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Ubiquitination-mediated degradation of cell cycle-related proteins by F-box proteins

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Abstract

F-box proteins, subunits of SKP1-cullin 1-F-box protein (SCF) type of E3 ubiquitin ligase complexes, have been validated to play a crucial role in governing various cellular processes such as cell cycle, cell proliferation, apoptosis, migration, invasion and metastasis. Recently, a wealth of evidence has emerged that F-box proteins is critically involved in tumorigenesis in part through governing the ubiquitination and subsequent degradation of cell cycle proteins, and dysregulation of this process leads to aberrant cell cycle progression and ultimately, tumorigenesis. Therefore, in this review, we describe the critical role of F-box proteins in the timely regulation of cell cycle. Moreover, we discuss how F-box proteins involve in tumorigenesis via targeting cell cycle-related proteins using biochemistry studies, engineered mouse models, and pathological gene alternations. We conclude that inhibitors of F-box proteins could have promising therapeutic potentials in part through controlling of aberrant cell cycle progression for cancer therapies.

Keywords

Cell cycle; F-box protein; Ubiquitination; UPS; Cancer; Degradation

1. Introduction

Ubiquitin proteasome system (UPS) governs the process of cellular protein degradation, known as ubiquitination, and subsequently controls various cellular processes such as cell proliferation, cell cycle progression, transcription and apoptosis (Eldridge and O'Brien,

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

2010, Hershko and Ciechanover, 1998, Hoeller and Dikic, 2009, Komander and Rape, 2012, Varshavsky, 2012). It has been known that ubiquitinated proteins are degraded by the 26S proteasome complex after the ubiquitin molecules are conjugated to the targeted substrate proteins. These processes include a three-step enzymatic reaction, which is catalyzed by the ubiquitin-activating enzyme (E1), the ubiquitin-conjugating enzyme (E2), and the ubiquitin ligase (E3). Specifically, ubiquitin molecule is activated by the E1 using an ATP, and transfers to the E2. Then, ubiquitin ligase E3 binds to, and facilitates the transfer of the ubiquitin moiety to its substrates, leading to degradation by the 26S proteasome in an ATP-dependent manner (Nakayama and Nakayama, 2006, Nalepa et al., 2006, Pickart, 2001) (Figure 1). It is noteworthy that the E3 ubiquitin ligase is most important to specifically determine the substrates for ubiquitination and further degradation.

Up to date, more than 600 E3 ubiquitin ligases have been discovered in the human genome (Li et al., 2008). According to their protein sequence homology, the major types of E3 ubiquitin ligases consist of the HECT (homologous to the E6-AP carboxyl terminus) type, the RING (really interesting new gene) finger type, and the RBR (ring between ring fingers) domain-containing ubiquitin ligases (Bedford et al., 2011, Deshaies and Joazeiro, 2009, Petroski and Deshaies, 2005). The Cullin-Ring Ligases (CRL-type of E3s) are the most well-studied RING type of E3 ubiquitin ligases (Hua and Vierstra, 2011, Sarikas et al., 2011), which contain CRL-1, CRL-2, CRL-3, CRL-4A, CRL-4B, CRL-5, CRL-7 and CRL-9 subfamilies (Duda et al., 2011, Metzger et al., 2012). CRL-1, also known as the SKP1-cullin 1-F-box protein (SCF) type of E3 ubiquitin ligase complex, has been most well characterized (Frescas and Pagano, 2008, Skaar et al., 2013). The SCF complex consists of cullin1 as the scaffold protein, the RING finger protein Rbx1 to recruit the E2 enzyme, and Skp1 (S phase kinase associated protein 1) as the adaptor protein to bridge F-box proteins (Peters, 2006, Zheng et al., 2002). It has been validated that the human genome encodes 69 F-box proteins, which contain several functional domains such as various carboxy-terminal domain for binding specific substrates and the F-box motif (Bai et al., 1996). Depending on the different binding domains, F-box proteins are classified into three major sub-families: the FBXW sub-family (contains WD40 substrate binding domains), the FBXL sub-family (contains leucine-rich repeats substrate binding domains), and the FBXO sub-family (contains other motifs such as kelch repeats or proline-rich motifs to bind substrates) (Frescas and Pagano, 2008, Welcker and Clurman, 2008).

The SCF complex has been reported to regulate multiply cell processes including cell cycle (Eldridge and O'Brien, 2010, Hershko and Ciechanover, 1998, Hoeller and Dikic, 2009, Komander and Rape, 2012, Varshavsky, 2012). Dysregulation of cell cycle progression is a key event in cancer development since it causes uncontrolled cell growth. It is clear that the cell cycle is mainly governed by cyclin-dependent kinases (Cdks) (Besson et al., 2008, Malumbres and Barbacid, 2009). Specifically, Cdks are activated by Cyclins and inhibited by Cdk inhibitors (CdkIs). Multiple mechanisms are involved in strictly controlling cell cycle progression such as regulatory factors (Cyclins and CdkIs), posttranslational modifications (phosphorylation, acetylation, or methylation), and degradation of cell cycle related proteins (Dai and Grant, 2003). A wealth of evidence has emerged that F-box proteins targets certain regulatory proteins as ubiquitin substrates that are critically involved in cell cycle regulation. Therefore, in this review, we describe the function of F-box proteins

in regulation of cell cycle. Moreover, we elucidate how F-box proteins involve in tumorigenesis via targeting cell cycle regulatory proteins. We conclude that targeting F-box proteins could be a novel strategy for the control of cell cycle and cancer therapies.

2. Roles of FBXW sub-family in the regulation of cell cycle

The FBXW sub-family comprises 10 proteins including FBXW-1 (also known as β-TRCP1), FBXW-2, FBXW-4, FBXW-5, FBXW-7, FBXW-8, FBXW-9, FBXW-10, FBXW-1 1 (also known as β-TRCP2), and FBXW-12 (Wang et al., 2014b). The FBXW sub-family has been revealed to be critically involved in the regulation of cell cycle. In the following paragraphs, we will discuss how the FBXW sub-family governs the cell cycle progression through targeting cell cycle regulatory proteins for ubiquitination and destruction (Table 1).

2.1 FBXW1 (β-TRCP1) and FBXW11 (β-TRCP2)

It has been well documented 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 (Wertz et al., 2011). It has been known that β-TRCP includes two homologues, namely β-TRCP1 and β-TRCP2, which have similar structure with an F-box domain and seven WD-40 repeats. These two isoforms have noticeable sequence differences in their N-terminal regions (Yaron et al., 1998). In addition, the functions of β-TRCP1 and β-TRCP2 are non-distinguishable as least using *in vitro* biochemical assays (Nakayama et al., 2003). Some studies have demonstrated that β-TRCP plays a vital regulatory role by recognizing specific substrates in cell cycle process. For instance, certain cell cycle regulators including Emi1, Cdc25A, Cdc25B, Wee1A, Cyclin D1, BTG, Plk4, Bora, and Securin have been identified as the substrates of β-TRCP. Specifically, the dysregulation of Emi1 by β-TRCP led to mitotic catastrophe (Margottin-Goguet et al., 2003). Similarly, it has been previously shown that the dysregulation of Emi1 by β-TRCP caused delayed progression through mitosis (Guardavaccaro et al., 2003). Another independent study showed that cdc25A is required for the S-phase entry and its phosphorylation can be targeted by β-TRCP and thus slow down cell-cycle progression to response to DNA damage (Busino et al., 2003, Jin et al., 2003). Besides Cdc25A, Cdc25B can also be recognized by β-TRCP and subsequently degraded to mediate the stress-activated MAPK signaling pathway (Kanemori et al., 2005, Uchida et al., 2011). Similarly, β-TRCP targets the Wee1, a Cdc2 inhibitory kinase, to ensure normal mitosis (Watanabe et al., 2004). Moreover, Cyclin D1 has been recently found to be degraded by SCF/β-TRCP, leading to regulating the cell cycle and cell proliferation (Wei et al., 2008).

Additionally, both β-TRCP1 and β-TRCP2 can recognize and degrade BTG (B-cell translocation gene), thereby regulating the cell cycle and cell proliferation (Sasajima et al., 2012). The centriolar protein Plk4 (Polo-like kinase 4) plays a role in cell cycle via regulation of centriole biogenesis and maintaining constant centriole number. β-TRCP was found to induce Plk4 degradation after Plk4 autophosphorylates itself and bound to β-TRCP (Cunha-Ferreira et al., 2009, Guderian et al., 2010). One study also showed that Plk1 (Polo-like kinase 1) can phosphorylate Bora and promote its degradation by β-TRCP, resulting in subsequent regulation of mitotic progression (Seki et al., 2008). Similarly, β-TRCP was reported to govern centrosome separation in part by targeting CEP68 for proteasomal

degradation (Pagan et al., 2015). Moreover, Securin is a complicated protein with its bifunctional properties in cell cycle. In the expose of UV irradiation, Securin is found to be degraded by β-TRCP and leads to a sharp decrease both in nucleus and cytoplasm, resulting in cell cycle arrest (Limon-Mortes et al., 2008). Moreover, it has been reported that REST (repressor-element-1-silencing transcription factor) is degraded by β-TRCP during the G2 phase of the cell cycle, leading to derepression of Mad2, which is a key component of the spindle assembly checkpoint (Guardavaccaro et al., 2008). Therefore, the overexpression of REST found in certain human cancers could be partly due to dysregulation of β-TRCP, which contributed to cellular transformation through enhancing genomic instability (Guardavaccaro, Frescas, 2008). In keeping with this notion, another study showed that β-TRCP-dependent degradation of Claspin is important for the efficient and timely termination of the DNA replication checkpoint (Peschiaroli et al., 2006). Specifically, inhibition of Claspin proteolysis by β-TRCP led to subsequent activation of Chk1 and attenuating the recovery from the DNA replication stress response, thereby delaying entry into mitosis (Peschiaroli, Dorrello, 2006). Recently, we reported that β-TRCP earmarks Set8 for ubiquitination and degradation in a casein kinase I-dependent manner, leading to control of cell cycle progression, and governing the onset of DNA damage-induced checkpoints (Wang et al., 2015). However, further in-depth studies are required to fully understand the critical role for both β-TRCP1 and β-TRCP2 and their potential redundancy in governing cell cycle progression.

2.2 FBXW2 and FBXW4

FBXW2 has been reported to regulate cell cycle in part via targeting hGCMa (human glial cell missing homolog 1) protein for degradation (Yang et al., 2005). It has been known that hGCMa, a zinc-containing transcription factor, regulates the syncytin-1 gene, which takes part in cell cycle progression (Zhuang et al., 2014). FBXW2 was found to promote the degradation of hGCMa by ubiquitination (Yang, Yu, 2005). Mechanistically, FBXW2 interacts with hGCMa in a phosphorylation-dependent manner and promotes hGCMa ubiquitination. Moreover, depletion of *FBXW2* using its siRNA led to lower level ubiquitination of hGCMa and increased hGCMa protein stability (Yang, Yu, 2005). These findings suggest that hGCMa is a substrate of FBXW2. Due to the fact that hGCMa plays a key role in regulation of cell cycle, FBXW2 could be involved in cell cycle regulation through targeting hGCMa. However, further investigation is required to discover the direct evidence of FBXW2-regulated cell cycle.

FBXW4, encoded by gene *dactylin*, plays a critical role in SHFM (split hand/foot malformation) diseases. The level of FBXW4 is decreased in the mouse dactylaplasia mutant, suggesting that FBXW4 could have an important function in SHFM (Basel et al., 2003, Ianakiev et al., 1999, Sidow et al., 1999). Recently, it has been reported that FBXW4 interacts with COP9 signalosome and mediates the specific protein degradation and maintains the normal cell growth. Furthermore, mutation, lost and low expression of FBXW4 were found in multiple cancer cell lines, indicating that FBXW4 may be a tumor suppressor by controlling cell cycle progression (Lockwood et al., 2013). Without a doubt, in-depth exploration is necessary to determine the mechanism how FBXW4 regulates cell cycle in human cancer cells.

2.3 FBXW5

Several studies have highlighted the important role of FBXW5 in regulation of cell cycle. For example, Eps8, a regulator in cell proliferation, is stable in G1 and S phase, but its expression drops in G2 by ubiquitination-mediated degradation (Werner et al., 2013). To this end, FBXW5 targets and degrades Eps8 to maintain the proper mitotic progression. Moreover, in NSCLC (non-small cell lung cancer), tumor suppressor DLC1 is degraded by the FBXW5-CRL4A E3 ubiquitin ligase, leading to promoting cell growth (Jiang et al., 2015, Kim et al., 2013). Consistently, inhibition of FBXW5 causes cell proliferation (Kim, Jackson, 2013). Since HsSAS-6 is a centriolar protein and plays important role in centrosome duplication, FBXW5 targets and ubiquitylates HsSAS-6, resulting in controlling centrosome number (Pagan and Pagano, 2011, Puklowski et al., 2011). Consistently, depletion or mutation of *FBXW5* causes centrosome overduplication and formation of multipolar spindles (Puklowski, Homsi, 2011). Another independent study identified that FBXW5 regulates TSC2 (tuberous sclerosis 2) protein stability, indicating that FBXW5 might regulate the cell cycle and growth partly via targeting TSC2 (Hu et al., 2008). Furthermore, it was found that FBXW5 itself is controlled by PLK4 and APC/C (anaphase-promoting) complex for degradation during mitosis and G1 (Puklowski, Homsi, 2011). Taken together, FBXW5 plays a critical role in cell cycle regulation, but in-depth studies are required in the future to fully dissect the downstream targets that may mediate the critical function of FBXW5 in cell cycle progression.

2.4 FBXW7

Some FBXW7 downstream substrates are vital regulatory effectors involved in cell cycle. For instance, Cyclin E is a critical regulator of cell cycle procession (Siu et al., 2012). It binds to and activates Cdk2 and thus promotes the entry from the G1 phase to the S phase of the cell cycle, while the mount of the Cyclin E is tightly controlled by ubiquitin- mediated proteolysis (Perciavalle and Opferman, 2013, Siu, Rosner, 2012, Spruck et al., 1999). FBW7 interacts specifically with phosphorylated Cyclin E, leading to its ubiquitination and subsequent degradation by the 26S proteasome (Minella et al., 2007). Deregulation of Cyclin E has been frequently found in cancer, and overexpression of Cyclin E leads to genomic instability and tumorigenesis (Spruck, Won, 1999). Importantly, deletion of *FBW7* caused accumulation and stabilization of Cyclin E in various types of human malignances (Koepp et al., 2001). Aurora kinases play important roles in mitosis (Carmena and Earnshaw, 2003, Ducat and Zheng, 2004, Fu et al., 2007, Katayama et al., 2003, Lens et al., 2010, Lindqvist et al., 2009, Ruchaud et al., 2007). Notably, there are three Aurora kinase family members, namely Aurora A, Aurora B, and Aurora C, which are highly expressed during mitosis. Aurora A is initially located at the centrosomes during prophase and later moved to the spindle poles during prometaphase and metaphase. Aurora B and Aurora C are chromosomal passenger proteins. Aurora B is located on the chromosome arms during the prophase and at the centromeres during prometaphase and metaphase (Carmena and Earnshaw, 2003, Sampath et al., 2004). Both Aurora A and Aurora B play pivotal roles in mitosis by ensuring correct chromosome segregation and normal progression through mitosis (Kwon et al., 2012, Teng et al., 2012). Interestingly, the function of Aurora C is similar as Aurora B (Slattery et al., 2008). Hence, the abundance of Aurora kinases is strictly

controlled during each stage of mitosis, primarily through ubiquitination-mediated degradation (Teng, Hsieh, 2012). It has been found that FBXW7 interacts with and negatively regulates Aurora A and Aurora B via the ubiquitination pathway (Kwon, Kim, 2012, Teng, Hsieh, 2012). Notably, loss of *FBXW7* in various cancers leads to an abnormal elevation of Aurora A and B and results in deregulated mitosis, which misleads cell cycle and accelerates cancer cell growth (Kwon, Kim, 2012, Rajagopalan et al., 2004). Collectively, FBW7 is considered as a key regulator in cell cycle, but further study is warranted to understand the physiological downstream substrate through which Fbw7 suppresses cell cycle progress to inhibit tumorigenesis.

2.5 Other FBXW proteins

FBXW8 (also known as FBW6, FBW8, FBX29, FBXW6, or FBXO29) plays a critical role in cancer cell proliferation by increasing the degradation of Cyclin D1 (Okabe et al., 2006). Interestingly, FBXW8 did not regulate the proteolysis of Cyclin D in normal cell cycle (Kanie et al., 2012). Furthermore, depletion of *FBXW8* results in pre- and postnatal growth retardation in mice, suggesting that FBXW8 is important in regulating cell growth (Tsutsumi et al., 2008). Lin et al. reported that FBXW8 regulated the G2/M phase transition to control the proliferation of human choriocarcinoma cells, which is associated with several cell cycle regulators such as CDK1, CDK2, Cyclin A, Cyclin B1 and p27 expression (Lin et al., 2011). In pancreatic cancer cells, FBXW8 increases the degradation of HPK1 (hematopoietic progenitor kinase 1) and promotes the cell growth (Wang et al., 2014a). Moreover, miR-218 targets the FBXW8 and inhibits the proliferation of human choriocarcinoma cells (Shi et al., 2014).

It has been recently reported that the protein level and function of FBXW10 depend on the protein O-GlcNAcylation as the levels of FBXW10 mRNA and protein were reduced in GlcN-treated cell (Feng et al., 2013). Furthermore, O-GlcNA protein modification exerts function in many cellular processes such as cell cycle, insulin signaling, calcium handling as well as the cellular stress response (Zachara and Hart, 2006). This indicates that FBXW10 could be associated with regulation of cell cycle. On the other hand, FBXW12 is reported to be deleted or methylated in epithelial ovarian cancer (Chesnaye Ede et al., 2015). Interestingly, knockdown of *FBXW12* increases human epithelial cell growth and cell cycle progression (Franz et al., 2015), suggesting that FBXW12 is an epithelial growth suppressor probably by inhibiting cell cycle progression.

3. Roles of FBXL sub-family in cell cycle

The FBXL sub-family composes 22 members including FBXL1 (also known as Skp2) and FBXL2 to FBXL21. All of FBXL proteins contain an F-box motif and a C-terminal Leu-rich repeat (LRR) domain. The FBXL proteins have been characterized as cell cycle regulators in the control of cell cycle. In this section, we will describe the roles of FBXL proteins in governing cell cycle (Table 2).

3.1 FBXL1 (Skp2)

FBXL1, also called Skp2 (S-phase kinase-associated protein 2), is one of the well-characteristic F-box proteins (Chan et al., 2010). Some studies have demonstrated that Skp2 is a key cell cycle regulator through targeting multiple cell cycle related proteins such as p27, p21, p57, p130, Cyclin A, Cyclin E, Cyclin D1 and Cyclin G2. It has been reported that p27 is a primary target of Skp2 (Nakayama et al., 2001, Suzuki et al., 2012), and it is inversely related to Skp2 expression during the differentiation of human embryonic stem cells and in many human tumors (Dombrowski et al., 2013, Egozi et al., 2007, Kitagawa et al., 2009). The higher expression of Skp2 induces the degradation of p27 and promotes the entry of S phase from G phase, leading to induction of the immortalized cell proliferation (Carrano and Pagano, 2001). In mammalian cells, silencing *Skp2* induced the accumulation of Cyclin D and p21 (Bornstein et al., 2003, Nakayama et al., 2004, Yu et al., 1998). In some cancer cells, p57 (also name as KIP2) plays important roles in controlling cell cycle and is reported to be negatively correlated with Skp2 (Pateras et al., 2006, Yang et al., 2015). Moreover, p130, a member of the retinoblastoma family of pocket proteins, decreases sharply in the mid-G1 phase. This is due to its hyperphosphorylation on Serine 672 and degradation by Skp2, and subsequently promoting the cell into S phase (Bhattacharya et al., 2003, Tedesco et al., 2002).

Notably, Cyclin A can promote G1 entering into the S phase. Previous studies have shown that the kinase activity of Cdk2/Cyclin A was blocked by the p27, while Skp2 binds with Cyclin A and conceals the site targeted by p27, suggesting that Skp2 has a crucial role in cell cycle via regulation of Cyclin A (Ji et al., 2006, Michel and Xiong, 1998, Yam et al., 1999). In addition, Skp2 combines with the Cyclin E and mediates its degradation (Yeh et al., 2001). Interestingly, Cyclin E also involves in the degradation of p27 (Li et al., 2004, Ungermannova et al., 2005). Overexpression of Cyclin G2 inhibits cell proliferation and the normal amount of Cyclin G2 is controlled by Skp2 through promoting its degradation (Xu et al., 2008). Our previous study also demonstrated Skp2 expression reaches its summit during the entry to S phase from G1 when the protein levels of Cdh1 are low (Wei et al., 2004). Notably, Cdh1 can bind the N-terminal D-box motif of Skp2 and the deficiency or mutation of the motif leads to resistance of Skp2 to ubiquitination and degradation mediated by Cdh1 (Kurland and Tansey, 2004). Altogether, Skp2 is an essential regulator to control cell cycle progression and its own expression is also subjected to cell cycle dependent regulation to achieve timely entry into the S phase at optimized growth conditions.

3.2 FBXL2 and FBXL3

FBXL2 has a CAAX motif that targets it to cell membranes. Interestingly, one of identified substrates of FBXL2, p85-beta, is localized to cell membrane. FBXL2-mediated degradation of p85-beta is essential for the efficient response of quiescent cells to mitogens and their reentry into the cell cycle (Kuchay et al., 2013). Additionally, FBXL2 targets and degrades Cyclin D2 in leukemic and B-lymphoblastoid cell lines, leading to G0 phase arrest and apoptosis (Chen et al., 2012b). Depletion of endogenous *FBXL2* stabilizes Cyclin D2 levels, while overexpression of FBXL2 promotes Cyclin D2 degradation (Chen, Glasser, 2012b). Additionally, Cyclin D3 was identified as a substrate of FBXL2 as well (Chen et al., 2011a, 2012a). Moreover, degradation of Cyclin D3 inhibits lung cancer proliferation and cell cycle

arrest. This could be due to that ectopically expressed FBXL2 elicits G2/M-phase arrest and thus suppressed tumorigenesis (Chen, Glasser, 2011a, 2012a). Overexpression of FBXL2 also hinders tumor formation in athymic nude mice, implicating that FBXL2 could serve as a tumor suppressor in part via governing cell cycle in human cancer cells (Chen, Glasser, 2012a).

FBXL3 has been reported to regulate circadian clock by directly degrading CRY (cryptochrome) protein (Busino et al., 2007, Godinho et al., 2007, Siepka et al., 2007). In normal conditions, mammalian CRY interacts with Per (PERIOD) and together depresses their own genes expression, while FBXL3 negatively controls this loop by inducing the ubiquitination and degradation of CRY (Anand et al., 2013, Busino, Bassermann, 2007, Xing et al., 2013). Furthermore, FBXL3 interacts with the cofactor pocket, which is formed by both FAD (flavin adenine dinucleotide) and CRY, to insure the timely degradation process (Xing, Busino, 2013). Deletion of *FBXL3* results in the stabilization of CRY and thus inhibits the expression of CRY and Per proteins, and subsequently interferes the normal circadian clock (Siepka, Yoo, 2007). Furthermore, CRY1 is critical in formation of functional E3 complex (Yumimoto et al., 2013). However, it is required to investigate whether FBXL3 could regulate cell cycle via targeting CRY and Per proteins, which will reveal an intrinsic connection between circadian and cell cycle machineries.

3.3 FBXL4 and FBXL5

FBXL4 targets and degrades JMJD2A (Jumonji domain-containing 2A), which plays an essential role in cell cycle (Van Rechem et al., 2011). The overexpression of JMJD2A promotes the S phase and cancer cell proliferation, while depletion of *JMJD2A* suppresses cell growth in lung and bladder cancer cells (Kogure et al., 2013, Van Rechem, Black, 2011). JMJD2A attenuation affects cell cycle and tumourigenic inflammatory gene regulation in lipopolysaccharide syimulated neurodermal stem cells (Das et al., 2014), suggesting that FBXL4 could be involved in cell cycle through targeting JMJD2A.

Notably, FBXL5 is reported as a substrate of miR-290-295 (Lichner et al., 2011). Specially, miR-290-295 expresses specifically in mouse ESC (embryonic stem cells) and ECC (embryonic carcinoma cells). Overexpression of miR-290-295 promotes the entry of S phase from G1 phase, indicating that this cell cycle process may be controlled by the substrate of miR-290-295, FBXL5 (Lichner, Pall, 2011). Another independent study revealed that FBXL5 targets CITED2 (with Glu/Asp-Rich Carboxy-Terminal Domain, 2) for degradation to regulate the HIF-1α (hypoxia-inducible factor-1α) (Machado-Oliveira et al., 2015). Moreover, Snail 1 is validated as a substrate of FBXL5 and the degradation of Snail 1 leads to inhibition of metastasis in gastric cancer cells (Vinas-Castells et al., 2014, Wu et al., 2015). Additionally, the ubiquitination and degradation of cortactin by FBXL5 suppresses the migration and invasion of gastric cancer cells (Cen et al., 2014). One group reported that FBXL5 regulates the DNA damage response by targeting the hSSB1 (Human single-strand DNA binding proteins 1) (Chen et al., 2014). It is required to define mechanistically whether FBXL5 directly targets cell cycle regulatory proteins in the near future.

3.4 FBXL7 and FBXL10

FBXL7 exerts a critical role in mitotic process through targeting Aurora A and thus disturbing spindle formation and cell proliferation (Coon et al., 2012). Consistently, the deregulation of FBXL7 results in G2/M arrest, and subsequently leads to mitotic arrest (Coon, Glasser, 2012). FBXL10, also named as JHDM1B or Kdm2b, which is an H3K36 demethylase, regulates cell proliferation and senescence by regulating p15 (He et al., 2008). Depletion of *FBXL10* induces the expression of let-7 and miR-101 and inhibits their target EZH2 (zester homolog 2). On the other hands, overexpression of FBXL10 inhibits the let-7 and miR-101 and subsequently promotes the level of EZH2, leading to increased immortal cells, suggesting that the FBXL10-let-7-EZH2 pathway plays an important role in cell cycle and cell progression (Tzatsos et al., 2011). In NPC (nasopharyngeal carcinoma), FBXL10 promotes cell progression in part by controlling the PI3K/mTOR pathway (Ren et al., 2015). Moreover, loss of *FBXL10* induces the genomic DNA hyper-methylation (Boulard et al., 2015). As a nucleolar protein, FBXL10 represses transcription of ribosomal RNA genes and involves in cancer development (Frescas et al., 2007). Furthermore, FBXL10 captures PRC1 (polycomb repressive complex 1) to CpG islands and regulates H2A ubiquitination (Wu et al., 2013). In pancreatic cancer, FBXL10 promotes tumorigenesis by Polycomb-dependent and independent transcriptional programs (Tzatsos et al., 2013). Taken together, FBXL10 plays a central role in cell progression and involves in cancer development, but further studies are warranted to fully understand its physiological contribution to this process.

3.5 FBXL11 and FBXL12

FBXL11 as a histone demethylase, also known as Kdm2a, plays a role in cell proliferation, apoptosis and senescence (Ishimura et al., 2012, Kawakami et al., 2015). *FBXL11* KO mice exhibit embryonic lethality with growth defects. Cells without *FBXL11* decrease proliferation and promote apoptosis. Moreover, knockout of *FBXL11* depresses the level of EZH2, the ubiquitination of H2A and upregulates of p21 (Kawakami, Tokunaga, 2015). Thus, FBXL11 is important in cell cycle regulation. Additionally, overexpression of FBXL11 inhibits activity of NF-κB, while knockdown of FBXL11 promotes NF-κB binding DNA and activates its gene expression (Lu et al., 2009).

The mechanism of regulating NF-κB may be due to the reversible lysine methylation of p65 (Lu et al., 2010). In NSCLC, FBXL11 promotes lung tumorigenesis by epigenetically enhancing ERK1/2 signaling (Wagner et al., 2013). Additionally, transcriptional repression of histone deacetylase 3 by FBXL11 is coupled to tumorigenicity of lung cancer cells (Dhar et al., 2014). On the other hand, FBXL12 targets and degrades CaMK1 (calmodulin kinase 1) to induce G1 arrest (Mallampalli et al., 2013). Interestingly, one group independently showed that FBXL12 has a novel function in regulating the DNA damage by inducing Ku80 ubiquitination (Postow and Funabiki, 2013). Taken together, FBXL12 may be considered as a cell cycle regulator but its role in tumorigenesis warrants further investigation.

3.6 other FBXL proteins

FBXL15 interacts with the Smurf1 (Smad ubiquitination regulatory factor 1) E3 ubiquitin ligase and directly degrades Smurfe (Cui et al., 2011, Fei et al., 2014). Notably, the C2 domain of Smurf1 performs a critical role in targeting Axin for ubiquitination. The

interaction between Smurf1 and Axin locates Smurf1 to membrane and decreases the process of G2/M phase of cell cycle, and this state promotes the response to Wnt stimulation (Fei, He, 2014). The degradation of Smurf1 mediated by FBXL15 also involves the BMP (bone morphogenetic protein) signaling pathway during embryonic development and adult bone formation (Cui, He, 2011).

Notably, FBXL18 could bind Lys 109 site of FBXL7 and then ubiquitinate and degrade FBXL7, indicating that FBXL18 regulates cell cycle possibly by controlling the level of FBXL7 (Liu et al., 2015). On the other hand, FBXL20, known as SCRAPPER, has been reported to involve in tumorigenesis (Yao et al., 2007). Depletion of *FBXL20* causes inhibition of cell proliferation, G1 cell cycle arrest and induction of apoptosis in colorectal adenocarcinoma cells (Zhu et al., 2012). Furthermore, overexpression of FBXL20 increases cell viability and invasion capacity in colon cancer cells, accompanied by the upregulation of β-catenin and c-Myc, and downregulation of E-cadherin (Zhu et al., 2014). Therefore, FBXL20 plays a critical role in colon cancer development and cell cycle. Notably, FBXL21 interacts with CRY and to promote its degradation (Hirano et al., 2013, Yoo et al., 2013). Since FBXL3 could lengthen and FBXL21 shorten circadian period (Yoo, Mohawk, 2013), FBXL21 could antagonize the function of FBXL3 and their combined actions ensure the stable oscillation of the circadian clock (Hirano, Yumimoto, 2013), but additional studies are required to understand the physiological role and their functional interplay between FBXL3 and FBXL21 in both cell cycle regulation and tumorigenesis.

4. Roles of FBXO sub-family in cell cycle

Except for FBXW sub-family and the FBXL sub-family, the last 36 F-box proteins are defined as F-box only (FBXO) proteins. FBXO sub-family proteins contain the F-box motif in its N-terminus and multiple types of functional domains in its C-terminus. Different from the FBXW with the WD40 motif and FBXL proteins with the LRR motif, the FBXO sub-family contains 21 functional homology domains. The function of FBXO subfamily proteins is not fully characterized and we will focus on the role of FBXO subfamily in cell cycle in the following paragraphs (Table 3).

4.1 FBXO1

FBXO1 (also known as FBX1 or Cyclin F), which localizes to both the centrosome and nucleus, is believed as a novel mammalian cyclin because its amino acid sequences are much similar to Cyclin A. The amount of FBXO1 accumulates in the S phase and summits in G2 and finally disappears in mitosis (Bai et al., 1994, Fung et al., 2002). FBXO1 has a critical function in cell cycle while the mechanism is still unclear. It has been believed that FBXO1 binds Cyclin B and transports it into the nucleus, leading to governing Cyclin B/Cdk1 localization and functions during mitosis (Fung, Siu, 2002, Kong et al., 2000). Moreover, FBXO1 targets CP110 protein for degradation, which is essential in centrosome duplication, subsequently regulates the fidelity of mitosis and genome integrity (D'Angiolella et al., 2010). RRM2 is identified as a degraded substrate of FBXO1. The decrease of RRM2 controls the amount of dNTP pools and genome stability, and thus provides the DNA repair from genotoxic stress (D'Angiolella et al., 2012). Furthermore, FBXO1 targets NUSAP1 during the S and G2 phases in cell cycle, leading to sensitizing

cells to microtubule-based chemotherapeutics (Emanuele et al., 2011). Notably, deletion of *FBXO1* results in cell cycle doubling time and delays cell cycle reentry from quiescence (Tetzlaff et al., 2004). In support of this, MEFs without *FBXO1* displays cell cycle defects, suggesting that FBXO1 is critical in cell cycle progression (Tetzlaff, Bai, 2004).

4.2 FBXO3 and FBXO4

FBXO3 targets and degrades Smurf1 to regulate cell cycle (Li et al., 2015). Unlike FBXL15, FBXO3 targets all the Nedd4 family and controls their stability (Li, Xie, 2015). On the other hand, FBXO4 (also known as FBX4) binds chaperone αβ-crystallin to form an active SCF E3 ubiquitin ligase. The SCF FBXO4-aβ-crystallin complex mediates the ubiquitination of Cyclin D1 in cytoplasm. Mutation or deletion of *FBXO4* attenuates degradation of Cyclin D1 and leads to Cyclin D1 accumulation and promotion of cell cycle progression (Barbash et al., 2008, Lin et al., 2006). Moreover, control of FBXO4 activity attenuates the degradation of Cyclin D1 and oncogenic transformation. Mutation of FBXO4 inhibits dimerization of SCF (FBXO4) ligase and leads to tumorigenesis (Barbash, Zamfirova, 2008). However, there are no changes in genetic analysis or protein level of Cyclin D1 in *Fbxo4*$^{-/-}$ mice, suggesting that the regulatory of FBXO4 may be compensated by others proteins (Kanie, Onoyama, 2012).

4.3 FBXO5 and FBXO6

FBXO5, also named as EMI1 and FBX5, is an endogenous inhibitor of APC/C. FBXO5 could play an oncogenic role in human cancers. For instance, the high expression of FBXO5 contributes to increased proliferation, tetraploidy and instability of *p53*-deficient cells, indicating that loss of *p53* may contribute to tumorigenesis together with FBXO5 (Lehman et al., 2006). Additionally, FBXO5 has been reported to promote the entry of S phase and mitosis by controlling the Cyclin A, Cyclin B or securin (Hsu et al., 2002). Interestingly, the stability of FBXO5 is promoted by BCR-ABL fusion oncoprotein, and inhibits SKP2 degradation, subsequently increases cell proliferation in chronic myeloid leukaemia cells (Chen et al., 2011b). Notably, FBXO6 binds the carboxyl terminus of Chk1, which plays a key role in replication checkpoint with ATR, and then degrades Chk1 (Zhang et al., 2009). The protein levels of FBXO6 and Chk1 are negatively correlated in both cultured cancer cells and human breast tumor tissues. Conclusively, FBXO6-dependent Chk1 degradation leads to S phase checkpoint arrest and cell cycle defection (Zhang, Brognard, 2009), but their physiological role in cell cycle regulation warrants further in-depth studies.

4.4 FBXO7

FBXO7 have a C-terminal specific proline-rich region (PRR) that binds various substrates (Chang et al., 2006, Hsu et al., 2004). Multiple reports showed FBXO7 function in a tissue-specific manner (Hsu, Lee, 2004, Laman et al., 2005, Lomonosov et al., 2011, Meziane el et al., 2011). FBXO7 was defined as a putative proto-oncogene and directly bound to the Cyclin D/Cdk6/p27 complex in immortalized fibroblasts. The binding activates Cdk6 and promotes the cell cycle progression and tumorigenesis (Laman, Funes, 2005). Conversely, reduction of FBXO7 promotes cell progression, decreases cell size and shortens G1 phase due to enhanced Cyclins in S phase and CDK2 activity (Meziane el, Randle, 2011). Notably,

FBXO7 targets HURP (hepatoma upregulated protein), a cell cycle regulated oncogene, and controls cell growth in human liver cancer (Hsu, Lee, 2004). Moreover, one independent study revealed that depletion of *FBXO7* promotes cell proliferation by shortening G1 phase (Meziane el, Randle, 2011). Altogether, FBXO7 may be a tumor suppressor through regulation of cell cycle in human cancer, but its physiological contribution to this process awaits further investigation.

4.5 FBXO11, FBXO18, FBXO21 and FBXO22

The CRL4 (Cdt2) E3 ubiquitin ligase controls the cell cycle progression by regulating Cdt1, p21 and Set8 during S phase (Abbas et al., 2013a, Abbas et al., 2013b, Rossi et al., 2013). Importantly, Cdt2 is polyubiquitylated and degraded by FBXO11, and decrease of Cdt2 stabilizes cell cycle regulators including Cdt1, p21 and Set8. The stability of Set8 regulates cell response to TGF-β exiting from the cell cycle and cellular migration (Abbas, Keaton, 2013a). This cross-regulation between specific Cullin 4 and Cullin 1 E3 ubiquitin ligase may play a critical role in cell cycle regulation (Abbas, Mueller, 2013b). Notably, FBXO11 targets BCL6, a repressor of the cell cycle regulator p53, for degradation (Duan et al., 2012). FBXL11 is inactivated in diffuse large B-cell lymphomas, indicating that *FBXO11* is a haplo-insufficient tumor suppressor gene (Duan, Cermak, 2012). Furthermore, FBXO11 promotes the neddylation of p53 both *in vivo* and *in vitro* and thus inhibits its function of transcription (Abida et al., 2007).

In addition, upon DNA replication stress, FBXO18 (FBHI) promotes double-strand breakage, leading to activation of the DNA-PK and ATM signaling cascades and apoptosis (Jeong et al., 2013). On the other hand, FBXO21 targets EID1 (EP300-interacting inhibitor of differentiation 1) for degradation in G0 phase cells. The peptidic degron of EID1 is a binding site of FBXO21 and the polyubiquitylation is required in both cycling and quiescent cells (Zhang et al., 2015). FBXO21 may regulate cell cycle in part by mediating the protein level of EID1. Moreover, KDM4A is regulated by FBXO22 since overexpression or knockdown of FBXO22 decreases or increases the protein level of KDM4A, which oscillates the cell cycle progression (Tan et al., 2011).

4.6 FBXO31

FBXO31 is a senescence-related gene that located in the chromosome 16q24.3 (Kumar et al., 2005). FBXO31 targets and degrades Cyclin D1 that plays a critical role in G1/S entry. Overexpression of FBXO31 leads to low level of Cyclin D1 and subsequently causes G1 arrest in cell cycle (Santra et al., 2009). This happens specifically after DNA damage, but FBXO31 may not degrade Cyclin D1 in normal cell cycle progression (Kanie, Onoyama, 2012). Moreover, FBXO31 is identified as a tumor suppressor in breast, ovarian, hepatocellular and prostate cancers (Johansson et al., 2014, Kumar, Neilsen, 2005). Consistently, FBXO31 targets Cdt1 for degradation in G2 phase of cell cycle to prevent re-replication and tumorigenesis (Johansson, Jeffery, 2014). Notably, MDM2, a negative regulator of p53, has been identified as a substrate of FBXO31. In this context, FBXO31 promotes cell growth arrest by degrades MDM2 in genotoxic stress (Malonia et al., 2015). In gastric cancer cells, FBXO31 is negatively regulated by miR-17 and miR-20a (Zhang et al., 2014). The depression of FBXO31 promotes the expression of Cyclin D1 and decreases

G1 phase (Zhang, Kong, 2014). Taken together, FBXO31 may act as a tumor suppressor by regulating cell cycle progression, but its downstream effect pathway as well as its own regulation in cell cycle progress and tumorigenesis awaits further investigation.

4.7 FBXO44 and FBXO45

BRCA1 is associated in sporadic cancer cases and plays a role in cell cycle checkpoint and DNA repair. The N terminus of BRCA1 has a binding site of FBXO44, and FBXO44 targets BRCA1 for degradation and regulates cell cycle in sporadic breast cancer (Lu et al., 2012). On the other hand, FBXO45 has been found to play a role in neural development and tumorigenesis (Peschiaroli et al., 2009, Saiga et al., 2009, Wang and Wei, 2014). To this end, previous studies have shown that FBXO45 is an estrogen-induced gene that contains estrogen receptor-binding sequences (Han et al., 2016, Yoshida, 2005). Further study suggests that Era could be a substrate of FBXO45 (Han, Begum, 2016). Par-4 (prostate apoptosis response protein 4), a novel specific substrate of FBXO45, is a tumor suppressor by inducing cancer cells apoptosis (Wang and Wei, 2014). Moreover, FBXO45 ubiquitylates and degrades p73, which is a member of p53 family that responses to DNA damage by mediating cell cycle arrest and apoptosis.(Peschiaroli, Scialpi, 2009). Taken together, FBXO45 may control cell cycle by regulating its substrates such as p73 and Par-4, but its physiological role in cell cycle and tumorigenesis warrant further in-depth studies.

5. Conclusions

In conclusion, F-box proteins exert their function in cell cycle regulation mainly via targeting the various cell cycle regulatory substrates. Since most studies focus on the role of Fbw7, Skp2, and β-TRCP among the identified 69 F-box proteins in cell cycle and tumorigenesis, the remaining members are required to elucidate their biological functions by genetic, biochemical, and cell biological approaches. Due to the fact that dysregulation of cell cycle contributes to tumorigenesis, comprehensively understanding of cellular functions for all 69 F-box proteins could be helpful for finding a novel strategy via targeting F-box proteins for the treatment of human cancers. It is known that F-box proteins play an oncogenic or tumor suppressive role in context-dependent manner. Therefore, we need develop the inhibitors of oncogenic F-box proteins to suppress their expression. As many F-box proteins such as FBXW7 act as tumor suppressors, discovering inhibitors for upstream regulatory proteins to activate them, or inhibiting their downstream oncoprotein targets would be viable therapeutic approaches (Skaar et al., 2014). Without a doubt, it is essential to design personalized medicine targeting the individual dysregulated F-box protein. To this end, in-depth investigation of functions of F-box proteins will elucidate their role in cell cycle and develop novel strategies for the treatment and prevention of human cancers.

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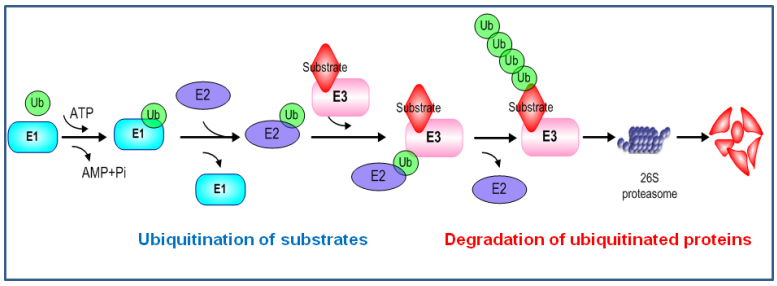

Figure 1.

A schematic illustration of the E1-E2-E3 cascade-mediated ubiquitin transfer process to a given ubiquitin substrate.

Table 1

A list of reported representative substrates of FBXW sub-family proteins in cell cycle regulation.

Substrates	F-box	Functions	References
Emi1	β-TRCP	Inhibitor of APC/C, Cell cycle	(Guardavaccaro, Kudo, 2003, Margottin-Goguet, Hsu, 2003)
Cdc25A	β-TRCP	Protein phosphatase, Cell cycle	(Busino, Donzelli, 2003, Jin, Shirogane, 2003)
Cdc25B	β-TRCP	Protein phosphatase, Cell cycle	(Kanemori, Uto, 2005, Uchida, Watanabe, 2011)
Wee1A	β-TRCP	Protein kinase, Cell cycle	(Watanabe, Arai, 2004)
Cyclin D1	β-TRCP	Cyclin, Cell cycle	(Seki, Coppinger, 2008, Wei, Yang, 2008)
BTG	β-TRCP	Transcription factor, Cell cycle	(Sasajima, Nakagawa, 2012)
Plk4	β-TRCP	Protein kinase, Centrosome duplication	(Cunha-Ferreira, Rodrigues-Martins, 2009, Guderian, Westendorf, 2010)
CEP68	β-TRCP	Centrosome separation	(Pagan, Marzio, 2015)
Bora	β-TRCP	Aurora A kinase activator, Cell cycle	(Seki, Coppinger, 2008)
Securin	β-TRCP	Regulatory protein, Cell cycle	(Limon-Mortes, Mora-Santos, 2008)
REST	β-TRCP	Spindle assembly checkpoint	(Guardavaccaro, Frescas, 2008)
Claspin	β-TRCP	DNA replication checkpoint	(Peschiaroli, Dorrello, 2006)
hGCMa	FBXW2	Transcription factor, Cell cycle	(Yang, Yu, 2005) (Zhuang, Li, 2014)
COP9	FBXW4	Cell growth, Cell cycle	(Lockwood, Chandel, 2013)
Eps8	FBXW5	Mitosis, Cell cycle	(Werner, Disanza, 2013)
DLC1	FBXW5	Tumor suppressor, Cell growth	(Jiang, Li, 2015, Kim, Jackson, 2013)
HsSAS-6	FBXW5	Centrosome duplication, Cell cycle	(Hu, Zacharek, 2008, Pagan and Pagano, 2011, Puklowski, Homsi, 2011)
Cyclin E	FBXW7	Protein kinase, Cell cycle	(Perciavalle and Opferman, 2013, Siu, Rosner, 2012, Spruck, Won, 1999)
Aurora A/B	FBXW7	Mitosis, Cell cycle	(Kwon, Kim, 2012, Slattery, Moore, 2008, Teng, Hsieh, 2012)
Cyclin D1	FBXW8	Cell growth, Cell cycle	(Okabe, Lee, 2006)
HPK1	FBXW8	Cell growth, Cell cycle	(Wang, Chen, 2014a)

Table 2

A list of reported representative substrates of FBXL sub-family proteins in cell cycle regulation.

Substrates	F-box	Functions	References
P27	FBXL1	Cdk inhibitor, Cell cycle	(Nakayama, Hatakeyama, 2001, Suzuki, Fukasawa, 2012)
P21	FBXL1	Cdk inhibitor, Cell cycle	(Bornstein, Bloom, 2003, Nakayama, Nagahama, 2004, Yu, Gervais, 1998)
Cyclin D1	FBXL1	Cyclin, Cell cycle	(Nakayama, Nagahama, 2004, Yu, Gervais, 1998)
P57	FBXL1	Cdk inhibitor, Cell cycle	(Pateras, Apostolopoulou, 2006, Yang, Nan, 2015)
P130	FBXL1	Rb protein family, Cell cycle	(Bhattacharya, Garriga, 2003, Tedesco, Lukas, 2002)
Cyclin A	FBXL1	Cyclin, Cell cycle	(Ji, Goldin, 2006, Michel and Xiong, 1998, Yam, Ng, 1999)
Cyclin E	FBXL1	Cyclin, Cell cycle	(Li, Li, 2004, Ungermannova, Gao, 2005)
Cyclin G2	FBXL1	Cyclin, Cell cycle	(Xu, Bernaudo, 2008)
Cdh1	FBXL1	DNA replication factor, Cell cycle	(Kurland and Tansey, 2004)
Cyclin D2	FBXL2	Cyclin, Cell cycle	(Chen, Glasser, 2012b)
Cyclin D3	FBXL2	Cyclin, Cell cycle	(Chen, Glasser, 2011a, 2012a)
P85beta	FBXL2	Cell cycle	(Kuchay, Duan, 2013)
CRY	FBXL3 FBXL21	Circadian clock, Cell cycle	(Busino, Bassermann, 2007, Godinho, Maywood, 2007, Siepka, Yoo, 2007) (Hirano, Yumimoto, 2013, Yoo, Mohawk, 2013)
JMJD2A	FBXL4	Cell cycle	(Das, Chai, 2014)
CITED2	FBXL5	Cell cycle	(Machado-Oliveira, Guerreiro, 2015)
Aurora A	FBXL7	Mitosis, Cell cycle	(Coon, Glasser, 2012)
EZH2	FBXL10 FBXL11	Cell cycle	(Kawakami, Tokunaga, 2015, Tzatsos, Paskaleva, 2011)
CaMK1	FBXL12	Cell cycle	(Mallampalli, Kaercher, 2013)
Smurf1	FBXL15	Cell cycle	(Fei, He, 2014)

Table 3

A list of reported representative substrates of FBXO sub-family prorteins in cell cycle.

Substrates	F-box	Functions	References
Cyclin B	FBXO1	Cyclin, Cell cycle	(Fung, Siu, 2002, Kong, Barnes, 2000)
CP110	FBXO1	Centrosome duplication, Cell cycle	(D'Angiolella, Donato, 2010)
RRM2	FBXO1	DNA repair, Cell cycle	(D'Angiolella, Donato, 2012)
NUSAP1	FBXO1	Microtubule, Cell cycle	(Emanuele, Elia, 2011)
Smurf1	FBXO3	Cell cycle	(Li, Xie, 2015)
Cyclin D1	FBXO4	Cyclin, Cell cycle	(Barbash, Zamfirova, 2008, Lin, Barbash, 2006, Santra, Wajapeyee, 2009)
P53	FBXO5, FBXO11	Tumor suppressor, Cell cycle	(Lehman, Verschuren, 2006)
Chk1	FBXO6	Replication checkpoint, Cell cycle	(Zhang, Brognard, 2009)
Cyclin D/Cdk6/p27	FBXO7	Cyclin, Cell cycle	(Laman, Funes, 2005)
HURP	FBXO7	Oncogene, Cell cycle	(Hsu, Lee, 2004)
Cdt2	FBXO11	Cell cycle	(Abbas, Keaton, 2013a)
Bcl6	FBXO11	Cell cycle	(Duan, Cermak, 2012)
EID1	FBXO21	Cell cycle	(Zhang, Li, 2015)
KDM4A	FBXO22	Cell cycle	(Tan, Lim, 2011)
Cdt1	FBXO11, FBXO31	Cell cycle	(Johansson, Jeffery, 2014)
MDM2	FBXO31	Cell cycle	(Malonia, Dutta, 2015)
BRCA1	FBXO44	DNA repair, Cell cycle	(Lu, Li, 2012)
Par-4	FBXO45	Apoptosis, Cell cycle	(Wang and Wei, 2014)
P73	FBXO45	Tumor suppressor, Cell cycle	(Peschiaroli, Scialpi, 2009)