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Review

Recent advances in SCF ubiquitin ligase complex: Clinical implications

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ABSTRACT

F-box proteins, which are subunit recruiting modules of SCF (SKP1-Cullin 1-F-box protein) E3 ligase complexes, play critical roles in the development and progression of human malignancies through governing multiple cellular processes including cell proliferation, apoptosis, invasion and metastasis. Moreover, there are emerging studies that lead to the development of F-box proteins inhibitors with promising therapeutic potential. In this article, we describe how F-box proteins including but not restricted to well-established Fbw7, Skp2 and β-TRCP, are involved in tumorigenesis. However, in-depth investigation is required to further explore the mechanism and the physiological contribution of undetermined F-box proteins in carcinogenesis. Lastly, we suggest that targeting F-box proteins could possibly open new avenues for the treatment and prevention of human cancers.

Contents

1. Introduction

The UPS (ubiquitin–proteasome system) governs the degradation of target proteins and plays critical roles in multiple cellular processes including cell proliferation, apoptosis, migration, invasion and cell cycle [1]. It has been known that conjugation of ubiquitin to the targeted substrates and subsequent degradation of the ubiquitinated proteins are two processes in governing protein degradation [2]. There are three enzymes including the ubiquitin-activating enzyme (E1), the ubiquitin-conjugating enzyme (E2), and the ubiquitin ligase (E3) to catalyze these reactions. Specifically, ubiquitin molecules are activated by the E1 enzyme via utilizing ATP and then transferred to the E2 enzyme, and subsequently recruited into the E3 ligases. The E3 complex binds to substrate proteins and further leads to their degradation by the 26S proteasomes [2] (Fig. 1). It is acceptable that the substrate specificity for ubiquitination is largely controlled by E3 ligases. Among approximately 600 E3 ligases, they are characterized as multiple families according to their protein sequence homology including the HECT (Homologous to the E6-AP Carboxyl Terminus) family, the RING (Really Interesting New Gene) finger family and the REB (Ring-between-ring) family [3–5].

Among the RING type of E3 ligases, the SCF (Skp1-Cullin1-F-box) complex has been well studied. It has been identified that the SCF complex consists of the scaffold protein Cullin1, the RING finger protein Rbx1, the linker protein Skp1 (S phase kinase associated protein 1), and

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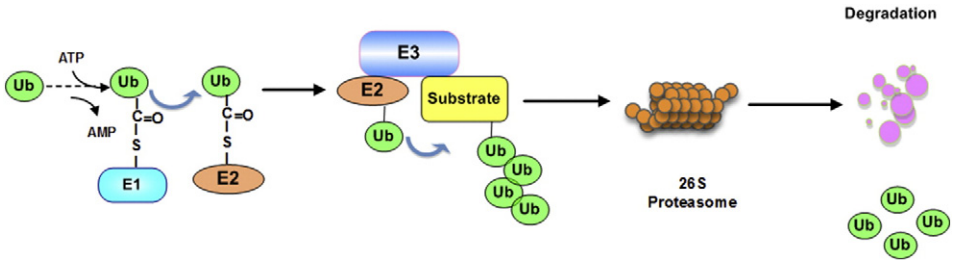

Fig. 1. A schematic illustration of the E1–E2–E3 cascade-mediated ubiquitin transfer process.

F-box protein [4] (Fig. 2). The function of Rbx1 is to recruit the E2 enzyme, while Skp1 binds to F-box proteins. F-box proteins often recognize substrates when they are properly modified, most of cases involving phosphorylation of the degron motif within the specific substrate, and then recruit the substrates to the SCF complex for ubiquitination [6]. It has been identified that there are 69 F-box proteins in human genome [7,8]. Based on the substrate binding domains, F-box proteins are characterized as three major subfamilies: the FBXW (F-box with the WD40 motif), FBXL (F-box with the LRR motif), and the FBXO (F-box only) subfamily [8]. These F-box proteins target a wide range of substrates for ubiquitination and destruction and subsequently regulate cellular processes such as cell cycle, cell proliferation, apoptosis, angiogenesis, and metastasis [6]. Thus, dysregulation of F-box proteins contributes to the development and progression of various human diseases including human cancer. Recently, a wealth of literature has shown that aberrant expression of F-box proteins is critically involved in tumorigenesis [6]. Furthermore, F-box proteins have been suggested as biomarkers in clinical implications. Therefore, in this article, we will review the recent advances in our biochemical understanding of how various F-box proteins are dysregulated and lead to tumorigenesis. Moreover, we will summarize possible clinical implications of F-box proteins and further discuss whether some F-box proteins could be biomarkers and therapeutic targets of a variety of human cancers.

2. F-box proteins

Over the past decades, F-box proteins have been intensively investigated using both biochemical approaches and mouse genetic models. It is well documented that F-box proteins could exert their oncogenic or tumor suppressive function, which depends on misregulated degradation of oncoproteins or tumor suppressors by SCF E3 ligases [7]. In this section, we will summarize the recent pathological and biochemical evidence revealing a potential role of F-box proteins in the development and progression of human cancers. Furthermore, given the critical role of F-box proteins in tumorigenesis, the potential clinical implications via targeting F-box proteins will be described.

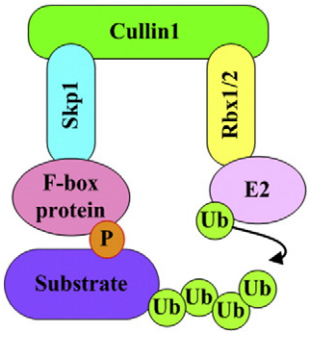

Fig. 2. A schematic illustration of structural organization of the multiple-subunit SCF E3 ubiquitin ligase complexes.

2.1. Role of the FBXW subfamily in clinical implications

FBXW subfamily contains the WD40 repeat domain and includes 11 proteins, namely FBXW-1 (also known as beta transducin repeat-containing protein, β-TRCP1), FBXW-2, FBXW-4, FBXW-5, FBXW-7, FBXW-8, FBXW-9, FBXW-10, FBXW-11 (also known as β-TRCP2), FBXW-12, and FBXW-15 [6] (Table 1). Many excellent studies have demonstrated that FBXW1 (β-TRCP1) and FBXW11 (β-TRCP2) have context-dependent functions in cancer. It is worthy to mention that β-TRCP recognizes the consensus sequence D-pS-G-X-X-pS (X represents any amino acid) degron and phosphorylation of both serine residues by specific kinases is required for β-TRCP-mediated ubiquitination [9]. β-TRCP1 and β-TRCP2 are two homologs, although

Table 1
Representative substrates of the FBXW subfamily of F-box proteins in clinical implications.

Substrates	F-box	Functions	References
Emi1	β-TRCP	Cell cycle	[12]
Cdc25A	β-TRCP	Cell cycle	[13,14]
Wee1A	β-TRCP	Cell cycle	[15]
cyclin D1	β-TRCP	Cyclin, cell cycle	[16]
BTG	β-TRCP	Cell cycle	[17]
REST	β-TRCP	Cell cycle	[18]
PLK4	β-TRCP	Cell cycle	[19]
CEP68	β-TRCP	Cell cycle	[20]
Snail	β-TRCP	Cell migration	[21]
ECMFn	β-TRCP	Cell migration	[22]
Twist	β-TRCP	Cell migration	[23]
Mcl-1	β-TRCP	Apoptosis	[24]
BimEL	β-TRCP	Apoptosis	[25]
PDCD4	β-TRCP	Apoptosis	[26]
Pro-caspase-3	β-TRCP	Apoptosis	[27]
hGCM1	FBXW2	Transcription factor, cell cycle	[38]
RACK1	FBXW2	Cell migration and invasion	[40]
DLC1	FBXW5	Tumor suppressor, cell growth	[43]
Aurora A	FBXW7	Cell cycle	[47]
cyclin E	FBXW7	Protein kinase, cell cycle	[48]
C-Myc	FBXW7	Transcription factor	[49]
C-Jun	FBXW7	Oncogene	[50,51],
C-Myb	FBXW7	Transcription factor	[52–54]
G-CSFR	FBXW7	Cell proliferation	[55]
HIF-1α	FBXW7	Transcription factor	[56,57]
KLF2/5	FBXW7	Cell proliferation	[58,59]
Mcl-1	FBXW7	Cell death	[9,60]
MED13	FBXW7	Transcription factor	[61]
mTOR	FBXW7	Cell proliferation	[62,63]
NF1	FBXW7	Tumor suppressor	[64]
Notch	FBXW7	Transcription factor	[65,66]
NF-κB2	FBXW7	Transcription factor	[67,68]
NRF1	FBXW7	Transcription factor	[69]
JUNB	FBXW7	Oncogene, tumor suppressor	[70,71]
SREBP	FBXW7	Transcription factor	[72,73]
cyclin D1	FBXW8	Cyclin, cell cycle	[83]
CDK1/2	FBXW8	Cell cycle	[86]
cyclin A	FBXW8	Cyclin, cell cycle	[86]
cyclin B1	FBXW8	Cyclin, cell cycle	[86]
P27	FBXW8	Cell cycle	[86]
HPK1	FBXW8	Cell growth, cell cycle	[87]
HBO1	FBXW15	Cell proliferation	[93]