Roles of F-box proteins in human digestive system tumors (Review)

JIAN GONG, LIANG LV and JIRONG HUO

Department of Gastroenterology, The Second Xiangya Hospital,
Central South University, Changsha, Hunan 410011, P.R. China

Abstract. F-box proteins (FBPs), the substrate-recognition subunit of E3 ubiquitin (Ub) ligase, are the important components of Ub proteasome system (UPS). FBPs are involved in multiple cellular processes through ubiquitylation and subsequent degradation of their target proteins. Many studies have described the roles of FBPs in human cancers. Digestive system tumors account for a large proportion of all the tumors, and their mortality is very high. This review summarizes for the first time the roles of FBPs in digestive system tumorigenesis and tumor progression, aiming at finding new routes for the rational design of targeted anticancer therapies in digestive system tumors.

Contents

1. Introduction

Protein ubiquitylation by the ubiquitin (Ub) proteasome system (UPS) is a post-translational modification that governs a broad array of basic cellular processes, and its defective

Correspondence to: Dr Jirong Huo, Department of Gastroenterology, The Second Xiangya Hospital, Central South University, 139 Middle Renmin Road, Changsha, Hunan 410011, P.R. China
E-mail: huojir008@126.com

regulation is manifested in various human diseases (1-3). UPS has a crucial role in maintaining and regulating cellular homeostasis (4). The change of ubiquitination is closely related to the occurrence of a wide variety of tumors. The UPS exerts its functions mainly through the concerted efforts of a group of enzymes (5-7) (Fig. 1): the E1 Ub-activating enzyme, E2 Ub-conjugating enzyme, and E3 Ub ligase and 26S proteasome. Ub is activated in an ATP-dependent manner by an Ub-activating enzyme (E1), and then transferred to the active site cysteine of a conjugating enzyme (E2) through a thioester bond. The E3 ligase facilitates the attachment of Ub onto the substrate protein from the E2 enzyme. Next, the Ub proteins are recognized and then degraded by 26S proteasome to several small peptides. There are >1,000 putative E3 Ub ligases belonging to two major families, the homologous to E6-APC terminus (HECT) type and Ring/Cullin Ligase (RCL) type (8,9). Among the E3 Ub ligase enzymes, the RCL type of E3 ligases contain the largest number of family members, among them, the Skp1-Cullin1-F-box (SCF) E3 ligase complex has recently come to prominence (10-12). The SCF-type E3 ligase complex consists of four units: Skp1, Rbx1 and Cullin1, and F-box protein (FBP), the latter of which being responsible for the substrate targeting specificity of the complex (13,14). FBPs are characterized by ~40 amino acids. Because this kind of structure domain was originally found in the cycle of F protein (FBXO1), it is named 'F-box structure domain'. Without taking into account the various isoforms that may be produced, 69 human FBPs have been identified so far (10), but only few of them have been well characterized. FBPs have been classified into three categories according to their specific substrate recognition domains (Fig. 2) (15-17). The FBXW subclass containing WD40 repeat domains is composed of 10 proteins. The FBXL family comprises of 22 proteins which are leucine-rich repeat proteins. Other 37 F-box members containing other domains such as zinc finger or ring finger constitute FBXO family. FBPs are attractive candidates for drug discovery because they play pivotal roles in various cancers.

The common digestive system tumors are colorectal cancer, gastric cancer, liver cancer, esophagus cancer and pancreatic cancer (PC). According to the latest global cancer statistics (Table I), colorectal cancer is the third most common malignancy, while gastric cancer, liver cancer and esophagus cancer are ranked the fourth, the fifth, and the

Table I. Percentage of the five digestive system cancers in all cancers.

Cancer site	The rank in cancers	New cases	The rank in cancers	Cancer deaths
Colon/rectum	3	1,233,700	4	608,700
Stomach	4	989,600	2	738,000
Esophageal	7	464,500	6	406,800
Liver	5	748,300	3	695,900
Pancreas	13	277,000	8	266,000
All site but skin		12,668,500		7,571,500
Percentage		29.30%		35.86%

According to the crude global new cancer cases and deaths in cancer registries in 2008. All global new cases of the five digestive system cancers in 2008 are 3,713 thousand, 29.30% is estimated to account for all new cancers. All cancer deaths of the five digestive system cancers in 2008 were 271,000, of these 35.86% accounts for all the cancer deaths. The percentage given means the estimated percentage of the five digestive system tumors in all global cancers.
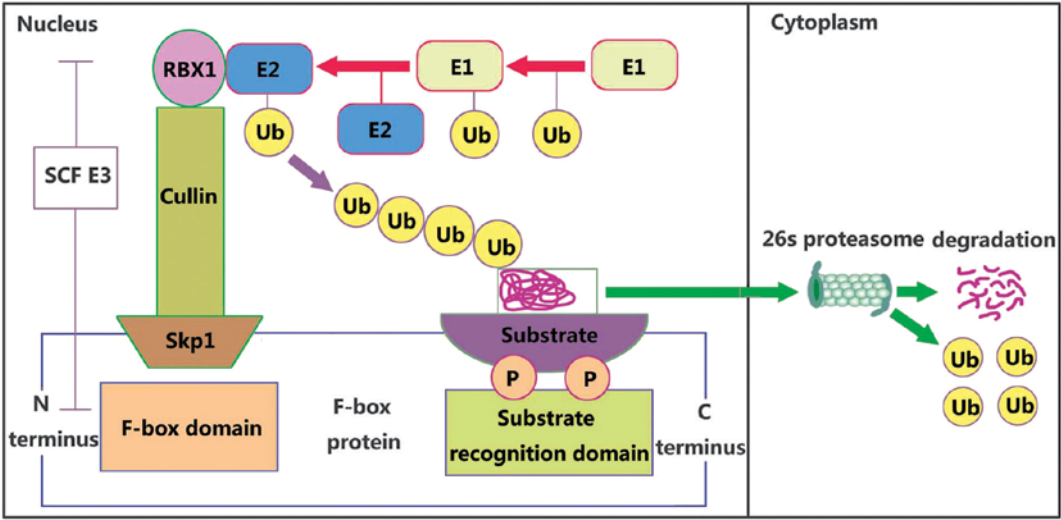

Figure 1. The functions of ubiquitin (Ub) proteasome system (UPS). The E1 enzyme functions as an activator by creating a high-energy thioester bond between a cysteine of the E1 enzyme and the Ub molecule via ATP hydrolysis, which is subsequently transferred to conjugating enzyme (E2). The function of E2 is the transfer of activated Ub to the site of conjugation in the form of an E2-Ub thiolester intermediate. Ub is then transferred from the E2 to lysine residues in the target through an E3-Ub ligase. Finally the Ub proteins were recognized and then degraded by the 26s proteasome to several small peptides in the cytoplasm.
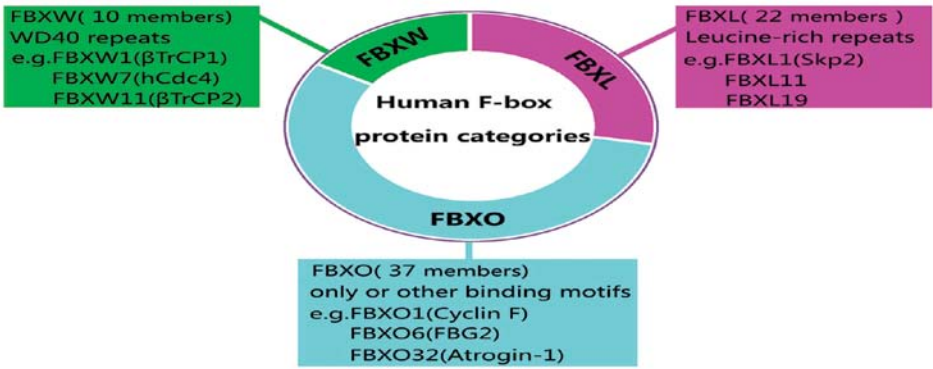

Figure 2. Human F-box protein (FBP) catagories. The large circle stands for the whole FBP family. The three rectangles indicate the three different kinds of FBPs and the typical representatives of each type.

seventh respectively in all cancers. A total of 3,713,100 new cancer cases and 2,715,400 cancer deaths are responsible for 29.30% of worldwide total new cancer cases and 35.86% of deaths in 2008. There is a high necessity for accurate

diagnosis of digestive system tumors because of their poor prognosis due to chemoresistance and a high recurrence rate. The main functions of the digestive tract are the absorption, digestion and excretion. The occurrence and development of digestive system tumors are strongly associated with all sorts of stimulations and the subsequently signal pathway activations caused by stimulations. Studies have shown that FBP, one component of E3 ligase, can be activated by the cell's DNA damage caused by certain stimuli such as heat and chemotherapy drugs (18,19). Therefore, it is necessary and important to summarize the function of FBPs in digestive system cancers.

2. The main FBPs Skp2, FBXW7 and βTrCP in digestive system tumors

The misregulated degradation of tumor suppressor proteins or oncoproteins can drive tumorigenesis. Accordingly, FBPs can function as oncoproteins when overexpressed (if their substrates are tumor suppressors) or as tumor suppressors (if their substrates are oncoproteins).

FBXW7 is focused on as a tumor suppressor gene in human tumorigenesis in large due to the fact that FBXW7 targets multiple well-known oncoproteins including Cyclin E (20,21), c-Myc (22,23), c-Jun (24,25), Notch (25,26) and tumor suppressor neurofibromatosis type 1 (NF1) (27) for ubiquitination. Gene mutations of FBXW7 are frequently discovered in a variety of human cancers such as cholangiocarcinomas (35%) (28), digestive system tumors such as colorectal cancer (6-9%) (29-31), intrahepatic cholangiocarcinoma (ICC) (32) and gastric cancer (3.7%) (33), esophageal adenocarcinoma (55.6%) (34), PC (35) and other solid tumors (36-39). Notably, recent studies have also demonstrated that FBXW7 is also involved in the regulation of drug resistance (40-42). Furthermore, FBXW7 is a tumor suppressor and evidence shows that mouse FBXW7 is essential for normal vascular development (43).

S-phase kinase-associated protein 2 (Skp2) is an authenticated oncogenic protein (44). It was first discovered as an element of CDK2/Cyclin A (45). Then it was identified as a Skp1-binding protein to regulate cell cycle progression (46). Skp2 drives cells from G1 to S phase through ubiquitylation and degrading the p27 (47). p27, a Cyclin-dependent kinase (CDK) inhibitor, is a negative regulator of the cell cycle which is found decreased in cancers. So far, all studied cases of cancer have indicated that high levels of Skp2 correlate with poor overall survival. The dysregulation of Skp2 and p27 was found to be associated with tumor progression in human oral (48), colon (49,50), esophageal squamous cell carcinoma (ESCC) (51), gastric (52) and prostate cancer (53). Mouse models unequivocally confirmed the role of the Skp2-p27 axis in tumorigenesis (54). Thus, Skp2 may serve as an attractive target for the treatment of cancer.

β-transducin repeat-containing protein (βTrCP) including βTrCP1 and βTrCP2 is overexpressed in multiple cancers, such as colorectal cancer, pancreatic cancer, breast cancer and melanoma, which supports an oncogenic function for these proteins (55). However, in sharp contrast to the tumor-promoting role of βTrCP described above, in gastric cancer tumors, it has been shown to suppress tumor development (56). Thus, βTrCP

might have a greater role as an oncogenic protein than as a tumor suppressor in digestive system cancers (55).

3. Roles of FBPs in esophageal cancer

Esophageal carcinoma is an age-related neoplasm with a 5-year overall survival rate of <35% (57,58). Esophageal cancer is one of the most frequently occurring malignancies and the seventh leading cause of cancer-related deaths in the world. ESCC is the most prevalent type of esophageal cancer in China and the survival rate of ESCC patients is <10% (59,60). Due to the changes in lifestyle such as smoking and physical inactivity, the incidence of cancer becomes increasingly high.

Fukuchi *et al* (51) first analyzed Skp2 and p27 expression in 32 early ESCC surgical specimens. Their findings suggest that the target substrate of Skp2 is mainly p27, and that failure of Skp2-induced degradation of p27 leads to a poor prognosis, especially in the primary stages. Another study (61) reported that Skp2 increases during esophageal squamous cell cancer progression from esophageal intraepithelial dysplasia to ESCC (62). In addition, the elevated expression of Skp2 promoted the radioresistance of ESCC cell line EC9706. Another member of the FBP family, FBXL19, exhibits antitumor property via targeting Rac3 for its degradation, thereby inhibiting TGFβ1-induced E-cadherin downregulation in esophageal cancer cells OE19 and OE33 (63). Rac3 is a small GTPase multifunctional protein that regulates cell adhesion, migration and differentiation. It has been considered as an oncogene in breast cancer and prostate cancer (64,65). Transforming growth factor-β (TGFβ), can reduce the tumor suppressor. E-cadherin is a key component in the formation of cell-cell adherens-type junctions in epithelial tissues (66). E-cadherin plays a critical role as a tumor suppressor in cancers (67).

The team of Barbash *et al* (68) found 14% (16/116) missense mutations in 116 primary ESCC patients in FBXO4 directly promotes Cyclin D1 accumulation. Taken together, FBXO4 has biological properties consistent with a tumor suppressor in ESCC. As these researchers also found that FBXW8 is not expressed in either normal esophageal epithelium or associated tumor tissues, they speculated that an FBXW8-based E3 ligase is unlikely to contribute to Cyclin D1 proteolysis in ESCC. Cyclin D1 is overexpressed in various types of malignant tumors such as breast cancer (69), and esophageal cancer (70,71). Over the last decade, articles have been published demonstrating that FBPs including FBXO4, FBXW8, Skp2 and FBXO31, independently contribute to Cyclin D1 ubiquitylation (19,68,72,73). However, other researchers found different results (74). Naganawa *et al* (75) investigated the relationship between the expression of FBXW7 and the tumor progression of 43 primary ESCC patients. The patients with low levels of FBXW7 expression had a significantly shorter postoperative survival time than the patients with high levels of FBXW7 expression.

Kogo *et al* (76) reported that higher expression of FBXO31 determines poor prognosis in esophageal squamous carcinoma. On the contrary, a substantial body of evidence implicates that FBXO31 functions as a tumor suppressor in cancers such as breast cancer and hepatocellular carcinoma (77-79). So, the molecular mechanism for these discrepancies is so far

unclear prompting further investigations to identify FBXO31 regulated pathways. A recent study (18) found that FBXO31 downregulates p38 mitogen-activated protein (MAP) kinase via degradation of MAP kinase kinase 6 (MKK6) in ESCC cell lines. p38 MAP plays an important role in a wide range of complex biologic processes, such as cell proliferation, cell differentiation, cell death, cell migration, and invasion, and p38 MAP enhances migration and invasion of many cancers (80). MKK6 is a p38 activator. FBXO32, also known as Atrogin-1, has been reported as an apoptosis regulator and a tumor suppressor (81). FBXO32 has recently been identified as TGF-β target gene involved in regulating cell survival and it may be transcriptionally silenced by epigenetic mechanisms in some carcinomas. The mRNA and protein expression of FBXO32 is decreased in esophageal cancer cell lines because of the aberrant methylation and histone deacetylation of FBXO32. The silencing of FBXO32 could be reversed by treatment with 5-aza-2'-deoxycytidine (DNA methylation inhibitor) in the esophageal cancer cell line TE13. This study indicates that FBXO32 may be a functional tumor suppressor in ESCC carcinogenesis and its abnormal methylation leads to the occurrence of ESCC (82).

4. Roles of FBPs in gastric cancer

A total of 989,600 new stomach cancer cases and 738,000 deaths are estimated to have occurred in 2008, accounting for 8% of the total cases and 10% of total deaths (83). The morbidity of gastric cancer is the second most common, after lung cancer according to global cancer statistics (83).

One study (16) showed that Skp2 is overexpressed in human gastric carcinomas with corresponding reduction of p27 and poor prognosis. Consistently, another study showed that the activation of Skp2 accelerates both p27 and phosphatase and tensin homolog on chromosome 10 (PTEN) degradation in gastric carcinoma (84,85). These studies indicated that p27 and PTEN are the possible substrates of Skp2 in gastric cancers. PTEN is a tumor suppressor. Reduced expression of PTEN protein contributes to carcinogenesis and progression of gastric carcinoma (86). Skp2 expression was gradually increased during the course of intestinal metaplasia, dysplasia and primary gastric carcinoma (84). Knockdown of Skp2 suppressed the ability of gastric cancer MGC803 cells to form tumors and metastasize to the lungs of mice and the growth of established tumors via inhibiting cell proliferation and enhancing cell apoptosis (87). Moreover, another member of the FBXL family, FBXL5, targets cortactin for ubiquitination in gastric cancer cells, thus decreasing cell migration and invasion (88). Cortactin, an actin-interacting protein, is implicated in cytoskeletal architecture and often amplified in advanced, invasive cancers. In other words, FBXL5 may be a tumor suppressor in gastric cancer.

βTrCP1 is not expressed in primary gastric cancer (89). Genetic alterations of βTRCP2 were identified in gastric cancer cell lines and primary gastric cancers (89). Complementing this study, an analysis of somatic mutations in 95 gastric cancer specimens found five missense mutations in βTRCP2, and in these particular tissues, with oncogene β-catenin level higher than controls (56), which means that βTrCP2 may function as a suppressor in gastric cancer. FBXW7 mutation has been confirmed in gastric cancer (33). The loss of heterozygosity of FBXW7 has reached 32% in 37 early-onset gastric carcinomas cases (90). Yokobori and colleagues reported the relationship of FBXW7 and p53 in gastric cancer (91). The low expression of FBXW7 mostly results from p53 mutation, which brings about poor prognosis in gastric cancer patients. p53 is well acknowledged as a tumor suppressor gene, and p53 mutation is often found in cancers. Several studies have demonstrated that restoration of wild-type p53 expression can eliminate tumors (92-94).

FBXO6, also named Fbg2, mainly targets checkpoint kinase 1 (Chk1) for ubiquitination and degradation. Low expression of FBXO6 causing Chk1 accumulation might increase tumor cell resistance to chemotherapy drugs (95,96). Chk1 is the main replication checkpoint for cellular sensitivity to replicative stress. It has been proved to be overexpressed in cancers (97). Intriguingly, recent evidence questions the role of FBXO6 in gastric cancer. Zhang *et al* (98) reported that FBXO6 promotes the growth, proliferation and invasion of gastric cancer cells as well as normal gastric cells. FBXO32 is also involved in promoting tumorigenesis in gastric cancer cells (99).

5. Roles of FBPs in hepatobiliary tumors

The mortality rate of liver cancer is second in the ranking in China (100).

There is evidence showing that, troglitazone (101) or LK-A (102) can lower the expression of Skp2 in human hepatoma cells or xenograft models. Troglitazone is a synthetic ligand of peroxisome proliferator-activated receptor-γ (PPARγ), and it has an inhibitory effect on cancers (103). LK-A, a natural ent-kaurene diterpenoid isolated from Isodon genus, has an antitumor effect on nasopharyngeal carcinoma (104). Furthermore, Xu *et al* (105) first reported that knocking down kinesin family member 14 (KIF14) could reduce the expression of Skp2 and elevated p27 in hepatocellular carcinoma cells. KIF14 is a mitotic kinesin and acts as oncogene in cancers (106).

Acetaldehyde contributing to more aggressive phenotypes in hepatocellular carcinoma cell line HEPG2 might result from activating the expression of βTrCP (107). *FBXW7*, a universally acknowledged tumor suppressor gene, decreased in hepatocellular carcinoma tissues. FBXW7 was thought to be the strongest independent risk factor for hepatocellular carcinoma recurrence or prognostic marker (108). A recent study shows that Yes-associated protein (YAP) may be a potential target of FBXW7 in hepatocellular carcinoma (109). YAP is often overexpressed in various types of human cancers (110). FBXW7 protein expression was negatively correlated with c-Myc, Cyclin E and p53 in hepatocellular carcinoma tissues (111). Recombinant human adenovirus-p53 can inhibit tumor cell growth with FBXW7 upregulation in murine hepatocellular carcinoma model (112). This provides a new potential therapy for HCC.

Notably, Cyclin F (FBXO1), is downregulated in liver cancer, indicating poor survival and recurrence (113). FBXO5, named early mitotic inhibitor-1 (Emi1), is highly expressed in 114 human hepatocellular carcinoma samples. Emi1 increases hepatocellular carcinoma cell proliferation
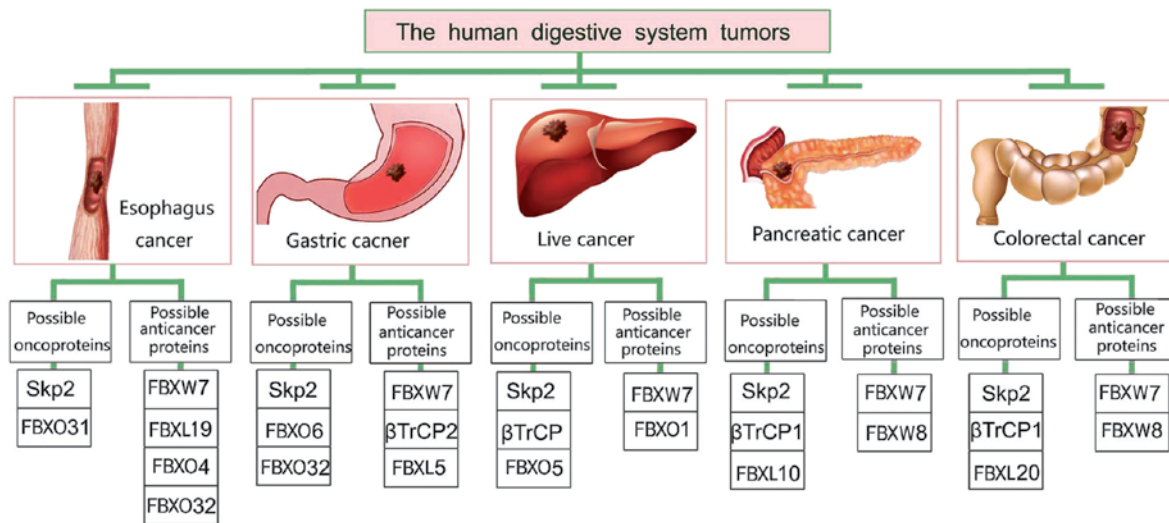
Figure 3. The five common digestive system tumors and the possible oncoproteins or anticancer proteins in the corresponding tumor.

by inhibiting the degradation of Skp2, thus reducing the expression of p27 (114). This result indicates possible cross-talk between individual FBPs. FBXO31 functions as a tumor suppressor mainly through the degradation of Cyclin D1 in liver cancer (77), which is consistent with the results in breast cancer (79).

One study showed that Skp2 is also overexpressed in both biliary tract carcinoma (BTC) cell lines and primary BTC predicting poor prognosis. However, the levels of Skp2 in BTC and p27 proteins were not correlated inversely with other tumors (115). Also p27 can be degraded by other means in BTC. Data from another study reported that the expression of p27 and Skp2 are significantly inversely correlated in 74 patients with ICCs (116). Silencing of the *Skp2* gene can on one hand slow down the growth in a nude mouse tumor model, and on the other hand, inhibit the proliferation, migration and invasiveness of gallbladder carcinoma cell line GBC-SD by enhancing the expression of the p27 protein (117). Loss of FBXW7 expression is correlated with lymph node metastasis in ICC, which tends to be an independent prognostic factor for both overall and disease-free survival (32).

6. Roles of FBPs in pancreatic cancer

Pancreatic cancer (PC) is rare, with the incidence rate 2.5% of all forms of cancers, while the mortality rate has reached 96% (118). Because the conventional treatments of PC have little effect on disease course, the 5-year survival of PC is <5% (119,120). Most patients die within the first year of diagnosis (121). Therefore, better in-depth knowledge of the molecular mechanisms might reveal new avenues for early diagnosis, and treatment of patients.

The FBPs have rarely been studied in human PC. It has been accepted by researchers that expression of Skp2 is high in many advanced cancers. Consistent with a putative oncogenic role, high expression level of Skp2 correlating with histological grade, lymph node metastasis, lymphatic permeation and poor outcome has been implicated in human pancreatic ductal carcinoma tissue (122). Schüler *et al*

disclosed for Skp2 a novel function in pancreatic ductal adenocarcinoma (PDAC) cells. Skp2 can resist TNF-related apoptosis-inducing ligand (TRAIL)-induced apoptosis (123). Blocking the expression of βTRCP1 in PC cell line PancTu-1 can reduce nuclear factor-κB (NF-κB) activation and chemo-resistance (124). FBXW7 mutations were found in PC (35). Genistein, a soy derived isoflavone, exerts its antitumor activity partly through the upregulation of FBXW7 and downregulation of miR-223 in PC cells (125). Knockdown of FBXW8 can inhibit cell proliferation of PC cells (126). FBXL10, a nucleolar protein that represses transcription of ribosomal RNA genes (127), can promote leukemia mouse model development (128), but its expression is low in aggressive brain tumors (127). The expression of FBXL10 is high in human PC tissues, and higher expression levels of FBXL10 are correlated with disease grade and stage, as well as metastasis. FBXL10 overexpression co-operated with KrasG12D, which promotes PDAC formation in mouse models (129).

7. Roles of FBPs in colorectal cancer

Colorectal cancer is the second most diagnosed cancer in females and the third leading cause of cancer-related death for females with an estimated 1.2 million new cases and 608,700 deaths in 2008 (3). Colorectal cancer incidence rates are rapidly increasing in several areas (130,131).

Li *et al* (132) reported a progressive increase of Skp2 from normal mucosa through adenoma to primary carcinoma during all stages of colorectal carcinogenesis. In the contrary, expression of Skp2, was decreased during invasion but increased again in colorectal tumor metastases. Similar results were also detected in melanoma (133). Overexpression of Skp2 accompanied with reduced p27 indicates overall survival in colorectal carcinoma patients (134). Xu *et al* (135) reported the effect of interfering Skp2 expression in colon carcinoma cell line SW480. Their results showed that knock-down of Skp2 expression induced p27 and p16 upregulation. It can also block tumor cell growth and induce cell apoptosis

in colorectal cancer nude mice. Recently, another study (136) also revealed that siRNA knockdown of Skp2 caused p27 accumulation in colon carcinoma cell line SW620, as well as increased the survival rate of nude mice. Zhu *et al* (137) reported that FBXL20 promotes carcinogenesis through activating of the Wnt signaling pathway and caspase in human colorectal adenocarcinoma. Later, it was reported that FBXL20 overexpression increases the invasiveness of colorectal cancer cell line Lovo by mediating the ubiquition and degradation of E-cadherin (138). These findings collectively indicate that FBXL20 might also govern tumorigenesis in colorectal adeno-carcinoma.

Okabe *et al* (72) reported that FBXW8 targets Cyclin D1, and FBXW7 targets Cyclin E for degration in colorectal cancer cells HCT116 and SW480. Babaei-Jadidi *et al* (139) specifically deleted FBXW7 in the murine gut, and their results showed that the loss of FBXW7 accelerated intestinal tumorigenesis, promoting accumulation of β-catenin in adenomas at late but not early time points. Somatic mutations of FBXW7 in colorectal adenocarcinoma tissues were first detected by Rajagopalan *et al* (140) and later verified by many studies (29-31). The absence of FBXW7 enhanced expression of c-Myc and Cyclin E proteins and upregulated cell prolifera-tion (30) as well as activated Wnt and Notch signaling pathway in human colorectal carcinoma (141). Jahid *et al* (142) reported that miR-27a can directly downregulate FBXW7 and promote cell proliferation through activating Notch, Jun and Myc signaling in colorectal cancer cell lines. Wang *et al* (143) first reported that depletion of FBXW7 induces epithelial-mesen-chymal transition (EMT) in human colon cancer cells, which can be suppressed by mTOR inhibitor rapamycin. This result indicates that FBXW7/mTOR axis could be a novel EMT pathway that mediates cancer invasion.

Earlier observation demonstrates that IκB and β-catenin have a similar motif for the degradation via UPS pathway, indicating that the ubiquitination of the two proteins is mediated by the same E3 ligase (144). IκB, inhibitor of NF-κB, functions as a tumor suppressor. β-catenin is a downstream molecule of Wnt signaling pathways. β-catenin is an oncoprotein that was found routinely activated in tumors and has been correlated with poor prognosis and short survival (145,146). βTrCP targeting the degradation of both β-catenin and IκB has been verified (147,148). Ougolkov *et al* (149) reported that 56% (25/45) of the tumors had increased βTrCP1 mRNA aånd protein levels in colorectal cancer compared to the normal colorectal tissues. Increased βTrCP1 levels were significantly associated with β-catenin activation. This result indicated that βTrCP1 may act as an oncogene in colorectal cancer.

8. Conclusions and perspectives

During the last 10 years since the identification and annota-tion of the FBP family, the continued identification and characterization of novel substrates has greatly expanded our knowledge. To date, 69 FBPs have been identified in humans. However, only Skp2, FBXW7 and βTrCP are well recognized with their matched downstream substrate in different cancers. The identification of substrates for FBPs in different tissues remains a major endeavor for researchers.

Above all, FBPs are important in the occurrence and development of digestive system tumorigenesis, leading the high level research into the pathogenesis of these tumors. We should reveal further mechanism of the FBPs on the cellular and molecular levels. Although a great number of FBPs have been identified in digestive system tumors (Fig. 3), this area of research and our current understanding of the FBP family remains in its infancy. Plenty of questions remain to be answered. Do the FBPs in a cell compete for binding to the Cullin scaffold and consequently are unable to participate in ubiquitination reactions in digestive system tumors? Will a certain FBP function as a tumor suppressor or be oncogenic in different stages of disease or different tissues of the same digestive system tumor? Does intricate crosstalk exist among FBPs in digestive system tumors? How does the FBP's expression vary after primary carcinomas metastasizing to lymph nodes in digestive system tumors? Future study on FBP activity in these digestive system tumors will be of great interest and the different biological characteristics of a given FBP in different tissues will surely bring us new insight. Bortezomib, a reversible inhibitor of the catalytic activity of the 26S proteasome, has revealed effectiveness in the treatment of mantle cell lymphoma and multiple myeloma (150,151). In addition, we believe inhibi-tors targeting the FBPs are promising in the prevention and treatment of digestive system tumors.

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