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Review Article

The role of Fbxo5 in the development of human malignant tumors

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Abstract: Fbxo5 (F-Box only protein 5), as a substrate recognition subunit of SCF (SKP1-Cullin1-Fbox) protein, plays a crucial role in various cellular processes through ubiquitination and degradation of multiple proteins. In recent years, many studies have pointed out that Fbxo5 is critically involved in carcinogenesis. Moreover, targeting Fbxo5 could have a therapeutic potential for cancer therapy. This review focuses on the functions of Fbxo5 in various types of human malignancies and its underlying molecular mechanisms. This review might lay the foundation for enhancing future investigation on Fbxo5 functions in cancer development and progression.

Keywords: SCF, APC/C, F-box family protein, Fbxo5, cancer

Introduction

Ubiquitin proteasome systems (UPS) targets numerous substrate proteins for degradation to regulate biological processes, such as cell proliferation, cell cycle, apoptosis, differentiation and motility [1]. Ubiquitin protease pathway is one of the most important ways for selective protein degradation in mammalian cells, which has important regulatory effects on the degradation of intracellular misfolded proteins and regulates key physiological processes [2]. The UPS relies on the cascade activation of E1, E2, and E3 enzymes, also known as ubiquitin-activating enzyme, ubiquitin-binding enzyme, and ubiquitin ligase, to perform its biological functions [3]. Ubiquitin, consisting of 76 amino acids with a molecular weight of 8.5 KDa, can be transferred to the E1 enzyme in an ATP-dependent manner. The activated ubiquitin can be transferred to the E2 enzyme [4]. Then, the ubiquitin molecule is connected with the target protein by the E3 ubiquitin ligase. The target protein is finally recognized and destroyed by the 26S proteasome [4].

Numerous studies have shown that E3 ubiquitin ligases are divided into four main types, namely HECT-type, RING-finger type, U-box type, and PHD-finger type [5]. Ubiquitination and substrate-specific degradation are mainly determined by E3 ubiquitin ligases. The E3 ligase family of mammalian cells is composed of over 600 E3 ligases [6]. The representative RING-type E3 is a multi-subunit assembly containing the cullin family of scaffolding proteins, which has eight members: CRL1, CRL2, CRL3, CRL4A, CRL4B, CRL5, CRL7 and CRL9 [7-9]. Among them, CRL1 or SCF (Skp1-CUL1-F-box protein) ubiquitin ligase complex is well-described CRL member [10]. SCF consists of three components: Skp1 (S-phase kinase-related protein-1), CUL1 (Cullin1) and RBX1/ROC1, and a variable component FBP (F-box protein, a variable element capable of selecting substrates) [11]. FBP is a substrate recognition subunit of the SCF E3 ligase complex, which can determine the specificity of the SCF complex substrates [12, 13].

Current studies show that F-box proteins serve as substrate receptors in the SCF ubiquitin ligase complex [14]. FBPs affect the growth and differentiation of cells through multi-channel regulation of numerous substrates [3]. To date, 69 FBPs have been identified in the human genome [15]. According to the existence of spe-

cific substrate recognition domains, F-box proteins can be divided into three subclasses, FBXW subclass, FBXL subclass, and FBXO subclass [16]. FBXW subclass contains 10 family members, which have WD40 substrate-binding domains, including the well-studies members: β-TRCP1, FBXW7, and β-TRCP2 (also known as FBXW11). The FBXL subclass with leucine-rich repeat domain has 22 family members, including Skp2 (also known as FBXL1). The FBXO subclass is the most diverse subfamily of FBPs, and FBXO has 21 functionally homologous structural domains [17]. This class of FBP members contains zinc finger domains, carbohydrate interaction domains (CASH), and proline-rich domains that interact with other proteins, but not WD40 and LRR domains [18]. There are 37 family members in FBXO family such as FBXO1, FBXO5 (also known as Fbxo5 and Fbx5), and FBXO45. FBP has been identified to play a critical role in regulation of proliferation, apoptotic death, drug resistance, cancer stem cells, EMT and metastasis [19, 20].

The anaphase promoting complex/cyclosome (APC/C), an E3 ubiquitin ligase, has a similar structure to SCF, which controls cell cycle and cell mitosis by regulating the degradation of cyclin [21]. The APC/C ubiquitin ligase is activated by Cdc20 and Cdh1 and can be inhibited by Mad2 and Mad2B and Fbxo5 [22]. Fbxo5 was mapped in chromosome position at 6q25-q26 in human tumors [23]. One study found a dramatic change in poly (A) tail lengths of Fbxo5, resulting in its translational repression in M phase [24]. Triethylene glycol dimethacrylate (TEGDMA) induced oxidative stress response due to regulation of several genes including Fbxo5 in human fibroblasts, leading to cell cycle delay [25]. Additionally, replication stress led to a decrease of Fbxo5 via suppression of FOXO-mediated inhibition of E2F1 in damaged cells, indicating that Fbxo5 plays a role in replication checkpoint in damaged cells [26]. Evidence has suggested that Fbxo5 participate in oncogenesis and tumor progression in several types of malignancies. Here, our review focuses on the role of Fbxo5 in the development of tumors and its underlying mechanisms. We hope our review will lay the foundation for enhancing future research on Fbxo5 in cancer development.

Fbxo5 is overexpressed in cancer

Fbxo5 is an endogenous inhibitor of APC/C and was originally identified in yeast two-hybrid screening [27]. In humans, Drosophila and Xenopus extract, Fbxo5 has been recognized as an important cell cycle regulator [28-30], which enters S and M phases and induces S and M phases by driving the accumulation of Cyclin A and Cyclin B period entry. Cell cycle regulation is mediated by the Fbxo5-APC/C^{Cdh1} double-negative feedback switch, where Fbxo5 is both a substrate and an inhibitor of APC/C^{Cdh1} [31]. At the same time, the ability of Fbxo5 to inhibit APC/C is negatively regulated by cyclin-dependent kinase CDKs [32]. Fbxo5 is first synthesized during the G1-S transition, and accumulated in the S and G2 phases, and is finally degraded by the $SCF^{β\text{-}trcp}$ pathway in the first and middle stages [33, 34].

Fbxo5 is essential for accurate mitotic progression because $Fbxo5^{-/-}$ embryos died from preimplantation developmental defects [29]. In vivo defects caused by Fbxo5 deficiency are caused by the imbalance of APC/C^{Cdh1} molecules [35]. The stabilization of Fbxo5 involves in two different mechanisms. Pin1 can degrade Fbxo5 in the G2 phase in large quantities [36], and Evi5 can be used as a stabilizer, which maintains the level of Fbxo5 in the S and G2 phase [37]. These two paths ensure that Fbxo5 is degraded at the right time, ensuring the fidelity of mitosis. Before of early mitotic degradation by $SCF^{β\text{-}TrCP}$ ubiquitination, Fbxo5 maintains genomic integrity by keeping high levels of Geminin and Cyclin A to prevent re-replication [38]. The C-terminal domain of Fbxo5 combines with multiple sites in APC/C for multimodal inhibition, which can block the substrate pathways and prevent the extension of the ubiquitin chain [39]. Fbxo5 effectively stabilizes the APC substrate by inhibiting the extension of the ubiquitin chain [40].

Studies have shown that Fbxo5 expression is significantly related to Skp2 expression, which leads to down-regulation of $p27^{Kip1}$, suggesting that Fbxo5 might be an oncogenic protein [41]. Fbxo5 overexpression can lead to the proliferation of p53 gene-deficient cells, tetraploid and genomic instability [42], suggesting that the loss of p53 may promote tumorigenesis with Fbxo5 [43]. At the same time, the cluster statistical analysis found that the expression of Fbxo5 in malignant tumors is stronger than that of benign tumors, that is, malignant tumors usually show extensive dysregulation of mitotic APC/C substrates, but not seen in benign

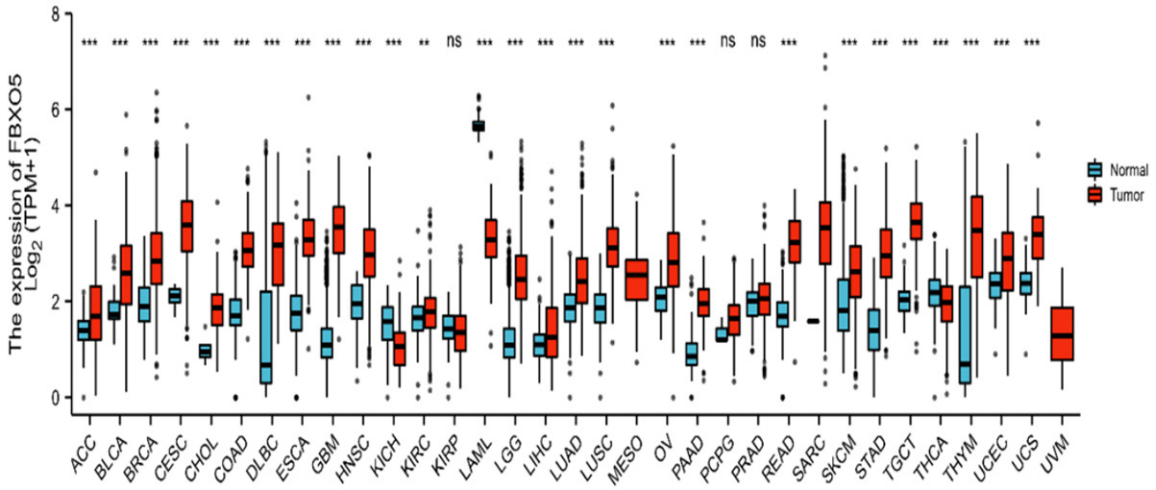

Figure 1. Fbxo5 expression levels in different cancer tissues and corresponding normal tissues are illustrated.

tumors [44]. Consistently, Fbxo5 is upregulated in breast cancer tissues and is associated with the pathological stage groups and poor prognosis [45]. Taken together, Fbxo5 is overexpressed in a variety of human tumors (**Figure 1**).

Role of Fbxo5 in various human cancers

Liver cancer

A global ranking of cancer-related causes of death indicates that liver cancer is the fourth leading cause of death and the sixth leading cancer cases worldwide, with more than one million people expected to die from liver cancer and its complications by 2030 [46]. In Asian countries, liver cancer is mainly caused by long-term chronic hepatitis B virus (HBV) infection, while in European countries, it is driven primarily by long-term excessive alcohol consumption [47]. Recent studies have reported that Fbxo5 is involved in the proliferation of liver cancer cells, and this progress is controlled by APC/C inhibition. APC/C inhibits Skp2 stable and degrades $p27^{kip1}$. The expression of Fbxo5 is positively correlated with the stage and adverse prognosis of hepatocellular carcinoma (HCC) [41]. One study screened therapeutic targets of ribavirin and pointed out that Fbxo5 mRNA levels may be related to the effect of ribavirin on HCC [48].

Esophageal cancer

About 455,800 new cases of esophageal cancer was reported each year worldwide, of which 400,200 patients died [49]. According to the reports, the global incidence and mortality of esophageal cancer will continue to increase, which enhances the global burden [50]. Recent research found that Fbxo5 may be a key factor in judging the prognosis of patients with esophageal squamous cell carcinoma (ESCC). Studies have shown that Fbxo5 is up-regulated in ESCC tissues. The expression of Fbxo5 is closely related to the degree of tissue differentiation and lymph node metastasis [51]. The high expression of Fbxo5 is closely related to the poor prognosis. Moreover, the expression of Fbxo5 protein in ESCC is increased, and it is positively correlated with the proliferation of esophageal cancer cells [51].

Lung cancer

Epidemiological surveys show that approximately 6% of the global population dies from lung cancer, making it the leading cause of cancer-related deaths [46]. Clinically, lung cancer is divided into two major categories: small cell lung cancer and non-small cell lung cancer (NSCLC). Of these, NSCLC accounts for 85%, and NSCLC mainly includes adenomyoma (ADC) (60%) and squamous cell carcinoma (SqCC) (35%) [52]. One study has pointed out that Fbxo5 plays a key role in the occurrence and prognosis of lung squamous cell carcinoma (SqCC) [53]. Moreover, downregulation of Fbxo5 enhanced apoptosis in lung cancer cells [53].

Breast cancer

Breast cancer is one of the common types of tumors in women, and it is also the second

leading cause of cancer-related deaths after lung disease [54]. Fbxo5, as a new breast cancer-related gene, plays an important role in the invasion and metastasis of breast cancer [55]. Studies have found that Fbxo5 is a regulator of PARPI sensitivity in triple-negative breast cancer (TNBC) cells. FBXO5 can degrade RAD51 to regulate the biological function of breast cancer cells and the sensitivity of PARPis [56]. In breast cancer tissues, Fbxo5 induced the proliferation of PI3K inhibitors through the PI3K/Akt pathway and reduced Fbxo5 expression [57]. According to TCGA and research data, Fbxo5 is closely related to poor prognosis of breast cancer [58] and poor survival rate, especially in patients with lumen type A breast cancer [59]. Zhang et al. reported that Fbxo5 is a candidate gene in regulation of autophagy in breast cancer via analysis of TCGA database [60].

Ovarian cancer

Ovarian cancer is the deadly cancer in women. About 230,000 women will be diagnosed every year worldwide, of which 150,000 patients will die [61]. Some scholars have pointed out that significant overexpression of Fbxo5 was detected in ovarian tumor tissues [62]. Fbxo5 expression was directly associated with Cyclin E and inversely associated with ER in ovarian clear cell cancer [62]. Ovarian cancer patients with high expression of Fbxo5 had worse prognosis and also positively correlated with higher pathological histological grade [63]. Fbxo5 inhibitors may be used as a treatment for clear cell ovarian cancer in the future [64, 65].

Bladder cancer

Because Fbxo5 inhibited the late promotion complex, which controls the cell cycle progression through the sequential degradation of various substrates, Fbxo5 can also be involved in cell cycle regulation [66]. While previous studies have shown that Polo-like kinase 1 (Plk1) can be involved in mitotic progression, recent studies have found that PLK1 can also play a role in DNA synthesis and cell cycle regulation and tumor regulation [67]. Fbxo5 is degraded in the pre-mitotic phase via a PLK1-dependent pathway [32, 68]. PLK1 phosphorylates Fbxo5 to ensure mitotic entry [69]. One study has pointed out that Fbxo5, as a downstream gene of PLK1, is negatively associated with cell proliferation, invasion, and stem cell and PLK1 expression in bladder cancer [70]. Moreover, Fbxo5 has a negative correlation with clinical stage and metastasis of bladder cancer patients [70]. Taken together, Fbxo5 might be a potential biomarker and target for bladder cancer therapy.

Chronic myelogenous leukemia

Chronic myelogenous leukemia (CML) is a malignant hematopoietic stem cell (HSC) disease that accounts for 15%-20% of all leukemia cases in adults [71]. Studies have found that this disease is caused by mutual translocation of chromosomes, leading to the formation of a carcinogenic BCR-ABL gene fusion [71]. Recently, one study indicated that BCR-ABL can activate Src kinase (or related tyrosine kinase), and then phosphorylate Fbxo5 to enhance its stability. The increase of Fbxo5 inhibited the activity of APC/C^{Cdh1} E3 ligase, reduced the ubiquitination and degradation of Skp2 protein, suggesting that targeting Skp2 and Fbxo5 may have a significant effect on the treatment of CML [72].

Other cancers

Fbxo5 is highly expressed in a variety of cancers, including head and neck cancers [73]. Patients with head and neck tumors that overexpress Fbxo5 show poor differentiation and lymph node metastasis symptoms [73]. Knockdown of Fbxo5 inhibited the expression of Cdc20, Cyclin A, Cyclin B, geminin, TPX2 and Aurora-A in Ca9-22 and Ho-1-U-1 head and neck cancer cells [73]. Recently, Yuan et al. used microRNA sequencing and bioinformatics analysis and found that ten genes, including Fbxo5, may be related to the development of HPV-positive cervical cancer [74]. One group performed a lentiviral screening of F-box protein and identified that Fbxo5 is a potential therapeutic target for neuroblastoma [75]. In addition, two transcripts of Fbxo5, transcript a and transcript b isoforms, increased migration, and osteogenic differentiation via induction of ALP activity and mineralization and promotion of RUNX2, OSX and OCN expression in human periodontal ligament mesenchymal stem cells [76]. In mantle cell lymphoma, integrated genomic and expression profiling demonstrated that Fbxo5 is involved in maintenance of chromosome stability and prevention of replication [77]. In gastric cancer, CRIP1 depletion

Table 1. The functions of Fbxo5 in human cancers

Cancer type	Function	Targets	Reference
Liver cancer	Promotes proliferation of liver cancer cells; positively correlates with the stage and poor prognosis; related to the effect of ribavirin on HCC.	Skp2, p27, Cyclin A, Cyclin B	[41, 48]
Esophageal cancer	Closely related to the degree of tissue differentiation and lymph node metastasis, and high expression is related to poor prognosis and proliferation.	Cyclin A, Cyclin B	[51]
Lung cancer	Plays a key role in occurrence and prognosis.	Cell cycle genes	[53]
Breast cancer	Poor prognosis and poor survival rate.	PI3K/Akt, Rad51, autophagy	[55-59]
Ovarian cancer	Overexpression is associated with high histological grade and low survival rate.	Cyclin E, ER	[62-65]
Bladder cancer	Involved in proliferation, invasion and migration; negatively correlated with clinical stage and metastasis.	PLK1 regulates Fbxo5	[69, 70]
Chronic myelogenous leukemia	Potential therapeutic target.	Cdh1, Skp2	[71, 72]
Head and neck cancers	High expression of Fbxo5 shows poor differentiation and lymph node metastasis; doxorubicin resistance.	Aurora-A, geminin, Cdc20, Cyclin A, B, TPX2	[73]
Cervical cancer	Related to the occurrence of HPV-positive cervical cancer	Correlated with TOP2A	[74, 79]
Neuroblastoma	Potential therapeutic target.		[75]
Gastric cancer	Increases cisplatin, epirubicin resistance	Rad51	[78]
Retinoblastoma	Involves in cell cycle and survival	APC/C, Skp2	[80]

enhanced RAD51 and Fbxo5 interaction, leading to promotion of Fbxo5-mediated RAD51 degradation, which reduced homologous repair upon DNA damage induced by cisplatin and epirubicin [78]. In cervical cancer, Fbxo5 and TOP2A were reported to be a potential target for the diagnosis and therapy [79]. In retinoblastoma cells, thyroid hormone receptor b2 (TRb2) can enable Fbxo5 to inhibit APC/C-involved Skp2 degradation, leading to regulation of cell cycle progression and cell survival [80].

Conclusion and future perspective

Fbxo5 as an endogenous and SCF-independent suppressor of APC/C negatively regulates APC/C activity by binding to Cdc20 and Cdh1 [81]. Among the 69 FBPs identified, four FBPs, namely FBXW7, FBXW1, FBXW11, and FBXL1, have been highly regarded and extensively studied. Little is known about the remaining members of the FBP family. In this review, we introduce the function of Fbxo5 in various types of human cancers (**Table 1**). Fbxo5 as an oncogene is overexpressed in a variety of human tumors, and has a significant correlation with the prognosis, stage, and lymph node metastasis of tumor patients. At the same time, Fbxo5 as a cell cycle regulator has an effect on the proliferation, differentiation and apoptosis of tumor cells. Targeting Fbxo5 will provide new insights for the development of cancer treatment. However, these studies did not provide a theoretical basis for whether and how Fbxo5 has carcinogenic activity in other tissue environments. Targeting Fbxo5 by activation or inhibition of upstream signaling pathways requires extensive research. What are the other physiological substrates of Fbxo5? Which methods are needed to screen other substrates of Fbxo5 and verify the physiological functions of Fbxo5? To solve these problems, specific animal models and cell lines are needed. There is also a need for novel methods to identify other ubiquitin substrates to determine the direct mechanism of action of Fbxo5 in the development and progression of cancer. In order to determine the different functions of Fbxo5, a lot of research is still necessary. We believe that answering these questions will promote Fbxo5 study to provide a greater value in future clinical diagnosis and treatment.

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Disclosure of conflict of interest

None.

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