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FBXW7 in gastrointestinal cancers: from molecular mechanisms to therapeutic prospects

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F-box and WD repeat domain-containing 7 (FBXW7), formerly known as hCdc4, hAGO Fbw7, or SEL10, plays a specific recognition function in SCF-type E3 ubiquitin ligases. FBXW7 is a well-established cancer suppressor gene that specifically controls proteasomal degradation and destruction of many key oncogenic substrates. The FBXW7 gene is frequently abnormal in human malignancies especially in gastrointestinal cancers. Accumulating evidence reveals that mutations and deletions of FBXW7 are participating in the occurrence, progression and treatment resistance of human gastrointestinal cancers. Considering the current therapeutic challenges faced by gastrointestinal cancers, elucidating the biological function and molecular mechanism of FBXW7 can provide new perspectives and references for future personalized treatment strategies. In this review, we elucidate the key molecular mechanisms by which FBXW7 and its substrates are involved in gastrointestinal cancers. Furthermore, we discuss the consequences of FBXW7 loss or dysfunction in tumor progression and underscore its potential as a prognostic and therapeutic biomarker. Lastly, we propose potential therapeutic strategies targeting FBXW7 to guide the precision treatment of gastrointestinal cancers.

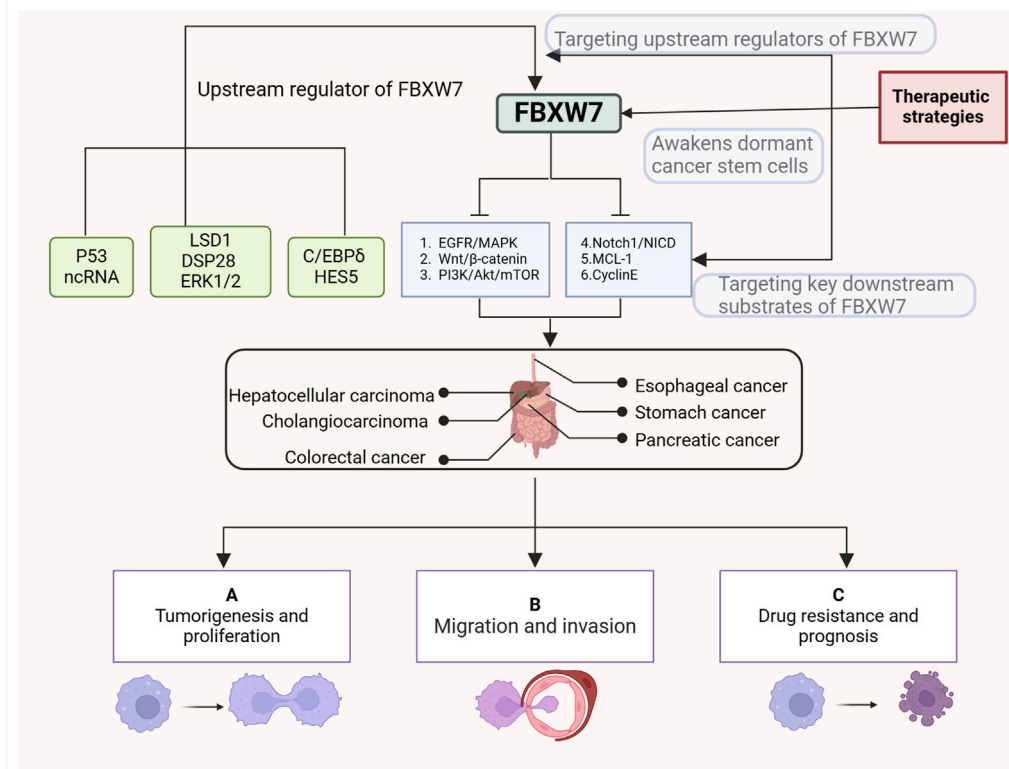
KEYWORDS

FBXW7, gastrointestinal cancers, molecular mechanism, therapeutic strategies, biomarker

1 Background

Globally, gastrointestinal cancers have high morbidity and mortality rates, especially in recent years, with a trend toward affecting younger individuals (I et al., 2023; Huang et al., 2023; Ben-Aharon et al., 2023). Gastrointestinal malignancies are estimated to account for 17.7% and 28.5% of all expected newly diagnosed cancer cases and fatalities respectively in the United States in 2024 (Siegel et al., 2024). Gastrointestinal cancers refer to malignant tumors originating from the digestive tract and digestive organs, mainly including esophageal cancer, colorectal cancer, stomach cancer, pancreatic cancer, hepatocellular carcinoma and cholangiocarcinoma (Li et al., 2021; Li et al., 2023a). With the development of medical technology, certain progress has been made in the prognosis of patients with gastrointestinal cancer (Chong et al., 2024). However, gastrointestinal cancers are relatively heterogeneous, and different individuals usually face dramatic differences in outcomes. Molecularly stratified markers are used for patients with gastrointestinal cancers as shown in Figure 1. Precision therapy is the future direction for gastrointestinal cancers, but current

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GRAPHICAL ABSTRACT

therapeutic and prognostic molecular markers are limited. Therefore, to achieve precision management of gastrointestinal cancers, it is necessary to explore novel biomarkers that can improve diagnosis and treatment.

The ubiquitin-proteasome system (UPS) regulates many cellular processes such as cell division, cell differentiation, DNA damage repair, and apoptosis by controlling the degradation of a variety of proteins in eukaryotes (Park et al., 2020; Liu et al., 2021a). The protein degradation function of UPS mainly depends on the sequential activation of three enzymes: ubiquitin-activating enzyme E1, ubiquitin couplingase E2 and ubiquitin protein ligase E3 (Tekcham et al., 2020). FBXW7 (also known as Ago, hCdc4, Fbw7, and Sel10) is involved in the formation of the SCF-type E3 enzyme complex and performs specific substrate recognition (Yeh et al., 2018). FBXW7 has been identified as a cancer suppressor gene that frequently malfunctions in a variety of human cancers (Yumimoto and Nakayama, 2020). According to the COSMIC database, the overall mutation rate of FBXW7 in human tumors is 7.79%, with the highest prevalence observed in gynecologic tumors, hematologic malignancies, and gastrointestinal cancers (Fan et al., 2022). Extensive research has demonstrated that abnormal FBXW7 expression contributes to tumor initiation, progression, treatment resistance, and poor prognosis in cancer patients (Qi et al., 2024). While the molecular mechanisms and clinical significance of FBXW7 in gynecologic cancers, breast cancer, and hematologic malignancies have been thoroughly reviewed, a comprehensive analysis of its role in gastrointestinal cancers remains lacking (Di Fiore et al., 2023; Chen et al., 2023; N

et al., 2015; Q et al., 2020). Therefore, further investigation into the role of FBXW7 in regulating various signaling pathways and key molecules in gastrointestinal cancers is warranted. It provides a reference for exploring biomarkers and molecular targets for the treatment of gastrointestinal cancers.

2 Structure and function of the FBXW7

The degradation of proteins in eukaryotes requires the coordinated activity of E1, E2, and E3 enzymes (Liu et al., 2017; Hershko and Ciechanover, 1998). First, the E1 enzyme activates and binds to the ubiquitin molecule (Ub) by consuming ATP (Bakos et al., 2018). Subsequently, the Ub bound to the E1 enzyme is transferred to the E2 enzyme (G and T, 2014). The SCF-type E3 enzyme transfers the Ub bound to the E2 enzyme to the specific substrate protein recruited (Pickart, 2001). Finally, the 26s proteasome degrades the target protein-Ub complex and releases Ub for recycling (Xu et al., 2015). F-box proteins are the recognition subunits of the SCF E3 ubiquitin ligase complex, and about 70 F-box proteins have been identified in humans (Ge et al., 2020). Based on their structure, F-box proteins are classified into three families: FBXW (WD40 repeat-containing domains), FBXL (leucine-rich repeats), and FBXO (other structural domains) (Ge et al., 2020; Skaar et al., 2013). FBXW7, due to its involvement in the destruction of many oncogenic proteins, is the most extensively

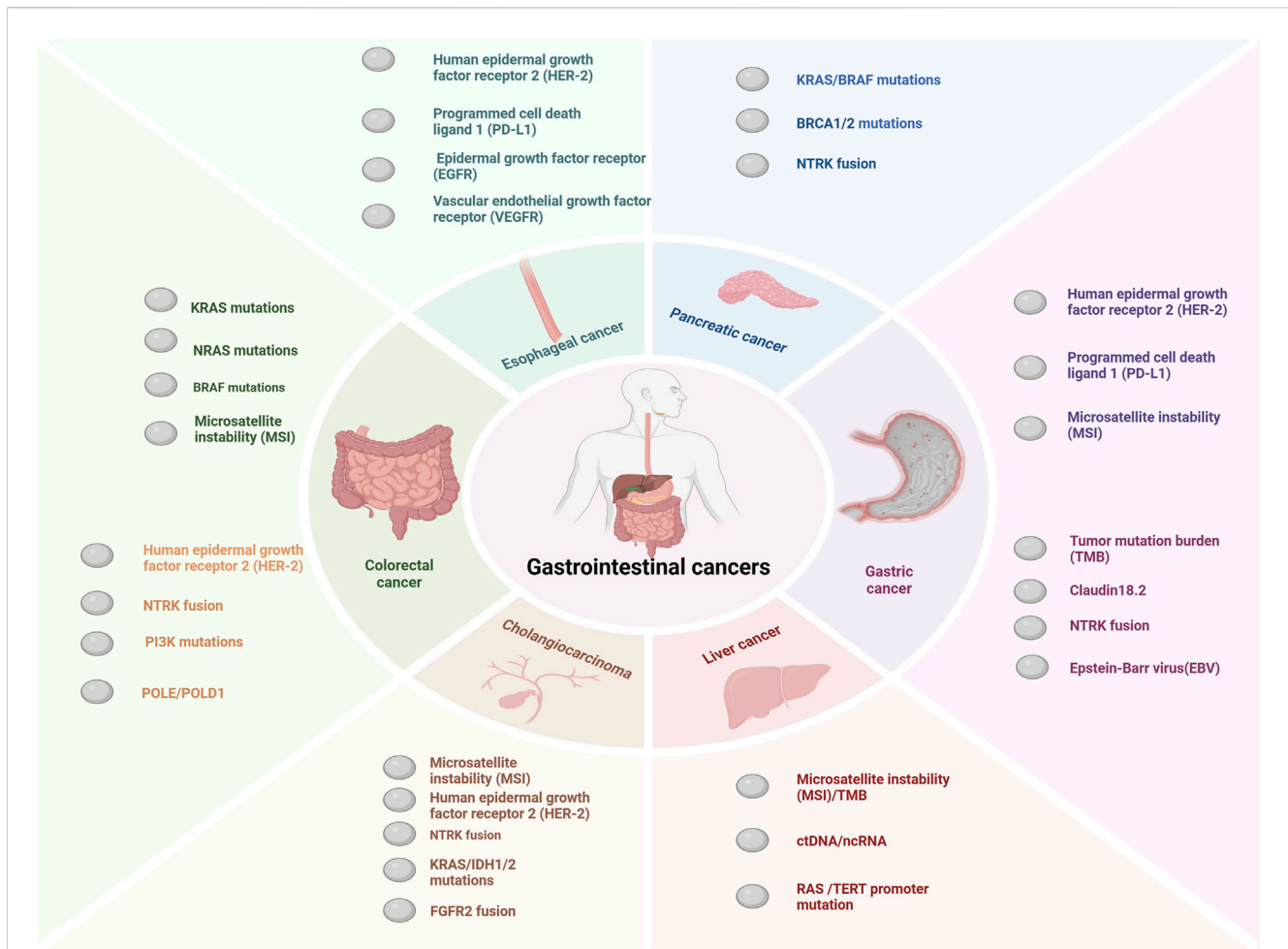


FIGURE 1

Major molecular markers of gastrointestinal cancers. The key molecular markers for esophageal cancer include HER2 amplification or overexpression, PD-L1, EGFR, and VEGFR (Liu et al., 2020; Zhou and Hofstetter, 2020; Wang et al., 2025). For pancreatic cancer, the main molecular markers are NTRK fusion, BRCA1/2 mutations, KRAS mutations, BRAF mutations, and MSI (Collisson et al., 2019; Buscail et al., 2020; Wang S. et al., 2021; Schlick et al., 2021). Molecular markers for cholangiocarcinoma mainly include MSI, HER-2 amplification or overexpression KRAS mutations, IDH1/2 mutations, FGFR2 fusion and NTRK fusion (Rodrigues et al., 2021; Pavicevic et al., 2022; Kam et al., 2021). The major molecular markers for colorectal cancer include MMR/MSI, RAS/BRAF mutations, NTRK fusion, POLE/POLD1 mutations, PI3K mutations, and HER2 amplification or overexpression (Martelli et al., 2022; Taieb et al., 2019; Sepulveda et al., 2017). The main molecular markers for gastric cancer include MSI, PD-L1, HER-2 amplification or overexpression, Claudin18.2, TMB, and EBV (Guan et al., 2023; Joshi and Badgwell, 2021; Elimova et al., 2015). So far the molecular alterations in hepatocellular carcinoma have not led to effective treatments (Nault and Villanueva, 2021). In the figure we show several promising molecular markers such as ctDNA, ncRNA, TERT promoter mutation and MSI (Nault and Villanueva, 2021; Llovet et al., 2018; Chan et al., 2024a).

studied F-box protein (Welcker and Clurman, 2008; Zhang et al., 2019). The structure and function of FBXW7 within the UPS are illustrated in Figure 2.

The FBXW7 gene consists of 13 exons and 4 introns and is located on chromosome 4q31q.3 (Fan et al., 2022; Sailo et al., 2019). As shown in Figure 2, the proteins encoded by the FBXW7 gene contain three domains: F-box, dimerization (D-D), and WD40 (Roling et al., 2022). The F-box domain functions as a linker to the SCF E3 ligase complex by binding to the adaptor protein SKP1 (Welcker and Clurman, 2008; Thirimanne et al., 2022). The WD40 repeat domains fold into β -propeller-like structures, forming binding pockets that specifically recognize and bind phosphorylated substrates (Zhang et al., 2019; Schapira et al., 2017). The dimerization domain contributes to the specificity and stability of FBXW7 and substrate interactions (Welcker et al., 2013).

The FBXW7 gene encodes three different mRNAs, which are translated into three isoforms: FBXW7 α , FBXW7 β and FBXW7 γ , differing at the N-terminus (Kitade et al., 2016). These isoforms exhibit distinct subcellular localizations and functional roles.

FBXW7 α is distributed in the nucleus and mediates the degradation of the majority of FBXW7 substrates (Kar et al., 2021). FBXW7 β isoforms and FBXW7 γ are distributed in the endoplasmic reticulum and nucleolus, respectively (Lee et al., 2020). FBXW7 β isoforms are involved in cellular lipid metabolism whereas the function of FBXW7 γ is unclear (Wei et al., 2023). The range of substrate proteins degraded by FBXW7 is broad, including Notch1, c-Jun, c-Myc, mTOR, MCL-1, cyclin E, TGF- β , and YAP (Tekcham et al., 2020; Welcker and Clurman, 2008; Sailo et al., 2019; Mao et al., 2008; Bengoechea-Alonso and Ericsson, 2010; Tu et al., 2014). In addition to genetic alterations, the function of FBXW7 is regulated

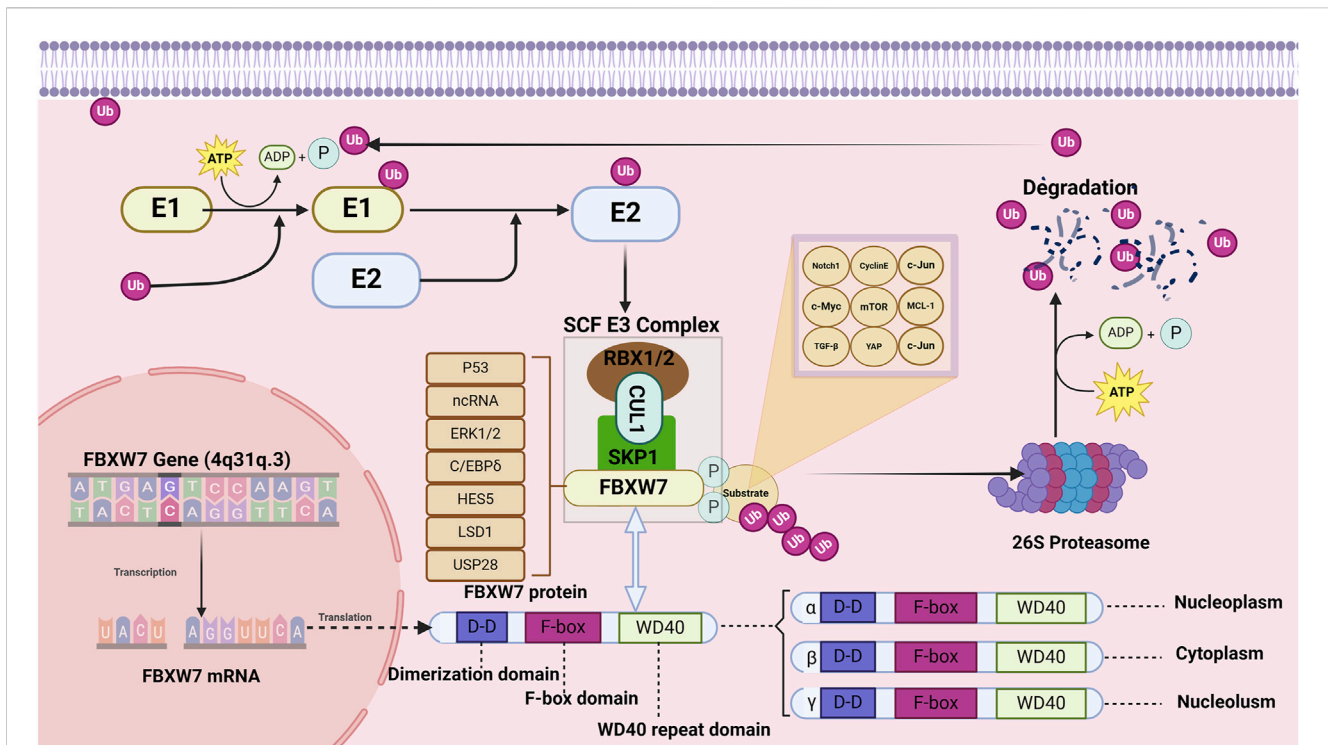


FIGURE 2

Structure and function of FBXW7. The FBXW7 gene is located on 4q31.3 and encodes three FBXW7 isoforms: FBXW7 α , FBXW7 β , and FBXW7 γ . Despite differences at their N-terminal regions, all three isoforms share dimerization domains, F-box domains, and WD40 repeat domains. FBXW7 primarily targets substrates such as TGF- β , c-Jun, Cyclin E, c-Myc, Notch1, MCL-1, YAP, and mTOR for degradation. Additionally, the expression of FBXW7 is regulated by p53, non-coding RNAs, LSD1, ERK1/2, USP28, HES5, and C/EBP δ .

by the P53, transcriptional (HES5 and C/EBP δ), translational (non-coding RNA), and post-translational regulators (LSD1, ERK1/2, USP28) (Chen et al., 2023). Given the carcinogenic effects of various regulatory proteins and molecules, FBXW7 has a broad and profound role in the occurrence and progression of human cancer (Fan et al., 2022).

3 Upstream regulatory mechanism and downstream key substrates of FBXW7

FBXW7 plays a pivotal role in various processes, including cancer cell proliferation, metastasis, invasion, apoptosis, and treatment resistance (Davis et al., 2014). Understanding the functional regulatory network of FBXW7 in greater depth is essential to elucidate its tumor-suppressive effects and to identify potential avenues for developing new cancer treatment strategies. The subsequent sections discuss the upstream regulatory mechanisms of FBXW7 and its downstream carcinogenic substrates.

3.1 Upstream regulation mechanism of FBXW7

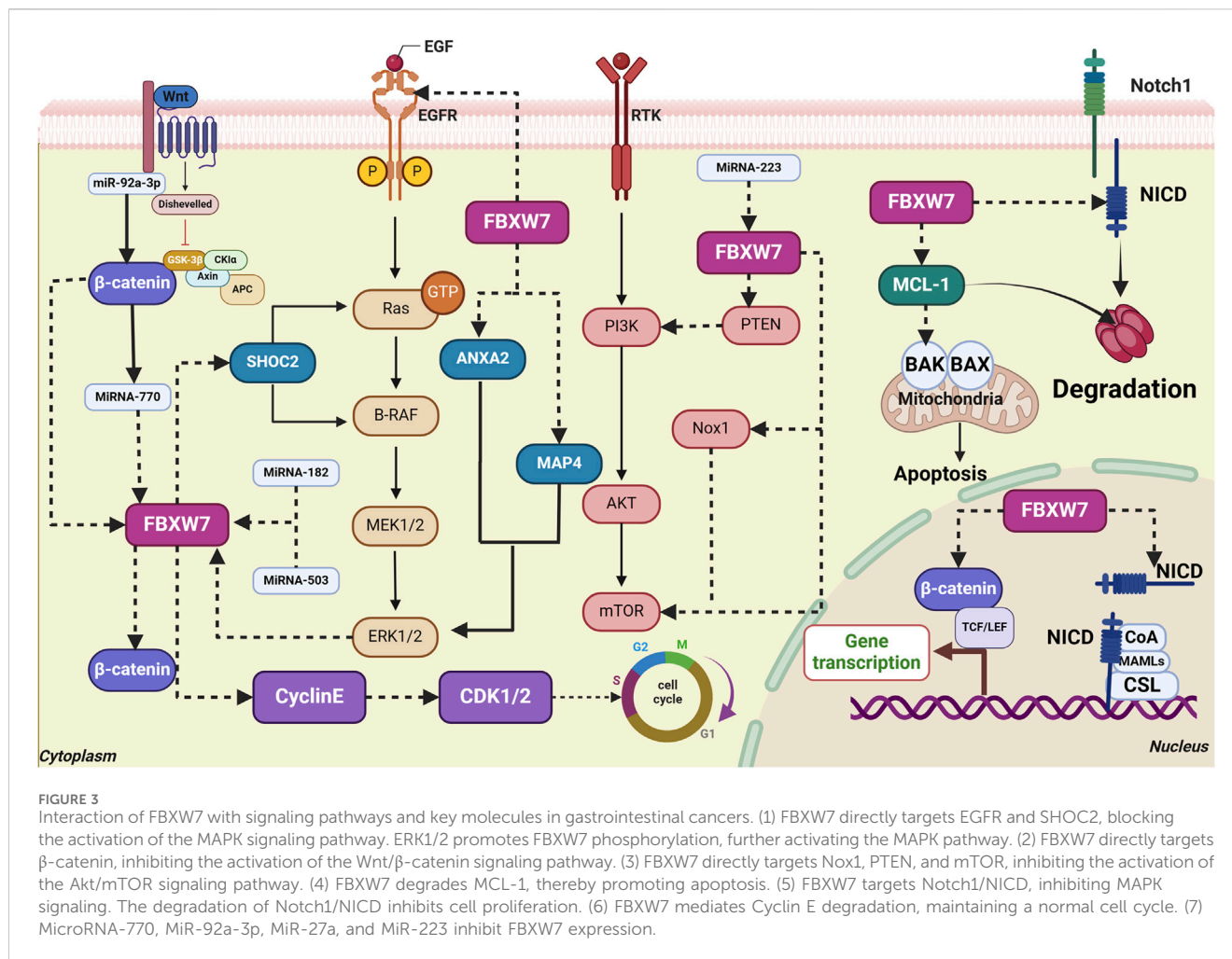
3.1.1 Transcriptional regulation of FBXW7

The expression of the FBXW7 gene is regulated by various transcription factors, including TP53, C/EBP δ , PHF1, and Hes5.

Mao et al. discovered that the exons of FBXW7 contain p53 binding sites and that heterozygous mutations in TP53 in mouse tumors are frequently accompanied by FBXW7 mutations (Mao et al., 2004). Subsequent studies have confirmed that FBXW7 gene expression depends on the TP53 gene status during tumor development (Perez-Losada et al., 2005; Grim et al., 2012). C/EBP δ directly binds to the FBXW7 α promoter to inhibit FBXW7 expression, leading to reduced degradation of mTOR (Balamurugan et al., 2010). Elevated mTOR levels activate HIF-1 protein activity, thereby promoting metastatic tumorigenesis. Similarly, PHF1 regulates FBXW7 transcription by negatively affecting the expression of both the FBXW7 protein and E-cadherin, which promotes tumor proliferation and invasion (Liu et al., 2018a). HES5, a downstream effector of Notch signaling, directly suppresses the transcription of FBW7 β , influencing the differentiation patterns of intestinal cells in mice (Sancho et al., 2013). Since Notch is negatively regulated by FBXW7, a significant feedback loop exists between HES5, FBXW7, and Notch. Additionally, the inactivation of the TGF- β signaling pathway is strongly associated with HES5-mediated inhibition of FBXW7 transcription (Chen et al., 2021).

3.1.2 Non-coding RNA regulation of FBXW7

Non-coding RNAs (ncRNAs), which are not translated into proteins, play critical roles in various physiological and pathological processes, primarily by regulating messenger RNA (mRNA) at the post-transcriptional level (Anastasiadou et al., 2018). Several types of ncRNAs, including microRNAs (MiRNAs), Circular RNAs



(CircRNAs), and Long non-coding RNAs (LncRNAs), have been implicated in the post-transcriptional regulation of FBXW7 (Lin et al., 2019). In cancer, miRNAs can suppress FBXW7 expression, thereby disrupting its tumor-suppressive functions (Lin et al., 2019; Ling et al., 2016). For instance, MiR-27a-3p and MiR-92a-3p downregulate FBXW7 mRNA expression, promoting tumor cell proliferation and invasion (Wang et al., 2021a; Ben et al., 2020). Similarly, MiRNAs such as MiR-182, MiR-25, and MiR-32 inhibit FBXW7 expression in various cancers, facilitating tumor growth and migration (Chang et al., 2018; Xiang et al., 2015; Xia et al., 2017). LncRNAs often function as miRNA sponges to regulate FBXW7 expression. For example, LncRNA-MIF acts as a competing endogenous RNA (ceRNA) for miR-586, counteracting miR-586-mediated inhibition of FBXW7, which in turn suppresses c-Myc activity and tumorigenesis (Zhang et al., 2016a). Additionally, circular RNA circPSD3 sponges MiR-25-3p, thereby restoring FBXW7 expression and inhibiting epithelial-mesenchymal transition (EMT) and tumor metastasis (Xie et al., 2022).

3.1.3 Post-translational modifications of FBXW7

3.1.3.1 Phosphorylation

The function and expression of FBXW7 are regulated by phosphorylation through several post-translational kinases, including ERK1/2, PI3K, Polo-like kinase-1 and -2 (PLK1/2), and

cyclin-dependent kinase 5 (CDK5) (L et al., 2022; D et al., 2016; Cizmecioglu et al., 2012; Ko et al., 2019). ERK1/2 activation induces the phosphorylation of FBXW7 at Thr205, reducing its stability and leading to the accumulation of heat shock factor 1 (HSF1) (Gi et al., 2020). Similarly, PLK family members phosphorylate FBXW7, promoting its ubiquitin-mediated degradation and enhancing the oncogenic potential of Myc (D et al., 2016). The FBXW7 α isoform is also phosphorylated in a PI3K-dependent manner at the S227 site (Schülein et al., 2011). Additionally, CDK5 phosphorylates FBXW7 at Ser349 and Ser372, resulting in its ubiquitination and degradation [22]. Phosphorylation by dual-specificity tyrosine-phosphorylation-regulated kinase 2 (DYRK2) has been reported to promote FBXW7 degradation via the proteasome, thereby impairing the turnover of oncogenic proteins (Jiménez-Izquierdo et al., 2023).

3.1.3.2 Auto-ubiquitination and deubiquitination

At the post-translational level, autoubiquitination and deubiquitinating enzymes (DUBs) collaboratively regulate the levels and functions of the FBXW7 protein (Xu et al., 2016). Sang's colleagues demonstrated that Pin1 promotes FBXW7 autoubiquitination and degradation by disrupting its dimerization, thereby impairing its function (Min et al., 2012).

Concurrently, Pin1 negatively regulates FBXW7-mediated substrate degradation, contributing to tumor development (Min et al., 2012). Additionally, tripartite motif-containing 25 (TRIM25) mediates the ubiquitination and degradation of FBXW7 α , leading to increased stability and accumulation of Myc (Zhang et al., 2020). The HECT domain-based E3 ligase thyroid hormone receptor interactor 12 (TRIP12) promotes autoubiquitination and proteasomal degradation of FBXW7 by mediating K11-linked ubiquitination of lysine residues K404 and K412 (Khan et al., 2021a). Beyond genetic alterations, FBXW7 function is modulated by deubiquitinases. USP9X inhibits FBXW7 autoubiquitination, thereby reducing the activity of its downstream substrate c-Myc and suppressing tumor formation in mice (Khan et al., 2018). Similarly, USP28 prevents FBXW7 self-degradation in chronic lymphocytic leukemia (CLL), leading to elevated levels of Notch1 (Close et al., 2018).

3.1.3.3 Dimerization

FBXW7 forms dimers through its conserved D-domain to maintain stability and functional activity. This structural mechanism enhances the specificity and stability of FBXW7 binding to specific substrates (Welcker et al., 2013; Welcker and Clurman, 2007). Impaired dimerization of FBXW7 not only increases its autoubiquitination but also disrupts substrate ubiquitination and degradation. For instance, as previously discussed, Pin1 promotes FBXW7 autoubiquitination and degradation by interfering with its dimerization (Min et al., 2012). Similarly, LSD1 directly disrupts FBXW7 dimerization, leading to reduced stability and proteasomal degradation (Lan et al., 2019). These findings underscore the critical role of dimerization in regulating FBXW7 stability and its anti-tumor functions.

3.2 Downstream carcinogenic substrates of FBXW7

Cyclin E plays a critical role in the transition from the G1 phase to the S phase and regulates tumorigenesis, cell proliferation, and resistance to anticancer therapies (Chu et al., 2021; T et al., 2004). The normal progression of the cell cycle relies on the proper expression of cyclins and cyclin-dependent kinases (CDKs) (Mammalian cell cycle cyclins, 2024; Targeting cell, 2024). FBXW7 deficiency has been shown to enhance Cyclin E1/CDK activation, contributing to genomic instability and tumorigenesis (Minella et al., 2007; Grim et al., 2008; Takada et al., 2017). Cyclin E is a key downstream substrate of the miR-223/FBXW7 and miR-92a/FBXW7 regulatory pathways (Xu et al., 2010; M et al., 2011). Low levels of miR-223 or miR-27a result in FBXW7 upregulation, thereby inhibiting the ubiquitination and degradation of cyclin E (Xu et al., 2010; M et al., 2011). Consequently, FBXW7 plays a vital role in maintaining Cyclin E levels, and its dysfunction is sufficient to cause Cyclin E dysregulation (Ekholm-Reed et al., 2004).

Notch1, a member of the Notch family, plays a critical role in the initiation and progression of human malignancies (Notch1 in Cancer Therapy, 2024). The Notch signaling pathway is primarily involved in regulating embryonic development, normal cell growth, apoptosis, and differentiation (Notch signaling pathway

in cancer, 2024). The intracellular domain of Notch1 (NICD) is a key target for FBXW7-mediated degradation (Kar et al., 2021). In mouse embryonic fibroblasts (MEFs), selective knockout of FBXW7 leads to aberrant activation of the Notch1/NICD signaling pathway, disrupting normal cell cycle regulation (Y et al., 2008). In various hematopoietic and solid tumors, impaired FBXW7-mediated degradation of Notch1 is associated with reduced drug response and poor patient prognosis (Close et al., 2019; Mori et al., 2018).

MCL-1, a member of the anti-apoptotic Bcl-2 protein family, is critically involved in tumor cell proliferation, apoptosis, and drug resistance (Wang et al., 2021b). The function and expression of MCL-1 are tightly regulated by various factors, including VEGF, IL-6, FBXW7, MULE, and miRNAs (Mojsa et al., 2014; L et al., 2009; Shenoy et al., 2014; CXCR4, 2024; Inuzuka et al., 2011; Pervin et al., 2011). Specific alleles in the CPD domain of MCL-1—Ser159, Thr163, and Ser121—are phosphorylated by glycogen synthase kinase 3 β (GSK3 β) (Inuzuka et al., 2011; Morel et al., 2009; Senichkin et al., 2020). Subsequently, FBXW7 interacts with phosphorylated MCL-1, facilitating its degradation via the 26S proteasome (Yeh et al., 2018; Tang et al., 2023). Thus, FBXW7 influences multiple malignant processes in cancer, particularly drug resistance, by regulating MCL-1 activity or expression levels (Wu et al., 2024). In oral squamous cell carcinoma, FBXW7 has been reported to negatively regulate MCL-1 expression and autophagy (Sun et al., 2023). Furthermore, reduced FBXW7 expression decreases cisplatin sensitivity in oral squamous cell carcinoma (Yang et al., 2022). These findings suggest that targeting MCL-1 could enhance therapeutic sensitivity in patients with FBXW7-mutated gastrointestinal cancers (Wood, 2020; Mittal et al., 2021).

mTOR is a serine/threonine kinase belonging to the phosphoinositide 3-kinase-related kinase (PIKK) family, playing a pivotal role in tumor growth, metastasis, and drug resistance (Marques-Ramos and Cervantes, 2023; As, 2019). FBXW7 has been reported to recognize and degrade mTOR (Mao et al., 2008). Experiments have shown that the expression level of mTOR depends on the rhythmic change of FBXW7, which means that FBXW7 is a negative regulator of mTOR (Okazaki et al., 2014). This regulatory relationship has been well-demonstrated in breast cancer (Mao et al., 2008). Notably, FBXW7 knockout in tumor cells leads to increased epithelial-mesenchymal transition (EMT), enhanced stem cell properties, and greater migratory potential (Wang et al., 2013). Interestingly, mTOR inhibitors have been shown to suppress EMT and cancer stem cell traits induced by FBXW7 mutations (Wang et al., 2013). Furthermore, in murine tumor models undergoing radiotherapy, mTOR inhibitors delay tumor progression associated with FBXW7 mutations or deletions (Liu et al., 2013).

β -Catenin is a key effector of the canonical Wnt signaling pathway, which regulates cell proliferation, embryonic development, and homeostasis under physiological conditions (Liu et al., 2022; Song et al., 2024; Pai et al., 2017). Dysregulation of the Wnt/ β -catenin pathway promotes malignant tumor invasion (Song et al., 2024; Zhang and Wang, 2020). Extensive research has demonstrated that this pathway is frequently overactivated in various cancers, particularly in gastrointestinal malignancies (Is et al., 2022; Bd et al., 2012; X C. et al., 2019a; Wu et al., 2016).

FBXW7 plays a critical role in regulating the Wnt/ β -catenin pathway by mediating the degradation of β -catenin and associated transcription factors (Yu et al., 2021). Additionally, chromatin domain-helicase-DNA-binding protein 4 (CHD4) promotes Wnt/ β -catenin pathway activation, which FBXW7 counteracts by disrupting CHD4 (G et al., 2024). Overexpression of FBXW7 directly ubiquitinates and degrades β -catenin, thereby preventing pathway overactivation and inhibiting tumor growth and invasion (Jiang et al., 2016). Consequently, targeting the Wnt/ β -catenin pathway is a promising strategy for treating FBXW7-mutated tumors. However, recent studies reveal resistance to Wnt/ β -catenin inhibition therapy in FBXW7-mutant tumors, potentially due to increased activity of alternative FBXW7 substrates, such as Myc (Zhong and Virshup, 2024). This suggests that cancer proliferation and progression driven by FBXW7 mutations are not solely dependent on Wnt/ β -catenin signaling and that targeting a single FBXW7 substrate may have limited therapeutic efficacy.

c-Myc is a proto-oncogene encoding a protein implicated in the development of numerous human cancers (Dhanasekaran et al., 2021). Aberrant activation of c-Myc drives hallmark features of cancer, including cell proliferation, growth, differentiation, metabolism, angiogenesis, and tumor microenvironment remodeling, through various genetic mechanisms (M et al., 2014). FBXW7 suppresses the oncogenic effects of c-Myc by ubiquitinating and degrading phosphorylated c-Myc at Thr58 and Ser62 (Yeh et al., 2018; M Y. et al., 2004). At the single-cell level, loss of FBXW7 expression results in the accumulation of several substrates, most notably c-Myc and cyclins (Meyer et al., 2020). This loss leads to the activation of c-Myc, contributing to the progression of various malignancies, particularly hematologic cancers (B et al., 2024; B et al., 2013). Findings by Markus et al. indicate that FBXW7 deletion disrupts control over c-Myc, resulting in rapid tumor cell proliferation (M W. et al., 2004).

4 FBXW7 is involved in the occurrence and development of various gastrointestinal cancers

FBXW7 mediates the degradation of numerous proteins, and alterations in its expression are strongly associated with cell proliferation, invasion, metastasis, and drug resistance in gastrointestinal cancers. Understanding the molecular mechanisms and clinical significance of FBXW7 in these cancers can aid in the development of targeted therapies and biomarkers. The following sections discuss the role of FBXW7 in the onset and progression of gastrointestinal cancers by tumor type, and summarize the associated molecular mechanisms and signaling pathways, as illustrated in Figure 3.

4.1 Colorectal cancer (CRC)

CRC is a highly heterogeneous disease, with different molecular alterations and genetic subtypes closely related to the prognosis of CRC (Schell et al., 2016; Linnekamp et al., 2018). Currently, the treatment and prognostic classification of CRC primarily depend on

TNM staging, as well as molecular markers such as MMR/MSI, RAS, RAF, and PI3K. Mutations or deletions of FBXW7 are often found in patients with CRC, especially in younger patients (<45 years) (Kothari et al., 2016). A recent meta-analysis of 58 studies found that the overall mutation rate of FBXW7 in 13,974 CRC patients was 10.3% (Afolabi et al., 2024). Thus, investigating the possible role of the FBXW7 gene in CRC is essential. The role of FBXW7 in CRC is shown in Table 1.

4.1.1 FBXW7 is involved in regulating the growth and proliferation of CRC

FBXW7 influences the growth and proliferation of CRC by regulating the activity of various oncogenic substrates, including Notch, Akt/mTOR, Jun, and DEK (Babaei-Jadidi et al., 2011; Lu et al., 2019; Liu et al., 2021b). Mice with FBXW7 deficiency exhibit an increased likelihood of developing intestinal tumors (Babaei-Jadidi et al., 2011). For instance, the synergistic downregulation of FBXW7 expression by MiR-182 and MiR-503 has been shown to drive the progression of colon adenoma into adenocarcinoma (Li et al., 2014). Ou et al. reported that elevated expression of Polo-like kinase 2 (Plk2) in CRC samples stabilizes Cyclin E by suppressing FBXW7 expression, thereby promoting CRC growth (Ou et al., 2016). Similarly, the Rictor/FBXW7-mediated accumulation of c-Myc and Cyclin E plays a crucial role in CRC cell proliferation (Guo et al., 2012). Additionally, factors such as Serine/threonine/tyrosine interacting protein (STYX), MiR-223, MiR-92b-3p, FAM83D, USP9X, and KDM5c indirectly regulate various oncoproteins by modulating FBXW7 expression, contributing to CRC cell proliferation and apoptosis (Khan et al., 2018; Liu Z. et al., 2021; Gong et al., 2018; He et al., 2019; Mu et al., 2017; Lin H. et al., 2020). Fat metabolism, regulated by FBXW7, is also linked to tumor growth in CRC. The binding of COP9 signalosome subunit 6 (CSN6) to FBXW7 β inhibits the degradation of fatty acid synthase (FASN), promoting lipogenic CRC and tumor progression (Wei et al., 2023).

4.1.2 FBXW7 is involved in regulating the invasion and metastasis of CRC

FBXW7 plays a significant role in the invasion and metastasis of CRC. It has been reported to suppress the migration of CRC cells by regulating the HIF1 α /CEACAM5 axis (Li et al., 2018). Furthermore, the FBXW7 gene negatively regulates Enolase 1 (ENO1), thereby influencing the growth and metastasis of the CRC cell line HCT116 (163). SHOC2, a conserved protein that binds to RAS and RAF at its N-terminus, facilitates downstream signaling (Xie and Sun, 2019). FBXW7-mediated ubiquitination and degradation of SHOC2 block MAPK pathway activation, thereby inhibiting cancer growth signaling (Xie and Sun, 2019). In FBXW7 knockout CRC cells, increased epithelial-mesenchymal transition (EMT), enhanced stem cell properties, and elevated migration are observed (Wang et al., 2013). The use of mTOR inhibitors can mitigate EMT characteristics and cancer stem cell properties induced by FBXW7 mutations (Wang et al., 2013). Additionally, restoring FBXW7 expression partially suppresses CRC progression driven by the activation of the Wnt/ β -catenin signaling pathway (Hu et al., 2019).

TABLE 1 The role of FBXW7 in colorectal cancer.

Study	Source	FBXW7 status	Specific mechanisms	Significance
Babaei-Jadidi et al. (2011)	Mice	Deleted	FBXW7-Notch/c-Jun/ β -catenin	Reduced life span and elevated risk of intestinal cancers in mice
Li et al. (2014)	HCT116	Downregulated	MiR-182/MiR-503—FBXW7	Contribute to the malignant progression of colon adenoma to adenocarcinoma
Wei et al. (2023)	CRC tissues	Downregulated	CSN6—FBXW7 β	Reprogramming adipogenesis in CRC to increase tumour growth
Ou et al. (2016)	CRC tissues	Downregulated	Plk2—FBXW7—Cyclin E	Promotes tumor development by inhibiting CRC cell death
He et al. (2019)	CRC tissues	Downregulated	STYX -FBXW7	Stimulates CRC cell migration, invasion, proliferation, and EMT while preventing apoptosis
Liu et al. (2021b)	HCT11	Downregulated	MiR-223-FBXW7-Akt/mTOR/Notch1	CRC proliferation increased, whereas apoptosis reduced
Gong et al. (2018)	HT29 HCT116	Downregulated	MiR-92b-3p -FBXW7	Increased migration, invasion, and proliferation of CRC
Mu et al. (2017)	CRC cell lines CRC tissues	Downregulated	FAM83D-FBXW7 -Notch1	Encourages CRC cell growth, migration and invasion
Khan et al. (2018)	Mice model	Upregulated	Usp9x -FBXW7 -c-Myc	Inhibits tumor formation
Lin et al. (2020a)	Colon cancer cells	Downregulated	KDM5c- FBXW7 - c-Jun	Increase proliferation of colon cancer cells
Li et al. (2018)	CRC tissues	Low expression	FBXW7—HIF1 α /CEACAM5	Worse clinicopathologic features and poor patient outcome
Zhan et al. (2015)	HCT116	Depletion	FBXW7—ENO1	Lactate production, cell proliferation and migration
Kawashita et al. (2017)	CRC tissues	Low expression	MiR-223-FBXW7	Worse disease-free survival and more susceptibility to recurrence
Honma et al. (2019)	CRC tissues CRC cell lines	Downregulated	FBXW7 silence awakens CSCs	Enhanced susceptibility to anti-cancer medications both <i>in vivo</i> and <i>in vitro</i>
Izumi et al. (2017)	Colorectal CSCs	Upregulated	Elevated FBXW7 leads to cell cycle arrest of CSCs after chemotherapy	After chemotherapy, inhibiting FBXW7 overexpression in CSCs may improve their response to anticancer drugs
Huang and Long (2023); Wang et al. (2021c)	CRC cell lines HCT-116	Overexpression	FBXW7- Nox1- mTOR	CRC cells are sensitive to cisplatin and taxol
Li et al. (2019)	Mouse models	Depletion	FBXW7-ZEB2-EMT/CSCs	Causes chemoresistance and EMT.
J et al. (2017); Tong et al. (2017); Song et al. (2020); Lin et al. (2020b)	CRC cell lines	Inactivating mutations	FBXW7-MCL-1	Less sensitive to regorafenib, sorafenib, Trametinib and Hsp90 inhibitors
Boretto et al. (2024); Nemecek et al. (2016)	CRC tissues Colon organoids	Mutations	FBXW7-EGFR	Reduced effectiveness of anti-EGFR treatment
Liu et al. (2018b); Korphaisarn et al. (2017)	CRC tissues Clinical databases	Downregulated Missense mutations	Unclear	An independent unfavorable prognostic factor of CRC
Iwatsuki et al. (2010)	CRC tissues CRC cell lines	Low expression	FBXW7-c-Myc/CyclinE	The prognosis was worse
Shang et al. (2021)	Database	Mutation or Low expression	N/A	Poorer OS of the CRC
Kawaguchi et al. (2021)	Genetic sequencing data	Low expression	N/A	Worse survival after CLM resection
Chang et al. (2015)	MassArray system	Mutation	N/A	FBXW7 mutations and patient prognosis did not significantly correlate
Y et al. (2023)	CRC tissues	Mutation	N/A	FBXW7 R465C hotspot mutation-afflicted CRC patients had worse OS

4.1.3 FBXW7 affects the therapeutic sensitivity of CRC

Loss of FBXW7 function reduces the sensitivity of CRC cells to anticancer drugs. In CRC cell models, FBXW7 downregulation increases the activity of NADPH oxidase 1 (Nox1) and mTOR, leading to resistance to paclitaxel and cisplatin (Huang and Long, 2023; Wang HP. et al., 2021). Additionally, FBXW7 deletion upregulates ZEB2 protein levels, inducing chemoresistance to 5-fluorouracil and oxaliplatin (Li et al., 2019). Conversely, high FBXW7 expression downregulates Cryptochrome 2 (CRY2), reducing resistance to oxaliplatin treatment (Fang et al., 2015). FBXW7 also plays a critical role in the effectiveness of molecularly targeted therapies for CRC. Sequencing data from CRC patients reveal that mutations in FBXW7 and SMAD4 are common in those resistant to cetuximab or panitumumab (Lupini et al., 2015). Recently, FBXW7 was shown to mediate the ubiquitination and degradation of EGFR, influencing the efficacy of EGFR inhibitors in human CRC-derived organoid lines (Boretto et al., 2024; Nemecek et al., 2016). Moreover, CRC cells harboring FBXW7 mutations exhibit resistance to regorafenib and sorafenib due to MCL-1 accumulation (Tong et al., 2017; Song et al., 2020). However, inhibiting MCL-1 restores the sensitivity of these cells to regorafenib (Tong et al., 2017; Song et al., 2020). Similar mechanisms underlie resistance to trametinib and Hsp90 inhibitors in FBXW7-mutant CRC (Lin L. et al., 2020; J et al., 2017). Interestingly, FBXW7 downregulation has been reported to enhance the therapeutic response of CRC stem cells to anticancer drugs (Honma et al., 2019). CRC stem cells may develop chemoresistance to CPT-11 by upregulating FBXW7, which degrades c-Myc and arrests the cell cycle (Izumi et al., 2017). Thus, further research on FBXW7 could aid in identifying novel predictive markers and treatment strategies for CRC.

4.1.4 FBXW7 affects the prognostic outcome of CRC

The functional status of FBXW7 may be linked to poorer prognosis in CRC patients (Liu H. et al., 2018; Korphaisarn et al., 2017). Specifically, reduced FBXW7 mRNA expression in tumor tissues is inversely associated with CRC prognosis (Iwatsuki et al., 2010). A meta-analysis further confirmed that FBXW7 mutations or low expression levels correlate with advanced T stage, shorter overall survival (OS), and lymph node metastases in CRC patients (Shang et al., 2021). Additionally, CRC patients with liver metastases who have FBXW7 mutations exhibit significantly lower 5-year OS rates compared to those with FBXW7 wild-type tumors (Kawaguchi et al., 2021; Kawashita et al., 2017). However, some studies indicate that the relationship between FBXW7 and patient prognosis may not be strong (Chang et al., 2015). For instance, Liu et al. found that while the R465C hotspot mutation was associated with worse OS, other FBXW7 mutations did not significantly affect survival outcomes (Y et al., 2023). Although FBXW7 appears to influence CRC prognosis, further research is required to establish more conclusive evidence. Nonetheless, FBXW7 shows significant potential as a biomarker for CRC treatment and prognosis.

4.2 Gastric cancer (GC)

According to recent statistics, gastric cancer (GC) ranks fifth in cancer-related mortality (Bray et al., 2024). Molecular biomarker-based classification, including markers such as PD-L1, MSI, and HER-

2, has enabled some GC patients to benefit from immunotherapy or targeted therapies (Guan et al., 2023). However, there are few treatment options for patients with GC and the prognosis is still relatively poor (Sun et al., 2024). Thus, identifying more effective molecular markers is critical for improving the management of GC. Studies have reported mutations rate of FBXW7 in GC ranging from 9.2% to 18.5% (Li et al., 2016). More and more researchers have paid attention to the role of FBXW7 in GC (Table 2).

4.2.1 FBXW7 is involved in regulating the occurrence and development of GC

Studies have shown that FBXW7-deficient mice exposed to the chemical carcinogen N-methyl-N-nitrosourea (MNU) are more prone to genetic damage and c-Myc accumulation, increasing the risk of gastric cancer (GC) (Jiang et al., 2017). In addition, MiR-223 and MiR-25 can indirectly regulate GC cell proliferation, apoptosis, and invasiveness by controlling the post-transcriptional expression of FBXW7 (191,192). Certain compounds, such as Demethylzeylasteral (a naturally occurring monomer from *Tripterygium wilfordii*) and Lycorine hydrochloride (LH), can restore FBXW7 expression, thereby reducing the growth and invasiveness of GC cells (Y et al., 2021; Li et al., 2020). Growth factor independent 1 (GFI1) encourages the growth of GC cells and disease progression by inhibiting the transcription of gastric factor-2 (GKN2) (X K. et al., 2019). In GC patients with elevated GFI1 protein levels, FBXW7 function were reduced, leading to rapid GC cell proliferation and disease progression (X K. et al., 2019). Li et al. demonstrated that low FBXW7 expression activates the RhoA pathway in GC, promoting EMT and disease progression (Li et al., 2016). ZC3H15 inhibits FBXW7 expression at the transcriptional level, hindering c-Myc degradation and thereby contributing to GC development and progression (Hou et al., 2022). Higher Brg1 (also known as SMARCA4) expression has been linked to distant and lymph node metastasis in GC patients (Sentani et al., 2001). Huang et al. analyzed human GC tissue samples and found that increased Brg1, due to low FBXW7 expression, is a key mechanism driving GC metastasis (Huang et al., 2018). Moreover, FBXW7 is negatively regulated by lncRNA BDNF-AS and is involved in ferroptosis and peritoneal metastasis of GC in animal models (Huang et al., 2022).

4.2.2 FBXW7 affects the treatment and prognosis of GC

The functional status of FBXW7 also profoundly affects the treatment resistance and prognosis of GC patients. It has been reported that MiR-223 modulates the sensitivity of GC to chemotherapy and molecularly targeted therapy (Zhou et al., 2015; Eto et al., 2015). Mechanistic studies have shown that MiR-223 induces resistance to cisplatin and trastuzumab in GC cells by downregulating FBXW7 expression (Zhou et al., 2015; Eto et al., 2015). The restoration of FBXW7 function by consuming MiR-223 inhibits the resistance of GC cells to cisplatin trastuzumab (Zhou et al., 2015; Eto et al., 2015). Furthermore, in patients with GC, dysregulated FBXW7 is related to more severe clinical characteristics and a worse prognosis (Yokobori et al., 2009). For Chinese patients, the results also suggest that GC patients with low expression of FBXW7 have poor tumor differentiation and worse prognosis (Li MR. et al., 2017). In summary, the function of FBXW7 acts on the whole process of the occurrence and development of GC, which offers an innovative approach for the static treatment of patients.

TABLE 2 The role of FBXW7 in gastric cancer.

Study	Source	FBXW7 status	Specific mechanisms	Significance
Jiang et al. (2017)	Gene Knockout mouse	Haploinsufficiency	FBXW7-c-Myc/DNA damage	Increased the risk of gastric carcinogenesis
Li et al. (2012); Gong et al. (2015)	GC cell lines GC tissues	Downregulated	MiR-223/MiR-25-FBXW7	FBXW7 regulate cellular apoptosis, proliferation, and invasion in GC
Y et al. (2021); Li et al. (2020)	Xenograft tumor model GC cell lines	Upregulated	FBXW-c-Myc FBXW-MCL-1	Dem and Lycorine hydrochloride inhibits the proliferation, apoptosis, and invasion of GC cells
X et al. (2019b)	GC tissue	N/A	FBXW7/GSK3 β -GFI1-GKN2	Gastric cancer cell proliferation and tumorigenesis
Li et al. (2016)	GC tissue	Downregulated	FBXW7-Snail 1/ZEB 1-EMT FBXW7- RhoA	FBXW7 induces apoptosis and growth arrest and inhibits the EMT in GC
Hou et al. (2022)	GC cell lines	Downregulated	ZC3H15- FBXW-c-Myc	Promote GC cell proliferation, migration and invasion
Huang et al. (2018)	GC tissue	N/A	FBXW7- Brg1	Brg1 degradation by FBXW7 inhibits GC metastasis
Huang et al. (2022)	GC tissue	Downregulated	BDNF-AS-WDR5-FBXW7- VDAC3- Ferroptosis	Promotes progression of GC and peritoneal metastases
Zhou et al. (2015); Eto et al. (2015)	GC cell lines	Downregulated	MiR-223-FBXW7	FBXW7 is involved in cisplatin and trastuzumab resistance in GC cells
Yokobori et al. (2009)	GC tissue	Downregulated	P53-FBXW7	Disruption of both p53 and FBXW7 leads to poor GC prognosis
Li et al. (2017a)	GC tissue	Low expression	Unclear	Low FBXW7 expression is associated with poor differentiation and prognosis in GC

TABLE 3 The role of FBXW7 in esophageal squamous cell carcinoma.

Study	Source	FBXW7 status	Specific mechanisms	Significance
Bi et al. (2023)	TCGA database	Overexpression	ESCC stem cell formation	Inhibit ESCC cell proliferation, migration, invasion and angiogenesis
Li et al. (2023b)	Xenograft tumors	Loss of function	FBXW7- ANXA2-ERK	Promoting esophageal carcinogenesis through ANXA2 overexpression
Pan et al. (2023)	ESCC tissues	Inactivation	FBXW7-MAP4/ERK	Promote ESCC proliferation
Wu et al. (2015)	ESCC tissues and cell lines	Downregulated	MiR-27a-3p-FBXW7	Promoted ESCC cell proliferation
Yu et al. (2015)	ESCC tissues	Downregulated	N/A	Poor prognosis of ESCC.
Y et al. (2010)	ESCC tissues	Downregulated	N/A	Progression and local invasiveness
Yokobori et al. (2012)	ESCC tissues	Downregulated	FBXW7-cMyc	ESCC proliferation, worse prognosis
Kurashige et al. (2012)	ESCC tissues	Downregulated	MiR-223-FBXW7	Low FBXW7 expression adversely affects survival in ESCC patients
Gombodorj et al. (2018)	ESCC tissues and cell lines	Overexpression	FBXW7-MCL-1	ESCC patients have a favorable response to CRT.

4.3 Esophageal squamous cell carcinoma (ESCC)

In ESCC, low FBXW7 expression is related to high aggressiveness, while FBXW7 overexpression significantly inhibits tumor growth and invasion (Gong et al., 2016; Bi et al., 2023). FBXW7 deficiency in ESCC can overactivate the ANXA2-ERK pathway, worsening the tumor's biological behavior (Li Z. et al., 2023). In addition, FBXW7-MAP4-ERK axis is implicated in ESCC (207). MAP4 overexpression and ERK activation caused by FBXW7 inactivation can promote the growth, invasion and migration of ESCC cells (Pan et al., 2023). Upregulation of MiR-27a-3p in ESCC has been shown to reduce

FBXW7 expression, leading to accelerated tumor proliferation and disease progression (Wu et al., 2015). Moreover, the functional status of FBXW7 can also affect the prognosis of ESCC patients (Yu et al., 2015; Y et al., 2010). In ESCC, both FBXW7 mutations and copy number loss affect the prognosis of patients (Yokobori et al., 2012). When the expression of FBXW7 in ESCC is inhibited by MiR-223, the prognosis of patients becomes worse (Kurashige et al., 2012). A retrospective study found that high FBXW7 expression was correlated with a favorable response to chemoradiotherapy (CRT) in advanced ESCC (213). Therefore, the status of FBXW7 is also an important indicator for predicting the efficacy of ESCC treatment (Table 3).

TABLE 4 The Role of FBXW7 in hepatocellular carcinoma.

Study	Source	FBXW7 status	Specific mechanisms	Significance
Wang et al. (2015)	HCC tissues	Downregulated	FBXW7-Notch1	Promote HCC cell invasion and worse prognosis
Zhou et al. (2012)	HCC tissues	Downregulated	N/A	Adverse clinicopathologic features and cell proliferation
Feng et al. (2022)	HCC tissues	Downregulated	MiR-25-FBXW7-Autophagy	Sorafenib resistance and autophagy
Chan et al. (2024b)	HCC cell lines	Loss of function	ASPM-i1-FBXW7- Notch1	Leading to the occurrence of HCC
Zhang et al (2020)	HCC tissues	Downregulated	MAP3K13-TRIM25-FBXW7- Myc	Treatment resistance and poor prognosis
Nie et al. (2022)	TCGA database GEO database	Downregulated	FAM83D-FBXW7-MCL-1	Promote the proliferation and migration of HCC cells
Sun et al. (2016)	HCC tissues HCC cell lines	Downregulated	MiR-27b-FBXW7	Poor prognostic features and reduced survival
Yang et al. (2015)	HCC tissues	Downregulated	MiR-92a-FBXW7	Independent risk factors for tumor growth and prognosis
Tang et al. (2016)	HCC tissues HCC cell lines	Downregulated	MiR-155-3p-FBXW7	HCC cell proliferation
Tu et al. (2014)	HCC tissues	Downregulated	FBXW7-YAP	Poor clinicopathologic features and prognosis
Yu et al. (2014)	HCC cell lines	Downregulated	FBXW7-EMT	Diminished efficacy of adriamycin and increased HCC aggressiveness
Tang et al. (2019)	HCC cell lines	Downregulated	MiR-223-FBXW7	HCC cells develop resistance to sorafenib
S et al. (2014)	HCC tissues	Low expression	N/A	Low expression of FBXW7 is an independent risk factor for HCC recurrence
El-Mezayen et al. (2021)	HCC tissues	Downregulated	MiR-25-FBXW7	HCC tumor progression

4.4 Hepatocellular carcinoma (HCC)

Studies from small samples have reported that the frequency of FBXW7 mutations in hepatocellular carcinoma (HCC) tissues is approximately 7.7% (1/13) (Dl et al., 2014). Patients with HCC have a worse prognosis and a more aggressive tumor when FBXW7 expression is lost (Table 4) (Wang et al., 2015; Zhou et al., 2012; Feng et al., 2022). The functional impairment of FBXW7 in HCC is connected to accumulation of the Notch1 and poorer clinicopathological features (Wang et al., 2015). The Assembly Factor for Spindle Microtubules (ASPM) promotes tumorigenesis in HCC by preventing the binding and degradation of Notch1 by FBXW7 (218). Except for Notch1, FBXW7 can control the invasion ability and prognosis of HCC by regulating the stability of YAP protein and Myc protein (Tu et al., 2014; Zhang et al., 2020). Moreover, the level of FBXW7 in HCC cells was found to be controlled by a variety of regulators. For instance, by controlling FBXW7 expression, FAM83D, MiR-27b, MiR-92a, and MiR-155-3p affect the development and prognosis of HCC (219–222).

4.5 Pancreatic cancer (PC)

Pancreatic cancer (PC) is a high-threat gastrointestinal cancer characterized by its insidious onset and resistance to chemotherapy (Lin et al., 2022). Due to the significant heterogeneity and limited treatment options for PC, the survival rate for patients with

advanced disease remains extremely low (Pancreatic Cancer). Therefore, identifying new therapeutic targets and biomarkers is crucial. The mutation rate of FBXW7 in PC has been reported to be approximately 2%–3% (Heestand and Kurzrock, 2015).

FBXW7 plays a crucial role in the differentiation of pancreatic ductal epithelial cells (Sancho et al., 2014). Elevated levels of Ngn3 after FBXW7 inactivation can induce the differentiation potential of pancreatic ductal cells, which may lead to the development of PC (Sancho et al., 2014; Ba and Y, 2014). Zhang et al. showed that deletion of FBXW7 accelerates KRAS G12D-driven pancreatic tumorigenesis (Zhang Q. et al., 2016). Mechanistic studies have shown that FBXW7 loss in mice depends on Yap accumulation to drive pancreatic tumor formation (Zhang Q. et al., 2016). The activation of the KRAS-ERK pathway in PC further suppresses FBXW7 expression, facilitating cancer progression (Ji et al., 2015). This occurs because the ERK pathway degrades FBXW7 in a phosphorylation-dependent manner, and pancreatic cancer cells with defective FBXW7 phosphorylation sites exhibit oncogenic resistance to ERK pathway activation (Ji et al., 2015). FBXW7 has been reported to hinder PC cell growth and invasion by inhibiting Wnt/ β -catenin signaling (Jiang et al., 2016; Liu et al., 2019). Protein database analysis suggests that FBXW7 also inhibits the downstream TORC2/AKT signaling pathway by degrading salt-inducible kinase 2 (SIK2), thereby reducing pancreatic cancer cell proliferation (Mx et al., 2020). Moreover, FBXW7 suppresses tumor aggressiveness by degrading other substrates, such as Enhancer of zeste homolog 2 (EZH2) (Jin et al., 2017). The epigenetic regulator protein arginine methyltransferase 5 (PRMT5) stabilizes c-Myc

TABLE 5 The role of FBXW7 in pancreatic cancer.

Study	Source	FBXW7 status	Specific mechanisms	Significance
Zhang et al. (2016b)	Mice	Deletion	FBXW7-Yap	Induced pancreatic tumorigenesis
Ji et al. (2015)	PC tissues	Downregulated	KRAS-ERK-FBXW7	Promote PC progression
Jiang et al. (2016)	PC tissues	Inactivation	FBXW7-Wnt/ β -catenin	PC cell growth and invasion
Mx et al. (2020)	Human protein database	N/A	FBXW7- SIK2/TORC2/AKT	Suppress PC cell division and cell cycle progression
Jin et al. (2017)	PC cell lines	N/A	FBXW7-EZH2	Suppress PC cell invasion
Qin et al. (2019)	TCGA Mouse model	Downregulated	PRMT5 - FBW7-cMyc	Improvement in PC cell growth and aerobic glycolysis
Ye et al. (2020)	Xenograft tumors	Normal	FBXW7-NRA41-SCD1	Activating ferroptosis and apoptosis
Q et al. (2017)	PC cell lines	Overexpression	FBXW7-ENT1	Improving the therapeutic efficacy of gemcitabine
Ishii et al. (2017)	PC tissues PC cell lines	Downregulated	FBXW7-MCL-1	Improving gemcitabine and paclitaxel efficacy in PC cells

levels in pancreatic cancer cells by downregulating FBXW7, promoting tumor cell proliferation (Qin et al., 2019).

FBXW7 can predict the response of PC to chemotherapy drugs. On one hand, FBXW7 can enhance the therapeutic response to gemcitabine by inhibiting the expression of proteins like stearyl-CoA desaturase (SCD) or increasing the expression of equilibrative nucleoside transporter 1 (ENT1) (Ye et al., 2020; Q et al., 2017). And on the other hand, the low expression of FBXW7 can promote resistance to gemcitabine and paclitaxel in pancreatic cancer (PC) cells by leading to the accumulation of MCL-1 (240). Consequently, it is anticipated that FBXW7 function restoration will enhance the therapeutic efficacy and prognosis of PC patients (Table 5).

The invasiveness and sensitivity of HCC cells to doxorubicin are also affected by FBXW7 levels. Restoring FBXW7 expression in HCC cells reduces their invasiveness and enhances the efficacy of doxorubicin (Yu et al., 2014). Sorafenib, commonly used in patients with advanced liver cancer, faces significant challenges due to drug resistance. FBXW7 has been implicated in sorafenib resistance in HCC cells (Feng et al., 2022; Tang et al., 2019). This resistance is linked to the downregulation of FBXW7 by MiR-223 and MiR-25, and can be reversed by restoring FBXW7 levels (Feng et al., 2022; Tang et al., 2019). For prognosis, HCC patients with high FBXW7 mRNA expression exhibit better DFS compared to those with low expression (S et al., 2014). Survival analysis indicates that low FBXW7 expression is an independent risk factor for predicting HCC recurrence (S et al., 2014). Therefore, FBXW7 may be a molecular marker in the treatment and prognosis assessment of HCC (Tu et al., 2014; El-Mezayen et al., 2021).

4.6 Cholangiocarcinoma and other gastrointestinal cancers

The mutation rate of FBXW7 in extrahepatic cholangiocarcinoma (CCA) has been reported to be 15% (n = 20) (Churi et al., 2014). Wang et al. demonstrated that FBXW7 deletion and AKT pathway activation synergistically upregulated the expression of c-Myc in animal experiment, contributing to the occurrence of intrahepatic cholangiocarcinoma (iCCA) (Wang et al., 2019). Overexpression of

FBXW7 enables CCA cells to restore normal c-Myc expression levels, which inhibits cell proliferation and progression (Li M. et al., 2017). Consequently, they proposed a novel therapeutic strategy for iCCA that targets the FBXW7-c-Myc pathway (Wang et al., 2019; Li M. et al., 2017). Besides c-Myc, FBXW7 regulates the progression of CCA cells and their resistance to cisplatin by targeting other substrates, including Notch1 and MCL-1 (Mori et al., 2018). The loss of FBXW7 expression can promote EMT and CSC development in CCA, resulting in tumors with increased malignant potential (H et al., 2015). Studies indicate that FBXW7-deficient CCA exhibits poor differentiation, a propensity for regional lymph node metastasis, and a later tumor stage (H et al., 2015; Enkhbold et al., 2014). Furthermore, FBXW7 expression is closely linked to the prognosis of CCA patients. Patients with low FBXW7 expression have significantly poorer outcomes, indicating that FBXW7 levels are a critical prognostic factor for CCA (Mori et al., 2018; Enkhbold et al., 2014). Recent research has revealed that numerous cytokines and chemokines are upregulated in CCA with FBXW7 mutations, showing favorable responses to immunotherapy (Feng et al., 2024). These findings suggest that FBXW7-mutant CCA may possess a distinct tumor immune microenvironment, making FBXW7 expression status a potential indicator of immunotherapy efficacy.

Approximately 75% of patients with gastrointestinal stromal tumors (GIST) harbor functional mutations in KIT (Shima et al., 2024). Imatinib, a KIT inhibitor, is the primary treatment for inoperable or metastatic GIST. However, the occurrence of drug resistance remains inevitable (Blanke et al., 2008). Current research has emphasized the role of FBXW7 in predicting GIST treatment resistance and prognosis. Both *in vivo* and *in vitro* experiments demonstrate that FBXW7 expression enhances sensitivity to imatinib treatment in GIST by downregulating MCL-1 (Wu et al., 2024). Following radical resection, GIST patients with high FBXW7 expression exhibit better prognoses and lower recurrence rates (Koga et al., 2019). The incidence of FBXW7 mutations in rectal neuroendocrine tumors (NETs) is reported to be 25% (Venizelos et al., 2021). In rectal NETs, the levels of FBXW7 mutations and non-coding RNAs may correlate with the Ki67 index, though further research is required to confirm this relationship (Kang et al., 2023). Table 6 illustrates the role of FBXW7 in CCA and other gastrointestinal cancers.

TABLE 6 The role of FBXW7 in cholangiocarcinoma and other gastrointestinal cancers.

Study	Source	FBXW7 status	Specific mechanisms	Significance
Wang et al. (2019)	iCCA tissues Mouse model	Downregulated	FBXW7/AKT-c-Myc	Leading to tumorigenesis in mice
Li et al. (2017b)	CCA cell lines	Overexpression	FBXW7 -c-Myc	Restrained cell multiplication <i>in vitro</i> and CCA xenograft tumor growth
A et al. (2018)	CCA cell lines CCA tissues	Normal expression	FBXW7-MCL-1/Notch1	Inhibited CCA progression and CCA cells are sensitive to cisplatin
H et al. (2015)	CCA cell lines CCA tissues	Depletion	FBXW7-EMT/CSCS	Resulting in the metastasis of CCA cells
Enkhbold et al. (2014)	CCA tissues	Low expression	N/A	Tumor progression and poor prognosis
Feng et al. (2024)	CCA cell lines Mouse	Downregulated	FBXW7- Stat	Accelerating tumor formation and growth
Wu et al. (2024)	GIST tissues	N/A	FBXW7-MCL-1	Regulates the sensitivity of imatinib
Koga et al. (2019)	GIST tissues	Low expression	FBXW7-c-Myc/Notch 1	Potential predictive marker of recurrence
Kang et al. (2023)	Rectal NET tissues	Mutation	N/A	Playing critical roles in tumor behaviors

5 Strategies to target FBXW7 for the treatment of cancers

As previously noted, FBXW7 is pivotal in the pathogenesis, progression, treatment resistance, and poor prognosis of gastrointestinal cancers, thereby presenting opportunities for targeted therapy. We propose several promising strategies for the treatment of cancer by FBXW7 as shown in Figure 4. At the same time, we also propose the current challenges of FBXW7 in the treatment of cancer.

5.1 Targeting upstream regulators to increase FBXW7 expression levels

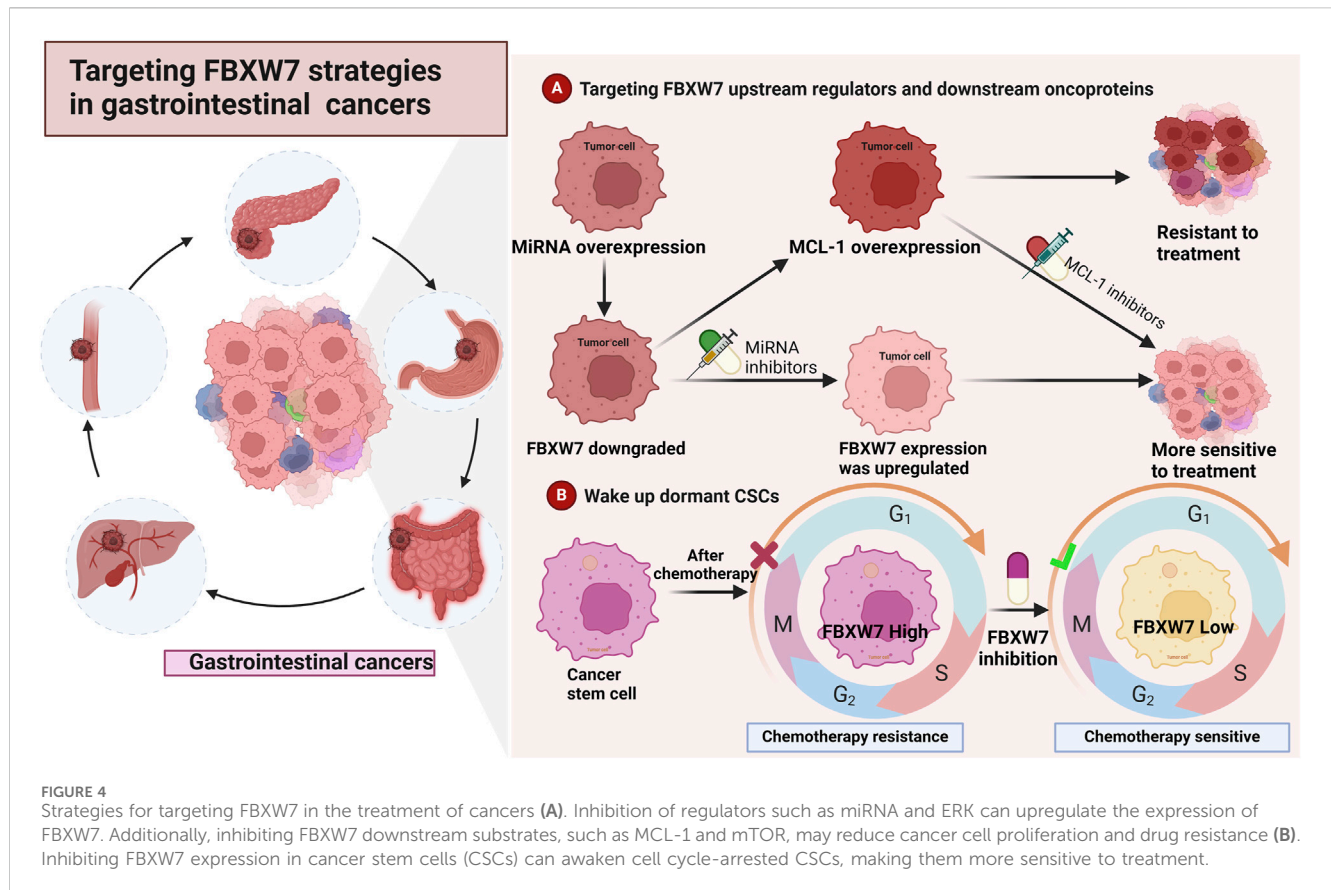
Aberrant FBXW7 expression is a key factor contributing to poor cancer prognosis, drug resistance, and treatment challenges (Khan AQ. et al., 2021). Restoring or increasing FBXW7 expression has been identified as a viable strategy to halt cancer progression and improve treatment outcomes (Figure 4). Several studies have shown that modulating MiR-223 levels can indirectly upregulate FBXW7 expression (Liu Z. et al., 2021; Kurashige et al., 2012). As previously reported, MiR-223-mediated inhibition of FBXW7 leads to GC resistance to trastuzumab and cisplatin, whereas reducing MiR-223 levels reverses this resistance (Zhou et al., 2015; Eto et al., 2015). Notably, genistein has been found to downregulate MiR-223 and upregulate FBXW7 expression (Ma et al., 2013). Elevated FBXW7 expression subsequently inhibits the growth and aggressiveness of PC cells (Ma et al., 2013). Recent findings also suggest that inhibiting ERK, another upstream regulator of FBXW7, improves the sensitivity of CRC cells to chemotherapeutic agents (Ruan et al., 2024). Mechanistically, this is attributed to Clitocine, an adenosine analog, which promotes FBXW7 expression and MCL-1 degradation by preventing the A2B/cAMP/ERK signaling axis (Ruan et al., 2024). Thus, targeting upstream regulators of FBXW7 presents a feasible approach to enhance drug sensitivity in gastrointestinal cancers.

5.2 Targeting key downstream substrates for FBXW7

FBXW7 exerts anti-tumor effects by regulating the degradation of various downstream oncoproteins. Thus, developing drugs that target key carcinogenic substrates may counteract the carcinogenic effects resulting from FBXW7 inactivation. For example, selective MCL-1 inhibitors restore the sensitivity of CRC cells with FBXW7 mutations to regorafenib (Tong et al., 2017). It has been found that deguelin can promote the destruction of MCL-1 by FBXW7, which is beneficial to the apoptosis of cancer cells (Gao et al., 2020). Furthermore, FBXW7 deficiency-induced resistance of CRC to Hsp90 inhibitors can be overcome by selective MCL-1 inhibitors (J et al., 2017). Research on MCL-1 inhibitors has garnered significant attention and may be applied in clinical treatment in the near future (Wang H. et al., 2021; Chen and Fletcher, 2017). Alongside MCL-1 inhibitors, mTOR inhibitors also exhibit significant anti-cancer effects on tumors with FBXW7 mutations (Mao et al., 2008). FBXW7 deletion leads to increased EMT and aggressiveness in CRC cell lines, which is mediated by overactivation of the mTOR pathway (Wang et al., 2013). Subsequently, mTOR inhibitors were applied to CRC cells with FBXW7 deficiency, resulting in significant inhibition of EMT and the aggressiveness of cancer cells (Wang et al., 2013). Therefore, inhibiting downstream oncoproteins to treat gastrointestinal cancers with FBXW7 deletions or mutations has the potential to enhance the efficacy of anticancer therapy.

5.3 Awakens dormant cancer stem cells (CSCs)

FBXW7 plays a critical role in regulating the differentiation and malignant transformation of various stem/progenitor cells, including pluripotent stem cells, hematopoietic stem cells, intestinal stem cells, and neural stem cells (N et al., 2015;



Takeishi and Nakayama, 2014). Additionally, FBXW7 is involved in the characterization of CSCs by modulating key oncoproteins, such as c-Myc and Notch1, in human malignancies (G et al., 2024; Li et al., 2019). For instance, FBXW7 contributes to the self-renewal and stem-like properties of hepatocellular carcinoma (HCC) cells by promoting the degradation of Actin-like 6A (ACTL6A) (X et al., 2022). CSCs, a small subset of tumor cells with the capacity for self-renewal and differentiation, play a pivotal role in tumor recurrence, progression, and resistance to treatment. While cytotoxic drugs target proliferating tumor cells, CSCs in a quiescent state are often resistant to such treatments (Takeishi and Nakayama, 2016). In non-small cell lung cancer (NSCLC), FBXW7 maintains gefitinib-resistant CSCs in a quiescent state by targeting the degradation of c-Myc (Hidayat et al., 2019). Moreover, downregulation of FBXW7 gene expression has been shown to significantly decrease the number of cells in the G0/G1 phase (Hidayat et al., 2019). In chronic myeloid leukemia, FBXW7 preserves dormant leukemia-initiating cells (LICs) through a similar mechanism, and its removal can awaken quiescent LICs, restoring sensitivity to imatinib (Takeishi et al., 2013). Elevated FBXW7 expression has also been detected in drug-resistant colorectal cancer (CRC) stem cells, with FBXW7 silencing enhancing sensitivity to anticancer drugs (Honma et al., 2019). These findings suggest that silencing FBXW7 may help convert CSCs from a quiescent to a proliferative state, potentially improving treatment resistance. However, this effect is primarily directed at CSCs or tumor cells with stem-like properties, which represent only a small portion of the overall tumor.

5.4 Other approaches to target FBXW7 for cancer treatment

FBXW7 is frequently inactivated in cancer through mutations, deletions, or promoter hypermethylation (Fan et al., 2022). Therefore, restoring the function of the FBXW7 cancer suppressor gene in tumor cells lacking expression at the molecular and genetic levels represents a potential therapeutic strategy. Evidence from mouse lung cancer models indicates that decitabine promotes FBXW7 expression, leading to MCL-1 degradation and enhanced sensitivity to anticancer drugs (DiNardo et al., 2018). Decitabine, as a DNMT1 inhibitor, induces a shift from hypermethylation to unmethylation of the FBXW7 promoter, thereby facilitating FBXW7 transcription (DiNardo et al., 2018). As discussed in Section 3, FBXW7 protein levels are regulated by autoubiquitination and deubiquitinases (DUBs). USP9X prevents the ubiquitination and degradation of FBXW7 in mouse models and inhibits intestinal tumor development (Khan et al., 2018). In tumors with downregulated FBXW7 expression, it may be possible to counteract FBXW7 self-ubiquitination and degradation by developing deubiquitinase-targeting chimeric (DUBTAC) technology to sustain FBXW7 expression and function (Henning et al., 2022; Willson, 2022). Furthermore, the development of proteolysis-targeting chimeric (PROTAC) technology, where two covalently linked PROTAC molecules recruit specific substrates and FBXW7, could enhance the degradation efficiency of FBXW7 (Li et al., 2022). Although research in this area is limited, the potential significance of DUBTACs and PROTACs will become clearer as the functional mechanisms of FBXW7 are further explored.

5.5 Current challenges in targeting FBXW7 in the treatment of cancer

The FBXW7 gene is frequently mutated or deleted in human tumors, leading to impaired tumor suppression. Currently, restoring the tumor-suppressive function of FBXW7 *in vivo* through gene editing or gene transfer therapies remains challenging (Fan et al., 2022). No drug or therapeutic technology currently available targets the FBXW7 gene directly for cancer treatment. While PROTAC and DUBTAC approaches may prove useful in tumors with low FBXW7 activity, they are ineffective in tumors with FBXW7 mutations or deletions. A large network of regulators and oncogenic substrates surrounds FBXW7, offering multiple potential pathways for cancer treatment. However, the tumor-suppressive effects of FBXW7 arise from the integrated function of this regulatory network, making it difficult to predict whether targeting a single pathway will produce the desired therapeutic effect. As noted earlier, there is resistance to Wnt/ β -catenin pathway inhibition in FBXW7-mutant tumors (Zhong and Virshup, 2024), which is linked to the activation of other carcinogenic substrates regulated by FBXW7. However, simultaneously targeting multiple oncogenic substrates or regulators may lead to unforeseen toxic side effects. Furthermore, the knockdown of FBXW7 to enhance the sensitivity of dormant cancer stem cells (CSCs) to therapeutic agents presents a dual challenge. CSCs, while a small fraction of the overall tumor, tend to increase as the disease progresses. Whether the enhanced drug sensitivity resulting from FBXW7 knockdown can counterbalance the tumor-suppressive dysfunction caused by FBXW7 deletion requires further investigation.

6 Discussion and conclusions

FBXW7 is a substrate recognition component of the SCF-type E3 ubiquitin ligase complex, frequently inactivated or mutated in human cancers. Given the wide range of FBXW7 functions in cancer, this review focuses on its role in gastrointestinal cancers. As a recognized tumor suppressor gene, the inactivation of FBXW7 promotes tumorigenesis, proliferation, differentiation, invasion, and apoptosis in gastrointestinal tumor cells by interacting with the EGFR-MAPK, Wnt/ β -catenin, and PI3K/Akt/mTOR signaling pathways (Wu et al., 2016; Liu Z. et al., 2021; Xie and Sun, 2019; Hu et al., 2019; Huang and Long, 2023; Pan et al., 2023; Ji et al., 2015; Escobar et al., 2022; R et al., 2023). In addition, FBXW7 is involved in the aggressiveness and drug resistance of gastrointestinal cancers by mediating the degradation of downstream substrates such as Cyclin E, MCL-1, and Notch1 (Ou et al., 2016; Guo et al., 2012; Lin et al., 2020b; J et al., 2017; Wang et al., 2015). Therefore, FBXW7 forms a complex and extensive regulatory network in gastrointestinal cancers by modulating various signaling pathways and substrate proteins. Both *in vitro* and *in vivo* studies have shown that the loss of FBXW7 expression leads to the accumulation of oncogenic proteins, which is strongly connected to the initiation, development, metastasis, and drug resistance of various gastrointestinal cancers, including CRC, GC, ESCC, HCC, CCA, and PC (Wei et al., 2023; Khan et al., 2018; Mori et al., 2018; Ou et al., 2016; Gong et al., 2018; He et al., 2019; Mu et al., 2017; Lin H. et al., 2020; Li et al., 2018; Zhan et al., 2015; Huang

and Long, 2023; Wang et al., 2021c; Kawashita et al., 2017; Jiang et al., 2017; Li et al., 2012; Gong et al., 2015; Y et al., 2021; Li et al., 2020; X et al., 2019b; Hou et al., 2022; Zhou et al., 2015; Eto et al., 2015; Bi et al., 2023; Li et al., 2023b; Wu et al., 2015; Y et al., 2010; Zhou et al., 2012; Feng et al., 2022; Chan et al., 2024b; Yang et al., 2015; Yu et al., 2014; Zhang Q. et al., 2016; Mx et al., 2020; Ye et al., 2020; Wang et al., 2019). Impaired FBXW7 function in gastrointestinal cancers is generally associated with poor patient outcomes (Liu H. et al., 2018; Iwatsuki et al., 2010; Kawaguchi et al., 2021; Yokobori et al., 2009; Li MR. et al., 2017; Gombodorj et al., 2018; S et al., 2014; Feng et al., 2024; Koga et al., 2019). Therefore, strategies aimed at targeting FBXW7 may offer potential therapeutic approaches for cancer treatment. Although no drugs currently directly target FBXW7, promising therapeutic strategies have been proposed based on existing research (Zeng et al., 2024). Future treatments may focus on restoring or replacing FBXW7 expression by targeting its upstream regulators, such as miRNA and ERK, or by inhibiting downstream oncoproteins such as MCL-1, mTOR, and c-Myc (Zhou et al., 2015; Eto et al., 2015; Ma et al., 2013; Ruan et al., 2024; Gao et al., 2020). The numerous regulators and substrates of FBXW7 provide a wide range of targets for treating gastrointestinal cancers. However, these treatment strategies are often difficult to implement, with uncertain efficacy and significant side effects. To address the key challenges currently faced, the following approaches may be considered: i) Identifying and inhibiting the most critical carcinogenic substrates or upstream regulators of FBXW7 to maximize its tumor-suppressive function. ii) Activating or enhancing the activity of other tumor suppressor genes in the presence of FBXW7 mutations or deletions. iii) Tailoring strategies based on tumor stage and the number of CSCs present to minimize the adverse effects of FBXW7 knockdown.

In conclusion, FBXW7 has the potential to be an important molecular marker for the treatment and prognosis of gastrointestinal cancers. Continued research into the tumor biology and molecular mechanisms of FBXW7 will offer valuable insights for improving the precision treatment of gastrointestinal cancer patients.

Author contributions

WW: Investigation, Project administration, Software, Visualization, Writing—original draft. XL: Investigation, Software, Writing—original draft. LZ: Supervision, Writing—original draft. KJ: Software, Writing—original draft. ZY: Software, Writing—original draft. RY: Investigation, Writing—original draft. WZ: Investigation, Writing—original draft. JC: Conceptualization, Supervision, Writing—review and editing. TL: Conceptualization, Funding acquisition, Resources, Supervision, Validation, Writing—review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

- Afolabi, H. A., Salleh, S. M., Zakaria, Z., Seng, C. E., Nafi, N. M., Bin AbdulAziz, A. A., et al. (2024). Targeted variant prevalence of FBXW7 gene mutation in colorectal carcinoma propagation. The first systematic review and meta-analysis. *Heliyon* 10 (11), e31471. doi:10.1016/j.heliyon.2024.e31471
- Anastasiadou, E., Jacob, L. S., and Slack, F. J. (2018). Non-coding RNA networks in cancer. *Nat. Rev. Cancer* 18 (1), 5–18. doi:10.1038/nrc.2017.99
- As, A. (2019). PI3K/Akt/mTOR inhibitors in cancer: at the bench and bedside. *Semin. Cancer Biol.* 59, 125–132. doi:10.1016/j.semcancer.2019.07.009
- B, K., T, T., L, R., L, X., J, M., P, N., et al. (2013). The ubiquitin ligase FBXW7 modulates leukemia-initiating cell activity by regulating MYC stability. *Cell* 153 (7), 1552–1566. doi:10.1016/j.cell.2013.05.041
- B, F., Pa, C., Bj, V. F., El, R., V, R., B, I., et al. (2024). A germline point mutation in the MYC-FBW7 phosphodegron initiates hematopoietic malignancies. *Genes Dev.* 38 (5–6), 253–272. doi:10.1101/gad.351292.123
- Ba, S., and Y, X. (2014). Out of the F-box: reawakening the pancreas. *Cell Stem Cell* 15 (2), 111–112. doi:10.1016/j.stem.2014.07.006
- Babaei-Jadidi, R., Li, N., Saadeddin, A., Spencer-Dene, B., Jandke, A., Muhammad, B., et al. (2011). FBXW7 influences murine intestinal homeostasis and cancer, targeting Notch, Jun, and DEK for degradation. *J. Exp. Med.* 208 (2), 295–312. doi:10.1084/jem.201100830
- Bakos, G., Yu, L., Gak, I. A., Roumeliotis, T. I., Liakopoulos, D., Choudhary, J. S., et al. (2018). An E2-ubiquitin thioester-driven approach to identify substrates modified with ubiquitin and ubiquitin-like molecules. *Nat. Commun.* 9, 4776. doi:10.1038/s41467-018-07251-5
- Balamurugan, K., Wang, J. M., Tsai, H. H., Sharan, S., Anver, M., Leighty, R., et al. (2010). The tumour suppressor C/EBP δ inhibits FBXW7 expression and promotes mammary tumour metastasis. *EMBO J.* 29 (24), 4106–4117. doi:10.1038/emboj.2010.280
- Bd, W., Aj, C., and Dw, D. (2012). Dysregulation of Wnt/ β -catenin signaling in gastrointestinal cancers. *Gastroenterology* 142 (2), 219–232. doi:10.1053/j.gastro.2011.12.001
- Ben, W., Zhang, G., Huang, Y., and Sun, Y. (2020). MiR-27a-3p regulated the aggressive phenotypes of cervical cancer by targeting FBXW7. *Cancer Manag. Res.* 12, 2925–2935. doi:10.2147/CMAR.S234897
- Ben-Aharon, I., van Laarhoven, H. W. M., Fontana, E., Obermannova, R., Nilsson, M., and Lordick, F. (2023). Early-onset cancer in the gastrointestinal tract is on the rise—evidence and implications. *Cancer Discov.* 13 (3), 538–551. doi:10.1158/2159-8290.CD-22-1038
- Bengochea-Alonso, M. T., and Ericsson, J. (2010). Tumor suppressor Fbxw7 regulates TGF β signaling by targeting TGF1 for degradation. *Oncogene* 29 (38), 5322–5328. doi:10.1038/onc.2010.278
- Bi, Y., Yang, Y., Zhang, Y., Cheng, C., Tang, P., Xiao, H., et al. (2023). FBXW7 inhibits the progression of ESCC by directly inhibiting the stemness of tumor cells. *Neoplasma* 70 (6), 733–746. doi:10.4149/neo_2023_230104N8
- Blanke, C. D., Rankin, C., Demetri, G. D., Ryan, C. W., von Mehren, M., Benjamin, R. S., et al. (2008). Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* 26 (4), 626–632. doi:10.1200/JCO.2007.13.4452
- Boretto, M., Geurts, M. H., Gandhi, S., Ma, Z., Staliarova, N., Celotti, M., et al. (2024). Epidermal growth factor receptor (EGFR) is a target of the tumor-suppressor E3 ligase FBXW7. *Proc. Natl. Acad. Sci. U. S. A.* 121 (12), e2309902121. doi:10.1073/pnas.2309902121
- Bray, F., Laversanne, M., Sung, H., Ferlay, J., Siegel, R. L., Soerjomataram, I., et al. (2024). Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* 74 (3), 229–263. doi:10.3322/caac.21834
- Buscaill, L., Bournet, B., and Cordelier, P. (2020). Role of oncogenic KRAS in the diagnosis, prognosis and treatment of pancreatic cancer. *Nat. Rev. Gastroenterol. Hepatol.* 17 (3), 153–168. doi:10.1038/s41575-019-0245-4
- Chan, Y. T., Zhang, C., Wu, J., Lu, P., Xu, L., Yuan, H., et al. (2024a). Biomarkers for diagnosis and therapeutic options in hepatocellular carcinoma. *Mol. Cancer* 23 (1), 189. doi:10.1186/s12943-024-02101-z
- Chan, T. S., Cheng, L. H., Hsu, C. C., Yang, P. M., Liao, T. Y., Hsieh, H. Y., et al. (2024b). ASPM stabilizes the NOTCH intracellular domain 1 and promotes oncogenesis by blocking FBXW7 binding in hepatocellular carcinoma cells. *Mol. Oncol.* 18 (3), 562–579. doi:10.1002/1878-0261.13589
- Chang, C. C., Lin, H. H., Lin, J. K., Lin, C. C., Lan, Y. T., Wang, H. S., et al. (2015). FBXW7 mutation analysis and its correlation with clinicopathological features and prognosis in colorectal cancer patients. *Int. J. Biol. Markers* 30 (1), e88–e95. doi:10.5301/ijbm.5000125
- Chang, H., Liu, Y. H., Wang, L. L., Wang, J., Zhao, Z. H., Qu, J. F., et al. (2018). MiR-182 promotes cell proliferation by suppressing FBXW7 and FBXW11 in non-small cell lung cancer. *Am. J. Transl. Res.* 10 (4), 1131–1142.
- Chen, L., and Fletcher, S. (2017). Mcl-1 inhibitors: a patent review. *Expert Opin. Ther. Pat.* 27 (2), 163–178. doi:10.1080/13543776.2017.1249848
- Chen, L. J., Hu, B., Han, Z. Q., Liu, W., Zhu, J. H., Chen, X. X., et al. (2021). Repression of FBXW7 by HES5 contributes to inactivation of the TGF- β signaling pathway and alleviation of endometriosis. *FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol.* 35 (2), e20938. doi:10.1096/fj.202000438RRR
- Chen, S., Leng, P., Guo, J., and Zhou, H. (2023). FBXW7 in breast cancer: mechanism of action and therapeutic potential. *J. Exp. Clin. Cancer Res. CR* 42 (1), 226. doi:10.1186/s13046-023-02767-1
- Chong, X., Madeti, Y., Cai, J., Li, W., Cong, L., Lu, J., et al. (2024). Recent developments in immunotherapy for gastrointestinal tract cancers. *J. Hematol. Oncol. Hematol. Oncol.* 17 (1), 65. doi:10.1186/s13045-024-01578-x
- Chu, C., Geng, Y., Zhou, Y., and Sicinski, P. (2021). Cyclin E in normal physiology and disease states. *Trends Cell Biol.* 31 (9), 732–746. doi:10.1016/j.tcb.2021.05.001
- Churi, C. R., Shroff, R., Wang, Y., Rashid, A., Kang, H. C., Weatherly, J., et al. (2014). Mutation profiling in cholangiocarcinoma: prognostic and therapeutic implications. *PLoS One* 9 (12), e115383. doi:10.1371/journal.pone.0115383
- Cizmecioglu, O., Krause, A., Bahtz, R., Ehret, L., Malek, N., and Hoffmann, I. (2012). Plk2 regulates centriole duplication through phosphorylation-mediated degradation of Fbxw7 (human Cdc4). *J. Cell Sci.* 125 (4), 981–992. doi:10.1242/jcs.095075
- Close, V., Close, W., Kugler, S. J., Reichenzeller, M., Yosifov, D. Y., Bloehdorn, J., et al. (2018). NOTCH1 signaling is activated in CLL by mutations of FBXW7 and low expression of USP28 at 11q23. *Blood* 132, 946. doi:10.1182/blood-2018-99-114491
- Close, V., Close, W., Kugler, S. J., Reichenzeller, M., Yosifov, D. Y., Bloehdorn, J., et al. (2019). FBXW7 mutations reduce binding of NOTCH1, leading to cleaved NOTCH1 accumulation and target gene activation in CLL. *Blood* 133 (8), 830–839. doi:10.1182/blood-2018-09-874529
- Collisson, E. A., Bailey, P., Chang, D. K., and Biankin, A. V. (2019). Molecular subtypes of pancreatic cancer. *Nat. Rev. Gastroenterol. Hepatol.* 16 (4), 207–220. doi:10.1038/s41575-019-0109-y
- CXCR4. CXCR4 inhibitor BL-8040 induces AML blast apoptosis by altering miR-15a/16-1 expression and downregulating ERK, BCL-2, MCL-1, and cyclin-D1 | Leukemia. (2024). Available at: <https://www.nature.com/articles/leu201782>
- D, X., M, Y., H, S., P, R., J, J., F, L., et al. (2016). Polo-like kinase-1 regulates myc stabilization and activates a feedforward circuit promoting tumor cell survival. *Mol. Cell* 64 (3), 493–506. doi:10.1016/j.molcel.2016.09.016
- Davis, R. J., Welcker, M., and Clurman, B. E. (2014). Tumor suppression by the Fbw7 ubiquitin ligase: mechanisms and opportunities. *Cancer Cell* 26 (4), 455–464. doi:10.1016/j.ccell.2014.09.013

- Dhanasekaran, R., Deutzmann, A., Mahaud-Fernandez, W. D., Hansen, A. S., Gouw, A. M., and Felsner, D. W. (2021). The MYC oncogene — the grand orchestrator of cancer growth and immune evasion. *Nat. Rev. Clin. Oncol.* 19 (1), 23–36. doi:10.1038/s41571-021-00549-2
- Di Fiore, R., Suleiman, S., Drago-Ferrante, R., Subbannayya, Y., Suleiman, S., Vasileva-Slaveva, M., et al. (2023). The role of FBXW7 in gynecologic malignancies. *Cells* 12 (10), 1415. doi:10.3390/cells12101415
- DiNardo, C. D., Pratz, K. W., Letai, A., Jonas, B. A., Wei, A. H., Thirman, M., et al. (2018). Safety and preliminary efficacy of venetoclax with decitabine or azacitidine in elderly patients with previously untreated acute myeloid leukaemia: a non-randomised, open-label, phase 1b study. *Lancet Oncol.* 19 (2), 216–228. doi:10.1016/S1470-2045(18)30010-X
- Di, J., Ji, W., K. H., Am, T., R. Z., J. F., et al. (2014). FBXW7 mutations in patients with advanced cancers: clinical and molecular characteristics and outcomes with mTOR inhibitors. *PLoS One* 9 (2), e89388. doi:10.1371/journal.pone.0089388
- Ekhholm-Reed, S., Spruck, C. H., Sangfelt, O., van Droogen, F., Mueller-Holzner, E., Widschwendter, M., et al. (2004). Mutation of hCDC4 leads to cell cycle deregulation of cyclin E in cancer. *Cancer Res.* 64 (3), 795–800. doi:10.1158/0008-5472.can-03-3417
- Elimova, E., Wadhwa, R., Shiozaki, H., Sudo, K., Estrella, J. S., Badgwell, B. D., et al. (2015). Molecular biomarkers in gastric cancer. *J. Natl. Compr. Cancer Netw. JNCCN* 13 (4), e19–e29. doi:10.6004/jnccn.2015.0064
- El-Mezayen, H., Yamamura, K., Yusa, T., Nakao, Y., Uemura, N., Kitamura, F., et al. (2021). MicroRNA-25 exerts an oncogenic function by regulating the ubiquitin ligase Fbxw7 in hepatocellular carcinoma. *Ann. Surg. Oncol.* 28 (12), 7973–7982. doi:10.1245/s10434-021-09778-2
- Enkhbold, C., Utsunomiya, T., Morine, Y., Imura, S., Ikemoto, T., Arakawa, Y., et al. (2014). Loss of FBXW7 expression is associated with poor prognosis in intrahepatic cholangiocarcinoma. *Hepatol. Res. Off. J. Jpn. Soc. Hepatol.* 44 (14), E346–E352. doi:10.1111/hepr.12314
- Escobar, D., Bushara, O., Sun, L., Liao, J., and Yang, G. Y. (2022). Clinicopathologic characteristics of FBXW7-mutated colorectal adenocarcinoma and association with aberrant beta-catenin localization. *Hum. Pathol.* 119, 51–58. doi:10.1016/j.humpath.2021.10.003
- Eto, K., Iwatsuki, M., Watanabe, M., Ishimoto, T., Ida, S., Imamura, Y., et al. (2015). The sensitivity of gastric cancer to trastuzumab is regulated by the miR-223/FBXW7 pathway. *Int. J. Cancer* 136 (7), 1537–1545. doi:10.1002/ijc.29168
- Fan, J., Bellon, M., Ju, M., Zhao, L., Wei, M., Fu, L., et al. (2022). Clinical significance of FBXW7 loss of function in human cancers. *Mol. Cancer* 21 (1), 87. doi:10.1186/s12943-022-01548-2
- Fang, L., Yang, Z., Zhou, J., Tung, J. Y., Hsiao, C. D., Wang, L., et al. (2015). Circadian clock gene CRY2 degradation is involved in chemoresistance of colorectal cancer. *Mol. Cancer Ther.* 14 (6), 1476–1487. doi:10.1158/1535-7163.MCT-15-0030
- Feng, X., Zou, B., Nan, T., Zheng, X., Zheng, L., Lan, J., et al. (2022). MiR-25 enhances autophagy and promotes sorafenib resistance of hepatocellular carcinoma via targeting FBXW7. *Int. J. Med. Sci.* 19 (2), 257–266. doi:10.7150/ijms.67352
- Feng, Y., Zhao, M., Wang, L., Li, L., Lei, J. H., Zhou, J., et al. (2024). The heterogeneity of signaling pathways and drug responses in intrahepatic cholangiocarcinoma with distinct genetic mutations. *Cell Death Dis.* 15 (1), 34. doi:10.1038/s41419-023-06406-7
- G, K., and T, M. (2014). Perilous journey: a tour of the ubiquitin-proteasome system. *Trends Cell Biol.* 24 (6), 352–359. doi:10.1016/j.tcb.2013.12.003
- G, X., W, L., J, Y., Z, L., P, W., and H, F. (2024). Fbxw7 suppresses carcinogenesis and stemness in triple-negative breast cancer through CHD4 degradation and Wnt/β-catenin pathway inhibition. *J. Transl. Med.* 22 (1), 99. doi:10.1186/s12967-024-04897-2
- Gao, F., Yu, X., Li, M., Zhou, L., Liu, W., Li, W., et al. (2020). Deguelin suppresses non-small cell lung cancer by inhibiting EGFR signaling and promoting GSK3β/FBW7-mediated Mcl-1 destabilization. *Cell Death Dis.* 11 (2), 143. doi:10.1038/s41419-020-2344-0
- Ge, M. K., Zhang, N., Xia, L., Zhang, C., Dong, S. S., Li, Z. M., et al. (2020). FBXO22 degrades nuclear PTEN to promote tumorigenesis. *Nat. Commun.* 11, 1720. doi:10.1038/s41467-020-15578-1
- Gi, M., E, C., Y, L., and Ys, L. (2020). Decreased expression of FBXW7 by ERK1/2 activation in drug-resistant cancer cells confers transcriptional activation of MDR1 by suppression of ubiquitin degradation of HSF1. *Cell Death Dis.* 11 (5), 395. doi:10.1038/s41419-020-2600-3
- Gombodorj, N., Yokobori, T., Tanaka, N., Suzuki, S., Kuriyama, K., Kumakura, Y., et al. (2018). Correlation between high FBXW7 expression in pretreatment biopsy specimens and good response to chemoradiation therapy in patients with locally advanced esophageal cancer: a retrospective study. *J. Surg. Oncol.* 118 (1), 101–108. doi:10.1002/jso.25127
- Gong, J., Cui, Z., Li, L., Ma, Q., Wang, Q., Gao, Y., et al. (2015). MicroRNA-25 promotes gastric cancer proliferation, invasion, and migration by directly targeting F-box and WD-40 Domain Protein 7, FBXW7. *Tumour Biol. J. Int. Soc. Oncodevelopmental Biol. Med.* 36 (10), 7831–7840. doi:10.1007/s13277-015-3510-3
- Gong, J., Huang, Z., and Huo, J. R. (2016). Involvement of F-box proteins in esophageal cancer (Review). *Int. J. Oncol.* 48 (3), 886–894. doi:10.3892/ijo.2016.3325
- Gong, L., Ren, M., Lv, Z., Yang, Y., and Wang, Z. (2018). miR-92b-3p promotes colorectal carcinoma cell proliferation, invasion, and migration by inhibiting FBXW7 *in vitro* and *in vivo*. *DNA Cell Biol.* 37 (5), 501–511. doi:10.1089/dna.2017.4080
- Grim, J. E., Gustafson, M. P., Hirata, R. K., Hagar, A. C., Swanger, J., Welcker, M., et al. (2008). Isoform- and cell cycle-dependent substrate degradation by the Fbw7 ubiquitin ligase. *J. Cell Biol.* 181 (6), 913–920. doi:10.1083/jcb.200802076
- Grim, J. E., Knoblaugh, S. E., Guthrie, K. A., Hagar, A., Swanger, J., Hespelt, J., et al. (2012). Fbw7 and p53 cooperatively suppress advanced and chromosomally unstable intestinal cancer. *Mol. Cell Biol.* 32 (11), 2160–2167. doi:10.1128/MCB.00305-12
- Guan, W. L., He, Y., and Xu, R. H. (2023). Gastric cancer treatment: recent progress and future perspectives. *J. Hematol. Oncol. Hematol. Oncol.* 16 (1), 57. doi:10.1186/s13045-023-01451-3
- Guo, Z., Zhou, Y., Evers, B. M., and Wang, Q. (2012). Rictor regulates FBXW7-dependent c-Myc and cyclin E degradation in colorectal cancer cells. *Biochem. Biophys. Res. Commun.* 418 (2), 426–432. doi:10.1016/j.bbrc.2012.01.054
- H, Y., X, L., Z, L., L, C., Y, X., Y, W., et al. (2015). FBXW7 suppresses epithelial-mesenchymal transition, stemness and metastatic potential of cholangiocarcinoma cells. *Oncotarget* 6 (8), 6310–6325. doi:10.18632/oncotarget.3355
- He, D., Ma, Z., Fang, C., Ding, J., Yang, W., Chen, P., et al. (2019). Pseudophosphatase STYX promotes tumor growth and metastasis by inhibiting FBXW7 function in colorectal cancer. *Cancer Lett.* 454, 53–65. doi:10.1016/j.canlet.2019.04.014
- Heestand, G. M., and Kurzrock, R. (2015). Molecular landscape of pancreatic cancer: implications for current clinical trials. *Oncotarget* 6 (7), 4553–4561. doi:10.18632/oncotarget.2972
- Henning, N. J., Boike, L., Spradlin, J. N., Ward, C. C., Liu, G., Zhang, E., et al. (2022). Deubiquitinase-targeting chimeras for targeted protein stabilization. *Nat. Chem. Biol.* 18 (4), 412–421. doi:10.1038/s41589-022-00971-2
- Hershko, A., and Ciechanover, A. (1998). The ubiquitin system. *Annu. Rev. Biochem.* 67, 425–479. doi:10.1146/annurev.biochem.67.1.425
- Hidayat, M., Mitsuishi, Y., Takahashi, F., Tajima, K., Yae, T., Miyahara, K., et al. (2019). Role of FBXW7 in the quiescence of gefitinib-resistant lung cancer stem cells in EGFR-mutant non-small cell lung cancer. *Bosn. J. Basic Med. Sci.* 19 (4), 355–367. doi:10.17305/bjbs.2019.4227
- Honma, S., Hisamori, S., Nishiuchi, A., Itatani, Y., Obama, K., Shimono, Y., et al. (2019). F-Box/WD repeat domain-containing 7 induces chemotherapy resistance in colorectal cancer stem cells. *Cancers* 11 (5), E635. doi:10.3390/cancers11050635
- Hou, J., Huang, P., Lan, C., Geng, S., Xu, M., Liu, Y., et al. (2022). ZC3H15 promotes gastric cancer progression by targeting the FBXW7/c-Myc pathway. *Cell Death Discov.* 8 (1), 32. doi:10.1038/s41420-022-00815-x
- Hu, J. L., Wang, W., Lan, X. L., Zeng, Z. C., Liang, Y. S., Yan, Y. R., et al. (2019). CAFs secreted exosomes promote metastasis and chemotherapy resistance by enhancing cell stemness and epithelial-mesenchymal transition in colorectal cancer. *Mol. Cancer* 18 (1), 91. doi:10.1186/s12943-019-1019-x
- Huang, G., and Long, K. (2023). Sensitization of colon cancer cells to cisplatin by Fbxw7 via negative regulation of the Nox1-mTOR pathway. *Pathol. Res. Pract.* 247, 154479. doi:10.1016/j.prp.2023.154479
- Huang, L. Y., Zhao, J., Chen, H., Wan, L., Inuzuka, H., Guo, J., et al. (2018). SCFFBW7-mediated degradation of Brg1 suppresses gastric cancer metastasis. *Nat. Commun.* 9, 3569. doi:10.1038/s41467-018-06038-y
- Huang, G., Xiang, Z., Wu, H., He, Q., Dou, R., Lin, Z., et al. (2022). The lncRNA BDNF-AS/WDR5/FBXW7 axis mediates ferroptosis in gastric cancer peritoneal metastasis by regulating VDAC3 ubiquitination. *Int. J. Biol. Sci.* 18 (4), 1415–1433. doi:10.7150/ijbs.69454
- Huang, J., Lucero-Prisno, D. E., Zhang, L., Xu, W., Wong, S. H., Ng, S. C., et al. (2023). Updated epidemiology of gastrointestinal cancers in East Asia. *Nat. Rev. Gastroenterol. Hepatol.* 20 (5), 271–287. doi:10.1038/s41575-022-00726-3
- I, B. A., Hwm van, L., E, F., R, O., M, N., and F, L. (2023). Early-onset cancer in the gastrointestinal tract is on the rise—evidence and implications. *Cancer Discov.* 13 (3), 538–551. doi:10.1158/2159-8290.CD-22-1038
- Inuzuka, H., Shaik, S., Onoyama, I., Gao, D., Tseng, A., Maser, R. S., et al. (2011). SCF(FBW7) regulates cellular apoptosis by targeting MCL1 for ubiquitylation and destruction. *Nature* 471 (7336), 104–109. doi:10.1038/nature09732
- Is, H., A, G., W, S., Ap, K., G, S. M. G., and Garg, M. (2022). The multidimensional role of the Wnt/β-catenin signaling pathway in human malignancies. *J. Cell Physiol.* 237 (1), 199–238. doi:10.1002/jcp.30561
- Ishii, N., Araki, K., Yokobori, T., Gantumur, D., Yamanaka, T., Altan, B., et al. (2017). Reduced FBXW7 expression in pancreatic cancer correlates with poor prognosis and chemotherapeutic resistance via accumulation of MCL1. *Oncotarget* 8 (68), 112636–112646. doi:10.18632/oncotarget.22634
- Iwatsuki, M., Mimori, K., Ishii, H., Yokobori, T., Takatsuno, Y., Sato, T., et al. (2010). Loss of FBXW7, a cell cycle regulating gene, in colorectal cancer: clinical significance. *Int. J. Cancer* 126 (8), 1828–1837. doi:10.1002/ijc.24879
- Izumi, D., Ishimoto, T., Miyake, K., Eto, T., Arima, K., Kiyozumi, Y., et al. (2017). Colorectal cancer stem cells acquire chemoresistance through the upregulation of

- F-box/WD repeat-containing protein 7 and the consequent degradation of c-myc. *Stem Cells Dayt Ohio* 35 (9), 2027–2036. doi:10.1002/stem.2668
- J, T., S, T., Z, N. C., J, Y., F, Z., and L, Z. (2017). FBW7-Dependent mcl-1 degradation mediates the anticancer effect of Hsp90 inhibitors. *Mol. Cancer Ther.* 16 (9), 1979–1988. doi:10.1158/1535-7163.MCT-17-0032
- Ji, S., Qin, Y., Shi, S., Liu, X., Hu, H., Zhou, H., et al. (2015). ERK kinase phosphorylates and destabilizes the tumor suppressor FBW7 in pancreatic cancer. *Cell Res.* 25 (5), 561–573. doi:10.1038/cr.2015.30
- Jiang, J. X., Sun, C. Y., Tian, S., Yu, C., Chen, M. Y., and Zhang, H. (2016). Tumor suppressor Fbxw7 antagonizes WNT signaling by targeting β -catenin for degradation in pancreatic cancer. *Tumour Biol. J. Int. Soc. Oncodevelopmental Biol. Med.* 37 (10), 13893–13902. doi:10.1007/s13277-016-5217-5
- Jiang, Y., Qi, X., Liu, X., Zhang, J., Ji, J., Zhu, Z., et al. (2017). Fbxw7 haploinsufficiency loses its protection against DNA damage and accelerates MNU-induced gastric carcinogenesis. *Oncotarget* 8 (20), 33444–33456. doi:10.18632/oncotarget.16800
- Jiménez-Izquierdo, R., Morrugares, R., Suanes-Cobos, L., Correa-Sáez, A., Garrido-Rodríguez, M., Cerero-Tejero, L., et al. (2023). FBXW7 tumor suppressor regulation by dual-specificity tyrosine-regulated kinase 2. *Cell Death Dis.* 14 (3), 202. doi:10.1038/s41419-023-05724-0
- Jin, X., Yang, C., Fan, P., Xiao, J., Zhang, W., Zhan, S., et al. (2017). CDK5/FBW7-dependent ubiquitination and degradation of EZH2 inhibits pancreatic cancer cell migration and invasion. *J. Biol. Chem.* 292 (15), 6269–6280. doi:10.1074/jbc.M116.764407
- Joshi, S. S., and Badgwell, B. D. (2021). Current treatment and recent progress in gastric cancer. *CA Cancer J. Clin.* 71 (3), 264–279. doi:10.3322/caac.21657
- Kam, A. E., Masood, A., and Shroff, R. T. (2021). Current and emerging therapies for advanced biliary tract cancers. *Lancet Gastroenterol. Hepatol.* 6 (11), 956–969. doi:10.1016/S2468-1253(21)00171-0
- Kang, H. S., Park, H. Y., Lim, H., Son, I. T., Kim, M. J., Kim, N. Y., et al. (2023). Different miRNAs related to FBXW7 mutations or high mitotic indices contribute to rectal neuroendocrine tumors: a pilot study. *Int. J. Mol. Sci.* 24 (7), 6329. doi:10.3390/ijms24076329
- Kar, R., Jha, S. K., Ojha, S., Sharma, A., Dholpuria, S., Raju, V. S. R., et al. (2021). The FBXW7-NOTCH interactome: a ubiquitin proteasomal system-induced crosstalk modulating oncogenic transformation in human tissues. *Cancer Rep.* 4 (4), e1369. doi:10.1002/cnr2.1369
- Kawaguchi, Y., Newhook, T. E., Tran Cao, H. S., Tzeng, C. W. D., Chun, Y. S., Aloia, T. A., et al. (2021). Alteration of FBXW7 is associated with worse survival in patients undergoing resection of colorectal liver metastases. *J. Gastrointest. Surg. Off. J. Soc. Surg. Aliment. Tract.* 25 (1), 186–194. doi:10.1007/s11605-020-04866-2
- Kawashita, Y., Morine, Y., Ikemoto, T., Saito, Y., Iwahashi, S., Yamada, S., et al. (2017). Loss of Fbxw7 expression is a predictor of recurrence in colorectal liver metastasis. *J. Hepato-Biliary-Pancreat Sci.* 24 (10), 576–583. doi:10.1002/jhbp.500
- Khan, O. M., Carvalho, J., Spencer-Dene, B., Mitter, R., Frith, D., Snijders, A. P., et al. (2018). The deubiquitinase USP9X regulates FBW7 stability and suppresses colorectal cancer. *J. Clin. Invest.* 128 (4), 1326–1337. doi:10.1172/JCI97325
- Khan, O. M., Almagro, J., Nelson, J. K., Horswell, S., Encheva, V., Keyan, K. S., et al. (2021a). Proteasomal degradation of the tumour suppressor FBW7 requires branched ubiquitylation by TRIP12. *Nat. Commun.* 12 (1), 2043. doi:10.1038/s41467-021-22319-5
- Khan, A. Q., Al-Tamimi, M., Uddin, S., and Steinhoff, M. (2021b). F-box proteins in cancer stemness: an emerging prognostic and therapeutic target. *Drug Discov. Today* 26 (12), 2905–2914. doi:10.1016/j.drudis.2021.07.006
- Kitade, S., Onoyama, I., Kobayashi, H., Yagi, H., Yoshida, S., Kato, M., et al. (2016). FBXW7 is involved in the acquisition of the malignant phenotype in epithelial ovarian tumors. *Cancer Sci.* 107 (10), 1399–1405. doi:10.1111/cas.13026
- Ko, Y. U., Kim, C., Lee, J., Kim, D., Kim, Y., Yun, N., et al. (2019). Site-specific phosphorylation of Fbxw7 by Cdk5/p25 and its resulting decreased stability are linked to glutamate-induced excitotoxicity. *Cell Death Dis.* 10 (8), 579. doi:10.1038/s41419-019-1818-4
- Koga, Y., Iwatsuki, M., Yamashita, K., Kiyozumi, Y., Kurashige, J., Masuda, T., et al. (2019). The role of FBXW7, a cell-cycle regulator, as a predictive marker of recurrence of gastrointestinal stromal tumors. *Gastric Cancer Off. J. Int. Gastric Cancer Assoc. Jpn. Gastric Cancer Assoc.* 22 (6), 1100–1108. doi:10.1007/s10120-019-00950-y
- Korhaisarn, K., Morris, V. K., Overman, M. J., Fogelman, D. R., Kee, B. K., Raghav, K. P. S., et al. (2017). FBXW7 missense mutation: a novel negative prognostic factor in metastatic colorectal adenocarcinoma. *Oncotarget* 8 (24), 39268–39279. doi:10.18632/oncotarget.16848
- Kothari, N., Teer, J. K., Abbott, A. M., Srikumar, T., Zhang, Y., Yoder, S. J., et al. (2016). Increased incidence of FBXW7 and POLE proofreading domain mutations in young adult colorectal cancers. *Cancer* 122 (18), 2828–2835. doi:10.1002/cncr.30082
- Kurashige, J., Watanabe, M., Iwatsuki, M., Kinoshita, K., Saito, S., Hiyoshi, Y., et al. (2012). Overexpression of microRNA-223 regulates the ubiquitin ligase FBXW7 in oesophageal squamous cell carcinoma. *Br. J. Cancer* 106 (1), 182–188. doi:10.1038/bjc.2011.509
- L, V., O, T., P, V., F, D., G, D., E, C., et al. (2009). Strong correlation between VEGF and MCL-1 mRNA expression levels in B-cell chronic lymphocytic leukemia. *Leuk. Res.* 33 (12), 1623–1626. doi:10.1016/j.leukres.2009.05.003
- L, S., A, C., L, L., L, Y., Y, H., J, X., et al. (2022). NRG1 regulates Fra-1 transcription and metastasis of triple-negative breast cancer cells via the c-Myc ubiquitination as manipulated by ERK1/2-mediated Fbxw7 phosphorylation. *Oncogene* 41 (6), 907–919. doi:10.1038/s41388-021-02142-4
- Lan, H., Tan, M., Zhang, Q., Yang, F., Wang, S., Li, H., et al. (2019). LSD1 destabilizes FBXW7 and abrogates FBXW7 functions independent of its demethylase activity. *Proc. Natl. Acad. Sci. U. S. A.* 116 (25), 12311–12320. doi:10.1073/pnas.1902012116
- Lee, C. J., An, H. J., Kim, S. M., Yoo, S. M., Park, J., Lee, G. E., et al. (2020). FBXW7-mediated stability regulation of signal transducer and activator of transcription 2 in melanoma formation. *Proc. Natl. Acad. Sci. U. S. A.* 117 (1), 584–594. doi:10.1073/pnas.1909879116
- Li, J., Guo, Y., Liang, X., Sun, M., Wang, G., De, W., et al. (2012). MicroRNA-223 functions as an oncogene in human gastric cancer by targeting FBXW7/hCdc4. *J. Cancer Res. Clin. Oncol.* 138 (5), 763–774. doi:10.1007/s00432-012-1154-x
- Li, L., Sarver, A. L., Khatri, R., Hajeri, P. B., Kamenev, I., French, A. J., et al. (2014). Sequential expression of miR-182 and miR-503 cooperatively targets FBXW7, contributing to the malignant transformation of colon adenoma to adenocarcinoma. *J. Pathol.* 234 (4), 488–501. doi:10.1002/path.4407
- Li, H., Wang, Z., Zhang, W., Qian, K., Xu, W., and Zhang, S. (2016). Fbxw7 regulates tumor apoptosis, growth arrest and the epithelial-to-mesenchymal transition in part through the RhoA signaling pathway in gastric cancer. *Cancer Lett.* 370 (1), 39–55. doi:10.1016/j.canlet.2015.10.006
- Li, M. R., Zhu, C. C., Ling, T. L., Zhang, Y. Q., Xu, J., Zhao, E. H., et al. (2017a). FBXW7 expression is associated with prognosis and chemotherapeutic outcome in Chinese patients with gastric adenocarcinoma. *BMC Gastroenterol.* 17 (1), 60. doi:10.1186/s12876-017-0616-7
- Li, M., Ouyang, L., Zheng, Z., Xiang, D., Ti, A., Li, L., et al. (2017b). E3 ubiquitin ligase FBXW7a inhibits cholangiocarcinoma cell proliferation by downregulating c-Myc and cyclin E. *Oncol. Rep.* 37 (3), 1627–1636. doi:10.3892/or.2017.5432
- Li, Q., Li, Y., Li, J., Ma, Y., Dai, W., Mo, S., et al. (2018). FBW7 suppresses metastasis of colorectal cancer by inhibiting HIF1 α /CEACAM5 functional axis. *Int. J. Biol. Sci.* 14 (7), 726–735. doi:10.7150/ijbs.24505
- Li, N., Babaei-Jadidi, R., Lorenzi, F., Spencer-Dene, B., Clarke, P., Domingo, E., et al. (2019). An FBXW7-ZEB2 axis links EMT and tumour microenvironment to promote colorectal cancer stem cells and chemoresistance. *Oncogenesis* 8 (3), 13. doi:10.1038/s41389-019-0125-3
- Li, C., Deng, C., Pan, G., Wang, X., Zhang, K., Dong, Z., et al. (2020). Lycorine hydrochloride inhibits cell proliferation and induces apoptosis through promoting FBXW7-MCL1 axis in gastric cancer. *J. Exp. Clin. Cancer Res. CR* 39, 230. doi:10.1186/s13046-020-01743-3
- Li, J., Xu, Q., Huang, Z., Jian, Mao, N., Lin, Z., tao, Cheng, L., et al. (2021). CircRNAs: a new target for the diagnosis and treatment of digestive system neoplasms. *Cell Death Dis.* 12 (2), 205–213. doi:10.1038/s41419-021-03495-0
- Li, X., Pu, W., Zheng, Q., Ai, M., Chen, S., and Peng, Y. (2022). Proteolysis-targeting chimeras (PROTACs) in cancer therapy. *Mol. Cancer* 21 (1), 99. doi:10.1186/s12943-021-01434-3
- Li, X. P., Qu, J., Teng, X. Q., Zhuang, H. H., Dai, Y. H., Yang, Z., et al. (2023a). The emerging role of super-enhancers as therapeutic targets in the digestive system tumors. *Int. J. Biol. Sci.* 19 (4), 1036–1048. doi:10.7150/ijbs.78535
- Li, Z., Pan, Y., Yao, J., Gao, Y., Qian, Y., Zheng, M., et al. (2023b). ANXA2 as a novel substrate of FBXW7 promoting esophageal squamous cell carcinoma via ERK phosphorylation. *Biochem. Biophys. Res. Commun.* 649, 93–100. doi:10.1016/j.bbrc.2023.01.082
- Lin, M., Xu, Y., Gao, Y., Pan, C., Zhu, X., and Wang, Z. W. (2019). Regulation of F-box proteins by noncoding RNAs in human cancers. *Cancer Lett.* 466, 61–70. doi:10.1016/j.canlet.2019.09.008
- Lin, H., Ma, N., Zhao, L., Yang, G., and Cao, B. (2020a). KDM5c promotes colon cancer cell proliferation through the FBXW7-c-jun regulatory Axis. *Front. Oncol.* 10, 535449. doi:10.3389/fonc.2020.535449
- Lin, L., Ding, D., Xiao, X., Li, B., Cao, P., and Li, S. (2020b). Trametinib potentiates TRAIL-induced apoptosis via FBW7-dependent Mcl-1 degradation in colorectal cancer cells. *J. Cell Mol. Med.* 24 (12), 6822–6832. doi:10.1111/jcmm.15336
- Lin, J., Wang, X., Zhai, S., Shi, M., Peng, C., Deng, X., et al. (2022). Hypoxia-induced exosomal circPDK1 promotes pancreatic cancer glycolysis via c-myc activation by modulating miR-628-3p/BPTF axis and degrading BIN1. *J. Hematol. Oncol. Hematol. Oncol.* 15 (1), 128. doi:10.1186/s13045-022-01348-7
- Ling, H., Pickard, K., Ivan, C., Isella, C., Ikuo, M., Mitter, R., et al. (2016). The clinical and biological significance of mir-224 expression in colorectal cancer metastasis. *Gut* 65 (6), 977–989. doi:10.1136/gutjnl-2015-309372
- Linnkamp, J. F., Hooff, S. R. van, Prasetyanti, P. R., Kandimalla, R., Buikhuisen, J. Y., Fessler, E., et al. (2018). Consensus molecular subtypes of colorectal cancer are recapitulated in *in vitro* and *in vivo* models. *Cell Death Differ.* 25 (3), 616–633. doi:10.1038/s41418-017-0011-5

- Liu, Y., Huang, Y., Wang, Z., Huang, Y., Li, X., Louie, A., et al. (2013). Temporal mTOR inhibition protects Fbxw7-deficient mice from radiation-induced tumor development. *Aging* 5 (2), 111–119. doi:10.18632/aging.100535
- Liu, X., Zhao, B., Sun, L., Bhuripanyo, K., Wang, Y., Bi, Y., et al. (2017). Orthogonal ubiquitin transfer identifies ubiquitination substrates under differential control by the two ubiquitin activating enzymes. *Nat. Commun.* 8, 14286. doi:10.1038/ncomms14286
- Liu, R., Gao, J., Yang, Y., Qiu, R., Zheng, Y., Huang, W., et al. (2018a). PHD finger protein 1 (PHF1) is a novel reader for histone H4R3 symmetric dimethylation and coordinates with PRMT5–WDR77/CRL4B complex to promote tumorigenesis. *Nucleic Acids Res.* 46 (13), 6608–6626. doi:10.1093/nar/gky461
- Liu, H., Wang, K., Fu, H., and Song, J. (2018b). Low expression of the ubiquitin ligase FBXW7 correlates with poor prognosis of patients with colorectal cancer. *Int. J. Clin. Exp. Pathol.* 11 (1), 413–419.
- Liu, F., Xia, Z., Zhang, M., Ding, J., Feng, Y., Wu, J., et al. (2019). SMARCD1 promotes pancreatic cancer cell growth and metastasis through wnt/ β -catenin-mediated EMT. *Int. J. Biol. Sci.* 15 (3), 636–646. doi:10.7150/ijbs.29562
- Liu, Y., Zhao, L., Xue, L., and Hou, Y. (2020). Selected updates in molecular and genomic pathology of esophageal cancer. *Ann. N. Y. Acad. Sci.* 1482 (1), 225–235. doi:10.1111/nyas.14527
- Liu, Q., Aminu, B., Roscow, O., and Zhang, W. (2021a). Targeting the ubiquitin signaling cascade in tumor microenvironment for cancer therapy. *Int. J. Mol. Sci.* 22 (2), 791. doi:10.3390/ijms22020791
- Liu, Z., Ma, T., Duan, J., Liu, X., and Liu, L. (2021b). MicroRNA-223-induced inhibition of the FBXW7 gene affects the proliferation and apoptosis of colorectal cancer cells via the Notch and Akt/mTOR pathways. *Mol. Med. Rep.* 23 (2), 154. doi:10.3892/mmr.2020.11793
- Liu, J., Xiao, Q., Xiao, J., Niu, C., Li, Y., Zhang, X., et al. (2022). Wnt/ β -catenin signalling: function, biological mechanisms, and therapeutic opportunities. *Signal Transduct. Target Ther.* 7, 3. doi:10.1038/s41392-021-00762-6
- Llovet, J. M., Montal, R., Sia, D., and Finn, R. S. (2018). Molecular therapies and precision medicine for hepatocellular carcinoma. *Nat. Rev. Clin. Oncol.* 15 (10), 599–616. doi:10.1038/s41571-018-0073-4
- Lu, H., Yao, B., Wen, X., and Jia, B. (2019). FBXW7 circular RNA regulates proliferation, migration and invasion of colorectal carcinoma through NEK2, mTOR, and PTEN signaling pathways *in vitro* and *in vivo*. *BMC Cancer* 19 (1), 918. doi:10.1186/s12885-019-6028-z
- Lupini, L., Bassi, C., Mlcochova, J., Musa, G., Russo, M., Vychytilova-Faltejskova, P., et al. (2015). Prediction of response to anti-EGFR antibody-based therapies by multigene sequencing in colorectal cancer patients. *BMC Cancer* 15, 808. doi:10.1186/s12885-015-1752-5
- M, Y., S, H., T, K., M, N., R, T., H, I., et al. (2004a). Phosphorylation-dependent degradation of c-Myc is mediated by the F-box protein Fbw7. *EMBO J.* 23 (10), 2116–2125. doi:10.1038/sj.emboj.7600217
- M, W., A, O., J, J., Je, G., Jw, H., Rn, E., et al. (2004b). The Fbw7 tumor suppressor regulates glycogen synthase kinase 3 phosphorylation-dependent c-Myc protein degradation. *Proc. Natl. Acad. Sci. U. S. A.* 101 (24), 9085–9090. doi:10.1073/pnas.0402770101
- M, L., J, L., S, A., A, J., Hf, N., F, A. M., et al. (2011). MiRNA-27a controls FBW7/hCDC4-dependent cyclin E degradation and cell cycle progression. *Cell Cycle Georget Tex* 10 (13), 2172–2183. doi:10.4161/cc.10.13.16248
- M, G., Y, L., and Dw, F. (2014). MYC activation is a hallmark of cancer initiation and maintenance. *Cold Spring Harb. Perspect. Med.* 4 (6), a014241. doi:10.1101/cshperspect.a014241
- Ma, J., Cheng, L., Liu, H., Zhang, J., Shi, Y., Zeng, F., et al. (2013). Genistein down-regulates miR-223 expression in pancreatic cancer cells. *Curr. Drug Targets* 14 (10), 1150–1156. doi:10.2174/13894501113149990187
- Mammalian cell cycle cyclins (2024). Available at: <http://pubmed6.0089.lunwenlib.com/32334991/>
- Mao, J. H., Perez-Losada, J., Wu, D., Delrosario, R., Tsunematsu, R., Nakayama, K. I., et al. (2004). Fbxw7/Cdc4 is a p53-dependent, haploinsufficient tumour suppressor gene. *Nature* 432 (7018), 775–779. doi:10.1038/nature03155
- Mao, J. H., Kim, I. J., Wu, D., Climent, J., Kang, H. C., DelRosario, R., et al. (2008). FBXW7 targets mTOR for degradation and cooperates with PTEN in tumor suppression. *Science* 321 (5895), 1499–1502. doi:10.1126/science.1162981
- Marques-Ramos, A., and Cervantes, R. (2023). Expression of mTOR in normal and pathological conditions. *Mol. Cancer* 22 (1), 112. doi:10.1186/s12943-023-01820-z
- Martelli, V., Pastorino, A., and Sobrero, A. F. (2022). Prognostic and predictive molecular biomarkers in advanced colorectal cancer. *Pharmacol. Ther.* 236, 108239. doi:10.1016/j.pharmthera.2022.108239
- Meyer, A. E., Furumo, Q., Stelloh, C., Minella, A. C., and Rao, S. (2020). Loss of Fbxw7 triggers mammary tumorigenesis associated with E2F/c-Myc activation and Trp53 mutation. *Neoplasia* N. Y. N. 22 (11), 644–658. doi:10.1016/j.neo.2020.07.001
- Min, S. H., Lau, A. W., Lee, T. H., Inuzuka, H., Wei, S., Huang, P., et al. (2012). Negative regulation of the stability and tumor suppressor function of Fbw7 by the Pin1 prolyl isomerase. *Mol. Cell* 46 (6), 771–783. doi:10.1016/j.molcel.2012.04.012
- Minella, A. C., Grim, J. E., Welcker, M., and Clurman, B. E. (2007). p53 and SCFFbw7 cooperatively restrain cyclin E-associated genome instability. *Oncogene* 26 (48), 6948–6953. doi:10.1038/sj.onc.1210518
- Mittal, P., Singh, S., Sinha, R., Shrivastava, A., Singh, A., and Singh, I. K. (2021). Myeloid cell leukemia 1 (MCL-1): structural characteristics and application in cancer therapy. *Int. J. Biol. Macromol.* 187, 999–1018. doi:10.1016/j.ijbiomac.2021.07.166
- Mojsa, B., Lassot, I., and Desagher, S. (2014). Mcl-1 ubiquitination: unique regulation of an essential survival protein. *Cells* 3 (2), 418–437. doi:10.3390/cells3020418
- Morel, C., Carlson, S. M., White, F. M., and Davis, R. J. (2009). Mcl-1 integrates the opposing actions of signaling pathways that mediate survival and apoptosis. *Mol. Cell Biol.* 29 (14), 3845–3852. doi:10.1128/MCB.00279-09
- Mori, A., Masuda, K., Ohtsuka, H., Shijo, M., Ariake, K., Fukase, K., et al. (2018). FBXW7 modulates malignant potential and cisplatin-induced apoptosis in cholangiocarcinoma through NOTCH1 and MCL1. *Cancer Sci.* 109 (12), 3883–3895. doi:10.1111/cas.13829
- Mu, Y., Zou, H., Chen, B., Fan, Y., and Luo, S. (2017). FAM83D knockdown regulates proliferation, migration and invasion of colorectal cancer through inhibiting FBXW7/Notch-1 signalling pathway. *Biomed. Pharmacother. Biomedicine Pharmacother.* 90, 548–554. doi:10.1016/j.biopha.2017.03.073
- Mx, Z., H, W., and Gp, S. (2020). Tumor-suppressor Fbxw7 targets SIK2 for degradation to interfere with TORC2-AKT signaling in pancreatic cancer. *Cell Biol. Int.* 44 (9), 1900–1910. doi:10.1002/cbin.11396
- N, K., A, S., and I, A. (2015). Emerging roles for the FBXW7 ubiquitin ligase in leukemia and beyond. *Curr. Opin. Cell Biol.* 37, 28–34. doi:10.1016/j.ccb.2015.09.003
- Nault, J. C., and Villanueva, A. (2021). Biomarkers for hepatobiliary cancers. *Hepatology* 73 (Suppl. 1), 115–127. doi:10.1002/hep.31175
- Nemecek, R., Berkovcova, J., Radova, L., Kazda, T., Mlcochova, J., Vychytilova-Faltejskova, P., et al. (2016). Mutational analysis of primary and metastatic colorectal cancer samples underlying the resistance to cetuximab-based therapy. *OncoTargets Ther.* 9, 4695–4703. doi:10.2147/OTT.S102891
- Nie, J., Lu, L., Du, C., and Gao, X. (2022). FAM83D promotes the proliferation and migration of hepatocellular carcinoma cells by inhibiting the FBXW7/MCL1 pathway. *Transl. Cancer Res.* 11 (10), 3790–3802. doi:10.21037/tcr-22-2069
- Notch signaling pathway in cancer: from mechanistic insights to targeted therapies. 2024. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11128457/>
- Notch1 in Cancer Therapy (2024). Possible clinical implications and challenges. Available at: <https://pubmed.ncbi.nlm.nih.gov/32913140/>.
- Okazaki, H., Matsunaga, N., Fujioka, T., Okazaki, F., Akagawa, Y., Tsurudome, Y., et al. (2014). Circadian regulation of mTOR by the ubiquitin pathway in renal cell carcinoma. *Cancer Res.* 74 (2), 543–551. doi:10.1158/0008-5472.CAN-12-3241
- Ou, B., Zhao, J., Guan, S., Wangpu, X., Zhu, C., Zong, Y., et al. (2016). Plk2 promotes tumor growth and inhibits apoptosis by targeting Fbxw7/Cyclin E in colorectal cancer. *Cancer Lett.* 380 (2), 457–466. doi:10.1016/j.canlet.2016.07.004
- Pai, S. G., Carneiro, B. A., Mota, J. M., Costa, R., Leite, C. A., Barroso-Sousa, R., et al. (2017). Wnt/beta-catenin pathway: modulating anticancer immune response. *J. Hematol. Oncol. Hematol. Oncol.* 10, 101. doi:10.1186/s13045-017-0471-6
- Pan, Y., Liu, J., Gao, Y., Guo, Y., Wang, C., Liang, Z., et al. (2023). FBXW7 loss of function promotes esophageal squamous cell carcinoma progression via elevating MAP4 and ERK phosphorylation. *J. Exp. Clin. Cancer Res. CR* 42 (1), 75. doi:10.1186/s13046-023-02630-3
- Pancreatic Cancer/Pancreatic cancer: changing epidemiology and new approaches to risk assessment, early detection, and prevention - PubMed Available at: <https://pubmed.ncbi.nlm.nih.gov/36804602/>. doi:10.1053/j.gastro.2023.02.012
- Park, J., Cho, J., and Song, E. J. (2020). Ubiquitin-proteasome system (UPS) as a target for anticancer treatment. *Arch. Pharm. Res.* 43 (11), 1144–1161. doi:10.1007/s12272-020-01281-8
- Pavicevic, S., Reichelt, S., Uluk, D., Lurje, I., Engelmann, C., Modest, D. P., et al. (2022). Prognostic and predictive molecular markers in cholangiocarcinoma. *Cancers* 14 (4), 1026. doi:10.3390/cancers14041026
- Perez-Losada, J., Mao, J. H., and Balmain, A. (2005). Control of genomic instability and epithelial tumor development by the p53-Fbxw7/Cdc4 pathway. *Cancer Res.* 65 (15), 6488–6492. doi:10.1158/0008-5472.CAN-05-1294
- Pervin, S., Tran, A., Tran, L., Urman, R., Braga, M., Chaudhuri, G., et al. (2011). Reduced association of anti-apoptotic protein Mcl-1 with E3 ligase Mule increases the stability of Mcl-1 in breast cancer cells. *Br. J. Cancer* 105 (3), 428–437. doi:10.1038/bjc.2011.242
- Pickart, C. M. (2001). Mechanisms underlying ubiquitination. *Annu. Rev. Biochem.* 70, 503–533. doi:10.1146/annurev.biochem.70.1.503
- Q, H., Y, Q., B, Z., C, L., S, J., S, S., et al. (2017). FBW7 increases the chemosensitivity of pancreatic cancer cells to gemcitabine through upregulation of ENT1. *Oncol. Rep.* 38 (4), 2069–2077. doi:10.3892/or.2017.5856
- Q, Z., L, H., Y, G., Z, X., Q, X., and X, T. (2020). FBW7 in hematological tumors. *Oncol. Lett.* 19 (3), 1657–1664. doi:10.3892/ol.2020.11264

- Qi, Y., Rezaeian, A. H., Wang, J., Huang, D., Chen, H., Inuzuka, H., et al. (2024). Molecular insights and clinical implications for the tumor suppressor role of SCFFBXW7 E3 ubiquitin ligase. *Biochim. Biophys. Acta Rev. Cancer* 1879 (5), 189140. doi:10.1016/j.bbcan.2024.189140
- Qin, Y., Hu, Q., Xu, J., Ji, S., Dai, W., Liu, W., et al. (2019). PRMT5 enhances tumorigenicity and glycolysis in pancreatic cancer via the FBW7/cMyc axis. *Cell Commun. Signal CCS* 17 (1), 30. doi:10.1186/s12964-019-0344-4
- R, S., S, M., J, X., X, R., P, G., H, L., et al. (2023). A novel polypeptide encoded by the circular RNA ZKSCAN1 suppresses HCC via degradation of mTOR. *Mol. Cancer* 22 (1), 16. doi:10.1186/s12943-023-01719-9
- Rodrigues, P. M., Vogel, A., Arrese, M., Balderramo, D. C., Valle, J. W., and Banales, J. M. (2021). Next-generation biomarkers for cholangiocarcinoma. *Cancers* 13 (13), 3222. doi:10.3390/cancers13133222
- Roling, L., Flammersfeld, A., Pradel, G., and Bennink, S. (2022). The WD40-protein PfWLP1 ensures stability of the PfCCP-based adhesion protein complex in plasmodium falciparum gametocytes. *Front. Cell Infect. Microbiol.* 12, 942364. doi:10.3389/fcimb.2022.942364
- Ruan, F., Ruan, Y., Gu, H., Sun, J., and Chen, Q. (2024). Clitocine enhances the drug sensitivity of colon cancer cells by promoting FBXW7-mediated MCL-1 degradation via inhibiting the A2B/cAMP/ERK axis. *Am. J. Physiol-Cell Physiol.* 327, C884–C900. doi:10.1152/ajpcell.00310.2024
- S, I., Lo, T., T, U., Y, M., T, I., Y, A., et al. (2014). Role of Fbxw7 expression in hepatocellular carcinoma and adjacent non-tumor liver tissue. *J. Gastroenterol. Hepatol.* 29 (10), 1822–1829. doi:10.1111/jgh.12623
- Sailo, B. L., Banik, K., Girisa, S., Bordoloi, D., Fan, L., Halim, C. E., et al. (2019). FBXW7 in cancer: what has been unraveled thus far? *Cancers* 11 (2), 246. doi:10.3390/cancers11020246
- Sancho, R., Blake, S. M., Tendeng, C., Clurman, B. E., Lewis, J., and Behrens, A. (2013). Fbw7 repression by hes5 creates a feedback loop that modulates Notch-mediated intestinal and neural stem cell fate decisions. *PLoS Biol.* 11 (6), e1001586. doi:10.1371/journal.pbio.1001586
- Sancho, R., Gruber, R., Gu, G., and Behrens, A. (2014). Loss of Fbw7 reprograms adult pancreatic ductal cells into α , δ , and β cells. *Cell Stem Cell* 15 (2), 139–153. doi:10.1016/j.stem.2014.06.019
- Schapira, M., Tyers, M., Torrent, M., and Arrowsmith, C. H. (2017). WD-repeat domain proteins: a novel target class? *Nat. Rev. Drug Discov.* 16 (11), 773–786. doi:10.1038/nrd.2017.179
- Schell, M. J., Yang, M., Teer, J. K., Lo, F. Y., Madan, A., Coppola, D., et al. (2016). A multigene mutation classification of 468 colorectal cancers reveals a prognostic role for APC. *Nat. Commun.* 7, 11743. doi:10.1038/ncomms11743
- Schlick, K., Kiem, D., and Greil, R. (2021). Recent advances in pancreatic cancer: novel prognostic biomarkers and targeted therapy—a review of the literature. *Biomolecules* 11 (10), 1469. doi:10.3390/biom11101469
- Schüle, C., Eilers, M., and Popov, N. (2011). PI3K-dependent phosphorylation of Fbw7 modulates substrate degradation and activity. *FEBS Lett.* 585 (14), 2151–2157. doi:10.1016/j.febslet.2011.05.036
- Senichkin, V. V., Streletskaia, A. Y., Gorbunova, A. S., Zhivotovsky, B., and Kopeina, G. S. (2020). Saga of Mcl-1: regulation from transcription to degradation. *Cell Death Differ.* 27 (2), 405–419. doi:10.1038/s41418-019-0486-3
- Sentani, K., Oue, N., Kondo, H., Kuraoka, K., Motoshita, J., Ito, R., et al. (2001). Increased expression but not genetic alteration of BRG1, a component of the SWI/SNF complex, is associated with the advanced stage of human gastric carcinomas. *Pathobiol. J. Immunopathol. Mol. Cell Biol.* 69 (6), 315–320. doi:10.1159/000064638
- Sepulveda, A. R., Hamilton, S. R., Allegra, C. J., Grody, W., Cushman-Vokoun, A. M., Funkhouser, W. K., et al. (2017). Molecular biomarkers for the evaluation of colorectal cancer: guideline from the American society for clinical pathology, college of American pathologists, association for molecular pathology, and the American society of clinical oncology. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* 35 (13), 1453–1486. doi:10.1200/JCO.2016.71.9807
- Shang, W., Yan, C., Liu, R., Chen, L., Cheng, D., Hao, L., et al. (2021). Clinical significance of FBXW7 tumor suppressor gene mutations and expression in human colorectal cancer: a systemic review and meta-analysis. *BMC Cancer* 21 (1), 770. doi:10.1186/s12885-021-08535-8
- Shenoy, A. R., Kirschnek, S., and Häcker, G. (2014). IL-15 regulates Bcl-2 family members Bim and Mcl-1 through JAK/STAT and PI3K/AKT pathways in T cells. *Eur. J. Immunol.* 44 (8), 2500–2507. doi:10.1002/eji.201344238
- Shima, T., Taniguchi, K., Inomata, Y., Arima, J., and Lee, S. W. (2024). Glycolysis in gastrointestinal stromal tumor: a brief overview. *Neoplasia N. Y.* 55, 101022. doi:10.1016/j.neo.2024.101022
- Siegel, R. L., Giaquinto, A. N., and Jemal, A. (2024). Cancer statistics, 2024. *CA Cancer J. Clin.* 74 (1), 12–49. doi:10.3322/caac.21820
- Skaar, J. R., Pagan, J. K., and Pagano, M. (2013). Mechanisms and function of substrate recruitment by F-box proteins. *Nat. Rev. Mol. Cell Biol.* 14 (6), 369–381. doi:10.1038/nrm3582
- Song, X., Shen, L., Tong, J., Kuang, C., Zeng, S., Schoen, R. E., et al. (2020). Mcl-1 inhibition overcomes intrinsic and acquired regorafenib resistance in colorectal cancer. *Theranostics* 10 (18), 8098–8110. doi:10.7150/tno.45363
- Song, P., Gao, Z., Bao, Y., Chen, L., Huang, Y., Liu, Y., et al. (2024). Wnt/ β -catenin signaling pathway in carcinogenesis and cancer therapy. *J. Hematol. Oncol. Hematol. Oncol.* 17 (1), 46. doi:10.1186/s13045-024-01563-4
- Sun, X. F., Sun, J. P., Hou, H. T., Li, K., Liu, X., and Ge, Q. X. (2016). MicroRNA-27b exerts an oncogenic function by targeting Fbxw7 in human hepatocellular carcinoma. *Tumour Biol. J. Int. Soc. Oncodevelopmental Biol. Med.* 37 (11), 15325–15332. doi:10.1007/s13277-016-5444-9
- Sun, Y., Nie, W., Qiu, B., Yang, Q., and Zhao, H. (2023). FBXW7 affects autophagy through MCL1 in oral squamous cell carcinoma. *Oral Dis.* 29, 3259–3267. doi:10.1111/odi.14325
- Sun, D., Mülder, D. T., Li, Y., Nieboer, D., Park, J. Y., Suh, M., et al. (2024). The effect of nationwide organized cancer screening programs on gastric cancer mortality: a synthetic control study. *Gastroenterology* 166 (3), 503–514. doi:10.1053/j.gastro.2023.11.286
- T, M., C, G., and Cyclin, E. (2004). *Int. J. Biochem. Cell Biol.* 36 (8). doi:10.1016/j.biocel.2003.12.005
- Taieb, J., Jung, A., Sartore-Bianchi, A., Peeters, M., Seligmann, J., Zaan, A., et al. (2019). The evolving biomarker landscape for treatment selection in metastatic colorectal cancer. *Drugs* 79 (13), 1375–1394. doi:10.1007/s40265-019-01165-2
- Takada, M., Zhang, W., Suzuki, A., Kuroda, T. S., Yu, Z., Inuzuka, H., et al. (2017). FBW7 loss promotes chromosomal instability and tumorigenesis via cyclin E1/CDK2-mediated phosphorylation of CENP-A. *Cancer Res.* 77 (18), 4881–4893. doi:10.1158/0008-5472.CAN-17-1240
- Takeishi, S., and Nakayama, K. I. (2014). Role of Fbxw7 in the maintenance of normal stem cells and cancer-initiating cells. *Br. J. Cancer* 111 (6), 1054–1059. doi:10.1038/bjc.2014.259
- Takeishi, S., and Nakayama, K. I. (2016). To wake up cancer stem cells, or to let them sleep, that is the question. *Cancer Sci.* 107 (7), 875–881. doi:10.1111/cas.12958
- Takeishi, S., Matsumoto, A., Onoyama, I., Naka, K., Hirao, A., and Nakayama, K. I. (2013). Ablation of Fbxw7 eliminates leukemia-initiating cells by preventing quiescence. *Cancer Cell* 23 (3), 347–361. doi:10.1016/j.ccr.2013.01.026
- Tang, B., Lei, B., Qi, G., Liang, X., Tang, F., Yuan, S., et al. (2016). MicroRNA-155-3p promotes hepatocellular carcinoma formation by suppressing FBXW7 expression. *J. Exp. Clin. Cancer Res. CR* 35 (1), 93. doi:10.1186/s13046-016-0371-6
- Tang, X., Yang, W., Shu, Z., Shen, X., Zhang, W., Cen, C., et al. (2019). MicroRNA-223 promotes hepatocellular carcinoma cell resistance to sorafenib by targeting FBW7. *Oncol. Rep.* 41 (2), 1231–1237. doi:10.3892/or.2018.6908
- Tang, G. L. Q., Lai, J. X. H., and Pervaiz, S. (2023). Ubiquitin-proteasome pathway-mediated regulation of the Bcl-2 family: effects and therapeutic approaches. *Haematologica* 109 (1), 33–43. doi:10.3324/haematol.2023.283730
- Targeting cell-cycle machinery in cancer - PubMed (2024). Available at: <http://pubmed6.0089.lunwenlib.com/33891890/>
- Tekcham, D. S., Chen, D., Liu, Y., Ling, T., Zhang, Y., Chen, H., et al. (2020). F-box proteins and cancer: an update from functional and regulatory mechanism to therapeutic clinical prospects. *Theranostics* 10 (9), 4150–4167. doi:10.7150/tno.42735
- Thirimanne, H. N., Wu, F., Janssens, D. H., Swanger, J., Diab, A., Feldman, H. M., et al. (2022). Global and context-specific transcriptional consequences of oncogenic Fbw7 mutations. *eLife* 11, e74338. doi:10.7554/eLife.74338
- Tong, J., Tan, S., Zou, F., Yu, J., and Zhang, L. (2017). FBW7 mutations mediate resistance of colorectal cancer to targeted therapies by blocking Mcl-1 degradation. *Oncogene* 36 (6), 787–796. doi:10.1038/ncr.2016.247
- Tu, K., Yang, W., Li, C., Zheng, X., Lu, Z., Guo, C., et al. (2014). Fbxw7 is an independent prognostic marker and induces apoptosis and growth arrest by regulating YAP abundance in hepatocellular carcinoma. *Mol. Cancer* 13 (1), 110. doi:10.1186/1476-4598-13-110
- Venizelos, A., Elvebakken, H., Perren, A., Nikolaienko, O., Deng, W., Lothe, I. M. B., et al. (2021). The molecular characteristics of high-grade gastroenteropancreatic neuroendocrine neoplasms. *Endocr. Relat. Cancer* 29 (1), 1–14. doi:10.1530/ERC-21-0152
- Wang, Y., Liu, Y., Lu, J., Zhang, P., Wang, Y., Xu, Y., et al. (2013). Rapamycin inhibits FBXW7 loss-induced epithelial-mesenchymal transition and cancer stem cell-like characteristics in colorectal cancer cells. *Biochem. Biophys. Res. Commun.* 434 (2), 352–356. doi:10.1016/j.bbrc.2013.03.077
- Wang, X., Zhang, J., Zhou, L., Sun, W., Zheng, Z. G., Lu, P., et al. (2015). Fbxw7 regulates hepatocellular carcinoma migration and invasion via Notch1 signaling pathway. *Int. J. Oncol.* 47 (1), 231–243. doi:10.3892/ijo.2015.2981
- Wang, J., Wang, H., Peters, M., Ding, N., Ribback, S., Utpatel, K., et al. (2019). Loss of Fbxw7 synergizes with activated Akt signaling to promote c-Myc dependent cholangiocarcinogenesis. *J. Hepatol.* 71 (4), 742–752. doi:10.1016/j.jhep.2019.05.027
- Wang, S., Zheng, Y., Yang, F., Zhu, L., Zhu, X. Q., Wang, Z. F., et al. (2021a). The molecular biology of pancreatic adenocarcinoma: translational challenges and clinical perspectives. *Signal Transduct. Target Ther.* 6 (1), 249. doi:10.1038/s41392-021-00659-4
- Wang, H., Guo, M., Wei, H., and Chen, Y. (2021b). Targeting MCL-1 in cancer: current status and perspectives. *J. Hematol. Oncol. Hematol. Oncol.* 14, 67. doi:10.1186/s13045-021-01079-1

- Wang, H. P., Chen, W. J., Shen, J. M., Ye, T., and Xie, H. W. (2021c). Attenuating glucose metabolism by Fbxw7 promotes Taxol sensitivity of colon cancer cells through downregulating NADPH oxidase 1 (Nox1). *Ann. Transl. Med.* 9 (10), 886. doi:10.21037/atm-21-2076
- Wang, W., Ye, L., Li, H., Chen, W., Hong, W., Mao, W., et al. (2025). A narrative review on advances in neoadjuvant immunotherapy for esophageal cancer: molecular biomarkers and future directions. *Int. J. Cancer* 156, 20–33. doi:10.1002/ijc.35153
- Wei, W., Qin, B., Wen, W., Zhang, B., Luo, H., Wang, Y., et al. (2023). FBXW7 loss-of-function enhances FASN-mediated lipogenesis and promotes colorectal cancer growth. *Signal Transduct. Target Ther.* 8 (1), 187. doi:10.1038/s41392-023-01405-8
- Welcker, M., and Clurman, B. E. (2007). Fbw7/hCDC4 dimerization regulates its substrate interactions. *Cell Div.* 2, 7. doi:10.1186/1747-1028-2-7
- Welcker, M., and Clurman, B. E. (2008). FBW7 ubiquitin ligase: a tumour suppressor at the crossroads of cell division, growth and differentiation. *Nat. Rev. Cancer* 8 (2), 83–93. doi:10.1038/nrc2290
- Welcker, M., Larimore, E. A., Swanger, J., Bengoechea-Alonso, M. T., Grim, J. E., Ericsson, J., et al. (2013). Fbw7 dimerization determines the specificity and robustness of substrate degradation. *Genes Dev.* 27 (23), 2531–2536. doi:10.1101/gad.229195.113
- Willson, J. (2022). DUBTACs for targeted protein stabilization. *Nat. Rev. Drug Discov.* 21 (4), 258. doi:10.1038/d41573-022-00039-9
- Wood, K. C. (2020). Overcoming MCL-1-driven adaptive resistance to targeted therapies. *Nat. Commun.* 11 (1), 531. doi:10.1038/s41467-020-14392-z
- Wu, X. Z., Wang, K. P., Song, H. J., Xia, J. H., Jiang, Y., and Wang, Y. L. (2015). MiR-27a-3p promotes esophageal cancer cell proliferation via F-box and WD repeat domain-containing 7 (FBXW7) suppression. *Int. J. Clin. Exp. Med.* 8 (9), 15556–15562.
- Wu, W. J., Shi, J., Hu, G., Yu, X., Lu, H., Yang, M. L., et al. (2016). Wnt/ β -catenin signaling inhibits FBXW7 expression by upregulation of microRNA-770 in hepatocellular carcinoma. *Tumor Biol.* 37 (5), 6045–6051. doi:10.1007/s13277-015-4452-5
- Wu, X., Iwatsuki, M., Takaki, M., Saito, T., Hayashi, T., Kondo, M., et al. (2024). FBXW7 regulates the sensitivity of imatinib in gastrointestinal stromal tumors by targeting MCL1. *Gastric Cancer* 27 (2), 235–247. doi:10.1007/s10120-023-01454-6
- X, C., X, X., D, C., F, Z., and W, W. (2019a). Therapeutic potential of targeting the Wnt/ β -catenin signaling pathway in colorectal cancer. *Biomed. Pharmacother. Biomedicine Pharmacother.* 110, 473–481. doi:10.1016/j.biopha.2018.11.082
- X, K., L, L., R, C., K, W., M, C., B, C., et al. (2019b). SCFFBXW7/GSK3 β -Mediated GFI1 degradation suppresses proliferation of gastric cancer cells. *Cancer Res.* 79 (17), 4387–4398. doi:10.1158/0008-5472.CAN-18-4032
- X, W., Y, L., P, L., S, L., Y, P., and Pan, Y. (2022). FBXW7 reduces the cancer stem cell-like properties of hepatocellular carcinoma by regulating the ubiquitination and degradation of ACTL6A. *Stem Cells Int.* 2022, 3242482. doi:10.1155/2022/3242482
- Xia, W., Zhou, J., Luo, H., Liu, Y., Peng, C., Zheng, W., et al. (2017). MicroRNA-32 promotes cell proliferation, migration and suppresses apoptosis in breast cancer cells by targeting FBXW7. *Cancer Cell Int.* 17, 14. doi:10.1186/s12935-017-0383-0
- Xiang, J., Hang, J. B., Che, J. M., and Li, H. C. (2015). miR-25 is up-regulated in non-small cell lung cancer and promotes cell proliferation and motility by targeting FBXW7. *Int. J. Clin. Exp. Pathol.* 8 (8), 9147–9153.
- Xie, C. M., and Sun, Y. (2019). The MTORC1-mediated autophagy is regulated by the FBXW7-SHOC2-RPTOR axis. *Autophagy* 15 (8), 1470–1472. doi:10.1080/15548627.2019.1609864
- Xie, X., Li, H., Gao, C., Lai, Y., Liang, J., Chen, Z., et al. (2022). Downregulation of circular RNA circPSD3 promotes metastasis by modulating FBXW7 expression in clear cell renal cell carcinoma. *J. Oncol.* 2022 (1), 5084631. doi:10.1155/2022/5084631
- Xu, Y., Sengupta, T., Kukreja, L., and Minella, A. C. (2010). MicroRNA-223 regulates cyclin E activity by modulating expression of F-box and WD-40 domain protein 7. *J. Biol. Chem.* 285 (45), 34439–34446. doi:10.1074/jbc.M110.152306
- Xu, D., Shan, B., Lee, B. H., Zhu, K., Zhang, T., Sun, H., et al. (2015). Phosphorylation and activation of ubiquitin-specific protease-14 by Akt regulates the ubiquitin-proteasome system. *eLife* 4, e10510. doi:10.7554/eLife.10510
- Xu, W., Taranets, L., and Popov, N. (2016). Regulating Fbw7 on the road to cancer. *Semin. Cancer Biol.* 36, 62–70. doi:10.1016/j.semcancer.2015.09.005
- Y, I., I, O., Ki, N., and K, N. (2008). Notch-dependent cell cycle arrest and apoptosis in mouse embryonic fibroblasts lacking Fbxw7. *Oncogene* 27 (47), 6164–6174. doi:10.1038/onc.2008.216
- Y, N., H, I., Y, K., M, K., A, M., T, K., et al. (2010). Decreased expression of FBXW7 is correlated with poor prognosis in patients with esophageal squamous cell carcinoma. *Exp. Ther. Med.* 1 (5), 841–846. doi:10.3892/etm.2010.115
- Y, L., Y, S., Y, Z., X, H., G, Z., J, H., et al. (2021). Demethylzeylasteral inhibits proliferation, migration, and invasion through FBXW7/c-Myc axis in gastric cancer. *MedComm* 2 (3), 467–480. doi:10.1002/mco2.73
- Y, L., H, C., H, B., J, Z., R, W., and L, Z. (2023). Comprehensive characterization of FBXW7 mutational and clinicopathological profiles in human colorectal cancers. *Front. Oncol.* 13, 1154432. doi:10.3389/fonc.2023.1154432
- Yang, W., Dou, C., Wang, Y., Jia, Y., Li, C., Zheng, X., et al. (2015). MicroRNA-92a contributes to tumor growth of human hepatocellular carcinoma by targeting FBXW7. *Oncol. Rep.* 34 (5), 2576–2584. doi:10.3892/or.2015.4210
- Yang, Q., Sun, Y., Qiu, B., and Zhao, H. (2022). FBXW7 enhances cisplatin-induced apoptosis in oral cancer cell lines. *Int. Dent. J.* 73 (5), 620–627. doi:10.1016/j.identj.2022.11.008
- Ye, Z., Zhuo, Q., Hu, Q., Xu, X., Liu, M., Zhang, Z., et al. (2020). FBW7-NRA41-SCD1 axis synchronously regulates apoptosis and ferroptosis in pancreatic cancer cells. *Redox Biol.* 38, 101807. doi:10.1016/j.redox.2020.101807
- Yeh, C. H., Bellon, M., and Nicot, C. (2018). FBXW7: a critical tumor suppressor of human cancers. *Mol. Cancer* 17 (1), 115. doi:10.1186/s12943-018-0857-2
- Yokobori, T., Mimori, K., Iwatsuki, M., Ishii, H., Onoyama, I., Fukagawa, T., et al. (2009). p53-Altered FBXW7 expression determines poor prognosis in gastric cancer cases. *Cancer Res.* 69 (9), 3788–3794. doi:10.1158/0008-5472.CAN-08-2846
- Yokobori, T., Mimori, K., Iwatsuki, M., Ishii, H., Tanaka, F., Sato, T., et al. (2012). Copy number loss of FBXW7 is related to gene expression and poor prognosis in esophageal squamous cell carcinoma. *Int. J. Oncol.* 41 (1), 253–259. doi:10.3892/ijfo.2012.1436
- Yu, J., Zhang, W., Gao, F., Liu, Y. X., Chen, Z. Y., Cheng, L. Y., et al. (2014). FBW7 increases chemosensitivity in hepatocellular carcinoma cells through suppression of epithelial-mesenchymal transition. *Hepatobiliary Pancreat. Dis. Int. HBPDI* 13 (2), 184–191. doi:10.1016/s1499-3872(14)60029-1
- Yu, H., Ling, T., Shi, R., Shu, Q., Li, Y., and Tan, Z. (2015). Expression of FBXW7 in esophageal squamous cell carcinoma and its clinical significance. *Zhonghua Zhong Liu Za Zhi* 37 (5), 347–351. doi:10.3760/cma.j.issn.0253-3766.2015.05.006
- Yu, F., Yu, C., Li, F., Zuo, Y., Wang, Y., Yao, L., et al. (2021). Wnt/ β -catenin signaling in cancers and targeted therapies. *Signal Transduct. Target Ther.* 6, 307. doi:10.1038/s41392-021-00701-5
- Yumimoto, K., and Nakayama, K. I. (2020). Recent insight into the role of FBXW7 as a tumor suppressor. *Semin. Cancer Biol.* 67 (Pt 2), 1–15. doi:10.1016/j.semcancer.2020.02.017
- Zeng, J., Chen, Z., He, Y., Jiang, Z., Zhang, Y., Dong, Q., et al. (2024). A patent review of SCF E3 ligases inhibitors for cancer: structural design, pharmacological activities and structure–activity relationship. *Eur. J. Med. Chem.* 278, 116821. doi:10.1016/j.ejmech.2024.116821
- Zhan, P., Wang, Y., Zhao, S., Liu, C., Wang, Y., Wen, M., et al. (2015). FBXW7 negatively regulates ENO1 expression and function in colorectal cancer. *Lab. Invest. J. Tech. Methods Pathol.* 95 (9), 995–1004. doi:10.1038/labinvest.2015.71
- Zhang, Y., and Wang, X. (2020). Targeting the Wnt/ β -catenin signaling pathway in cancer. *J. Hematol. Oncol. Hematol. Oncol.* 13 (1), 165. doi:10.1186/s13045-020-00990-3
- Zhang, P., Cao, L., Fan, P., Mei, Y., and Wu, M. (2016a). LncRNA-MIF, a c-Myc-activated long non-coding RNA, suppresses glycolysis by promoting Fbxw7-mediated c-Myc degradation. *EMBO Rep.* 17 (8), 1204–1220. doi:10.15252/embr.201642067
- Zhang, Q., Zhang, Y., Parsels, J. D., Lohse, I., Lawrence, T. S., Pasca di Magliano, M., et al. (2016b). Fbxw7 deletion accelerates KrasG12D-driven pancreatic tumorigenesis via Yap accumulation. *Neoplasia N. Y. N.* 18 (11), 666–673. doi:10.1016/j.neo.2016.08.009
- Zhang, Q., Mady, A. S. A., Ma, Y., Ryan, C., Lawrence, T. S., Nikolovska-Coleska, Z., et al. (2019). The WD40 domain of FBXW7 is a poly(ADP-ribose)-binding domain that mediates the early DNA damage response. *Nucleic Acids Res.* 47 (8), 4039–4053. doi:10.1093/nar/gkz058
- Zhang, Q., Li, X., Cui, K., Liu, C., Wu, M., Prochownik, E. V., et al. (2020). The MAP3K13-TRIM25-FBXW7 axis affects c-Myc protein stability and tumor development. *Cell Death Differ.* 27 (2), 420–433. doi:10.1038/s41418-019-0363-0
- Zhou, N., and Hofstetter, W. L. (2020). Prognostic and therapeutic molecular markers in the clinical management of esophageal cancer. *Expert Rev. Mol. Diagn.* 20 (4), 401–411. doi:10.1080/14737159.2020.1731307
- Zhou, Z., Yu, Sheng, Tu, K., Zhang, J., Zheng, X., Gao, J., Yao, Y. min, et al. (2012). [Expression of Fbxw7 and its correlation with cell proliferation in human hepatocellular carcinoma]. *Xi bao yu fen zi mian yi xue za zhi. Chin. J. Cell Mol. Immunol.* 28 (12), 1303–1306.
- Zhou, X., Jin, W., Jia, H., Yan, J., and Zhang, G. (2015). MiR-223 promotes the cisplatin resistance of human gastric cancer cells via regulating cell cycle by targeting FBXW7. *J. Exp. Clin. Cancer Res. CR* 34 (1), 28. doi:10.1186/s13046-015-0145-6
- Zhong, Z., and Virshup, D. M. (2024). Recurrent mutations in tumor suppressor FBXW7 bypass Wnt/ β -catenin addiction in cancer. *Sci. Adv.* 10 (14), eadk1031. doi:10.1126/sciadv.adk1031

Glossary

C/EBPδCCAAT	enhancer-binding protein-delta	MiRNA	micro-RNA
CHD4	Chromodomain helicase DNA-binding protein 4	MMR	Mismatch Repair
CLM	Colorectal cancer liver metastases	MSI	Microsatellite instability
CoA	Coactivator	mTOR	Mammalian target of rapamycin
CPD	Cdc4 phosphodegron	N/A	Not assessable
CRC	Colorectal cancer	ncRNA	Noncoding RNAs
CSCs	Cancer stem cells	NICD	NOTCH intracellular domain
CSL	CBF-1/suppressor of hairless/Lag1	Nox1	NADPH oxidase 1
CSN6	COP9 signalosome subunit 6	NTRK	Neurotrophic tyrosine receptor kinase
ctDNA	Circulating tumor DNA	NTRK	Neurotrophic tyrosine receptor kinase
E1	Ubiquitin-activating enzymes	PC	Pancreatic cancer
E2	Ubiquitin-conjugating enzymes	PD-L1	Programmed cell death ligand 1
E3	Ubiquitin ligase	PI3K	Phosphoinositide 3-kinase
EBV	Epstein-Barr virus	Plk2	Polo-like kinase 2
EGFR	Epidermal Growth Factor Receptor	PTEN	Phosphatase and tensin homolog
EMT	Epithelial-mesenchymal transition	SCF	Skp1-Cullin1-F-box
EMT	Epithelial-mesenchymal transition	SKP1	S-phase kinase-associated protein 1
ENO1	Enolase 1	STYX	Serine/threonine/tyrosine interacting protein
ERK1/2	Extracellular signal-regulated kinases 1 and 2	TCF	T cell factor
ESCC	Esophageal squamous cell carcinoma	TERT	Telomerase reverse transcriptase
FASN	Fatty acid synthase	TGF-β	Transforming growth factor beta
FBXW7	F-Box and WD Repeat Domain Containing 7	TMB	Tumor mutation burden
FGFR	Fibroblast growth factor receptor 2	TNBC	Triple negative breast cancer
GBM	Glioblastoma	UPS	Ubiquitin-proteasome system
GC	Gastric cancer	USP28	Ubiquitin-specific proteases 28
GIST	Gastrointestinal stromal tumors	Usp9x	Ubiquitin-specific peptidase 9X
GSK3β	Glycogen synthase kinase-3 β	VEGFR	Vascular endothelial growth factor
GSK3β	Glycogen synthase kinase-3 β	VEGFR	Vascular endothelial growth factor
HCC	Hepatocellular carcinoma	YAP	Yes-associated protein
HER-2	Human epidermal growth factor receptor 2		
HES5	HES family bHLH transcription factor 5		
Hsp90	Heat shock protein 90		
iCCA	Intrahepatic Cholangiocarcinoma		
IDH1/2	Isocitrate dehydrogenase 1 or 2		
KRAS	Kirsten rat sarcoma viral oncogene		
KRAS	Kirsten rat sarcoma viral oncogene		
LEF	lymphocyte enhancer factor-1		
LSD1	Lysine-specific demethylase 1		
MAMLs	Mastermind-like proteins		
MAP4	Microtubule-associated proteins 4		
MAPK	Mitogen-activated protein kinase		
MCL-1	Myeloid leukemia 1		