Animal Cells and Systems
Vol. 16, No. 3, June 2012, 173–182

Taylor & Francis
Taylor & Francis Group

REVIEW

Ubiquitin E3 ligases controlling p53 stability

Seong Won Lee, Min Woo Seong, Young Joo Jeon and Chin Ha Chung*

School of Biological Sciences, Seoul National University, Seoul 151-742, Korea

(*Received 13 March 2012; received in revised form 25 March 2012; accepted 23 April 2012*)

The p53 protein plays a pivotal role in tumor suppression. The cellular level of p53 is normally kept low by proteasome-mediated degradation, allowing cell cycle progression and cell proliferation. Under stress conditions, such as DNA damage, p53 is stabilized and activated through various post-translational modifications of itself as well as of its regulatory proteins for induction of the downstream genes responsible for cell cycle arrest, DNA repair, and apoptosis. Therefore, the level of p53 should be tightly regulated for normal cell growth and for prevention of the accumulation of mutations in DNA under stress conditions, which otherwise would lead to tumorigenesis. Since the discovery of Mdm2, a critical ubiquitin E3 ligase that destabilizes p53 in mammalian cells, nearly 20 different E3 ligases have been identified and shown to function in the control of stability, nuclear export, translocation to chromatin or nuclear foci, and oligomerization of p53. So far, a large number of excellent reviews have been published on the control of p53 function in various aspects. Therefore, this review will focus only on mammalian ubiquitin E3 ligases that mediate proteasome-dependent degradation of p53.

Keywords: p53; Mdm2; Pirh2; COP1; CARP1/CARP2; ARF-BP1; TOPORS; Synoviolin; CHIP; JFK; MKRN1; p300/CBP

Introduction

Nearly 50% of human cancers are attributed to the loss of p53 function. As to the importance of the tumor suppressive function of p53, a great deal of effort has been contributed to explore the mechanism for the control of p53 activity. One of the key mechanisms that control p53 activity is post-translational modification of the tumor suppressor protein. Nearly 100 proteins have been identified as the p53-binding proteins, which are involved in phosphorylation, methylation, acetylation, poly-ADP-ribosylation, glycosylation, ubiquitination, modification by ubiquitin-like proteins, such as SUMO and Nedd8, and their reversible processes. Of 393 amino acids that constitute the p53 protein, nearly 50 amino acids have been identified as the modification sites and perhaps many more of such sites are to be identified in the near future (Meek and Anderson 2009; Anderson and Appella 2010).

Of diverse post-translational modification processes, ubiquitination plays a fundamental role in the control of p53 function as it determines the cellular level of p53. The process of ubiquitination is catalyzed by three cascade enzyme system involving E1 activating enzymes, E2 conjugating enzymes, and E3 ligases (Hershko and Ciechanover 1998; Pickart 2001). Of these enzymes, E3 ligases determine the specificity of target proteins for ubiquitination. E6AP (human papilloma virus E6-associated cellular protein) is the first identified E3 ligase that targets p53 (Scheffner et al. 1993). The viral E6 protein promotes the human E6AP protein, also known as UBE3A (ubiquitin-protein ligase E3A), to destabilize p53 for viral replication in the host cells. Mouse double minute 2 (Mdm2) was then discovered as a major E3 ligase for p53 ubiquitination and degradation (Haupt et al. 1997; Honda et al. 1997; Kubbutat et al. 1997; Li et al. 2003). Since then, numerous other E3 ligases were identified and characterized for their function (Brooks and Gu 2011). Here, we summarize the functions of the E3 ligases that interact with and ubiquitinate p53 in mammalian cells.

Mdm2

Mouse double minute 2 is a major ubiquitin E3 ligase that mediates really interesting new gene (RING)-dependent ubiquitination of p53 (Haupt et al. 1997; Honda et al. 1997; Kubbutat et al. 1997; Fang et al. 2000). Its human homolog is called as HDM2, whose gene is located in chromosome 12q14.3-q15 (Oliner et al. 1992). Mdm2 has an N-terminal p53-binding domain, acidic and zinc finger domains in the middle, and a C-terminal RING finger domain (Figure 1).

Under normal conditions, p53 activates the expression of Mdm2, which in turn ubiquitinates p53 for proteasome-mediated degradation, forming a negative feedback loop for keeping p53 in low levels (Haupt et al. 1997; Honda et al. 1997; Kubbutat et al. 1997). Under DNA damage or other stress conditions, however, p53 level is increased by disruption of p53-mediated Mdm2 expression as well as by post-translational modifications that inhibit Mdm2 function

*Corresponding author. Email: chchung@snu.ac.kr

ISSN 1976-8354 print/ISSN 2151-2485 online

http://dx.doi.org/10.1080/19768354.2012.688769
http://www.tandfonline.com

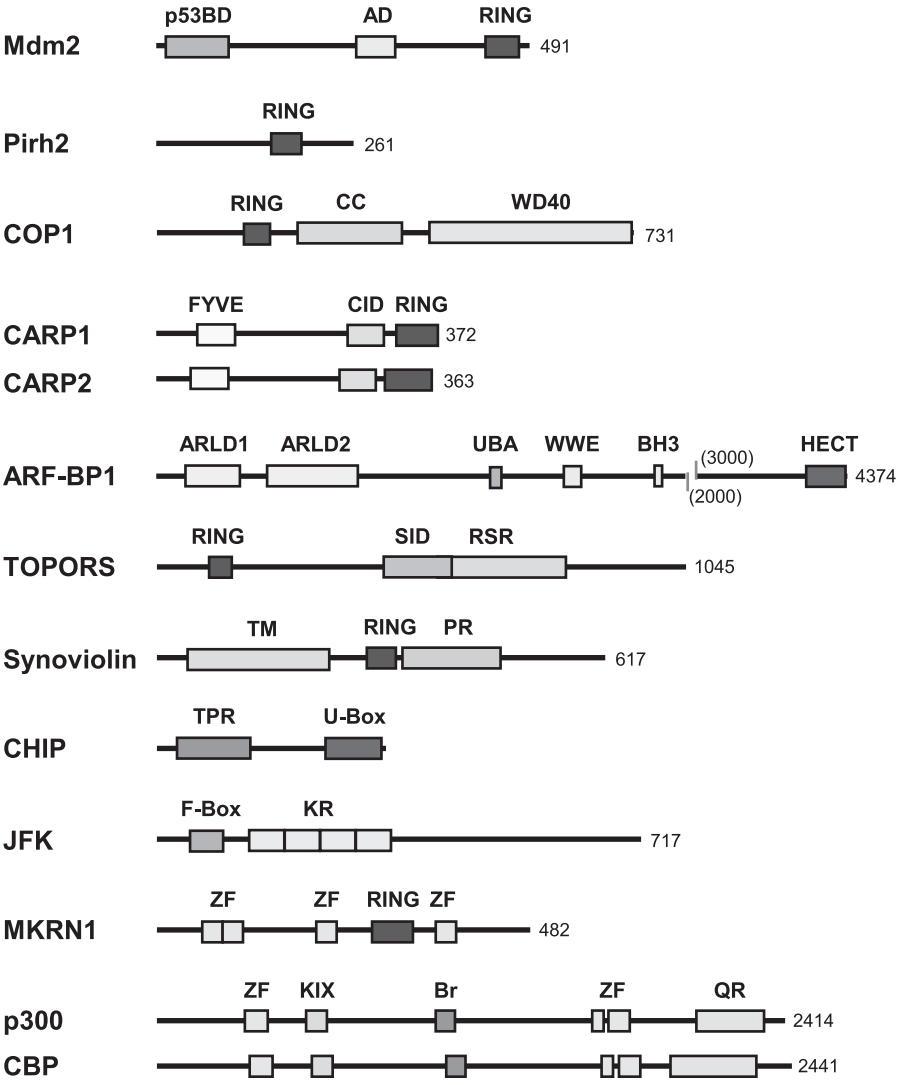

Figure 1. Domain structures of ubiquitin E3 ligases for p53 degradation. p53BD, p53-binding domain; AD, acidic domain; RING, really interesting new gene; CC, coiled coil; FYVE, Cys-rich zinc finger domain of Fab1, YOTB, Vac1, and EEA1; CID, caspase-interacting domain; ARLD, Armadillo repeat-like domain; UBA, ubiquitin-associated domain; BH3, Bcl-2 homology domain; HECT, homologous to the E6-AP carboxyl terminus; SID, SUMO-interacting domain; RSR, Arg/Ser-rich; TM, transmembrane; PR, Pro-rich; TPR, tetratricopeptide repeat; KR, Kelch repeat; ZF, zinc finger; KIX, CREB and MYB interaction domain; Br, bromo domain; QR, Gln-rich domain. The numerals shown at the right ends indicate the number of amino acids.

(Ashcroft et al. 2000; Meek and Knippschild 2003; Michael and Oren 2003). For example, phosphorylation of Ser15 and Ser20 of p53 by stress-induced kinases (such as ATM/ATR, Chk1/Chk2, and DNA-PK) disrupts its interaction with Mdm2, leading to the stabilization of p53 (Shieh et al. 1997; Shieh et al., 1999; Tibbetts et al. 1999; Hirao et al. 2000). In addition, alternate open reading frame (ARF) directly binds and inhibits Mdm2, leading to the stabilization of p53 and the promotion of p53-mediated cell cycle arrest and apoptosis (Zhang et al. 1998). Remarkably, the relative amount of Mdm2 is important to decide the fate of ubiquitinated p53 between proteasome-mediated destruction and translocation to the cytoplasm (Li et al. 2003). Low levels of Mdm2 activity induce mono-ubiquitination and nuclear export of p53, whereas high levels promote poly-ubiquitination and degradation of p53 in the nucleus.

MdmX, a structural homolog of Mdm2, which has a RING domain but lacks E3 ligase activity, ablates p53-mediated transcription by forming a ternary complex with Mdm2 and p53 (Shvarts et al. 1996; Stad et al. 2001). Knockout of MdmX is embryonic lethal. Knockout of Mdm2 is also embryonic lethal, and this phenotype can completely be rescued by knockout of both Mdm2 and p53 (Parant et al. 2001; Finch et al.

2002; Migliorini et al. 2002; Li et al. 2004). Elegant experiments involving the reintroduction of p53 to mice lacking p53 together with either Mdm2 or MdmX have shown that loss of Mdm2 promotes the activation of p53 target genes related to apoptosis, while loss of MdmX promotes the activation of genes mediating cell cycle arrest (Chavez-Reyes et al. 2003; Barboza et al. 2008). Human *MDM2* (*HDM2*) proto-oncogene is amplified in 30–40% of sarcomas and is overexpressed in leukemic cells (Oliner et al. 1992; Bueso-Ramos et al. 1993; Jones et al. 1995).

Other protein substrates that are ubiquitinated by Mdm2 for proteasome-mediated degradation include DYRK2 (dual-specificity tyrosine-regulated kinase 2), β-arrestin, IGF-1R (insulin-like growth factor-1 receptor), and androgen receptor (Shenoy et al. 2001; Lin et al. 2002; Girnita et al. 2003; Taira et al. 2010). Mdm2 also promotes proteasome-mediated degradation of Rb (retinoblastoma protein) and p21, but through an ubiquitin-independent pathway (Zhang et al. 2004; Sdek et al. 2005).

Pirh2

Pirh2 (p53-induced RING H2) was identified as an androgen receptor N-terminal interacting protein (ARNIP) and also known as Rchy 1 (RING finger and CHY zinc finger domain containing 1). Its gene is located in chromosome 4q21.1 (Beitel et al. 2002; Leng et al. 2003).

Like Mdm2, Pirh2 is transcriptionally activated by p53 and in turn negatively regulates p53 level by ubiquitination, forming a negative feedback loop (Leng et al. 2003; Feng et al. 2007; Sheng et al. 2008). However, unlike Mdm2, which promotes degradation of unmodified form of p53 under nonstressed conditions, Pirh2 preferentially ubiquitinates Ser15-phosphorylated p53, which can be generated under DNA damage conditions (e.g., IR or UV treatment), for proteasome-mediated degradation. Thus, Pirh2 negatively regulates the expression of p53 downstream genes for cell cycle arrest and apoptosis, because phosphorylation of Ser15 in p53 is critical for p53-dependent transactivation.

Pirh2 is mostly detected in the phosphorylated form in normal tissues, whereas it is present in unphosphorylated form in majority of tumors. Pirh2 is phosphorylated by calmodulin-dependent kinase II (CaMKII) in a cell cycle-dependent manner, and this phosphorylation promotes the localization of Pirh2 in the cytoplasm as well as self-ubiquitination, leading to p53 stabilization (Duan et al. 2007). Interestingly, the level of CaMKII is down-regulated in human tumors (Tombes et al. 1999). In addition, Pirh2 is overexpressed in a variety of human tumors, including prostate, lung, head-and-neck, and breast cancers, and this overexpression is independent of p53, implicating its role as an oncogenic protein (Duan et al. 2006; Wang et al. 2011).

Other proteins that are ubiquitinated by Pirh2 for proteasome-mediated degradation include DNA polymerase η, HDAC1, p27, and ε-COP (Logan et al. 2006; Hattori et al. 2007; Maruyama et al. 2008; Jung et al. 2010). Significantly, Pirh2 also ubiquitinates p73, a member of p53 family, which shows tumor suppressive functions by activating downstream target genes for cell cycle arrest and apoptosis (Jung et al. 2011; Wu et al. 2011).

COP1

COP1 (constitutive photomorphogenesis protein 1 homolog) was originally identified as a central regulator of photomorphogenic development in plant (Deng et al. 1991). Its gene is located in the human chromosome 1q25.1-q25.2. COP1 is also called as RFWD2 (RING finger and WD repeat domain 2) and RNF200 (RING finger protein 200). It contains an N-terminal RING finger domain, a coiled–coiled domain in the middle, and a C-terminal WD40 repeat domain. COP1 has a central bipartite nuclear localization signal (NLS), and is localized in both the nucleus and the cytoplasm (Yi et al. 2002; Bianchi et al. 2003).

Like Mdm2, COP1 is transcriptionally activated by p53 and in turn negatively regulates p53 level by ubiquitination in mammalian cells, forming a negative feedback loop. Under normal conditions, COP1 and Mdm2 may synergistically down-regulate p53 by ubiquitination, thus allowing cell growth and proliferation (Dornan et al. 2004b). In response to DNA damage, such as ionizing radiation (IR), however, ATM phosphorylates COP1 on Ser387, triggers its export from the nucleus to the cytoplasm, and stimulates its self-ubiquitination, resulting in the stabilization of p53 for cell cycle arrest or apoptosis (Dornan et al. 2006). COP1 is overexpressed in more than 80% of breast and nearly half of ovarian adenocarcinomas, implicating its role as an oncogenic protein (Dornan et al. 2004a).

However, recent studies have shown that COP1 acts as a tumor suppressor by promoting ubiquitination and degradation of the c-Jun oncoprotein in cooperation with DET1 (de-etiolated 1), DDB1 (DNA damage binding protein 1), cullin-4A, and Roc1 (Wertz et al. 2004). The tumor suppressive role of COP1 was further supported by the finding that *Cop1*-hypomorphic mice, which express only 10% of Cop1 with increased c-Jun accumulation, develop spontaneous malignancy and are more prone to radiation-induced lymphomagenesis (Migliorini et al. 2011; Wei and Kaelin 2011). COP1 also down-regulates ETV1, ETV4, and ETV5, which

are oncogenic transcription factors and most frequently rearranged and overexpressed in prostate cancers, providing an additional evidence for the role of COP1 as a tumor suppressor (Vitari et al. 2011).

Other COP1 substrates identified so far include ACC1 (acetyl-coenzyme A carboxylase alpha), MTA1 (metastasis-associated protein 1), FOXO1 (forkhead box protein O1), TORC2 (transducer of regulated CREB activity 2), and PEA3 (polyomavirus enhancer activator-3) (Qi et al. 2006; Kato et al. 2008; Li et al. 2009; Baert et al. 2010; Wei and Kaelin 2011).

CARP1 and CARP2

CARPs (caspase-8- and caspase-10-associated RING proteins) were identified as a family of apoptotic inhibitors that bind to and down-regulate the death effector domain (DED)-containing caspases (McDonald and El-Deiry 2004). Their genes are located in chromosomes 12q24.31 and 17q12 for CARP1 and CARP2, respectively. CARP1 is also called as RFI (RING finger homologous to inhibitor of apoptosis protein [IAP]) and RNF34, while CARP2, a splicing variant of CARP1, is also called as RNFL1 (RING finger and FYVE-like domain containing 1), RNF189, and RNF34L (RNF34-like). CARPs contain an N-terminal FYVE-type zinc finger domain, two CIDs (caspase-interacting domains) in the middle, and a C-terminal RING finger domain (Sasaki et al. 2002; Coumailleau et al. 2004).

Both CARP1 and CARP2 physically interact with and ubiquitinate p53 in the absence of Mdm2 for proteasome-mediated degradation. Interestingly, CARPs are also capable of down-regulating Ser20-phosphorylated p53. Under DNA damage conditions, such as treatment with adriamycin, phosphorylation of Ser20 of p53 as well as of Ser395 of Mdm2 occurs and disrupts their interaction, leading to p53 stabilization. Thus, the ability of CARPs, with that of Pirh2, in down-regulating phosphorylated-p53 may provide oncogenic potential capable of eliminating chemotherapy-induced p53 protein. Consistently, CARPs are frequently overexpressed in human tumors, such as esophageal cancers (Yang et al. 2007).

ARF-BP1

ARF-BP1 (ARF-binding protein 1) is the largest ubiquitin E3 ligase (~ 500 kDa) that harbors a HECT (homologous to E6AP carboxyl terminus) domain. It is also called as HectH9 (HECT homologous protein 9), UREB1 (upstream regulatory element-binding protein 1), LASU1 (large structure of UREB1), Mule (MCL-1 ubiquitin ligase E3), and HUWE1 (HECT, UBA, and WWE domain-containing protein 1). Its gene is located in chromosome Xp11.22 (Adhikary et al. 2005; Chen et al. 2005; Liu et al. 2005; Zhong et al. 2005).

Like Mdm2, ARF-BP1 directly binds and ubiquitinates p53, and this activity is strongly inhibited by ARF. Depletion of ARF-BP1 by RNA interference stabilizes p53 and induces apoptosis (Chen et al. 2005). However, ARF expression results in cell growth inhibition even in p53/Mdm2-double knockout MEF cells, indicating that ARF exerts its tumor-suppressive function in p53- and Mdm2-independent manner (Weber et al. 2000; Kuo et al. 2003). Moreover, ARF-BP1 depletion induces cell growth arrest in p53 null MEF cells. Thus, it appears that ARF-BP1 plays a role not only as an ubiquitin E3 ligase of p53 but also as a key target of ARF, which in turn exerts its tumor suppressive function in a p53-independent manner. However, target substrate(s) of ARF-BP1, which is stabilized by ARF and thereby induces cell growth inhibition, remains unknown (Chen et al. 2005, 2006). ARF-BP1 is overexpressed in a variety of primary tumor samples, including breast cancer cell lines (Adhikary et al. 2005; Yoon et al. 2005). Significantly, defects in ARF-BP1 are a causative of mental retardation syndromic X-linked Tuner type (MRXST), also known as mental retardation and macrocephaly syndrome (Froyen et al. 2008).

Other proteins that are ubiquitinated by ARF-BP1 for proteasome-mediated degradation include MCL1 (myeloid cell leukemia 1), DNA polymerase β, Cdc6, and MyoD (Zhong et al. 2005; Hall et al. 2007; Parsons et al. 2009; Noy et al. 2012). Interestingly, ARF-BP1 promotes the degradation of MyoD by ubiquitinating its N-terminus (Noy et al. 2012). ARF-BP1 also ubiquitinates Myc through Lys63-linked isopeptide bonds, leading to the stabilization of Myc rather than its degradation (Adhikary et al. 2005).

TOPORS

TOPORS was identified as topoisomerase I-binding protein containing RING finger and arginine/serine (R/S)-rich sequences. It is also called as p53BP3 because it binds to p53 and as LUN because it is highly expressed in the lung. Its gene is located in chromosome 9p21. TOPORS has an N-terminal RING domain, an R/S-rich domain and a bipartite NLS in the middle, and five PEST sequences (three in the N-terminus and two in the C-terminus) (Haluska et al. 1999; Chu et al. 2001). It dynamically associates with PML nuclear bodies in the nucleus (Rasheed et al. 2002).

TOPORS was shown to ubiquitinate p53, leading to proteasome-mediated degradation, albeit less efficiently than Mdm2 (Rajendra et al. 2004). By contrast,

it was also shown that TOPORS overexpression stabilizes p53 and in turn induces p53 downstream genes, such as p21 and Bax, for cell cycle arrest and apoptosis. Furthermore, in response to DNA damage, TOPORS accumulates and facilitates p53-mediated apoptosis in tumor and primary cells, implicating the role of TOPORS as a tumor suppressor (Lin et al. 2005). Interestingly, the expression of TOPORS is down-regulated during the development and metastasis of lung cancer, again suggesting the role of TOPORS in the suppression of tumorigenesis. However, it remains unclear how the ubiquitin ligase activity of TOPORS is related with its tumor suppressive function (Oyanagi et al. 2004; Saleem et al. 2004).

Remarkably, TOPORS also serves as a SUMO E3 ligase for p53 as well as other proteins, such as IKKε (Weger et al. 2005; Renner et al. 2010) . Although the physiological relevance for SUMO modification of p53 remains unclear, it has recently shown that in response to DNA damage TOPORS-mediated SUMO modification of IKKε is induced and triggers phosphorylation of NF-κB p65, contributing to the anti-apoptotic function of NF-κB (Renner et al. 2010).

Synoviolin

Synoviolin (synovial apoptosis inhibitor 1) is an endoplasmic reticulum (ER) stress-inducible ER membrane protein that acts as an ubiquitin E3 ligase with a RING finger motif, originally identified in yeast. It is also called as HRD1 (hydroxymethyl glutaryl CoA reductase degradation 1), named after its substrate. Synoviolin contains an N-terminal transmembrane domain, a RING finger domain in the middle, and a C-terminal cytoplasmic domain. Its gene is located in chromosome 11q13 (Kaneko et al. 2002; Amano et al. 2003; Nadav et al. 2003).

Synoviolin sequesters p53 in the cytoplasm and ubiquitinates it for proteasome-mediated degradation (Yamasaki et al. 2007). Synoviolin has been regarded as a causative factor of arthropathy, as it is highly expressed in the rheumatoid synovium and triggers the outgrowth of synovial cells due to its anti-apoptotic effects, and mice overexpressing this enzyme spontaneously develop arthropathy (Amano et al. 2003). Moreover, mice lacking p53 have severe collagen-induced arthritis, although they do not develop spontaneous arthropathy, suggesting the operation of the synoviolin–p53 pathway at least in controlling the severity of arthritis (Simelyte et al. 2005).

CHIP

CHIP (carboxyl terminus of Hsc70-interacting protein) is a cofactor that modulates the functions of cytosolic chaperones, such as Hsc/Hsp70. It contains an N-terminal TPR (tetratricopeptide repeat) domain and a C-terminal U-box domain, which forms a structure similar to a RING finger. Its gene is located in chromosome 16p13.3 (Min et al. 2008).

CHIP ubiquitinates p53 in cooperation with the chaperones Hsc70 and Hsp90 for degradation by proteasome, thereby negatively regulating p53-mediated transcription (Esser et al. 2005). Many transforming mutants of p53 display structural defects and associate with Hsc70 (Davidoff et al. 1992; Blagosklonny et al. 1995; Whitesell et al. 1998). For example, Arg175 mutations destabilize loop regions of the DNA-binding domain, leading to partial unfolding and more stable association of p53 mutants with Hsc70 (Gannon et al. 1990; Hinds et al. 1990; Bargonetti et al. 1993). CHIP promotes the degradation of both wild-type and mutant forms of p53. Interestingly, however, geldanamycin, an inhibitor of Hsp90, accelerates the degradation of oncogenic mutant forms but not that of wild-type p53, providing a relevance for the use of Hsp90 inhibitors as chemotherapeutics (Esser et al. 2005).

Other chaperone-assisted protein substrates for CHIP-mediated ubiquitination include glucocorticoid receptor (Connell et al. 2001; Demand et al. 2001), oncogenic receptor tyrosine kinase ErbB (Xu et al. 2002), and cystic fibrosis transmembrane conductance regulator (Meacham et al. 2001), and hyperphosphorylated Tau (Petrucelli et al. 2004; Shimura et al. 2004).

SCF^{JFK}

Among the total of 68 F-box proteins in human, JFK (just one F-box- and Kelch-domain contain protein) is the only F-box protein that also contains Kelch repeats. JFK is also called as FBXO42 (F-box protein 42). Its gene is located in 1p36.23-p36.11 (Sun et al. 2009).

JFK forms an SCF complex with Skp1, cullin-1, and Rbx1, and promotes ubiquitination of p53 for proteasome-mediated degradation. Depletion of JFK by RNA interference stabilizes p53, leading to promotion of cell cycle arrest and apoptosis. As SCF ligases mainly participate in the control of cell cycle, particularly on G1/S transition, and p53 plays a critical role in regulating the G1/S cell cycle checkpoint, JFK may contribute to the maintenance of p53 levels in unstressed cells (Sun et al. 2009).

MKRN1

MKRN1 (Makorin RING finger protein 1) was first identified as an intron-containing source gene for MKRN gene family, majority of which are intronless

and imprinted. MKRN1 is also called as RNF61, and its gene is located in chromosome 7q34.

MKRN1, like Mdm2, ubiquitinates and destabilizes p53 under normal conditions, but by targeting distinct Lys residues (i.e., K291 and K293). Under DNA damage conditions, however, MKRN1 ubiquitinates p21, but not p53, for proteasome-mediated degradation and thereby stimulates p53-mediated apoptosis (Lee et al. 2009). MKRN1 also ubiquitinates hTERT, the catalytic subunit of telomerase, for proteasome-mediated degradation, leading to a decrease in telomere length (Kim et al. 2005).

p300/CBP

Both p300 and CBP (CREB-binding protein) are transcriptional coactivators that have histone acetyltransferase (HAT) activity. Although both proteins are mainly localized in the nucleus, their substantial amounts also reside in the cytoplasm. Both contain three conserved Zn^{2+}-binding Cys/His-rich domains, one of which (C/H1-TAZ1) responsible for E3 and E4 ligase activity lies in the N-terminal region (Grossman et al. 2003). The genes for p300 and CBP are located in chromosome 22q13.2 and 16p13.3, respectively.

Under unstressed conditions, both p300 and CBP catalyze poly-ubiquitination of p53 that had been mono-ubiquitinated by Mdm2 in the cytoplasm, leading to destabilization of p53. Under stress conditions, however, both proteins catalyze acetylation of p53 for its stabilization and activation in the nucleus (Grossman et al. 2003; Shi et al. 2009). Thus, p300 and CBP appear to engage in compartmentalized control of p53 by ubiquitination in the cytoplasm and acetylation in the nucleus under normal and stress conditions, respectively.

Others

The E3 ligases described here ubiquitinate and destabilize p53 by proteasome-mediated degradation. In addition to these enzymes, mammalian cells contain a number of E3 ligases that catalyze ubiquitination of p53, but do not promote its proteasome-mediated degradation. Ubc13 that commonly acts as an E2 enzyme for the synthesis Lys63-linked poly-ubiquitin chains can directly ubiquitinate p53 without intervention of a partner E3 ligase, leading to prevention of p53 tetramerization (Laine et al. 2006). MSL2 (male-specific lethal 2) and WWP1 (WW domain-containing E3 ubiquitin protein ligase 1) ubiquitinate p53 and induce its nuclear export (Laine and Ronai 2007; Kruse and Gu 2009). On the other hand, E4F1 (E4F transcription factor 1) promotes translocation of p53 to chromatin by ubiquitination (Le Cam et al. 2006). Significantly, E4F1 promotes the ubiquitination of Lys residues in the hinge region of p53, which are acetylated by PCAF but distinct from those targeted by Mdm2, and this modification stimulates transcriptional activation of p53, specific for cell cycle arrest.

So many E3s for p53

Nearly 20 different E3 ligases for p53 have been identified in mammalian cells so far. Why the cells have so many E3 ligases for p53 ubiquitination? Based on their primary functions, they can at least be divided into two groups: one for the degradation of p53 by proteasome and the other for the proteasome-independent control of p53 activity, such as by subcellular localization and oligomerization. The E3 ligases that mediate proteasome-dependent p53 degradation can also be roughly divided into two groups: one, such as Mdm2, for the degradation of unmodified p53 for keeping p53 level low for cells to proliferate normally and the other, such as Pirh2 and CARP1/2, for the degradation of stress-induced, phosphorylated p53 to overcome p53-mediated cell cycle arrest and apoptosis. In addition, whole-mount *in situ* expression analysis has recently shown that E3 ligases for p53 display distinct expression pattern during mouse embryonic development, suggesting that the ligases may acquire specific functions at different stage of development (Jain and Barton 2010). Nonetheless, it remains largely unknown how different E3 ligase cooperates and cross talks with each other for the control of p53 function in tumor suppression.

Acknowledgements

This work was supported by the grants from the Korea Research Foundation (KRF-2005-084-C00025) and the Ministry of Education, Science, and Technology (M10533010001-05N3301). S.W. Lee was the recipient of BK21 fellowship. We apologize for the event that any relevant publications were inadvertently omitted.

References

Adhikary S, Marinoni F, Hock A, Hulleman E, Popov N, Beier R, Bernard S, Quarto M, Capra M, Goettig S, et al. 2005. The ubiquitin ligase HectH9 regulates transcriptional activation by Myc and is essential for tumor cell proliferation. Cell. 123:409–421.

Amano T, Yamasaki S, Yagishita N, Tsuchimochi K, Shin H, Kawahara K, Aratani S, Fujita H, Zhang L, Ikeda R, et al. 2003. Synoviolin/Hrd1, an E3 ubiquitin ligase, as a novel pathogenic factor for arthropathy. Genes Dev. 17:2436–2449.

Anderson CW, Appella E. 2010. Signaling to the p53 tumor suppressor through pathways activated by genotoxic and non-genotoxic stresses. In Ralph AB, Edward AD, editors. Handbook of cell signaling. 2nd ed. San Die-

go(CA): Academic Press. p. chapter 264, 2185–2204. Available from: http://www.sciencedirect.com/science/article/pii/B9780123741455002643

Ashcroft M, Taya Y, Vousden KH. 2000. Stress signals utilize multiple pathways to stabilize p53. Mol Cell Biol. 20:3224–3233.

Baert JL, Monte D, Verreman K, Degerny C, Coutte L, de Launoit Y. 2010. The E3 ubiquitin ligase complex component COP1 regulates PEA3 group member stability and transcriptional activity. Oncogene. 29:1810–1820.

Barboza JA, Iwakuma T, Terzian T, El-Naggar AK, Lozano G. 2008. Mdm2 and Mdm4 loss regulates distinct p53 activities. Mol Cancer Res. 6:947–954.

Bargonetti J, Manfredi JJ, Chen X, Marshak DR, Prives C. 1993. A proteolytic fragment from the central region of p53 has marked sequence-specific DNA-binding activity when generated from wild-type but not from oncogenic mutant p53 protein. Genes Dev. 7:2565–2574.

Beitel LK, Elhaji YA, Lumbroso R, Wing SS, Panet-Raymond V, Gottlieb B, Pinsky L, Trifiro MA. 2002. Cloning and characterization of an androgen receptor N-terminal-interacting protein with ubiquitin-protein ligase activity. J Mol Endocrinol. 29:41–60.

Bianchi E, Denti S, Catena R, Rossetti G, Polo S, Gasparian S, Putignano S, Rogge L, Pardi R. 2003. Characterization of human constitutive photomorphogenesis protein 1, a RING finger ubiquitin ligase that interacts with Jun transcription factors and modulates their transcriptional activity. J Biol Chem. 278:19682–19690.

Blagosklonny MV, Toretsky J, Neckers L. 1995. Geldanamycin selectively destabilizes and conformationally alters mutated p53. Oncogene 11:933–939.

Brooks CL, Gu W. 2011. p53 regulation by ubiquitin. FEBS Lett. 585:2803–2809.

Bueso-Ramos CE, Yang Y, deLeon E, McCown P, Stass SA, Albitar M. 1993. The human MDM-2 oncogene is overexpressed in leukemias. Blood. 82:2617–2623.

Chavez-Reyes A, Parant JM, Amelse LL, de Oca Luna RM, Korsmeyer SJ, Lozano G. 2003. Switching mechanisms of cell death in mdm2- and mdm4-null mice by deletion of p53 downstream targets. Cancer Res. 63:8664–8669.

Chen D, Kon N, Li M, Zhang W, Qin J, Gu W. 2005. ARF-BP1/Mule is a critical mediator of the ARF tumor suppressor. Cell. 121:1071–1083.

Chen D, Brooks CL, Gu W. 2006. ARF-BP1 as a potential therapeutic target. Br J Cancer. 94:1555–1558.

Chu D, Kakazu N, Gorrin-Rivas MJ, Lu HP, Kawata M, Abe T, Ueda K, Adachi Y. 2001. Cloning and characterization of LUN, a novel ring finger protein that is highly expressed in lung and specifically binds to a palindromic sequence. J Biol Chem. 276:14004–14013.

Connell P, Ballinger CA, Jiang J, Wu Y, Thompson LJ, Hohfeld J, Patterson C. 2001. The co-chaperone CHIP regulates protein triage decisions mediated by heat-shock proteins. Nat Cell Biol. 3:93–96.

Coumailleau F, Das V, Alcover A, Raposo G, Vandormael-Pournin S, Le Bras S, Baldacci P, Dautry-Varsat A, Babinet C, Cohen-Tannoudji M. 2004. Over-expression of Rififylin, a new RING finger and FYVE-like domain-containing protein, inhibits recycling from the endocytic recycling compartment. Mol Biol Cell. 15: 4444–4456.

Davidoff AM, Iglehart JD, Marks JR. 1992. Immune response to p53 is dependent upon p53/HSP70 complexes in breast cancers. Proc Natl Acad Sci USA. 89: 3439–3442.

Demand J, Alberti S, Patterson C, Hohfeld J. 2001. Cooperation of a ubiquitin domain protein and an E3 ubiquitin ligase during chaperone/proteasome coupling. Curr Biol. 11:1569–1577.

Deng XW, Caspar T, Quail PH. 1991. cop1: a regulatory locus involved in light-controlled development and gene expression in Arabidopsis. Genes Dev. 5:1172–1182.

Dornan D, Bheddah S, Newton K, Ince W, Frantz GD, Dowd P, Koeppen H, Dixit VM, French DM. 2004a. COP1, the negative regulator of p53, is overexpressed in breast and ovarian adenocarcinomas. Cancer Res. 64:7226–7230.

Dornan D, Wertz I, Shimizu H, Arnott D, Frantz GD, Dowd P, O'Rourke K, Koeppen H, Dixit VM. 2004b. The ubiquitin ligase COP1 is a critical negative regulator of p53. Nature. 429:86–92.

Dornan D, Shimizu H, Mah A, Dudhela T, Eby M, O'Rourke K, Seshagiri S, Dixit VM. 2006. ATM engages autodegradation of the E3 ubiquitin ligase COP1 after DNA damage. Science. 313:1122–1126.

Duan W, Gao L, Wu X, Zhang Y, Otterson GA, Villalona-Calero MA. 2006. Differential response between the p53 ubiquitin-protein ligases Pirh2 and MdM2 following DNA damage in human cancer cells. Exp Cell Res. 312:3370–3378.

Duan S, Yao Z, Hou D, Wu Z, Zhu WG, Wu M. 2007. Phosphorylation of Pirh2 by calmodulin-dependent kinase II impairs its ability to ubiquitinate p53. EMBO J. 26:3062–3074.

Esser C, Scheffner M, Hohfeld J. 2005. The chaperone-associated ubiquitin ligase CHIP is able to target p53 for proteasomal degradation. J Biol Chem. 280: 27443–27448.

Fang S, Jensen JP, Ludwig RL, Vousden KH, Weissman AM. 2000. Mdm2 is a RING finger-dependent ubiquitin protein ligase for itself and p53. J Biol Chem. 275:8945–8951.

Feng Z, Hu W, de Stanchina E, Teresky AK, Jin S, Lowe S, Levine AJ. 2007. The regulation of AMPK beta1, TSC2, and PTEN expression by p53: stress, cell and tissue specificity, and the role of these gene products in modulating the IGF-1-AKT-mTOR pathways. Cancer Res. 67:3043–3053.

Finch RA, Donoviel DB, Potter D, Shi M, Fan A, Freed DD, Wang CY, Zambrowicz BP, Ramirez-Solis R, Sands AT, et al. 2002. mdmx is a negative regulator of p53 activity in vivo. Cancer Res. 62:3221–3225.

Froyen G, Corbett M, Vandewalle J, Jarvela I, Lawrence O, Meldrum C, Bauters M, Govaerts K, Vandeleur L, Van Esch H, et al. 2008. Submicroscopic duplications of the hydroxysteroid dehydrogenase HSD17B10 and the E3 ubiquitin ligase HUWE1 are associated with mental retardation. Am J Hum Genet. 82:432–443.

Gannon JV, Greaves R, Iggo R, Lane DP. 1990. Activating mutations in p53 produce a common conformational effect. A monoclonal antibody specific for the mutant form. EMBO J. 9:1595–1602.

Girnita L, Girnita A, Larsson O. 2003. Mdm2-dependent ubiquitination and degradation of the insulin-like growth factor 1 receptor. Proc Natl Acad Sci USA. 100: 8247–8252.

Grossman SR, Deato ME, Brignone C, Chan HM, Kung AL, Tagami H, Nakatani Y, Livingston DM. 2003. Polyubiquitination of p53 by a ubiquitin ligase activity of p300. Science. 300:342–344.

Hall JR, Kow E, Nevis KR, Lu CK, Luce KS, Zhong Q, Cook JG. 2007. Cdc6 stability is regulated by the Huwe1 ubiquitin ligase after DNA damage. Mol Biol Cell. 18:3340–3350.

Haluska P, Jr., Saleem A, Rasheed Z, Ahmed F, Su EW, Liu LF, Rubin EH. 1999. Interaction between human topoisomerase I and a novel RING finger/arginine-serine protein. Nucleic Acids Res. 27:2538–2544.

Hattori T, Isobe T, Abe K, Kikuchi H, Kitagawa K, Oda T, Uchida C, Kitagawa M. 2007. Pirh2 promotes ubiquitin-dependent degradation of the cyclin-dependent kinase inhibitor p27Kip1. Cancer Res. 67:10789–10795.

Haupt Y, Maya R, Kazaz A, Oren M. 1997. Mdm2 promotes the rapid degradation of p53. Nature. 387:296–299.

Hershko A, Ciechanover A. 1998. The ubiquitin system. Annu Rev Biochem. 67:425–479.

Hinds PW, Finlay CA, Quartin RS, Baker SJ, Fearon ER, Vogelstein B, Levine AJ. 1990. Mutant p53 DNA clones from human colon carcinomas cooperate with ras in transforming primary rat cells: a comparison of the "hot spot" mutant phenotypes. Cell Growth Differ. 1:571–580.

Hirao A, Kong YY, Matsuoka S, Wakeham A, Ruland J, Yoshida H, Liu D, Elledge SJ, Mak TW. 2000. DNA damage-induced activation of p53 by the checkpoint kinase Chk2. Science. 287:1824–1827.

Honda R, Tanaka H, Yasuda H. 1997. Oncoprotein MDM2 is a ubiquitin ligase E3 for tumor suppressor p53. FEBS Lett. 420:25–27.

Jain AK, Barton MC. 2010. Making sense of ubiquitin ligases that regulate p53. Cancer Biol Ther. 10:665–672.

Jones SN, Roe AE, Donehower LA, Bradley A. 1995. Rescue of embryonic lethality in Mdm2-deficient mice by absence of p53. Nature. 378:206–208.

Jung YS, Liu G, Chen X. 2010. Pirh2 E3 ubiquitin ligase targets DNA polymerase eta for 20S proteasomal degradation. Mol Cell Biol. 30:1041–1048.

Jung YS, Qian Y, Chen X. 2011. The p73 tumor suppressor is targeted by Pirh2 RING finger E3 ubiquitin ligase for the proteasome-dependent degradation. J Biol Chem. 286:35388–35395.

Kaneko M, Ishiguro M, Niinuma Y, Uesugi M, Nomura Y. 2002. Human HRD1 protects against ER stress-induced apoptosis through ER-associated degradation. FEBS Lett. 532:147–152.

Kato S, Ding J, Pisck E, Jhala US, Du K. 2008. COP1 functions as a FoxO1 ubiquitin E3 ligase to regulate FoxO1-mediated gene expression. J Biol Chem. 283:35464–35473.

Kim JH, Park SM, Kang MR, Oh SY, Lee TH, Muller MT, Chung IK. 2005. Ubiquitin ligase MKRN1 modulates telomere length homeostasis through a proteolysis of hTERT. Genes Dev. 19:776–781.

Kruse JP, Gu W. 2009. MSL2 promotes Mdm2-independent cytoplasmic localization of p53. J Biol Chem. 284: 3250–3263.

Kubbutat MH, Jones SN, Vousden KH. 1997. Regulation of p53 stability by Mdm2. Nature. 387:299–303.

Kuo ML, Duncavage EJ, Mathew R, den Besten W, Pei D, Naeve D, Yamamoto T, Cheng C, Sherr CJ, Roussel MF. 2003. Arf induces p53-dependent and -independent antiproliferative genes. Cancer Res. 63:1046–1053.

Laine A, Topisirovic I, Zhai D, Reed JC, Borden KL, Ronai Z. 2006. Regulation of p53 localization and activity by Ubc13. Mol Cell Biol. 26:8901–8913.

Laine A, Ronai Z. 2007. Regulation of p53 localization and transcription by the HECT domain E3 ligase WWP1. Oncogene. 26:1477–1483.

Le Cam L, Linares LK, Paul C, Julien E, Lacroix M, Hatchi E, Triboulet R, Bossis G, Shmueli A, Rodriguez MS, et al. 2006. E4F1 is an atypical ubiquitin ligase that modulates p53 effector functions independently of degradation. Cell. 127:775–788.

Lee EW, Lee MS, Camus S, Ghim J, Yang MR, Oh W, Ha NC, Lane DP, Song J. 2009. Differential regulation of p53 and p21 by MKRN1 E3 ligase controls cell cycle arrest and apoptosis. EMBO J. 28:2100–2113.

Leng RP, Lin Y, Ma W, Wu H, Lemmers B, Chung S, Parant JM, Lozano G, Hakem R, Benchimol S. 2003. Pirh2, a p53-induced ubiquitin-protein ligase, promotes p53 degradation. Cell. 112:779–791.

Li M, Brooks CL, Wu-Baer F, Chen D, Baer R, Gu W. 2003. Mono- versus polyubiquitination: differential control of p53 fate by Mdm2. Science. 302:1972–1975.

Li M, Brooks CL, Kon N, Gu W. 2004. A dynamic role of HAUSP in the p53-Mdm2 pathway. Mol Cell. 13: 879–886.

Li DQ, Ohshiro K, Reddy SD, Pakala SB, Lee MH, Zhang Y, Rayala SK, Kumar R. 2009. E3 ubiquitin ligase COP1 regulates the stability and functions of MTA1. Proc Natl Acad Sci USA. 106:17493–17498.

Lin HK, Wang L, Hu YC, Altuwaijri S, Chang C. 2002. Phosphorylation-dependent ubiquitylation and degradation of androgen receptor by Akt require Mdm2 E3 ligase. EMBO J. 21:4037–4048.

Lin L, Ozaki T, Takada Y, Kageyama H, Nakamura Y, Hata A, Zhang JH, Simonds WF, Nakagawara A, Koseki H. 2005. Topors, a p53 and topoisomerase I-binding RING finger protein, is a coactivator of p53 in growth suppression induced by DNA damage. Oncogene. 24:3385–3396.

Liu Z, Oughtred R, Wing SS. 2005. Characterization of E3Histone, a novel testis ubiquitin protein ligase which ubiquitinates histones. Mol Cell Biol. 25:2819–2831.

Logan IR, Gaughan L, McCracken SR, Sapountzi V, Leung HY, Robson CN. 2006. Human PIRH2 enhances androgen receptor signaling through inhibition of histone deacetylase 1 and is overexpressed in prostate cancer. Mol Cell Biol. 26:6502–6510.

Maruyama S, Miyajima N, Bohgaki M, Tsukiyama T, Shigemura M, Nonomura K, Hatakeyama S. 2008. Ubiquitylation of epsilon-COP by PIRH2 and regulation of the secretion of PSA. Mol Cell Biochem. 307:73–82.

McDonald ER, 3rd, El-Deiry WS. 2004. Suppression of caspase-8- and -10-associated RING proteins results in sensitization to death ligands and inhibition of tumor cell growth. Proc Natl Acad Sci USA. 101:6170–6175.

Meacham GC, Patterson C, Zhang W, Younger JM, Cyr DM. 2001. The Hsc70 co-chaperone CHIP targets immature CFTR for proteasomal degradation. Nat Cell Biol. 3:100–105.

Meek DW, Anderson CW. 2009. Posttranslational modification of p53: cooperative integrators of function. Cold Spring Harb Perspect Biol. 1:a000950.

Meek DW, Knippschild U. 2003. Posttranslational modification of MDM2. Mol Cancer Res. 1:1017–1026.

Michael D, Oren M. 2003. The p53-Mdm2 module and the ubiquitin system. Semin Cancer Biol. 13:49–58.

Migliorini D, Lazzerini Denchi E, Danovi D, Jochemsen A, Capillo M, Gobbi A, Helin K, Pelicci PG, Marine JC. 2002. Mdm4 (Mdmx) regulates p53-induced growth

arrest and neuronal cell death during early embryonic mouse development. Mol Cell Biol. 22:5527–5538.
Migliorini D, Bogaerts S, Defever D, Vyas R, Denecker G, Radaelli E, Zwolinska A, Depaepe V, Hochepied T, Skarnes WC, et al. 2011. Cop1 constitutively regulates c-Jun protein stability and functions as a tumor suppressor in mice. J Clin Invest. 121:1329–1343.
Min JN, Whaley RA, Sharpless NE, Lockyer P, Portbury AL, Patterson C. 2008. CHIP deficiency decreases longevity, with accelerated aging phenotypes accompanied by altered protein quality control. Mol Cell Biol. 28: 4018–4025.
Nadav E, Shmueli A, Barr H, Gonen H, Ciechanover A, Reiss Y. 2003. A novel mammalian endoplasmic reticulum ubiquitin ligase homologous to the yeast Hrd1. Biochem Biophys Res Commun. 303:91–97.
Noy T, Suad O, Taglicht D, Ciechanover A. 2012. HUWE1 ubiquitinates MyoD and targets it for proteasomal degradation. Biochem Biophys Res Commun. 418: 408–413.
Oliner JD, Kinzler KW, Meltzer PS, George DL, Vogelstein B. 1992. Amplification of a gene encoding a p53-associated protein in human sarcomas. Nature. 358: 80–83.
Oyanagi H, Takenaka K, Ishikawa S, Kawano Y, Adachi Y, Ueda K, Wada H, Tanaka F. 2004. Expression of LUN gene that encodes a novel RING finger protein is correlated with development and progression of non-small cell lung cancer. Lung Cancer 46:21–28.
Parant J, Chavez-Reyes A, Little NA, Yan W, Reinke V, Jochemsen AG, Lozano G. 2001. Rescue of embryonic lethality in Mdm4-null mice by loss of Trp53 suggests a nonoverlapping pathway with MDM2 to regulate p53. Nat Genet. 29:92–95.
Parsons JL, Tait PS, Finch D, Dianova II, Edelmann MJ, Khoronenkova SV, Kessler BM, Sharma RA, McKenna WG, Dianov GL. 2009. Ubiquitin ligase ARF-BP1/Mule modulates base excision repair. EMBO J. 28:3207–3215.
Petrucelli L, Dickson D, Kehoe K, Taylor J, Snyder H, Grover A, De Lucia M, McGowan E, Lewis J, Prihar G, et al. 2004. CHIP and Hsp70 regulate tau ubiquitination, degradation and aggregation. Hum Mol Genet. 13: 703–714.
Pickart CM. 2001. Mechanisms underlying ubiquitination. Annu Rev Biochem. 70:503–533.
Qi L, Heredia JE, Altarejos JY, Screaton R, Goebel N, Niessen S, Macleod IX, Liew CW, Kulkarni RN, Bain J, et al. 2006. TRB3 links the E3 ubiquitin ligase COP1 to lipid metabolism. Science. 312:1763–1766.
Rajendra R, Malegaonkar D, Pungaliya P, Marshall H, Rasheed Z, Brownell J, Liu LF, Lutzker S, Saleem A, Rubin EH. 2004. Topors functions as an E3 ubiquitin ligase with specific E2 enzymes and ubiquitinates p53. J Biol Chem. 279:36440–36444.
Rasheed ZA, Saleem A, Ravee Y, Pandolfi PP, Rubin EH. 2002. The topoisomerase I-binding RING protein, topors, is associated with promyelocytic leukemia nuclear bodies. Exp Cell Res. 277:152–160.
Renner F, Moreno R, Schmitz ML. 2010. SUMOylation-dependent localization of IKKepsilon in PML nuclear bodies is essential for protection against DNA-damage-triggered cell death. Mol Cell. 37:503–515.
Saleem A, Dutta J, Malegaonkar D, Rasheed F, Rasheed Z, Rajendra R, Marshall H, Luo M, Li H, Rubin EH. 2004. The topoisomerase I- and p53-binding protein topors is differentially expressed in normal and malignant human tissues and may function as a tumor suppressor. Oncogene. 23:5293–5300.
Sasaki S, Nakamura T, Arakawa H, Mori M, Watanabe T, Nagawa H, Croce CM. 2002. Isolation and characterization of a novel gene, hRFI, preferentially expressed in esophageal cancer. Oncogene. 21:5024–5030.
Scheffner M, Huibregtse JM, Vierstra RD, Howley PM. 1993. The HPV-16 E6 and E6-AP complex functions as a ubiquitin-protein ligase in the ubiquitination of p53. Cell 75:495–505.
Sdek P, Ying H, Chang DL, Qiu W, Zheng H, Touitou R, Allday MJ, Xiao ZX. 2005. MDM2 promotes proteasome-dependent ubiquitin-independent degradation of retinoblastoma protein. Mol Cell. 20:699–708.
Sheng Y, Laister RC, Lemak A, Wu B, Tai E, Duan S, Lukin J, Sunnerhagen M, Srisailam S, Karra M, et al. 2008. Molecular basis of Pirh2-mediated p53 ubiquitylation. Nat Struct Mol Biol. 15:1334–1342.
Shenoy SK, McDonald PH, Kohout TA, Lefkowitz RJ. 2001. Regulation of receptor fate by ubiquitination of activated beta 2-adrenergic receptor and beta-arrestin. Science. 294:1307–1313.
Shi D, Pop MS, Kulikov R, Love IM, Kung AL, Grossman SR. 2009. CBP and p300 are cytoplasmic E4 polyubiquitin ligases for p53. Proc Natl Acad Sci USA. 106:16275–16280.
Shieh SY, Ikeda M, Taya Y, Prives C. 1997. DNA damage-induced phosphorylation of p53 alleviates inhibition by MDM2. Cell. 91:325–334.
Shieh SY, Taya Y, Prives C. 1999. DNA damage-inducible phosphorylation of p53 at N-terminal sites including a novel site, Ser20, requires tetramerization. EMBO J. 18:1815–1823.
Shimura H, Schwartz D, Gygi SP, Kosik KS. 2004. CHIP-Hsc70 complex ubiquitinates phosphorylated tau and enhances cell survival. J Biol Chem. 279:4869–4876.
Shvarts A, Steegenga WT, Riteco N, van Laar T, Dekker P, Bazuine M, van Ham RC, van der Houven van Oordt W, Hateboer G, van der Eb AJ, et al. 1996. MDMX: a novel p53-binding protein with some functional properties of MDM2. EMBO J. 15:5349–5357.
Simelyte E, Rosengren S, Boyle DL, Corr M, Green DR, Firestein GS. 2005. Regulation of arthritis by p53: critical role of adaptive immunity. Arthriris Rheum. 52: 1876–1884.
Stad R, Little NA, Xirodimas DP, Frenk R, van der Eb AJ, Lane DP, Saville MK, Jochemsen AG. 2001. Mdmx stabilizes p53 and Mdm2 via two distinct mechanisms. EMBO Rep. 2:1029–1034.
Sun L, Shi L, Li W, Yu W, Liang J, Zhang H, Yang X, Wang Y, Li R, Yao X, et al. 2009. JFK, a Kelch domain-containing F-box protein, links the SCF complex to p53 regulation. Proc Natl Acad Sci USA. 106:10195–10200.
Taira N, Yamamoto H, Yamaguchi T, Miki Y, Yoshida K. 2010. ATM augments nuclear stabilization of DYRK2 by inhibiting MDM2 in the apoptotic response to DNA damage. J Biol Chem. 285:4909–4919.
Tibbetts RS, Brumbaugh KM, Williams JM, Sarkaria JN, Cliby WA, Shieh SY, Taya Y, Prives C, Abraham RT. 1999. A role for ATR in the DNA damage-induced phosphorylation of p53. Genes Dev. 13:152–157.
Tombes RM, Mikkelsen RB, Jarvis WD, Grant S. 1999. Downregulation of delta CaM kinase II in human tumor cells. Biochim Biophys Acta. 1452:1–11.
Vitari AC, Leong KG, Newton K, Yee C, O'Rourke K, Liu J, Phu L, Vij R, Ferrando R, Couto SS, et al. 2011. COP1 is

a tumour suppressor that causes degradation of ETS transcription factors. Nature. 474:403–406.
Wang Z, Yang B, Dong L, Peng B, He X, Liu W. 2011. A novel oncoprotein Pirh2: rising from the shadow of MDM2. Cancer Sci. 102:909–917.
Weber JD, Jeffers JR, Rehg JE, Randle DH, Lozano G, Roussel MF, Sherr CJ, Zambetti GP. 2000. p53-independent functions of the p19(ARF) tumor suppressor. Genes Dev. 14:2358–2365.
Weger S, Hammer E, Heilbronn R. 2005. Topors acts as a SUMO-1 E3 ligase for p53 in vitro and in vivo. FEBS Lett. 579:5007–5012.
Wei W, Kaelin WG, Jr. 2011. Good COP1 or bad COP1? In vivo veritas. J Clin Invest. 121:1263–1265.
Wertz IE, O'Rourke KM, Zhang Z, Dornan D, Arnott D, Deshaies RJ, Dixit VM. 2004. Human De-etiolated-1 regulates c-Jun by assembling a CUL4A ubiquitin ligase. Science. 303:1371–1374.
Whitesell L, Sutphin PD, Pulcini EJ, Martinez JD, Cook PH. 1998. The physical association of multiple molecular chaperone proteins with mutant p53 is altered by geldanamycin, an hsp90-binding agent. Mol Cell Biol. 18:1517–1524.
Wu H, Zeinab RA, Flores ER, Leng RP. 2011. Pirh2, a ubiquitin E3 ligase, inhibits p73 transcriptional activity by promoting its ubiquitination. Mol Cancer Res. 9:1780–1790.
Xu W, Marcu M, Yuan X, Mimnaugh E, Patterson C, Neckers L. 2002. Chaperone-dependent E3 ubiquitin ligase CHIP mediates a degradative pathway for c-ErbB2/Neu. Proc Natl Acad Sci USA. 99:12847–12852.
Yamasaki S, Yagishita N, Sasaki T, Nakazawa M, Kato Y, Yamadera T, Bae E, Toriyama S, Ikeda R, Zhang L, et al. 2007. Cytoplasmic destruction of p53 by the endoplasmic reticulum-resident ubiquitin ligase 'Synoviolin'. EMBO J. 26:113–122.
Yang W, Rozan LM, McDonald ER, 3rd, Navaraj A, Liu JJ, Matthew EM, Wang W, Dicker DT, El-Deiry WS. 2007. CARPs are ubiquitin ligases that promote MDM2-independent p53 and phospho-p53ser20 degradation. J Biol Chem. 282:3273–3281.
Yi C, Wang H, Wei N, Deng XW. 2002. An initial biochemical and cell biological characterization of the mammalian homologue of a central plant developmental switch, COP1. BMC Cell Biol. 3:30.
Yoon SY, Lee Y, Kim JH, Chung AS, Joo JH, Kim CN, Kim NS, Choe IS, Kim JW. 2005. Over-expression of human UREB1 in colorectal cancer: HECT domain of human UREB1 inhibits the activity of tumor suppressor p53 protein. Biochem Biophys Res Commun. 326:7–17.
Zhang Y, Xiong Y, Yarbrough WG. 1998. ARF promotes MDM2 degradation and stabilizes p53: ARF-INK4a locus deletion impairs both the Rb and p53 tumor suppression pathways. Cell. 92:725–734.
Zhang Z, Wang H, Li M, Agrawal S, Chen X, Zhang R. 2004. MDM2 is a negative regulator of p21WAF1/CIP1, independent of p53. J Biol Chem. 279:16000–16006.
Zhong Q, Gao W, Du F, Wang X. 2005. Mule/ARF-BP1, a BH3-only E3 ubiquitin ligase, catalyzes the polyubiquitination of Mcl-1 and regulates apoptosis. Cell. 121:1085–1095.