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Chapter

Regulation of Selective Proteolysis in Cancer

Pai-Sheng Chen

Abstract

Proteins are the fundamental building blocks of cells for diverse cellular and physiological functions. The dynamic equilibrium of protein turnover is balanced by protein synthesis and proteolysis. The newly synthesized proteins undergo proper folding into the three-dimensional conformations for executing biological functions and constructing cellular components like organelles. On the other hand, ubiquitin-proteasome system (UPS) and lysosome are two major proteolytic systems by which the unneeded, misfolded, or damaged proteins are selectively sent for clearance to maintain the quality and quantity of cellular proteins. Loss of the ability to maintain cellular proteolysis in control has been known to contribute as disease-causing factors. In this chapter, the function, regulation, and pathological roles of dysregulated proteolysis will be described in a concise view, focusing on the link between cancer and UPS.

Keywords: ubiquitin-proteasome system, proteolysis, cancer

1. Introduction

Protein ubiquitination is a multistep process. It is initiated by an ATP-required activation and covalent binding of E1 ubiquitin-activating enzyme (E1) with ubiquitin [1]. The E1 then passes the ubiquitin to E2 ubiquitin-conjugating enzyme (E2) followed by forming complex with the E3 ubiquitin ligase (E3), which specifically recognizes substrate protein and catalyzes the ubiquitin transfer. Theoretically, E3s can function as oncogenes or tumor suppressors depending on the specificities on substrate proteins they targeted in cancer (**Figure 1**). For instance, MDM2 is oncogenic since it is the E3 for tumor-suppressive p53, while von Hippel–Lindau (VHL) disease tumor suppressor is tumor suppressive since it is the E3 for oncogenic HIF-1alpha (HIF-1α). However, alternative functions of E3 are also observed since multiple targets with diverse roles may be regulated by a common E3. Here, the selective ubiquitin-proteasome system (UPS) for p53, HIF-1α, and other cancer-related proteins are exemplified.

Modification of substrate proteins by ubiquitination is the major way for selective proteolysis by proteasome. Ubiquitination is a reversible process controlled by the balance of ubiquitination and deubiquitination systems. This balance of ubiquitination is regulated by E3 ubiquitin ligases (E3s) [2] and deubiquitylating enzymes (DUBs) [3]. In addition to UPS-mediated protein degradation, ubiquitination is also involved in diverse non-proteolytic molecular and cellular functions, such as protein trafficking, activation, DNA repair, and apoptosis [4]. For example, K63-linked chains regulate DNA repair and NF-κB activation [5–7]. The TNF-α

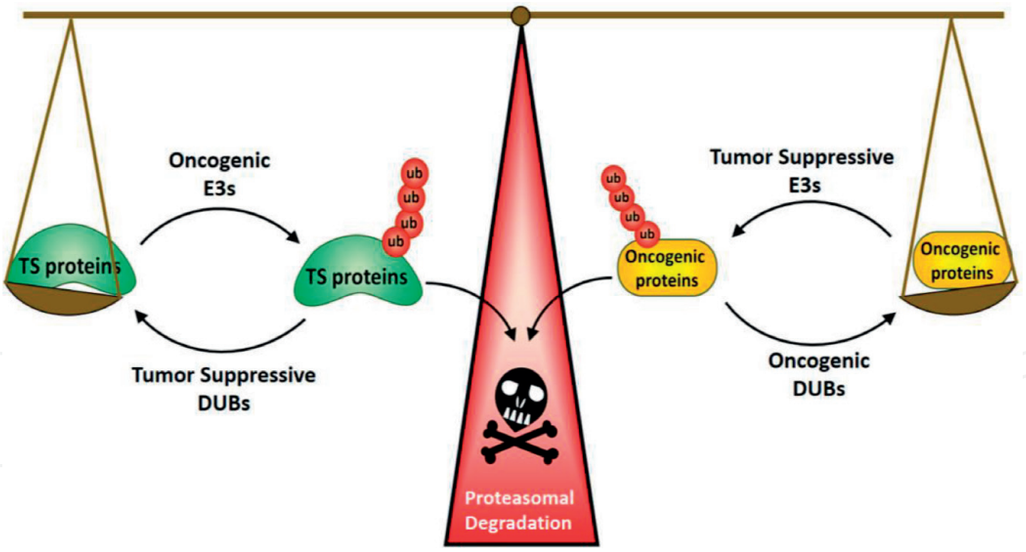

Figure 1.
Roles of E3s and DUBs in cancer.

receptor–associated factor 6 (TRAF6) mediated K63-linked polyubiquitination of NF-κB essential modulator (NEMO) for IκB kinase (IKK) activation [8]. These studies indicate the versatile function of ubiquitination machinery. In this section, we focus on the role of ubiquitination in proteasomal degradation. There are seven lysine residues at positions 6, 11, 27, 29, 33, 48, and 63 of ubiquitin, which are utilized for polyubiquitination. These lysine residues serve as acceptors for other ubiquitins. Different types (mono, multi, poly) and links (K6, K11, K27, K29, K33, K48, K63) of ubiquitination determine the fate of tagged substrates [9–11]. For proteasome degradation, K48- and K11-linked polyubiquitination is the canonical signal that tags substrate proteins [12–16]. Recent studies showed that branched K48- and K11-linked chains enhanced proteasomal degradation, whereas homotypic K11 linkages prevent substrate protein recognition by proteasome [17]. K29-linked polyubiquitin is the most abundant atypical linkage in mammalian cells [18]. But little is known about its cellular function. The use of K29-linked chains as a degradation signal is also unclear as these chains may accumulate as a consequence of proteosomal stress induced by proteasome inhibition rather than via the accumulation of K29-linkage-modified proteasome substrates. The K63 linkage, while it can be recognized by the proteasome [19], is widely regarded as a non-degradative signaling modification that is known to regulate signal transduction and endocytosis [20, 21]. In addition, efficient proteasome activity has also been found to rely on the presence of K6-linked ubiquitination [22].

2. UPS-mediated proteolysis in cancer

2.1 Regulatory network for p53 degradation

Tumor protein p53 is a well-known tumor suppressor [23]. As a guardian of genome, p53 can sense DNA damages, activate repair systems, pause cell growth, or initiate apoptosis when necessary [23]. These functions establish a cellular protective machinery, thus loss of expression or tumor-suppressive activities of p53 are observed as a hallmark in cancer. Deregulation of p53 is orchestrated by multiple pathways, such as gene mutation and enhanced proteasomal degradation. As an E3 for p53, overexpression of MDM2 in human cancers has been linked

to p53 degradation and tumorigenesis [24]. The transactivation domain of p53 is recognized by MDM2 and followed by MDM2-dependent ubiquitination and further proteasome degradation [25]. ATM serine/threonine kinase (ATM) is a DNA damage sensor participating in multiple mechanisms for p53 regulation. ATM-mediated phosphorylation of p53 at Ser15 is induced by genotoxic stress and therefore causes its escape from MDM recognition to further trigger cells to initiate DNA repair system through p53 [26–28]. Also, the MDM2-mediated p53 degradation is diminished when ATM-mediated MDM2 phosphorylation is induced by DNA damage [29]. Moreover, there is a negative feedback loop in which p53 activates the transcription of MDM2 [30]. Several inhibitors, such as Nutlin-3 and RG7112, were developed to disrupt the interaction between p53 and MDM2 and are currently undergoing clinical trials [31]. On the other hand, herpesvirus-associated ubiquitin-specific protease (HAUSP) is a deubiquitinase for p53. It removes ubiquitination and stabilizes p53 even in the presence of MDM2 [32]. Moreover, MDM2 is also stabilized by HAUSP through a p53-independent pathway [33, 34], suggesting a feedback regulatory loop between p53 and MDM2. The ATM-mediated phosphorylation, nuclear translocation, and stabilization of USP10 synergistically help nuclear HASUP stabilize p53 in the presence of DNA damage [35]. In addition, the constitutive photomorphogenesis protein 1 (COP1) forms an E3 ubiquitin ligase complex with cullin 4 (CUL4), DNA damage-binding protein 1 (DDB1), de-etiolated 1 (DET1), and ring-box 1 (RBX1) to target p53 [36]. Under genotoxic stress, ATM phosphorylates COP1 at Ser387 for degradation and subsequent p53 induction. Since p53 is targeted by COP1 for proteasomal degradation, downregulation or inactivation of COP1 subsequently activates p53 in cancer. Like MDM2, a transcriptional activation of COP1 by p53 forms a negative feedback loop [37]. Overexpression of COP1 is correlated with reduced p53 and has been observed in ovarian, breast, and liver cancers. P53-induced RING-H2 (Pirh2, also known as RCHY1) is another E3 ubiquitin ligase belonging to the RING finger family. Like MDM2, Pirh2 is considered as an oncogene to facilitate p53 protein degradation by UPS through a MDM2-independent manner [38, 39]. Notably, similar to the p53-MDM2 and p53-COP1 feedback loop, Pirh2 is also upregulated transcriptionally by p53. Interestingly, several researches suggested that Pirh2, but not MDM2, plays a major role in DNA damage-induced p53 degradation [38]. Moreover, in contrast to MDM2, Pirh2 can still recognize the p53 with Ser15 phosphorylation for UPS [40]. Elevated Pirh2 level has been found in human cancers and is correlated with unfavorable prognosis of cancer patients [41, 42]. The regulatory network for p53 degradation is illustrated in **Figure 2**.

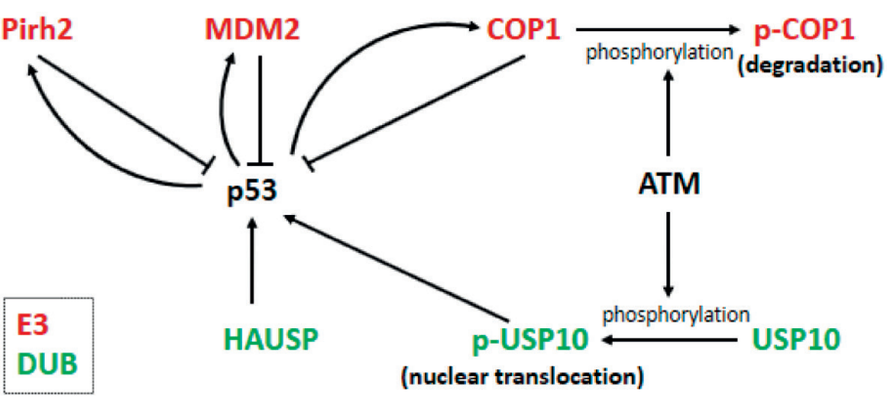

Figure 2.
Regulatory network for p53 degradation.

2.2 Ubiquitination system of HIF-1α

During tumorigenesis, the increased tumor mass leads to the reduction of available intratumoral oxygen, which is theoretically a survival stress to normal cells. However, cancer cells develop several mechanisms to face this stressful condition, such as the activation of hypoxia-inducible factor 1α (HIF-1α). Through transcriptional regulation of downstream genes, accumulation of HIF-1α is not only observed on facilitating angiogenesis at the initiation of rapid tumor growth (also called angiogenic switch) but also enhances metastasis and malignant progression of cancer [43]. Expression of HIF-1α is tightly controlled by ubiquitination in coordination with hypoxia (**Figure 3**). Inactivation of Von Hippel-Lindau (VHL) in familial kidney cancer syndrome contributes to oncogenic effects [44]. At the molecular level, VHL interacts with cullin 2, elongin B, elongin C, and Rbx [45–48]. This complex then targets HIF-1α for ubiquitination and proteasomal degradation [48, 49]. Under normoxia, prolyl hydroxylase (PHD) hydroxylates HIF-1α and facilitates its binding through N-TAD domain with VHL complex, leading to sustained ubiquitination and subsequent degradation of HIF-1α. The PHD-mediated post-translational modification (PTM) is abolished when cells encounter hypoxia during tumor growth. The stabilized HIF-1α is then accumulated in cancer cells and translocated to nucleus in complex with HIF-1β and other cofactors, resulting in transcriptional activation of downstream genes [50]. The transactivation activity of HIF-1α is also regulated by factor inhibiting HIF-1 (FIH-1). Through interaction with the ID and C-TAD domains, FIH-1 represses HIF-1α-mediated transactivation in association with histone deacetylase [51]. The HIF-1α-independent functions of VHL have also been pointed out. Besides HIF-1α, growing evidence has identified several targets of VHL with oncogenic properties in cancer [52]. It is well known that both downregulation of VHL and accumulation of HIF-1α are associated with cancer progression [53]. In addition to VHL, the chaperone-dependent E3 carboxy

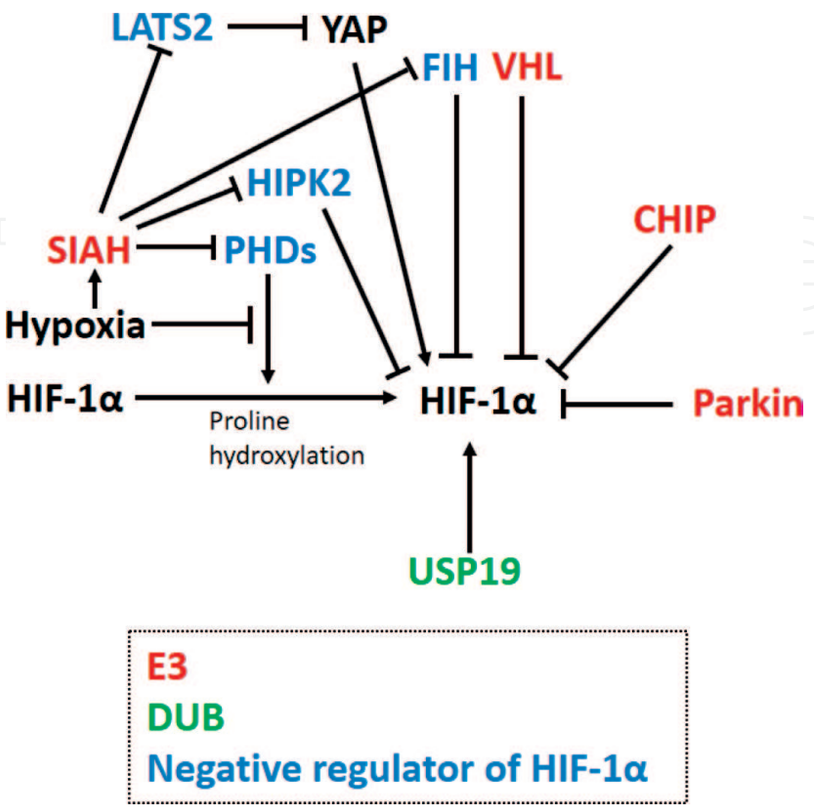

Figure 3.
Regulation of HIF-1α ubiquitination.

terminus of Hsp70-interacting protein (CHIP) is also identified to ubiquitinate HIF-1α for protein degradation [54]. Cellular response to hypoxia is also modulated by the E3s seven in absentia homolog (Siah) family proteins [55]. As another layer for HIF-1α regulation, Siah proteins are accumulated by transcriptional regulation and post-translational modification (PTM) under hypoxia [55]. The increased Siah proteins subsequently activate the degradation of PHDs and factors inhibiting HIF-1 (FIH) reduce prolyl hydroxylation of HIF-1α and consequently prevent VHL-mediated degradation [51, 55]. In addition to this regulation, there are several mechanisms known to cooperatively activate HIF-1α. For example, HIF-1α is stabilized when its ubiquitination is removed by ubiquitin-specific protease-19 (USP19) [56]. Siah proteins ubiquitinate the HIF-1α inhibitor, homeodomain-interacting protein kinase 2 (HIPK2), for degradation and thus enhance HIF-1α activity [57]. Siah2 also enhances the ubiquitination and degradation of large tumor suppressor kinase 2 (LATS2) resulting in suppressed HIPPO pathway and activated Yes-associated protein 1 (YAP1) that subsequently stabilizes HIF-1α [58]. Parkin is a recently-identified E3 for HIF-1α [59]. It facilitates HIF-1α polyubiquitination at K477 for proteasomal degradation through the interaction with HIF-1α. Alternatively, under the stimulations by hypoxia or growth factors, the induced HIF-1α brings Parkin and Dicer together, following by ubiquitination and autophagic degradation of Dicer, and eventually enhances cancer metastasis [60]. The findings exemplify the dual role of E3, which in this case, the target substrate (HIF-1α or Dicer) determines the fate of cellular function (**Figure 4**).

2.3 Cellular signaling regulated by UPS

Networks of signaling pathways coordinately orchestrate the cellular functions. Dysregulation of signal transduction pathways, especially those controlling oncogenic behaviors, is tightly regulated and also controlled by UPS. E3s play as modulators through regulating the proteolysis of key proteins in signaling networks. Several E3s can mediate substrate degradation to modulate PI3K/Akt/mTOR and RAS/MAPK, which are two central pathways, coordinately to control a broad range of tumor-promoting functions.

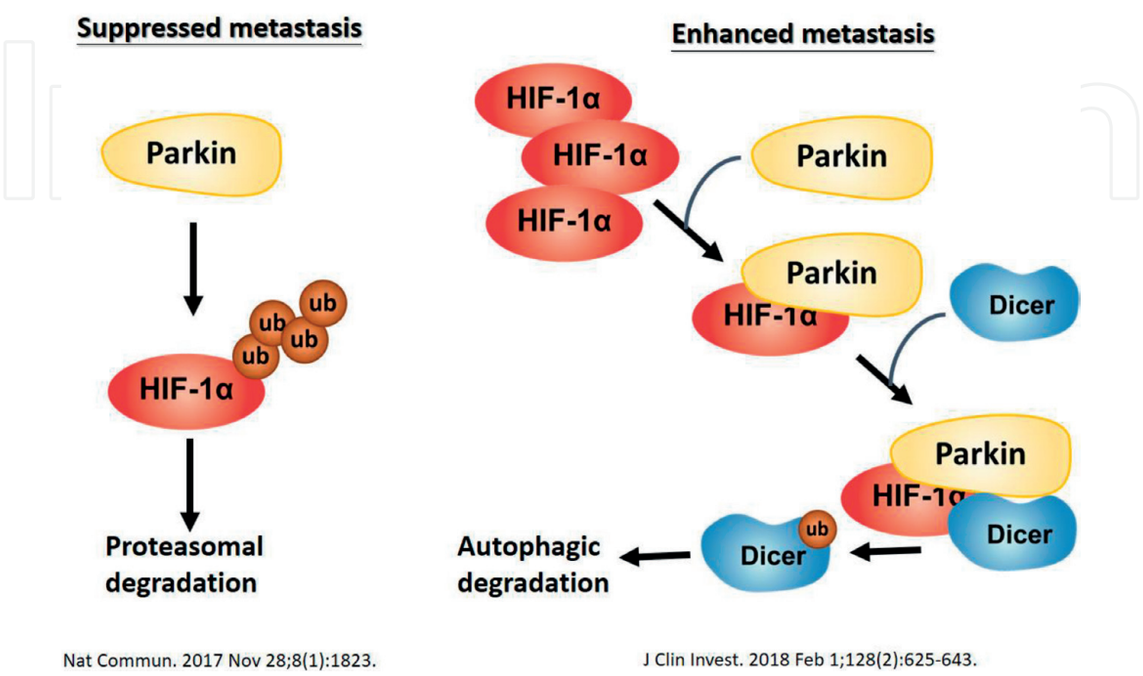

Figure 4.
Dual role of Parkin in cancer metastasis.

2.3.1 RAS/MAPK pathway

RAS oncogenes encode the highly-conserved RAS proteins as GTPases functioning in oncogenic transformation through the activation of MAPK pathway [61, 62]. Similar to p53, RAS mutations have been identified in human cancers, while stabilized RAS protein at post-translational level is also observed. The E3 ubiquitin-protein ligase, neural precursor cell-expressed developmentally downregulated protein 4 (NEDD4), is known to ubiquitinate RAS proteins for proteasomal degradation. NEDD4 targets KRAS, HRAS, NRAS for UPS, while its transcription is also activated by RAS signaling, which in turn, serves as a negative feedback to prevent the hyperactivation of RAS pathway [63]. More interestingly, this feedback mechanism is disrupted in cells expressing oncogenic RAS with activating mutation, exemplifying how an oncogenic protein (RAS) can escape from E3 (NEDD)-mediated degradation in cancer. Moreover, PTEN, a PI3K/Akt inhibitor, is another NEDD4 target, meaning that overexpression of NEDD4 facilitates PTEN degradation and activation of PI3K/Akt pathway. Thus, NEDD4 is supposedly to act as a tumor suppressor, but in cells expressing activating mutated RAS, NEDD4 no longer suppresses for RAS suppression and the concomitant PI3K/Akt activation corporately to amplify oncogenic signaling. In this case, NEDD4 functions as an oncogenic E3 [63]. However, a sustained RAS activation might be observed in lung cancer due to an elevated expression of DUB OTU domain-containing ubiquitin aldehyde-binding protein 1 (OTUB1), a deubiquitinase removing the ubiquitination of RAS and promoting the activation of RAS-mediated oncogenic downstream [64]. In addition to targeting RAS, several E3s are also identified to regulate downstream molecules of RAS. For example, ring finger protein 149 (RNF149) is an E3 targeting BRAF, a downstream kinase of RAS [65]. These machineries expend the complexity from reciprocal regulation in RAS/MAPK pathway.

2.3.2 PI3K/Akt pathway

PI3K/Akt pathway is induced by extracellular signaling such as activation of receptor tyrosine kinase (RTK) or G protein-coupled receptors (GPCRs). The regulatory subunit p85 and catalytic subunit p110 form heterodimer of PI3K [66]. In addition to p85, the p110 subunit also binds to Grb2 or insulin receptor substrate (IRS), and the competition from free p85 binding serves as an inhibitor for PI3K signaling [66, 67]. P85β is one of the variants of p85 subunits and is a target of the SCF-F-box and leucine-rich repeat protein 2 (FBXL2) complex [68]. SCF-FBXL2 enhances free p85β degradation through UPS and, consequently, disrupts the inhibitory effect of p85β pool on PI3K activation. Another layer of the regulation on this mechanism is controlled by dephosphorylation of p85β by PTPL1, which facilitates p85β degradation through enhanced interaction with FBXL2 [68]. The mechanistic target of rapamycin (mTOR) is a core component of PI3K/Akt pathway. The expression of mTOR is regulated by SCF-FBXW7 complex that triggers the ubiquitination and degradation of mTOR [69]. Loss of a single copy of FBXW7 in several breast cancer cell lines is observed to be incompatible with the loss of a single copy of PTEN, a negative regulator of mTOR, which further confirmed the significance of the stabilization of FBXW7-mediated mTOR in tumorigenesis. Therefore, loss of SCF-FBXW7 may motivate anabolic processes for tumor progression [69]. In addition to mTOR regulation, the F-box protein FBXW7 is a well-known tumor suppressor which recognizes and facilitates UPS of other oncogenic substrates including c-Myc, Notch1, and cyclin E [70–81]. The mechanism of cyclin E regulation will be discussed later in this chapter.

2.4 E3s as cell cycle regulators

Uncontrolled cell growth is one of the hallmarks of cancer [82]. Cell cycle progression is a fundamental process for cell survival and proliferation. Properly regulated cell cycle progression is required for the maintenance of genome stability, organismal development, tissue homeostasis that when deregulation coordinately leads to defect of cell growth control. Signals that control cell cycle entry, progression, and arrest are commonly malfunctioned in cancer, and the subsequent disruption of DNA replication, DNA repair, and chromosomal segregation often lead to genomic instability [83]. There is aberrant degradation caused by improper E3 activity in cancer. For example, abnormal expression of E3s regulates the degradation of cyclins and cyclin-dependent kinase (CDK) inhibitor proteins by UPS. The Anaphase Promoting Complex/Cyclosome (APC/C) and Skp1, Cullin1 F-box (SCF) E3 complexes that regulate cell cycle progression are the best-studied E3s, which further form different complexes with specific co-activators and provide the functional diversity of E3s to recognize different substrates at different phases for orchestrating cell cycle progression. In mitosis and G1 phase of cell cycle, APC/C is active to suppress mitotic CDKs [84]. In contrast, various SCF complexes formed by different protein partners contribute to multifaceted functions during the cell cycle progression. Here, we will discuss these two ubiquitin-protein ligases, and how they cooperatively regulate cell cycle progression.

APC/C is a well-studied E3 that recognizes the D-box sequence of substrate proteins and ubiquitinates them for proteasome degradation [85]. The recognition of substrates by APC/C is known to rely on a short linear motif called degron (derived from degradation motif) including KEN-box, D-box, and ABBA motif [86]. KEN-box is the prominent signal among APC/C degron and is contained in substrate proteins, such as CDC20 and securin. The substrates of APC/C cover numerous cell cycle regulators. Thus, APC/C contributes to the cell cycle regulation, especially during M phase to G1 phase. Cell division cycle 20 (CDC20) or CDC20-like protein 1 (CDH1) are two known activators for APC/C activation [87]. Interestingly, the two activators show opposite functions in cancer as oncogenic CDC20 or tumor-suppressive CDH1 interact with APC/C to exert their spatial and temporal functions during cell cycle [87]. It is widely observed that CDC20 is highly expressed in human malignancies and associates with poor prognosis of cancer patients [88–93]. Mechanistically, CDC20 recognizes securin [94], Cyclin A [95, 96], Cyclin B1 [97, 98], Nek2A [99], Mcl-1 [100], and p21 [101] as it substrates for ubiquitination. Cdc20 is primarily active in mid to late mitosis to promote ubiquitination and degradation of securin and cyclins to coordinately facilitate mitotic progression [87]. Thereafter, CDC20 degradation is triggered through ubquitination by APC/C-CDH1 or by itself in late M phase. As a result, the APC/C complex shifts from APC/C-CDC20 to APC/C-CDH1. APC/C-CDH1 is activated at late mitosis phase to degrade mitotic regulators, such as cyclins and kinases, and thereby promotes cells to exit from M phase and enter G1 phase to further prevent premature S phase entry [87]. Mutation or abnormal expression of CDH1 leads to genomic instability and premature S-phase entry [87, 102].

S-phase kinase-associated protein (Skp), cullin, and F-box domain containing proteins (F-box proteins) form SCF E3 ubiquitin ligase complex. Aurora kinase A and Cyclin E are substrates for SCF-FBXW7, thus inactivation of this complex causes defect in DNA repair system and sustained cell growth [103] suggesting the tumor-suppressive roles of SCF-FBXW7. As a key factor in SCF complex, dysregulation of F-box protein is frequently observed to affect SCF activity. SCF-Skp2 regulates cell cycle from G1/S to G2/M phase by targeting multiple CDK inhibitors for UPS degradation and consequently leads to enhanced cell cycle progression and tumorigenesis [104–111].

Interestingly, SCF-βTRCP complex also mediates the crosstalk between APC/C and SCF complex during cell cycle. Degradation of the APC/C inhibitor Emi1 during prometaphase and degradation of the Cdk1 inhibitor Wee1 during prophase are facilitated by SCF-βTRCP in cell cycle progression [112, 113]. Activation of SCF-Skp2 complex during G1 to S phase degrades cyclin-dependent kinase inhibitors (CKIs), thereby induces CDK activity. The CDK2-mediated phosphorylation and inactivation of CDH1 further stabilize Skp2 by phosphorylation. SKP2 is also a D-box-containing target of APC/C-CDH1 as an autoregulatory loop [114]. It is also noticed that the casein kinase I (CKI)-phosphorylated MDM2 is targeted and degraded by SCF-βTRCP complex and results in p53 stabilization and cell cycle arrest [115].

Parkin is another E3 participating in cell cycle regulation. Mutations and loss of copy number of *PARK2,* a gene encoding Parkin, are observed in cancer, which implies its tumor-suppressive role [116–121]. Loss of Parkin expression respectively results in the elevation of Cyclin D and Cyclin E owing to the suppression of FBXW7-containing Parkin-cullin-RING or F-box only protein 4 (FBXO4)-containing complexes [117]. In animal models, $Park2^{+/-}Apc^{Min/+}$ mice have higher rate of tumor formation than $Apc^{Min/+}$ mice, which may result from the accumulation of Cyclin E and uncontrolled cell growth when Parkin expression is lost [118, 120]. Similar associations between PARK2 mutations and Cyclin D, Cyclin E, and CDK4 are also observed in human cancers [117]. Therefore, Parkin may also regulate several cell cycle or mitotic regulators including CDC20, CDH1, Aurora kinase A, Aurora kinase B, NEK2, PLK1, Cyclin B1, and securin, suggesting its function in maintaining genomic stability and growth control to suppress tumor formation [119].

3. Conclusions

Malfunction of UPS machinery, especially the target selection factor E3, has been observed in cancer for a period of time. Abnormal expression, mutation, distribution of E3s, or even the degradation of themselves may affect the affinity or activity on substrate recognition and ubiquitination, and thus consequently regulate proteasomal degradation and cellular behaviors depending on the normal functions of dysregulated targets. Although we have focused on the selective proteolysis through UPS, E3-mediated ubiquitination is not the only way for proteasomal degradation and also, proteasomal degradation is not the only fate for ubiquitinated proteins. Oftentimes, these proteins undergo autophagic degradation, intracellular localization, functional inhibition, or activation. Moreover, the lysosomal and autolysosomal (autophagy-lysosomal) degradation, which are not described in detail in this chapter, are responsible for another side of selective proteolysis. In concert with the landscape of post-translational modification, the crosstalk and cooperation among these proteolysis systems enable our cells to maintain biological functions in control. Simply speaking, proteolysis serves as a dead end for protein, thus the selection of target substrates should be tightly controlled. This chapter introduces several pathways as examples of selective UPS. In addition, there are several clinical trials for drugs designed to target proteolysis. As we know more about the mechanisms, we are moving a step forward in developing strategies to fix the proteolytic chaos of cells.

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Conflict of interest

The author declares that there is no conflict of interest.

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