Abstract. Colorectal cancer (CRC) is one of the most common cancers worldwide with a high incidence and mortality rate. Integrative studies including systematic sequencing of colorectal tumors have provided an unprecedented insight into the molecular basis of CRC. Recently, evidence indicates that F-box proteins (FBPs) play a critical role in the oncogenesis, invasion, metastasis and prognostic assessment of CRC. Therefore, this review discusses the recent literature regarding the function and regulation of FBPs in the pathogenesis of CRC. Furthermore, we highlight that FBPs may represent an attractive therapeutic target for CRC.

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1. Introduction

CRC is one of the most common malignant tumors and is associated with poor overall survival (1,2). It is estimated that there were 1.2 million new cases and 608,700 deaths worldwide in 2008 (3). CRC is characterized by compounding genetic mutations in both oncogenes and tumor-suppressor genes that drive its initiation and promotion under various pathophysiological conditions. Despite advances in the prevention, early detection and treatment for advanced malignancies (4), the 5-year survival rate of CRC patients with distant metastases has decreased to less than 10% (5). Currently, CRC is mainly treated using surgery, chemoradiotherapy and biologically targeted therapy. Surgery is still the dominant treatment for CRC, yet many patients develop tumor recurrence after surgery. Chemotherapy is the first-line treatment for advanced CRC; however, chemotherapy drug resistance often results in treatment failure. Taken together, although surgery and chemotherapy are the leading treatments in clinical practice, they are of limited value for advanced CRC patients. Therefore, it is important to explore the mechanisms underlying tumorigenesis in CRC to assess the prognosis and to develop novel efficient primary or adjuvant drugs for CRC. Extensive cancer research over the last decade has uncovered numerous F-box protein (FBP) alterations in CRC.

2. SCF type of E3 ubiquitin ligases

E3 ubiquitin ligases are vital components of the ubiquitin-proteasome system (UPS) which governs a broad array of basic cellular processes such as cell proliferation, cell cycle progression, transcription and apoptosis (6). UPS is rather complex and consists of the ubiquitin-activating enzyme (E1), ubiquitin-conjugating enzyme (E2) and ubiquitin ligase (E3). These three enzymes act in concert to exert UPS function (7) (Fig. 1). E1 utilizes ATP to activate ubiquitin for conjugation and transfers it to E2. E2 interacts with a specific E3 partner and transfers the ubiquitin to the target protein, guiding the substrate to be destroyed by the proteasome (8). There are few studies to date, that have linked E1 and E2 to cancer (9). In general, it is FBPs that play a fundamental role in the proper functioning of SCF type E3 ligases for the timely degradation of various substrates thereby ensuring normal cell growth. This may be one of the reasons why deregulation of FBPs often leads to diseases including cancer development.

There are more than 1,000 types of E3 ubiquitin ligases based on the special domains they contain, such as the significantly new gene (RING)-domain, homologous to the E6-AP carboxyl terminus (HECT)-domain, U-box- and PHD-domain (10). Among them, RING-type E3 ligases are the best characterized and the most versatile class type of the E3 ligase complex (11). The SCF complex consists of

Key words: F-box proteins, colorectal cancer, SKP, FBXW7, β-TrCP
four components: an adaptor subunit (Skp1), a RING-domain protein (Rbx1/Roc1), a scaffold protein (Cullin1/Cullin) and a variable subunit denoted as FBP that binds the substrate. Above all, substrate-specific degradation is a main feature of the UPS.

3. FBPs are core components of E3 ubiquitin ligases

FBPs are the substrate recruiting components of E3 ubiquitin-ligase complexes, and they determine target specificity through recognition and binding target proteins for ubiquitination and then degradation. It is FBPs that are involved in cellular physiological processes through degradation of its ubiquitination protein. FBPs contain an N-terminal, an F-box domain and a C-terminal. The N-terminal is a 48-amino acid F-box domain, which binds SKP1 to create a link to Cullin1. The C-terminal is a variable protein-interaction domain, such as Trp-Asp repeats (also called WD40) and leucine-rich repeats (LRR), as well as unknown motifs, which are responsible for identifying specific substrates (12). According to the variable C-terminal, FBPs can be categorized into three subclasses, FBXW, FBXL and FBXO, family proteins. In humans, FBXW family proteins are those with the WD40 domain, which is composed of 10 proteins, and the FBXL family proteins are those with a Leu-rich repeat domain comprising 22 proteins. The remaining 37 F-box proteins with other diverse protein-interaction domains or no recognizable domains are called FBXO family proteins (Fig. 1).

Figure 1. Ubiquitin is first activated by ubiquitin-activating enzyme (E1), then transferred to ubiquitin-conjugating enzyme (E2), and finally transferred to substrates by ubiquitin ligases (E3). The ubiquitin proteins are recognized and then degraded by 26 proteasome to several small peptides. The SCF type of E3 ligase complex consists of Skp1, Rbx1, Cullin and a variable F-box protein. In humans, FBPs have been classified into three categories according to their specific substrate recognition domains. FBXL family proteins are those with Leu-rich repeat domains. FBXW family proteins are those with WD40 domain. The remaining F-box proteins that contain other diverse protein-interaction domains or no recognizable domains are called FBXO family proteins. FBPs, F-box proteins.

Research has elucidated that the aberrant regulation of FBPs is clinically related to the occurrence and development of cancers. For example, SKP2, a representative of the FBXW family proteins, is always highly expressed in cancers, while FBXW7, one member of the FBXW family, is often downregulated in cancers. Whether FBPs exert an antitumoral or a promoting effect depends on the specific substrates that they degrade. FBPs function as oncoproteins when overexpressed if their substrates are tumor suppressors or as tumor suppressors if their substrates are oncogenes. Each FBP has more than one substrate; for the same reason, one substrate can be degraded by different FBPs. F-box protein FBXO31 mediates the degradation of cyclin D1 in melanoma cells (13). In the breast cancer cell line MCF-7, cyclin D1 is degraded by the APC/cdc27 complex (14). Cyclin D1 is degraded by FBXW8 in the CRC cell line HCT116 (15). In addition, FBXO31 is downregulated in breast (16), liver (17) and gastric cancer (18). However, an opposite result was discovered in esophageal squamous cell carcinoma (ESCC). Kogo et al (19) showed that higher FBXO31 expression levels were significantly correlated with elevated tumor invasion and clinical stage and determine a poorer prognosis when compared with low expression. Therefore, the roles of FBPs in cancers are intricate. This review focuses on the current understanding of FBPs in CRC.

4. Possible oncogenes of FBPs, SKP2, FBXL20, β-TrCP, in CRC

SKP2. S-phase kinase-associated protein 2 (SKP2) gene, located on chromosome 5p13, is mainly responsible for ubiquitination and subsequent degradation of cell cycle regulators, in particular the cell cycle inhibitor p27 (Kip1). p27 (Kip1) is a negative regulator of the cell cycle that plays an important role in tumor suppression. SKP2 was originally discovered in 1995 due to its ability to interact with the cell cycle protein cyclin A (20). Most published studies have found that SKP2 is overexpressed in various tumor tissues and cell lines with downregulation of p27 expression (21-25). SKP2 was also found to be highly associated with histological grade, tumor size (26) and tumor metastasis (27-30) in these cancers. Over the past decade, overwhelming evidence has emerged supporting a role for SKP2 to function as an oncogene and an independent prognostic marker for disease-free survival and overall survival in patients diagnosed with cancer.

SKP2 protein overexpression interacts with ras mutations to exert an independent adverse prognostic impact on non-small cell lung carcinoma (31). A previous study (32) reported that SKP2 overexpression could only transform primary rat embryo...
fibroblasts when H-ras was also coexpressed. Furthermore, although the expression of SKP2 or N-ras alone failed to induce malignancy, the coexpression of SKP2 and N-ras was capable of inducing lymphoma (33). Both results indicated that SKP2 overexpression might function differently between normal ras and mutant ras cancers. Nevertheless, there is no literature to implicate their application in the clinical decision process for the appropriateness of adding adjuvant therapy in cancers.

Hershko et al (21) identified an inverse correlation between levels of SKP2 mRNA/protein and p27 (Kip1) in colorectal carcinomas. However, this relationship was not found in cervical cancer (34). Overexpression of SKP2 was observed in aggressive CRC and was responsible for downregulation of p27 levels (35). The data from Shapira et al (36) also confirmed this conclusion. Overexpression of SKP2 was found to be associated with colorectal carcinogenesis and subsequent metastasis to lymph nodes (37). Meanwhile, SKP2 was found to determine poor prognosis in colorectal carcinoma (38). Xu et al (39) knocked down the expression of SKP2 using an adenovirus expressing SKP2 shRNA in SW480 cells. Their results showed that the knockdown of SKP2 blocked growth and induced cell apoptosis in the CRC cell line SW480. At the same time, their results indicated that SKP2 stimulated colorectal tumor growth by inhibiting p27 and p63 expression. Moreover, the Notch1-dependent regulation of p27 determined cell fate in CRC (40). Tian et al (41) found for the first time that high expression of SKP2 predicted a poor response to neoadjuvant chemoradiotherapy in rectal cancer patients. Bortezomib, a proteasome inhibitor, is a modified dipeptidyl boronic acid derived from leucine and phenylalanine. Its effect on SKP2 suppression and p27 upregulation was demonstrated in the CRC cell lines HT29 and SW480. Oxyysterol receptors LXRa and LXRx were found to regulate the expression of SKP2 in human colon cancer cells Colo205 and HCT116 (42). SKP2 nuclear ubiquitination-dependent pathway played an important role in the regulation of nuclear p27 (Kip1) expression (43). The high copy amplification of the SKP2 gene was associated with chromosomal instability phenotype in CRC cell line WiDr (44). Moreover, Kleivi et al (45) compared the genetic profile from different tumor stages of CRC, including primary tumors, liver metastasis and peritoneum carcinomatosis, and they found that SKP2 played an important role in the metastatic process.

FBXL20. The FBXL20 gene is located on human chromosome 17q21.2. Zhu et al (46) reported that FBXL20 was involved in CRC tumorigenesis. Initially, this group observed the expression of FBXL20 mRNA in 30 pairs of human colorectal adenocarcinoma tissues and corresponding adjacent normal colorectal tissues. As the result showed, FBXL20 mRNA expression was upregulated in 76.7% of the tumor samples. Additionally, SET and E-cadherin were ubiquitinated and negatively regulated by FBXL20 in the CRC cell lines SW480 and SW620 which caused cell proliferation and reduced apoptosis. To further confirm the function of FBXL20 in CRC, the authors determined that FBXL20 might mediate the degradation of E-cadherin resulting in an increase in cell viability and invasive ability of the CRC cell line LoVo (47). Taken together, these findings indicate that FBXL20 may also control tumorigenesis in colorectal adenocarcinoma. However, data concerning FBXL20 in the promotion of tumorigenesis in animal models are lacking and further investigation is needed.

β-transducin repeat-containing protein (β-TrCP). β-TrCP has been shown to play important roles in tumorigenesis. Yet, its exact role in cancer remains controversial. β-TrCP mainly acts as an oncoprotein, yet in some situations as a tumor suppressor, depending on the function of the targeted substrates. Taken together, β-TrCP may play a greater role as an oncogenic protein than as a tumor suppressor in cancers.

Human β-TrCP was first identified in 1998 as a binding partner of HIV-1 Vpu protein in a yeast two-hybrid screening. Two typical substrates of β-TrCP are IκB in the NF-κB pathway and β-catenin in the wnt pathway (48,49). IκB, inhibitor of NF-κB, functions as a tumor suppressor. β-catenin has been identified as highly stable in various types of human cancers, and is always correlated with poor prognosis and reduced survival (50,51). Since IκB and β-catenin exert antagonistic functions and both exist in cells, it is difficult to make in vivo interpretations only targeting β-catenin but not IκB. The linkage between SCFβ-TrCP and NF-κB makes it a drug target. The development of β-TrCP inhibitors may be a feasible therapeutic approach for NF-κB-associated human disease. NF-κB is held in an inactive form within the cytoplasm through association with IκB. In response to cytokines and other extracellular signals, the IκB kinase complex phosphorylates IκB, thereby promoting its degradation through the UPS. This allows the relocation of NF-κB into the nucleus, where it activates the expression of genes important for cytokine and survival responses. The identification of SCFβ-TrCP as the E3 for IκB suggests that it may be a target for molecules that act as anti-inflammatory agents by blocking IκB degradation. Due to the specific substrate degraded by β-TrCP, β-TrCP also participates in cell adhesion and migration (52). Taken together, β-TrCP is a member of the SCF family with a complex body of literature with both oncogenic and tumor-suppressor properties.

Guardavaccaro et al (53) showed that IκBo and β-catenin were not elevated in the absence of β-TrCP1 mouse embryonic fibroblasts (MEFs), whose accumulation required additional silencing of β-TrCP2 by siRNA. Detailed analyses performed in this study also suggested that β-TrCP1 deletion in the mouse causes male fertility. Another study by Kanarek et al (54) showed that depletion of β-TrCP2 by inducible small hairpin RNA on a β-TrCP1 knockout background resulted in a severe testicular phenotype marked by a near absence of spermatids and meiotic cells. They also demonstrated that the two β-TrCP paralogs had a non-redundant role in spermatogenesis. It is generally implicated that β-TrCP functions in the promotion of various carcinomas (55-58). Moreover, many β-TrCP substrates are known tumor suppressors such as IκB (59) and FOXO3 (60). Finally, genetic depletion of β-TrCP1 shows no phenotype in mice (61). β-TrCP1 was found in 56% (25/45) of CRC tissues compared to normal colorectal tissues (56). Increased β-TrCP1 levels were significantly associated with β-catenin activation. This result indicated that β-TrCP1 acts as an oncogene in CRC. However, in sharp contrast to the tumor-promoting role in CRC, β-TrCP has been shown to act as an oncogenic protein in other cancers such as gastric
cancer (62,63). An analysis of somatic mutations in 95 gastric cancer specimens found 5 missense mutations in β-TrCP2. Moreover in these particular tissues the oncogene β-catenin level was higher than the controls, indicating that β-TrCP2 functions as a tumor suppressor in gastric cancer (63). Unfortunately, although multiple groups have tried to investigate the biological roles of β-TrCP in cancers, the physiological functions of β-TrCP remain largely elusive. Therefore, further investigation is needed to delineate the exact role of β-TrCP in tumorigenesis.

5. Possible tumor suppressor gene, FBXW7, in CRC

The first member of the FBXW7 gene family, Cdc4, was originally identified in budding yeast as a cell division cycle protein (64). It was then characterized in other species including Homo sapiens (FBW7, also known as FBXW7) (65). The FBXW7 gene is located on chromosome 4 (4q31.3), and it consists of 1 specific exon and 10 common exons. Human FBXW7 encodes three transcripts (FBXW7α, FBXW7β and FBXW7γ) derived from the alternative N-terminus (66). The three isoforms share conserved interaction domains in the C-terminus, all containing the F-box domain and WD repeat domain. Each isoform is differentially regulated both in tissue expression and cellular locale. FBXW7α is ubiquitously expressed in all tissues, while FBXW7β is restricted to the brain and testis and FBXW7γ to the heart and skeletal muscles (67). The localization of each isoform also varies within the cell and is located in distinct subcellular compartments. The three FBXW7α, β and γ isoforms localize to the nucleoplasm, cytoplasm and nucleolus, respectively (68).

FBXW7 is a well-characterized tumor suppressor that is frequently mutated or deleted in a variety of human malignances. FBXW7 exerts its antitumor function through the following ways. Firstly, FBXW7 mediates the degradation of various oncoproteins such as cyclin E, c-Myc, c-Jun and Notch-1, all of which regulate cellular proliferation, differentiation and cause genetic instability in a variety of human tumors. The dysregulation of FBXW7-mediated proteolysis of these substrates contributes to tumorigenesis. Secondly, 6% of all primary human tumors harbor mutations in the FBXW7 gene (69). Thirdly, FBXW7 mutation is associated with p53 gene mutation (70); FBXW7 and p53 cooperatively suppress advanced and chromosomally unstable intestinal cancer (71).

Roles of FBXW7 in in vitro models. Rajagopalan et al (72) first identified the mutation of hCDC4 in human CRC. They found an increase in cyclin E protein caused by loss of FBXW7 in the HCT116 or DLD-1 hCDC4-/- cell line resulting in chromosomal instability. Cyclin E is a pivotal regulator of cell cycle progression and is frequently upregulated in cancer (73). It was reported that FBXW8 targeted cyclin D1, and FBXW7 targeted cyclin E for degradation in CRC HCT116 and SW480 cells (15). Similar to cyclin E, cyclin D1 is an oncoprotein that was found routinely activated in human types of cancers (74-76). Sionov et al (77) and Grim et al (78) indicated that FBXW7α might be the major isoform that mediates the stability of cyclin E. However, the results from van Drogen et al (79) and Sangfelt et al (80) were different. The latter two research groups hypothesized that both FBXW7α and FBXW7γ were responsible for the degradation of cyclin E; FBXW7α did not directly mediate cyclin E degradation. Notably, substrate recognition by FBXW7 may be more complex than simple differences in isoform specificity and FBXW7 isoform dimerization may also have an affect (81,82). CRC LoVo cells depleted of FBXW7 by small interfering RNA underwent overproliferation (83). Fukushima et al (84) demonstrated that FBXW7α promoted NFκB2 ubiquitination and its restoration in a GSK3 phosphorylation-dependent manner in both HCT116 and DLD1 CRC cell lines. FBXW7 has also been reported to be regulated by others. Rapamycin-insensitive companion of mTOR (Rictor) binding to FBXW7 regulated ubiquitination and increased protein levels of c-Myc and cyclin E in the CRC cell line HCT116 (85). Consistent with this observation, Wang et al (86) also found that the tumour cell lines HCT116 and DLD-1 harboring inactivation of FBXW7 underwent epithelial-mesenchymal transition, and were particularly sensitive to mTOR inhibitor rapamycin. This result indicates that loss of FBXW7 could be a biomarker of human cancer susceptibility to mTOR inhibitor treatment. These results suggest that FBXW7 plays a pivotal role in colon cancer progression and may be used for drug screening.

Roles of FBXW7 in in vivo models. To explore the underlying mechanisms of the development and tumor formation in CRC due to the deregulation of FBXW7, several FBXW7-knockout mouse models have been generated to understand the anticancer function of FBXW7 in CRC. Tetzlaff et al (87) first reported that the functional ablation of FBXW7α resulted in embryonic lethality at around 10.5 days due to major developmental defects. Sancho et al (88) generated gut-specific knockout FBXW7α mice lacking one allele of FBXW7 to investigate the function of FBXW7. Their results indicated that the high expression of c-Jun and Notch-1 in the conditional FBXW7-intestine-deficient mice induced actively proliferating progenitor cells in spite of no developed intestinal tumors. The complete absence of FBXW7β caused increased tumor number and tumor size. Deletion of FBXW7 in the murine gut altered homeostasis of the intestinal epithelium, resulting in elevated Notch and c-Jun expression, and eventually led to intestinal and colonic polyposis (89). However, FBXW7 deletion alone cannot cause tumorigenesis in the gut, as both FBXW7 and p53 synergistically suppress adenocarcinomas (73). This result provides novel insight for CRC associated with ubiquitin pathway mutations. In support of this finding, Davis et al (90) firstly created an animal model FBXW7K14R/K14R, which could faithfully mimic human disease. This model has a stronger ability to increase polypl numbers and size and promote intestinal tumorigenesis on an Apc mutant background. Therefore, loss of FBXW7 combined with overexpression of oncogenes or deletion of tumor-suppressor genes may contribute to cancer under the proper conditions. Moreover, the substrate of this model was not c-Jun, but Klf5 and Tgif1 in both normal intestines and adenomas. In addition, absence of miR-27α was found to inhibit colon cancer stem cell proliferation in vitro and tumor formation in vivo by increasing FBXW7 protein level (91). A study carried out in breast cancer showed that hypermethylation of the FBXW7 promoter also contributed to inactivation of FBXW7 and was associated with poorly differentiated tumors (92). These results indicated that the upstream
regulator was another main factor to influence the function of FBXW7.

Several studies have demonstrated the role of FBXW7 in vivo. However, further in-depth investigation is required to define the exact molecular mechanism underlying the anti-tumor activity of FBXW7 as well as the mechanism by which the expression of FBXW7 is regulated, and how the loss of FBXW7 contributes to the development or the progression of CRC.

Roles of FBXW7 in CRC tissues. FBXW7 mutations have been thoroughly surveyed in CRC. Rajagopalan et al. (74) first reported that the mutation frequency of FBXW7 in CRC was 8% (44 of 532), which was related with chromosomal instability (CIN) in human types of cancers. The data from Kemp et al. (93) confirmed this. They used fluorescence single-strand conformational polymorphism (SSCP) analysis to screen 244 colorectal tumors and 40 cell lines. The results showed that 6% (18 of 284) of tumors harbored CDC4 mutations. The results differed from the former. Kemp et al. believed that FBXW7 mutations were not associated with chromosomal instability. A recent study from Mouradov et al. (94) provides an adequate explanation to the contradiction. They used microsatellite instability (MSI) and CIN are independent predictors for stage II/III CRC patients rather than specific gene mutations such as KRAS, NRAS, BRAF, PIK3CA, FBXW7 and TP53. Miyaki et al. (95) investigated the mutation of FBXW7 in hereditary colorectal tumors. Somatic FBXW7 mutations were detected in 9% of hereditary non-polyposis CRC (HNPPCC) or adenomatous polyposis (FAP) carcinomas. Comparing the FBXW7 mutation rate in flat adenomas to polyoid adenomas, the FBXW7 mutation frequency was 1.13 and 3.23%, respectively (96). FBXW7 mutation was also found to determine poor prognosis in CRC (86). Xie et al. (97) performed whole genome sequencing of two primary CRC tumors and their matched liver metastases. Their results indicated that FBXW7 contributed to the initiation and progression of distant metastasis. What is more, mutations of FBXW7 in CRC patients usually occur with other simultaneous molecular aberrations such as KRAS; one of the possible explanations why the KRAS mutation frequency in the CRC population was relatively high (98). Thus, whether there are any possible association between FBXW7 and KRAS mutations still needs further study. These data suggest that modulating ubiquitin ligases such as FBXW7 may impact the efficacy of cetuximab treatment for KRAS-negative CRC cancers.

6. Conclusions and future direction

Despite recent advances in detection and treatment, CRC is still a major global public health concern. It is the third most common cancer and the fourth leading cause of cancer-related deaths in the world (4); both the incidence and mortality rates of CRC are increasing rapidly in Asian countries (99). CRC is a consequence of the accumulation of both genetic and epigenetic genomic alterations. Over the past few years, a growing body of genetic alterations have been found to play an increasingly important role in CRC diagnosis and treatment. At present, kras alterations are identified for the purpose of guiding treatment with targeted therapies such as anti-endothelial growth factor receptor monoclonal antibodies clinically. Although our understanding of the molecular mechanisms of CRC has improved substantially, molecular biomarkers for predictive and prognostic purposes are still in the theory stage. Much remains to be discovered to fully appreciate the nature of FBPs in cancers. Identification of other FBPs and characterization of their contribution to CRC will be an important yet challenging task.

In the present review, we summarized the recent findings concerning FBPs in CRC (Fig. 2). Overall, on the basis of the data presented here, most studies have focused on characterizing the substrate networks of FBPs related with CRC, yet...
relatively little is known regarding the expression regulation of FBPs themselves that lead to human CRC carcinogenesis and development. In the future, it will be of great importance to identify novel FBPs and their substrates that regulate the development and progression of CRC. Recently, more and more data have shown that several molecules such as p53 and APC (14,70), miRNAs including miR-27a and miR-223 (95) as well as FBXW7 promoter hypermethylation (96) regulate the tumor suppressor functions of FBXW7. In this regard, a better understanding of the upstream regulators of FBPs in cancers is needed. We expect novel strategies that directly or indirectly target FBXW7 to obtain more effective treatment for cancer patients in the near future. In regards to CRC issues, a majority of studies were performed using immunohistochemistry (IHC) or polymerase chain reaction (PCR) to define a potential correlation in expression of FBPs and their substrates. Few studies have utilized in vivo mouse models. More genetically modified mouse models should be established for gut-specific transgenic expression to target relevant components. In addition, the FBXW7 status has currently been proven to be related to drug therapeutic effect (98,100). Recent evidence reveals that bortezomib, a reversible inhibitor of the catalytic activity of the 26S proteasome, can be efficacious in the treatment of human types of cancers (101,102). This finding has set the stage for attempts to selectively inhibit the activities of disease-specific components of the UPS. All of these studies, therefore, call for an urgent need to design additional small molecules targeting FBP to treat human cancers. Future efforts in this area of research should be devoted to the development of small-molecule inhibitors of SCF E3 ligases as a novel approach for the treatment of human CRC. Moreover, the level of certain FBPs in cancers could be possible markers to optimize treatment regimens to achieve better clinical results.

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