-32 expression in multiple myeloma disease and miR-32 targeting of FBXW7 and subsequent increases in the expression of c-Jun and c-Myc, two FBXW7 targets [67]. Oncogenic miR-24 increases proliferation and motility via downregulation of FBXW7 in tongue squamous cell carcinoma [68]. In summary, the regulation of FBXW7 by miRNAs has been well studied (Fig. 1).

1.3.2. The oncogenic protein FBXW8

One group has shown that deletion of FBXW8 in mice leads to pre- and postnatal growth inhibition, indicating that FBXW8 is significantly involved in growth control [69]. Moreover, FBXW8 controls cell proliferation through proteolysis of Cyclin D1 in various cancer cells [70]. Similarly, silencing FBXW8 retards cell growth and enhances cell cycle arrest in choriocarcinoma cells, whereas overexpression of FBXW8 has the opposite effect [71]. In line with the oncogenic role of FBXW8, one group has shown that FBXW8 promotes cell proliferation via suppression of hematopoietic progenitor kinase 1 (HPK1) in pancreatic cancer [72]. FBXW8 is a downstream target of miR-3160–5p in prostate cancer [73]. Consistently, miR-3160–5p is negatively associated with the expression of FBXW8 in prostate cancer cells. Moreover, miR-3160–5p upregulation represses cell growth and triggers cell cycle arrest via suppression of FBXW8 in prostate cancer cells [73]. Moreover, miR-218 directly targets FBXW8 in human choriocarcinoma cells [74]. Overexpression of miR-218 represses cell growth and induces cell cycle arrest as well as suppresses Cyclin A and increases p27 due to inhibition of FBXW8. Consistently, forced expression of FBXW8 in part rescues the function of miR-218 in choriocarcinoma cells [74].

1.3.3. FBXW1

FBXW1, also named β-transducin repeat-containing protein 1 (β-TrCP1), exerts its antitumor or oncogenic functions in various types of cancers [3]. One study has shown that miR-183 decreases β-TrCP expression, and inhibits β-TrCP-mediated ubiquitylation and degradation of SP1 in human leukemia cells [75]. Forkhead box p3 (FOXP3) can inhibit β-TrCP via upregulation of miR-183 in leukemia cells [75]. One elegant study has revealed that coding region determinant-binding protein (CRD-BP) binds to β-TrCP1 mRNA, leading to enhanced stability of β-TrCP1. Moreover, this group validated that CRD-BP prevents β-TrCP mRNA degradation via attenuating the interactions between Argonaute2 and β-TrCP1 mRNA in a miR-183-dependent manner in colorectal cancer cells [76]. Two studies have shown that Epstein-Barr virus (EBV) encoded-miR-BART 10–3p directly targets the beta-transducin repeat containing E3 ubiquitin protein ligase (BTRC) gene encoding β-TrCP, leading to EMT and enhanced metastasis in nasopharyngeal carcinoma (NPC) cells [77,78]. Consistently, miR-BART 10–3p expression is correlated with a poor prognosis in NPC patients, and it is negatively associated with the BTRC level in NPC tumor samples [77]. Additionally, BTRC and Myc-binding protein (MYCBP) are predicted to be two targets of miR-10b-5p in multiple myeloma [79]. Moreover, miR-10b-5p may serve as a putative tumor suppressor in part via repression of β-TrCP in multiple myeloma [79]. MiR-135b overexpression promotes migratory and invasive abilities via inhibition of several targets including β-TrCP, large tumor suppressor homolog 2 (LATS2), N-myc downstream regulated gene 2 (NDR2) and leucine zipper tumor suppressor gene 1 (LZTS1) in lung cancer and hepatocellular carcinoma cells [80,81]. Chen et al. proposed that miR-920 can mediate the β-TrCP regulation model in HCC [82].

1.3.4. FBXW11

FBXW11, also known as β-TrCP2, is regulated by several miRNAs in human tumors. One study has revealed that oncogenic miR-182 promotes cell growth, and cell cycle progression and suppresses apoptosis by directly targeting FBXW11 in NSCLC [40]. In line with this finding, miR-182 is significantly overexpressed in tumor tissue, and inversely associated with the FBXW11 protein level in NSCLC [40]. Similarly, miR-182 promotes cell growth and migration via targeting FBXW11 and increases β-catenin expression in pancreatic cancer [83]. In addition, overexpression of miR-182 enhances cell growth and motility by targeting FBXW11 in head and neck squamous cell carcinoma [84]. Moreover, the miR-106b-25 cluster promotes Snail expression and increases cell motility by targeting FBXW11 in NSCLC [85].

1.4. The FBXL family

1.4.1. Skp2 (FBXL1) oncoprotein

S-phase kinase associated protein 2 (Skp2) facilitates tumorigenesis and cancer progression due to targeting multiple tumor suppressors including p21, p27, forkhead box protein O1 (FOXO1), and E-cadherin [5,13]. Numerous studies have shown that multiple miRNAs target Skp2 in human cancer cells [86–89] (Fig. 2). For instance, one study revealed that miR-340 represses growth and triggers apoptosis via suppression of Skp2 in NSCLC [86]. The miR-30 family, including miR-30a-e, suppresses pulmonary vascular hyperpermeability of the pre-metastatic niche via Skp2 inhibition [87]. MiR-1236–3p suppresses cell proliferation and promotes cell cycle arrest partly by regulating Skp2 and p21 expression in bladder cancer cells [88]. Another study demonstrated that miR-186 represses cell proliferation and stimulates apoptosis via direct targeting of Skp2 in human ESCC [89]. Duan et al. found that miR-508–5p inhibits metastasis by targeting Skp2 in human gastric cancer [90]. Bu et al. reported that miR-1297 increases cell proliferation by regulating the phosphatase and tensin homolog (PTEN)/Akt/Skp2 signaling pathway in NSCLC, indicating that miR-1297 can indirectly regulate Skp2 expression [91]. Similarly, miR-200b/c induces cell growth by targeting the reversion-inducing cysteine-rich protein with Kazal motifs (RECK) in colorectal cancer. RECK represses the expression of Skp2 and subsequently increases the p27 level [92]. An elegant study has unveiled that miR-3163 and maternally expressed gene 3 (Meg3) synergistically inhibit the translation of Skp2 mRNA in NSCLC cells, leading to suppression of NSCLC cell growth [93]. Additionally, miR-340 suppresses cell growth and motility, and enhances apoptosis through the downregulation of Skp2 in hepatocellular carcinoma [94]. Similarly, miR-339 inhibits cell growth by directly inhibiting Skp2 in lung cancer [95]. MiR-30a-5p inhibits cell motility and invasion in part by downregulating Skp2 in ovarian cancer cells [96]. Moreover, overexpression of several miRNAs, miR-21–5p, miR-26–5p, and miR-30–5p, suppresses Skp2 mRNA in MCF-7 cells and tamoxifen-resistant MCF-7 cells, indicating that Skp2 could be one target of these miRNAs [97].

1.4.2. FBXL2

Several studies have demonstrated that FBXL2 critically participates in tumorigenesis and progression [98–100]. Chen et al. reported that overexpression of FBXL2 triggers cell apoptosis and cell cycle arrest and induces chromosomal anomalies via ubiquitination and degradation of cyclin D3, indicating that FBXL2 is a tumor suppressor in human lung cancer [98]. They also found that FBXL2 degrades cyclin D2 to repress cell proliferation in leukemia [100], and targets aurora B, leading to suppression of tumorigenesis [99]. One elegant study revealed that FBXL2-mediated degradation of p85β governs the phosphatidylinositol 3-kinase (PI3K) signaling cascade and subsequent regulation of autophagy [101]. Furthermore, PTEN counteracts FBXL2 to enhance inositol 1,4,5-trisphosphate receptors (IP3R3)- and Ca^{2+}-mediated apoptosis, leading to tumor growth inhibition [102]. Notably, the viral protein nonstructural protein 5A (NS5A) enhances the constitutive degradation of IP3R3 by FBXL2, resulting in apoptosis induced by hepatitis C virus [103]. Recently, FBXL2 was found to inhibit cell proliferation and invasion via promotion of ubiquitination and degradation of forkhead box protein M1 (FoxM1) in gastric cancer cells [104]. MiR-346 has been validated to promote cell growth, motility, and invasive activity through suppression of FBXL2 in liver cancer [105]. The other miRNAs that target FBXL2 in human cancer need to be identified in the near future.

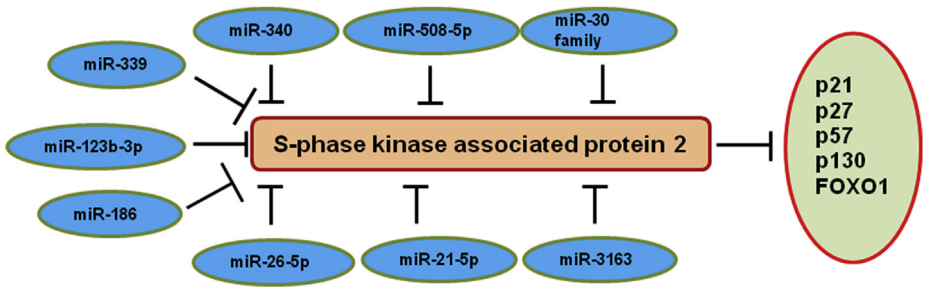

Fig. 2. Skp2 expression is regulated by several miRNAs. Multiple miRNAs exert their tumor suppressive functions by targeting Skp2 expression in various types of human cancers. Skp2 promotes the degradation of its substrates, includng p21, p27, p57, p130, and FOXO1.

1.4.3. FBXL3

FBXL3 governs the oscillation of the circadian clock via inhibition of the cryptochrome proteins, Cry1 and Cry2 [106]. FBXL3 and Cry2 cooperatively degrade c-Myc, providing new insights into the circadian control of cell growth [107]. MiR-181d enhances cell growth, motility, and invasion by stabilizing c-Myc via directly targeting FBXL3 and CRY2, leading to the promotion of glucose consumption and lactate production in colorectal cancer [108]. Moreover, c-Myc activates miR-181d expression, suggesting that miR-181d, CRY2, FBXL3, and c-Myc form a feedback loop to regulate metabolism in colorectal cancer [108]. Recently, FBXL3 was identified as one target of miR-4735–3p and retards cell growth and invasive functions in NSCLC [109]. It is necessary to elucidate the additional miRNAs that regulate FBXL3 expression.

1.4.4. FBXL5

FBXL5 plays an essential role in carcinogenesis. For example, FBXL5 promotes the ubiquitination and degradation of Snail1, an EMT inducer [110]. Similarly, FBXL5 inhibits cell invasiveness via suppression of Snail1 in gastric cancer, suggesting that FBXL5 is an attractive target for retardation of invasion and metastasis [111]. FBXL5 negatively regulates human single strand DNA binding protein 1 (hSSB1) expression to govern the DNA damage response in lung cancer, implicating FBXL5 as a useful therapeutic target in cancer [112]. Moreover, FBXL5 modulates gastric cancer migration through cortactin destruction, and depletion of FBXL5 promotes cisplatin resistance via extracellular signal regulated kinases (ERK) and p38 activation [113]. FBXL5 attenuates RhoGD12-mediated cisplatin resistance, but not by regulating the abundance and stability of RhoGD12 in gastric cancer cells [113]. FBXL5 promotes colon cancer progression by targeting PTEN and subsequent activation of PI3K, Akt and mammalian target of rapamycin (mTOR) expression [114]. It has been reported that inhibitor of apoptosis-stimulating protein of p53 (iASPP) mediates EMT and confers cisplatin resistance via the upregulation of miR-20 and subsequent downregulation of FBXL5 and BTG antiproliferation factor 3 (BTG3), two direct targets of miR-20a in cervical cancer [115]. Recently, miR-1306–3p has been shown to directly target FBXL5 and lead to the upregulation of Snail, resulting in EMT in hepatocellular carcinoma [116].

1.4.5. FBXL10

FBXL10 is also known as JmjC domain-containing histone demethylase 1b (JHDM1B), lysine-specific demethylase 2B (KDM2B), and Ndy1. The Pagano group reported that JHDM1B/FBXL10 suppresses the transcription of ribosomal RNA genes [117]. Moreover, low levels of FBXL10 expression are observed in aggressive brain tumors, defining a role for FBXL10 in tumorigenesis [117]. He et al. found that FBXL10 could be a histone H3 lysine 36 (H3K36) demethylase and control cell growth and senescence via p15 [118]. Furthermore, FBXL10 has been identified as an NF-κB-dependent antiapoptotic protein that inhibits tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis via regulation of the c-Fos/c-FLIP pathway [119]. One study showed that the FBXL10-let-7-enhancer of zester homolog 2 (EZH2) pathways contributes to cell cycle progression, cell proliferation, and senescence in primary cells [120]. FBXL10 promotes pancreatic cancer development and is markedly overexpressed in human pancreatic cancer tissues, which is correlated with the tumor grade, stage and metastases [121]. A transgenic mouse study demonstrated that overexpression of FBXL10 in hematopoietic stem cells (HSCs) leads to leukemia via metabolic activation and neuron-specific gene family member 2 (Nsg2) overexpression [122]. FBXL10 negatively regulates cell proliferation by targeting c-Fos protein degradation [123]. Zhao et al. found that FBXL10 knockdown suppresses cell proliferation and induces autophagy via downregulation of pAkt and mTOR, and upregulation of pERK in gastric cancer cells [124]. In addition, FBXL10 promotes cell proliferation and inhibits apoptosis via activation of the ERK1/2 signaling pathway in diffuse large B-cell lymphoma [125]. MiR-146a and miR-146b have been validated to regulate the expression of FBXL10 in human cancers. One study reported that miR-146b enhances cell proliferation, increases chemosensitivity, and retards cell motility and invasive activity through inhibition of FBXL10 in ovarian cancer [126]. Another study demonstrated that miR-146a directly targets FBXL10 and subsequently modulates cell apoptosis [127]. These studies suggest that FBXL10 could be regulated by miRNAs in human cancers.

1.4.6. FBXL20

Emerging evidence has shown that FBXL20 participates in colon tumorigenesis. FBXL20 is highly upregulated in tumor samples in colorectal adenocarcinoma. Downregulation of FBXL20 inhibits cell growth and induces apoptosis as well as triggers cell cycle arrest [128]. This study also showed that FBXL20 could regulate the expression of E-cadherin, c-Myc, cyclin D1, protein phosphate 2A (PP2A), p53, and β-catenin in colon cancer, indicating that FBXL20 induces tumorigenesis in part via regulation of Wnt signaling and caspase activation [128]. FBXL20 has been characterized as an invasion inducer in colorectal adenocarcinoma [129]. Overexpression of FBXL20 increases β-catenin and c-Myc levels, but decreases E-cadherin expression, leading to the promotion of invasion in colorectal cancer [129]. MiR-3151 is highly expressed in cytogenetically normal acute myeloid leukemia (CN-AML) patients, a phenomenon that is correlated with shorter disease-free and overall survival [130]. FBXL20 has been validated as a direct target of miR-3151, indicating that miR-3151 exerts its oncogenic functions partly through inhibition of FBXL20 in CN-AML [130].

1.5. The FBXO family

1.5.1. FBXO8

FBXO8, also known as FBX8, has been associated with tumor malignancies. FBXO8 overexpression inhibits small GTP-binding protein Arf6 (ADP ribosylation factor 6) activity and suppresses invasion in breast cancer cells [131]. It is noteworthy that FBXO8 suppresses Arf6 activity via noncanonical ubiquitination [131]. Strikingly, c-Myc induces cell invasion via inhibition of FBXO8-mediated inhibition of Arf6 [132]. Wang et al. reported lower expression of FBXO8 in HCC tissues, which is associated with a poor prognosis, suggesting that FBXO8 could be a prognostic factor [133]. In line with this finding, overexpression of FBXO8 inhibits growth and invasion in HCC cell lines and retards tumor size in mice [133]. Similarly, downregulation of FBXO8 has been observed in human glioma and correlates with tumor grade and a poor prognosis [134]. Another study revealed that FBXO8 is downregulated in tumor samples and is correlated with a shorter overall survival time and poor prognosis in gastric cancer [135]. Consistently, FBXO8 downregulation increases proliferation and invasion, whereas FBXO8 overexpression represses proliferation and motility in HCC cells [135]. Furthermore, FBXO8 inhibits GSTP1 via ubiquitin-mediated proteasome degradation in colorectal carcinoma, leading to an inhibition of proliferation, invasion and metastasis [136]. Lower expression of FBXO8 is observed in human colorectal carcinoma and is associated with poor overall survival of patients. FBXO8 suppresses metastasis via ubiquitin-mediated degradation of mTOR in colorectal carcinoma (CRC). Moreover, miR-223 has been identified to directly target FBXO8 in CRC cells [137]. Consistently, lower expression of FBXO8 is correlated with miR-223 and mTOR levels in human CRC tissues [137].

1.5.2. FBXO11

Increasing evidence has uncovered that the involvement of FBXO11 in carcinogenesis and cancer progression. One study has shown that FBXO11 promotes neddylation of p53 and leads to suppression of p53 functions [138]. FBXO11 mutations and deletions lead to lymphomagenesis via targeting BCL6 degradation in diffuse large B-cell lymphomas [139]. Moreover, FBXO11 regulates Cul4-RING protein ligase (CRL4) ubiquitin ligase and the timing of cell cycle exit [140]. Zheng et al. reported that FBXO11 degrades SNAIL in a polycystic kidney

disease associated protein 1 (PKD1) phosphorylation dependent manner in breast cancer, resulting in an inhibition of EMT and metastasis [141]. A similar study showed that FBXO11 promotes SNAIL ubiquitination and degradation during cancer progression [142].

One study reported that the upregulation of FBXO11 in HCC tissues and correlates with poor survival of HCC patients, but an inverse association with miR-26a expression in these tissues [143]. Moreover, miR-26a decelerates the behavior of HCC cells, including proliferation, colony formation, migration, and invasion, by regulating FBXO11 [143]. One group used Affymetrix Gene-Chip miRNA arrays and TaqMan MicroRNA Assays to verify the miRNA expression in dysplasia compared with the normal control [144]. This group identified high expression of miR-421, miR-29b-1-5p, and miR-27b-5p in gastric dysplasias [144]. According to miRNA-target interactions, FBXO11 and CREBZF are two key molecules for predicting gastric cancer progression [144]. Since this study did not identify FBXO11 as a direct target of these three miRNAs, further investigation is needed to verify this point. Moreover, miR-621 promotes cell apoptosis and increases chemosensitivity to paclitaxel and carboplatin via inhibition of FBXO11 and subsequent activation of p53 in breast cancer [145]. Furthermore, FBXO11 expression is negatively associated with miR-621 and positively correlated with a poor prognosis in breast cancer patients [145]. FBXO11 has been validated as a downstream molecule of miR-21, and miR-21 promotes tumorigenesis via inhibition of FBXO11. FBXO11 and miR-21 are inversely associated in tissue samples, and patients with high levels of FBXO11 show better survival [146].

1.5.3. FBXO31

FBXO31 has been characterized as a breast tumor suppressor that represses cell growth and colony growth in breast cancer [147]. Consistently, FBXO31 expression is decreased in breast tumors [147]. Moreover, FBXO31 induces G1 cell cycle arrest after DNA damage via the regulation of cyclin D1 degradation [148]. Similarly, FBXO31 is downregulated and exerts antitumor activity via the promotion of cyclin D1 degradation in hepatocellular carcinoma [149]. FBXO31 regulates the abundance of Cdt1, one DNA replication factor, via ubiquitination in G2 phase, and it prevents re-replication, which contributes to the function of FBXO31 as a tumor suppressor [150]. Higher levels of FBXO31 are correlated with the clinical stage and a poorer prognosis in ESCC patients [151]. Liu et al. found that FBXO31 negatively modulates p38 mitogen-activated protein kinase (MAPK) via degradation of mitogen-activated protein kinase kinase 6 (MKK6) [152]. Furthermore, FBXO31 can promote mouse double minute 2 (MDM2) degradation and leads to p53-mediated growth arrest following DNA damage [153]. Recently, FBXO31 was reported to target SNAIL1 for degradation, leading to inhibition of EMT in gastric cancer [154].

One study has unraveled that the oncogenic miRNAs miR-93 and miR-106a enhance breast cancer invasion and EMT via repression of the tumor suppressor protein FBXO31, leading to the upregulation of Slug [155]. MiR-93 and miR-106a are overexpressed in breast tumors, and their expression is driven by Slug, an FBXO31 ubiquitination target, indicating a positive feedback loop in the maintenance of the invasive phenotype [155]. Another study demonstrated that miR-210 promotes cell proliferation, the cell cycle, and migration by targeting FBXO31 in human breast cancer [156]. In line with this finding, miR-210 expression is inversely expressed with FBXO31 in breast cancer cell lines [156]. Lower levels of FBXO31 are observed in gastric cancer tissues and are associated with tumor grade and prognosis [157]. Overexpression of FBXO31 inhibits colony formation and induces cell cycle arrest via inhibition of cyclin D1 in gastric cancer cells. Strikingly, FBXO31 is negatively controlled by miR-20a and miR-17 in gastric cancer, suggesting that FBXO31 is a downstream molecule of miR-20a and miR-17 [157]. Recently, miR-29c has been found to override fluorouracil (5-FU) chemoresistance by directly targeting FBXO31, resulting in the upregulation of p38 MAPK in esophageal cancer [158]. Altogether, FBXO31 is regulated by several miRNAs in cancer cells (Fig. 3).

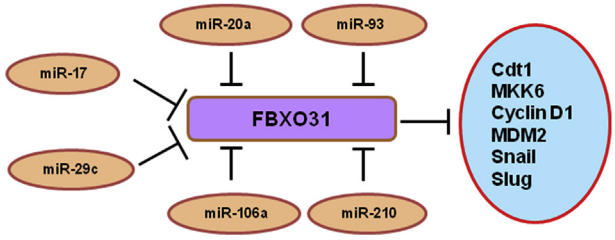

Fig. 3. FBXO31 expression is regulated by several miRNAs. Numerous miRNAs play a tumor suppressive role by targeting FBXO31 expression in human cancer. FBXO31 promotes the degradation of its substrates, including Cdt1, MKK6, cyclin D1, MDM2, Snail, and Slug.

1.6. LncRNAs regulate FBPs in cancer

LncRNAs can serve as cis and trans-acting modulators to interact with and recruit chromatin-modifying enzymes to a specific locus, leading to modulation of gene expression [159]. LncRNAs can interact with RNA-binding factors to promote or inhibit transcription [159]. LncRNAs can also regulate chromatin architecture and recruit factors to enhance gene transcription, and serve as decoys to repress gene transcription [159]. LncRNA plays an important role as a competing endogenous RNA (ceRNA) to modulate gene expression via sponging miRNAs. Evidence has indicated that lncRNAs regulate FBPs, leading to tumorigenesis and tumor progression. LncRNA MT1JP serves as a tumor suppressor via regulation of p53, RUNX3, and pTEN/Akt in human cancer [160–162]. LncRNA MT1JP inhibits growth, migration, and invasion by upregulating FBXW7 in gastric cancer cells [163]. In line with the tumor suppressive role of lncRNA MT1JP, its expression is downregulated in gastric cancer patient samples [163–165]. Similarly, lncRNA MT1JP modulates FBXW7 expression by competitively binding to miR-92a-3p in gastric cancer [164]. LncRNA cancer susceptibility candidate 2 (CASC2) is decreased in various cancer types such as lung cancer, gastric cancer, and colorectal cancer [166]. CASC2 exhibits a tumor suppressive function via sequestration of oncogenic miRNAs and inhibition of the signaling pathway in human cancer [166]. LncRNA CASC2 suppresses cell migration, invasive activity, and metastasis by inhibiting the EMT process via a competing ceRNA by sponging miR-367, resulting in the upregulation of FBXW7 in HCC cells [167]. Moreover, reduced CASC2 expression and miR-367 overexpression are associated with a poor clinical outcome [167].

LncRNA TINCR overexpression promotes tumor progression in colon and breast cancers [168–170]. TINCR modulates the 3-phosphoinositide-dependent protein kinase 1 (PDK1) expression level via sponging miR-375 in gastric cancer [171]. TINCR suppresses proliferation and invasive activity by sequestering miR-544a and subsequently upregulating FBXW7 in lung cancer [172]. Lower expression of TINCR and overexpression of miR-544a have been consistently observed in lung cancer tissues [172]. Notably, knockdown of FBXW7 abolishes the tumor suppressive function of TINCR in lung cancer cells, indicating a role for TINCR/miR-544a/FBXW7 in lung cancer [172]. Therefore, these lncRNAs regulate FBXW7 in cancer cells (Fig. 4). LncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) plays a key role in a variety of human cancers, which is dependent on the tumor type [173]. MALAT1 enhances cell growth by targeting miR-218 and subsequent upregulation of FBXW8 in choriocarcinoma cells, demonstrating that oncogenic MALAT1 could be a therapeutic target in choriocarcinoma [174]. We believe that additional lncRNAs will be discovered to regulate FBPs via targeting miRNAs in human cancers.

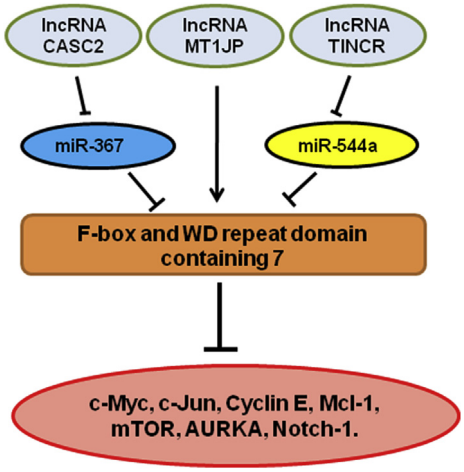

Fig. 4. FBXW7 is regulated by several lncRNAs. Tumor suppressor lncRNA MT1JP, lncRNA CASC2 and lncRNA TINCR inhibit tumor progression via increasing FBXW7 expression in human cancer. FBXW7 leads to the degradation of its substrates includng c-Myc, c-Jun, Mcl-1, cyclin E1, mTOR, AURKA, and Notch.

1.7. Role of circRNAs of FBP in cancer

CircRNAs as RNA transcripts participate in gene regulation and tumorigenesis. One study revealed that circ-FBXW7 is abundantly expressed in the normal human brain and is downregulated in glioblastoma clinical samples [175]. Moreover, circ-FBW7 expression is positively correlated with overall survival in glioblastoma patients [175]. The encoded protein of circ-FBXW7, FBW7-185aa, inhibits cell proliferation and cell cycle acceleration via antagonizing USP28-mediated c-Myc stabilization. This finding indicated that cicr-FBXW7 could have potential prognostic implications in glioblastoma.

2. Conclusions and perspectives

In conclusion, ncRNAs regulate the expression of FBPs and subsequently govern the turnover of substrates of FBPs, leading to the regulation of tumorigenesis. Thus, targeting these ncRNAs could be an alternative approach to control the level of FBPs. Indeed, some studies have described compounds that regulate the expression of FBPs via modulation of miRNAs in human cancers [176–178]. For example, the natural compound genistein has been reported to downregulate miR-223 expression and subsequently increase the FBXW7 level, leading to antitumor activity in pancreatic cancer cells [176]. Quinacrine, an antimalarial drug, induces cell apoptosis via targeting the FOXP3/miR-183/β-TrCP/SP1 axis in human leukemia cells [75]. Piceatannol evokes a downregulation of miR-183 and an upregulation of β-TrCP in human leukemia cells [178]. Arsenic trioxide inhibits cell growth and induces apoptosis via downregulation of Skp2 expression through the upregulation of miR-330–5p in pancreatic cancer cells [177]. These reports clearly indicate that targeting ncRNAs is useful for the treatment of human cancer. In addition, circulating ncRNAs have been known to serve as diagnostic and prognostic biomarkers that provide the prognosis and treatment efficacy information in human cancer [179].

Among the 69 FBPs, only a dozen FBPs are regulated by ncRNAs, with a prominent focus on FBPs such as FBXW7, Skp2, and β-TrCP1. Therefore, it is necessary to explore how other FBPs are regulated by ncRNAs. In addition, one FBP is regulated by multiple ncRNAs. What are the molecular mechanisms by which these ncRNAs target this FBP? Moreover, one ncRNA could target several FBPs. These issues should be considered if ncRNAs are used to treat human cancers in clinical trials. It is noteworthy that FBPs have various roles in different types of tumors, indicating that FBPs could play roles in a context-specific manner. Therefore, further exploration is necessary to investigate whether targeting FBPs by ncRNAs is a promising approach for anticancer therapy.

Authors' contributions

ML searched the literature regarding FBPs and ncRNA and made the figures and tables. YX, YG and CP searched the literature regarding FBPs and cancer. ML, XZ, and ZW wrote the manuscript. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.canlet.2019.09.008.

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