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PERSPECTIVE

A new layer of degradation mechanism for PR-Set7/Set8 during cell cycle

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ABSTRACT

Set8 is critically involved in transcription regulation, cell cycle progression and genomic stability. Emerging evidence has revealed that E3 ubiquitin ligases such as $CRL4^{cdt2}$ and SCF^{Skp2} regulate Set8 protein abundance. However, it is unclear whether other E3 ligase(s) could govern Set8 level for proper cell cycle progression in response to genotoxic stress such as UV irradiation. Recently, we report that the $SCF^{\beta\text{-TRCP}}$ complex regulates Set8 protein stability by targeting it for ubiquitination and subsequent degradation. Notably, Set8 interacts with the $SCF^{\beta\text{-TRCP}}$ E3 ligase complex. We further revealed a critical role of CKI in $SCF^{\beta\text{-TRCP}}$-mediated degradation of Set8. Mechanistically, CKI-mediated phosphorylation of Set8 at the S253 site promotes its destruction by $SCF^{\beta\text{-TRCP}}$. Importantly, $SCF^{\beta\text{-TRCP}}$-dependent Set8 destruction also contributes to the tight control of cell proliferation and cell cycle progression, in response to UV irradiation. Here, we summarize our new findings regarding the crucial role of β-TRCP in CKI-mediated Set8 degradation, which could provide new evidence to support that dysregulation of a tight regulatory network of Set8 could lead to aberrant cell cycle process.

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Set8 (also known as PR-Set7 and SETD8) has been previously characterized as a histone methyltransferase that specifically monomethylates Lys (20) of histone H4 (H4K20).[1,2] Set8 is critically involved in multiple cellular processes including transcription regulation, cell cycle, DNA repair, genome integrity and tumor metastasis.[3] The biological function of Set8 in cell cycle is largely exerted through suppressing DNA replication.[3,4] Further studies identified that Set8 could methylate non-histone proteins such as p53, Twist, Wnt-activated genes, PCNA (proliferating cell nuclear antigen), ERα (estrogen receptor) and AR (androgen receptor).[5] These results indicate that Set8 may play a key role in the development and progression of cancers. In keeping with this notion, multiple studies have demonstrated that high levels of Set8 are associated with tumor metastasis and poor survival of breast cancer patients.[6,11] Similarly, Set8 overexpression led to shorter survival time, suggesting that Set8 might be a predictor of worse outcome for gastric cancer.[6] Mechanistically, Set8 interacted with AR and promoted AR-mediated transcription activation, leading to enhanced prostate cancer cell proliferation.[7] Notably, Set8 interacted with Twist and induced epithelial-mesenchymal transition (EMT), and subsequently led to enhanced cell invasion in breast cancer.[8] Taken together, Set8 could play an oncogenic role to facilitate tumorigenesis.

Since Set8 is a key oncoprotein in a variety of human cancers, it is pivotal to determine how Set8 is regulated in cellular processes. A number of studies reported that Set8 is regulated at both the transcriptional level[9] and post-translational level.[10] Some enzymes have been validated to control Set8 modification, including kinases, SUMO (small ubiquitin-like modifier), and ubiquitin ligases. For example, the Ser29 residue of Set8 is phosphorylated by Cyclin B/Cdk1 (cyclin dependent kinase 1) during mitosis.[11] One E3 ligase $CRL4^{Cdt2}$(Cullin-RING ubiquitin ligase 4^{Cdt2}) controls the Set8 ubiquitination and degradation.[12-14] Moreover, the anaphase-promoting complex APC^{Cdh1} was also confirmed to govern the ubiquitination and degradation of Set8 during the G1 phase.[11] Recently, microRNAs (miRNAs) have been validated to control the Set8 expression in human malignancies. It has been known that miRNAs, small non-coding RNAs, largely exert their biological functions through inhibiting the translation or targeting the mRNAs for degradation through direct binding to the 3′-UTR region of mRNAs.[15] Several studies have revealed that Set8 is a direct target of miR-502.[16,17] In support of this concept, breast cancer patients with lower level of miR-502 have high level of Set8.[17] Moreover, the low expression ratio of miR-502 to Set8 mRNA is correlated to relatively poor overall survival in breast cancer patients.[17] Consistent with the findings, treatment with miR-502 inhibited cell proliferation and cell cycle and retarded cell migration, invasion and EMT partly through inhibition of Set8.[17] Another elegant study discovered that miR-7 inhibited cell invasion and sensitized tumor cells to DNA damages in part through targeting Set8 in breast cancer cells.[18] Interestingly, a polymorphism at the miR-502 binding site in the 3′ UTR of the Set8 gene is associated with the outcome of various types of human cancers including small-cell lung cancer, ovarian cancer, hepatocellular carcinoma, cervical cancer, and non-Hodgkin's lymphoma.[19-21] These experimental evidences

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together suggest a possible oncogenic role for Set8 in facilitating tumorigenesis.

It is known that ubiquitination leads to degradation of proteins, which controls a plethora of cellular functions such as cell proliferation, cell cycle and survival.[22-25] This process is catalyzed by a group of enzymes including ubiquitin activating enzyme (E1), an ubiquitin-conjugating enzyme (E2), and an ubiquitin ligase (E3). It is noteworthy that the E3 can specifically determine the substrates for ubiquitination and more than 600 E3 ligases have been reported in human genome.[26,27] Among these E3 enzymes, the CRLs are the largest E3 ligase family in eukaryotes.[28] It has been known that Cullins act as a scaffold protein, and its C-terminus is associated with the RING finger protein RBX1/ROC1 or RBX2/ROC2. The N-terminal region of Cullins binds with Cullin-specific adaptor protein to target diverse substrates.[29,30] Furthermore, CRLs activity is regulated by Nedd8 post-translational modification known as neddylation. Interestingly, this process can be reversed by COP9 signalosome (CSN)-mediated deneddylation, leading to inactivation of CRLs.[30-32]

Among eight Cullins (CUL1-7 and PARC), Cullin4 (CUL4) has been well studied. Cullin4 consists of 2 members, CUL4A and CUL4B, which share extensively sequence homology and functional redundancy.[28,30] CUL4 is expressed aberrantly in a wide range of human tumors and involves in tumor-related changes including cell cycle, DNA damage repair, histone methylation and oncoproteins turnover.[28,30] In particular, the aberrant expression of CUL4A has been identified in breast cancer, squamous cell carcinoma, pleural mesothelioma and non-small cell lung cancer.[33-37] Intriguingly, CUL4A induced EMT and promoted cancer metastasis in part via regulation of ZEB1 (zinc finger E-box-binding homebox 1) expression.[38] Strikingly, overexpression of CUL4 is associated with poor outcome in node-negative breast cancer.[39] In support of this notion, depletion of *CUL4A* inhibited cell proliferation, colony formation and breast cancer development.[40] Notably, Liu et al. generated *Cul4a* conditional knockout mice and found that skin-specific *Cul4a* ablation enhanced resistance to UV-induced skin carcinogenesis due to potential augmentation of cellular DNA repair proficiency.[41] Moreover, transgenic mice with cre-inducible overexpression of the *Cul4a* gene exhibited hyperplasia.[42] Therefore, CUL4A could play an oncogenic role in the tumorigenesis.

Emerging evidence has suggested that the abnormal cell cycle is a common feature of cancer cells. Remarkably, CRL4 has been validated to control cell cycle through regulation of multiple proteins including cell cycle proteins (Cyclins), cyclin-dependent kinases (CDKs), and cyclin-dependent kinase inhibitors (CDKIs), which are critical for cell cycle process.[30] For example, Cyclin E is a key regulator of the entry from G1 phase to S phase and its aberrant expression is observed in several types of human cancers.[43,44] Studies have discovered that CRL4 regulated the degradation of Cyclin E.[45,46] Overexpression of CRL4 decreased Cyclin E protein level, while down-regulation of CRL4 increased Cyclin E expression.[45,46] Clearly, p21 is an inhibitor of CDK and prevents the occurrence of the S phase as well as regulates the tumor development and progression.[47] Consistently, silencing *CRL4* by its siRNA increased the level of p21, indicating that CRL4 may regulate p21 expression.[48,49] In addition, p27 and p16, 2 key CDKIs, are also regulated by CRL4.[46,50],[51] These reports indicate that CRL4 exerts its oncogenic function partly through dysregulation of cell cycle.

β-TRCP (beta-transducin repeats containing proteins) belongs to the SCF (Skp1-Cullin-1-F-box protein) type of E3 ligase complexes. The SCF ligase complex included Skp1, Cullin-1, Rbx1/Roc1, and one of the 69 F-box proteins. Notably, β-TRCP recognizes the consensus sequence D-pS-G-X-X-pS (X represents any amino acid) degron of substrates.[52] Moreover, phosphorylation of both serine residues by specific kinases is required for β-TRCP-mediated degradation.[52] Dysregulation of β-TRCP is involved in regulation of several cellular processed such as cell cycle, apoptosis, invasion, and tumorigenesis through recognizing specific substrates including EMI-1 (early mitotic inhibitor-1),[53,54] Wee1,[55] and Cdc25A (cell division cycle 25 homolog A).[56,57] For example, the degradation of EMI-1 by β-TRCP induced mitotic catastrophe.[53,54] β-TRCP targeted Wee1, a Cdc2 inhibitory kinase, leading to abnormal mitosis.[55] Biologically, β-TRCP regulated Cdc25A to promote the cell cycle progression.[56,57] Moreover, β-TRCP recognized and degraded BTG (B-cell translocation gene) and thus controlled the cell cycle and cell proliferation.[58] The centriolar protein Plk4 (polo-like kinase 4) is a regulator of centriole biogenesis, and β-TRCP can bind and degrade Plk4, which is phosphorylated by itself.[59,60] Another elegant report shows that Plk1 can phosphorylate Bora and promote its degradation by β-TRCP, leading to subsequent regulation of mitotic progression.[61] Similarly, β-TRCP was reported to regulate centrosome separation partly via targeting CEP68 for degradation.[62] Interestingly, after exposure to UV irradiation, Securin is degraded by β-TRCP and results in cell cycle arrest.[63] Moreover, REST (repressor element-1-silencing transcription factor), which participates in cell cycle, is also degraded by β-TRCP.[64] In line with this observation, β-TRCP-mediated degradation of Claspin is important for the efficient and timely termination of the DNA replication checkpoint.[65] Intriguingly, inhibition of Claspin proteolysis led to subsequent activation of Chk1 and attenuated the recovery from the DNA replication stress response, thereby delaying entry into mitosis.[65] These findings strongly suggest that β-TRCP plays a critical role in regulation of cell cycle progression.

A number of evidence indicates that β-TRCP could be an oncoprotein in certain types of human cancers. In support of this notion, overexpression of β-TRCP has been observed in a variety of human cancers such as colorectal cancer,[66] hepatoblastoma,[67] pancreatic cancer,[68] and melanoma.[69] Consistent with an oncogenic role in human cancers, β-TRCP enhanced cell growth and tumor growth in mice.[70,71] Surprisingly, studies have argued that β-TRCP could also play tumor suppressive role in a tissue-specific manner. In keeping with this note, mutations of β-TRCP were observed in several human cancers including gastric cancer,[72,73] prostate cancer[74] and breast cancer.[75] Since β-TRCP targets both oncoproteins and tumor suppressors for proteolysis, β-TRCP could play an oncogenic or tumor suppressive role in the tissue-specific or cellular context-dependent manner. Without a doubt, conditional engineered animal models are necessary to further parse the exact function of β-TRCP in tumorigenesis.

As we described before, Set8 is a cell-cycle-regulated enzyme and promotes chromatin compaction.[10] CRL4 E3 ligase ubiquitinated and degraded Set8 in S phase of the cell cycle, which required the interaction between PCNA and Set8.[13,14] The inhibition of the CRL4-Cdt2-PCNA-Set8 degradation axis delayed

the progression from G2 phase and cell proliferation.[13,14] Moreover, the dysregulation of the CRL4-Cdt2-PCNA-Set8 axis led to DNA damage and induction of p53 and p53-transactivated proapoptotic genes.[13] Additionally, depletion of *CRL4* (or *Cdt2*) increased Set8 stability and the level of aberrant H4K20me1. A checkpoint-mediated G2 arrest happened due to the dysregulation of Set8, and destruction of Set8 preserved genome stability through preventing aberrant chromatin compaction during DNA synthesis.[14] Furthermore, the ultraviolet irradiation accelerated the degradation of Set8 in the CRL4 (Cdt2) ubiquitination way.[76] Interestingly, there is a cross-regulation between Cullin 4 and Cullin 1 E3 ubiquitin ligases. For example, Cdt2 is autoubiquitylated by the CRL4A E3 ubiquitin ligase and it is also additionally polyubiquitylated and degraded by CRL1-FBXO11.[77] CRL1 (FBXO11)-mediated degradation of Cdt2 promoted the stabilization of Set8 and p21.[77] The degradation of Cdt2 also stimulated the migration of epithelial cells and subsequently the stabilization of Set8.[77] One study showed that Cdt2 is a prognostic marker and a therapeutic target in melanoma. With the treatment of pevonedistat, Cdt2 is suppressed and melanoma cell growth is promoted due to the stabilization of Set8.[78] Taken together, these results demonstrate that CRL4 (Cdt2)-dependent cell-cycle regulation of Set8 for the maintenance of cell viability and chromatin compaction.

Importantly, Set8 has been reported to be degraded after UV exposure, but the exact mechanism remains largely unclear. Our study first investigated that Set8 interacts with the $SCF^{\beta\text{-TRCP}}$ E3 ligase complex.[79] The co-immunoprecipitation experiments are performed to find that exogenously expressed Set8 was associated with endogenous β-TRCP1, and β-TRCP1 mutant (R474A) reduced the interaction between the β-TRCP1 and Set8.[52] Moreover, our results indicated that Set8 interacted with SCF components including Skp1 and Rbx1.[79] Importantly, depletion of endogenous *β-TRCP* extended the half-life of endogenous Set8 protein and increased the level of Set8 protein. In support of the notion that both Cullin1 and Cullin 4 are involved in controlling Set8 stability, the protein level of Set8 was upregulated after depletion of either *Cullin1* or *Cullin4*. It is known that substrates are phosphorylated by kinase and then degraded in the SCF type of E3 ligases-dependent way.[52,80] We found that CKI (casein kinase I) phosphorylated Set8 at Ser253 and subsequently triggered its destruction by $SCF^{\beta\text{-TRCP}}$, suggesting that CKI could be a key upstream kinase to govern Set8 degradation.[79] Consistently, the inactivation of CKI also disrupted the interaction between Set8 and β-TRCP1.

Previous studies showed that Set8 levels are significantly reduced after DNA damage.[13,14] In line with this concept, we also observed that the levels of endogenous Set8 are significantly reduced in cells after UV treatment.[79] Intriguingly, UV-triggered reduction of Set8 was partially reversed by depletion of endogenous *β-TRCP1*. Biologically, overexpression of Set8 inhibited cell proliferation.[14] In line with this notion, we also found that ectopic expression of $Set8^{WT}$ inhibited cell proliferation, while the $Set8^{S253A}$ mutants caused a more marked effect in cell proliferation inhibition.[79] Accumulating evidence indicated that acute expression of an oncogene such as Ha-Ras,[81] Akt,[82,83] BRAF[84,85] or HIF (hypoxia-inducible factor 1),[86] could lead to cell growth arrest but not accelerate cell proliferation. This phenomenon is called OIS (oncogene-induced senescence). In concert with these observations, deletion of tumor suppressor *PTEN (phosphatase and tensin homolog 10)*[87,88] or *VHL (Von Hippel-lindau)*[89] also led to the onset of senescence, which could be due to the aberrant expression of pAkt and HIF oncoproteins. Ectopic expression of BRAF directly caused senescence in melanocytes.[84] Logically, the disruption of $CRL4^{cdt2}$ or the $SCF^{\beta\text{-TRCP}}$ pathway led to Set8 stabilization, and subsequently triggered cell growth arrest partly via OIS mechanism.

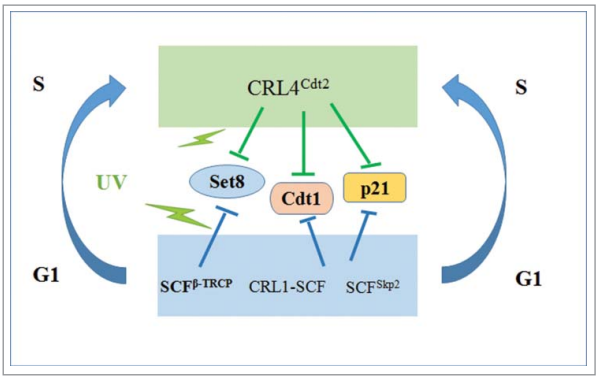

Figure 1. A schematic model illustrating how β-TRCP, Skp2 and Cdt2 govern the protein stability of Set8 during the cell cycle procession. In G1 phase, Set8 could be controlled by SCF^{Skp2} and $SCF^{\beta\text{-TRCP}}$. However, in S phase, Set8 destruction is largely governed by $CRL4^{Cdt2}$.

In summary, there are at least 2 major ways for Set8 degradation during the cell cycle transitions. Importantly, different E3 ligases could regulate different cell cycle regulators such as p21, Cdt2, and Set8. Set8 could be governed by Skp2 and β-TRCP in G1 phase, whereas Set8 destruction is controlled by $CRL4^{cdt2}$ in S phase (Fig. 1). Although these findings dissect the regulation of Set8 by 3 E3 ligases, how these ligases fine-tune the control of the timely destruction of Set8 to ensure proper cell cycle process is not elucidated. Moreover, tissue specific knockout mice or transgenic mice are required to further determine contribution of Set8 in tumorigenesis. As Set8 is tightly associated with tumorigenesis, targeting Set8 could be a potential strategy for the treatment of human cancers. To this end, one study has discovered that Set8 could be regulated by estradiol and bisphenol A in ovarian cancer cells.[90] Moreover, a natural compound curcumin has been reported to exert its anti-tumor activity through regulation of Set8 in pancreatic cancer.[91] Further investigations are needed to develop and discover new safer inhibitors of Set8 for human cancer patients with overexpressing Set8.

Disclosure of potential conflicts of interest

The authors declare no conflict of interest.

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References

[1] Jorgensen S, Elvers I, Trelle MB, Menzel T, Eskildsen M, Jensen ON, Helleday T, Helin K, Sorensen CS. The histone methyltransferase SET8 is required for S-phase progression. J Cell Biol 2007; 179:1337-45; PMID:18166648; http://dx.doi.org/10.1083/jcb.200706150

[2] Couture JF, Collazo E, Brunzelle JS, Trievel RC. Structural and functional analysis of SET8, a histone H4 Lys-20 methyltransferase. Genes Dev 2005; 19:1455-65; PMID:15933070; http://dx.doi.org/10.1101/gad.1318405

[3] Yin Y, Yu VC, Zhu G, Chang DC. SET8 plays a role in controlling G1/S transition by blocking lysine acetylation in histone through binding to H4 N-terminal tail. Cell Cycle 2008; 7:1423-32; PMID:18418072; http://dx.doi.org/10.4161/cc.7.10.5867

[4] Huen MS, Sy SM, van Deursen JM, Chen J. Direct interaction between SET8 and proliferating cell nuclear antigen couples H4-K20 methylation with DNA replication. J Biol Chem 2008; 283:11073-7; PMID:18319261; http://dx.doi.org/10.1074/jbc.C700242200

[5] Liu B, Zhang X, Song F, Liu Q, Dai H, Zheng H, Cui P, Zhang L, Zhang W, Chen K. A functional single nucleotide polymorphism of SET8 is prognostic for breast cancer. Oncotarget 2016; 7(23):34277-87; http://dx.doi.org/10.18632/oncotarget.9099

[6] Shi XL, Guo ZJ, Wang XL, Liu XL, Shi GF. SET8 expression is associated with overall survival in gastric cancer. Genet Mol Res 2015; 14:15609-15; PMID:26634528; http://dx.doi.org/10.4238/2015.December.1.12

[7] Yao L, Li Y, Du F, Han X, Li X, Niu Y, Ren S, Sun Y. Histone H4 Lys 20 methyltransferase SET8 promotes androgen receptor-mediated transcription activation in prostate cancer. Biochem Biophys Res Commun 2014; 450:692-6; PMID:24937452; http://dx.doi.org/10.1016/j.bbrc.2014.06.033

[8] Yang F, Sun L, Li Q, Han X, Lei L, Zhang H, Shang Y. SET8 promotes epithelial-mesenchymal transition and confers TWIST dual transcriptional activities. EMBO J 2012; 31:110-23; PMID:21983900; http://dx.doi.org/10.1038/emboj.2011.364

[9] Wakabayashi K, Okamura M, Tsutsumi S, Nishikawa NS, Tanaka T, Sakakibara I, Kitakami J, Ihara S, Hashimoto Y, Hamakubo T, et al. The peroxisome proliferator-activated receptor gamma/retinoid X receptor alpha heterodimer targets the histone modification enzyme PR-Set7/Setd8 gene and regulates adipogenesis through a positive feedback loop. Mol Cell Biol 2009; 29:3544-55; PMID:19414603; http://dx.doi.org/10.1128/MCB.01856-08

[10] Beck DB, Oda H, Shen SS, Reinberg D. PR-Set7 and H4K20me1: at the crossroads of genome integrity, cell cycle, chromosome condensation, and transcription. Genes Dev 2012; 26:325-37; PMID:22345514; http://dx.doi.org/10.1101/gad.177444.111

[11] Wu S, Wang W, Kong X, Congdon LM, Yokomori K, Kirschner MW, Rice JC. Dynamic regulation of the PR-Set7 histone methyltransferase is required for normal cell cycle progression. Genes Dev 2010; 24:2531-42; PMID:20966048; http://dx.doi.org/10.1101/gad.1984210

[12] Oda H, Hubner MR, Beck DB, Vermeulen M, Hurwitz J, Spector DL, Reinberg D. Regulation of the histone H4 monomethylase PR-Set7 by CRL4(Cdt2)-mediated PCNA-dependent degradation during DNA damage. Mol Cell 2010; 40:364-76; PMID:21035370; http://dx.doi.org/10.1016/j.molcel.2010.10.011

[13] Abbas T, Shibata E, Park J, Jha S, Karnani N, Dutta A. CRL4(Cdt2) regulates cell proliferation and histone gene expression by targeting PR-Set7/Set8 for degradation. Mol Cell 2010; 40:9-21; PMID:20932471; http://dx.doi.org/10.1016/j.molcel.2010.09.014

[14] Centore RC, Havens CG, Manning AL, Li JM, Flynn RL, Tse A, Jin J, Dyson NJ, Walter JC, Zou L. CRL4(Cdt2)-mediated destruction of the histone methyltransferase Set8 prevents premature chromatin compaction in S phase. Mol Cell 2010; 40:22-33; PMID:20932472; http://dx.doi.org/10.1016/j.molcel.2010.09.015

[15] Lin S, Gregory RI. MicroRNA biogenesis pathways in cancer. Nat Rev Cancer 2015; 15:321-33; PMID:25998712; http://dx.doi.org/10.1038/nrc3932

[16] Song F, Zheng H, Liu B, Wei S, Dai H, Zhang L, Calin GA, Hao X, Wei Q, Zhang W, et al. An miR-502-binding site single-nucleotide polymorphism in the 3′-untranslated region of the SET8 gene is associated with early age of breast cancer onset. Clin Cancer Res 2009; 15:6292-300; PMID:19789321; http://dx.doi.org/10.1158/1078-0432.CCR-09-0826

[17] Liu B, Zhang X, Song F, Zheng H, Zhao Y, Li H, Zhang L, Yang M, Zhang W, Chen K. MiR-502/SET8 regulatory circuit in pathobiology of breast cancer. Cancer Lett 2016; 376:259-67; PMID:27080302; http://dx.doi.org/10.1016/j.canlet.2016.04.008

[18] Yu N, Huangyang P, Yang X, Han X, Yan R, Jia H, Shang Y, Sun L. microRNA-7 suppresses the invasive potential of breast cancer cells and sensitizes cells to DNA damages by targeting histone methyltransferase SET8. J Biol Chem 2013; 288:19633-42; PMID:23720754; http://dx.doi.org/10.1074/jbc.M113.475657

[19] Ding C, Li R, Peng J, Li S, Guo Z. A polymorphism at the miR-502 binding site in the 3′ untranslated region of the SET8 gene is associated with the outcome of small-cell lung cancer. Exp Ther Med 2012; 3:689-92; PMID:22969952

[20] Guo Z, Wu C, Wang X, Wang C, Zhang R, Shan B. A polymorphism at the miR-502 binding site in the 3′-untranslated region of the histone methyltransferase SET8 is associated with hepatocellular carcinoma outcome. Int J Cancer 2012; 131:1318-22; PMID:22095217; http://dx.doi.org/10.1002/ijc.27352

[21] Wang C, Guo Z, Wu C, Li Y, Kang S. A polymorphism at the miR-502 binding site in the 3′ untranslated region of the SET8 gene is associated with the risk of epithelial ovarian cancer. Cancer Genet 2012; 205:373-6; PMID:22867998; http://dx.doi.org/10.1016/j.cancergen.2012.04.010

[22] Eldridge AG, O'Brien T. Therapeutic strategies within the ubiquitin proteasome system. Cell Death Differ 2010; 17:4-13; PMID:19557013; http://dx.doi.org/10.1038/cdd.2009.82

[23] Hoeller D, Dikic I. Targeting the ubiquitin system in cancer therapy. Nature 2009; 458:438-44; PMID:19325623; http://dx.doi.org/10.1038/nature07960

[24] Komander D, Rape M. The ubiquitin code. Annu Rev Biochem 2012; 81:203-29; PMID:22524316; http://dx.doi.org/10.1146/annurev-biochem-060310-170328

[25] Varshavsky A. The ubiquitin system, an immense realm. Annu Rev Biochem 2012; 81:167-76; PMID:22663079; http://dx.doi.org/10.1146/annurev-biochem-051910-094049

[26] Li W, Bengtson MH, Ulbrich A, Matsuda A, Reddy VA, Orth A, Chanda SK, Batalov S, Joazeiro CA. Genome-wide and functional annotation of human E3 ubiquitin ligases identifies MULAN, a mitochondrial E3 that regulates the organelle's dynamics and signaling. PLoS One 2008; 3:e1487; PMID:18213395; http://dx.doi.org/10.1371/journal.pone.0001487

[27] Zheng N, Wang Z, Wei W. Ubiquitination-mediated degradation of cell cycle-related proteins by F-box proteins. Int J Biochem Cell Biol 2016; 73:99-110; PMID:26860958; http://dx.doi.org/10.1016/j.biocel.2016.02.005

[28] Lee J, Zhou P. Pathogenic Role of the CRL4 Ubiquitin Ligase in Human Disease. Front Oncol 2012; 2:21; PMID:22649780

[29] Hellmann H, Estelle M. Plant development: regulation by protein degradation. Science 2002; 297:793-7; PMID:12161644; http://dx.doi.org/10.1126/science.1072831

[30] Sang Y, Yan F, Ren X. The role and mechanism of CRL4 E3 ubiquitin ligase in cancer and its potential therapy implications. Oncotarget 2015; 6:42590-602; PMID:26460955

[31] Duda DM, Borg LA, Scott DC, Hunt HW, Hammel M, Schulman BA. Structural insights into NEDD8 activation of cullin-RING ligases: conformational control of conjugation. Cell 2008; 134:995-1006; PMID:18805092; http://dx.doi.org/10.1016/j.cell.2008.07.022

[32] Lyapina S, Cope G, Shevchenko A, Serino G, Tsuge T, Zhou C, Wolf DA, Wei N, Shevchenko A, Deshaies RJ. Promotion of NEDD-CUL1 conjugate cleavage by COP9 signalosome. Science 2001; 292:1382-5; PMID:11337588; http://dx.doi.org/10.1126/science.1059780

[33] Melchor L, Saucedo-Cuevas LP, Munoz-Repeto I, Rodriguez-Pinilla SM, Honrado E, Campoverde A, Palacios J, Nathanson KL, Garcia MJ, Benitez J. Comprehensive characterization of the DNA amplification at 13q34 in human breast cancer reveals TFDP1 and CUL4A as likely candidate target genes. Breast Cancer Res 2009; 11:R86; PMID:19995430; http://dx.doi.org/10.1186/bcr2456

[34] Yasui K, Arii S, Zhao C, Imoto I, Ueda M, Nagai H, Emi M, Inazawa J. TFDP1, CUL4A, and CDC16 identified as targets for amplification at 13q34 in hepatocellular carcinomas. Hepatology 2002; 35:1476-84; PMID:12029633; http://dx.doi.org/10.1053/jhep.2002.33683

[35] Shinomiya T, Mori T, Ariyama Y, Sakabe T, Fukuda Y, Murakami Y, Nakamura Y, Inazawa J. Comparative genomic hybridization of squamous cell carcinoma of the esophagus: the possible involvement of the DPI gene in the 13q34 amplicon. Genes Chromosomes Cancer 1999; 24:337-44; PMID:10092132; http://dx.doi.org/10.1002/(SICI)1098-2264(199904)24:4%3c337::AID-GCC7%3e3.0.CO;2-O

[36] Hung MS, Mao JH, Xu Z, Yang CT, Yu JS, Harvard C, Lin YC, Bravo DT, Jablons DM, You L. Cul4A is an oncogene in malignant pleural mesothelioma. J Cell Mol Med 2011; 15:350-8; PMID:19929949; http://dx.doi.org/10.1111/j.1582-4934.2009.00971.x

[37] Wang Y, Zhang P, Liu Z, Wang Q, Wen M, Wang Y, Yuan H, Mao JH, Wei G. CUL4A overexpression enhances lung tumor growth and sensitizes lung cancer cells to erlotinib via transcriptional regulation of EGFR. Mol Cancer 2014; 13:252; PMID:25413624; http://dx.doi.org/10.1186/1476-4598-13-252

[38] Wang Y, Wen M, Kwon Y, Xu Y, Liu Y, Zhang P, He X, Wang Q, Huang Y, Jen KY, et al. CUL4A induces epithelial-mesenchymal transition and promotes cancer metastasis by regulating ZEB1 expression. Cancer Res 2014; 74:520-31; PMID:24305877; http://dx.doi.org/10.1158/0008-5472.CAN-13-2182

[39] Schindl M, Gnant M, Schoppmann SF, Horvat R, Birner P. Overexpression of the human homologue for Caenorhabditis elegans cul-4 gene is associated with poor outcome in node-negative breast cancer. Anticancer Res 2007; 27:949-52; PMID:17465225

[40] Saucedo-Cuevas LP, Ruppen I, Ximenez-Embun P, Domingo S, Gayarre J, Munoz J, Silva JM, Garcia MJ, Benitez J. CUL4A contributes to the biology of basal-like breast tumors through modulation of cell growth and antitumor immune response. Oncotarget 2014; 5:2330-43; PMID:24870930; http://dx.doi.org/10.18632/oncotarget.1915

[41] Liu L, Lee S, Zhang J, Peters SB, Hannah J, Zhang Y, Yin Y, Koff A, Ma L, Zhou P. CUL4A abrogation augments DNA damage response and protection against skin carcinogenesis. Mol Cell 2009; 34:451-60; PMID:19481525; http://dx.doi.org/10.1016/j.molcel.2009.04.020

[42] Li T, Hung MS, Wang Y, Mao JH, Tan JL, Jahan K, Roos H, Xu Z, Jablons DM, You L. Transgenic mice for cre-inducible overexpression of the Cul4A gene. Genesis 2011; 49:134-41; PMID:21381181; http://dx.doi.org/10.1002/dvg.20708

[43] Stein GS, van Wijnen AJ, Stein JL, Lian JB, Montecino M, Zaidi SK, Braastad C. An architectural perspective of cell-cycle control at the G1/S phase cell-cycle transition. J Cell Physiol 2006; 209:706-10; PMID:17001681; http://dx.doi.org/10.1002/jcp.20843

[44] Lopez-Beltran A, MacLennan GT, Montironi R. Cyclin E as molecular marker in the management of breast cancer: a review. Anal Quant Cytol Histol 2006; 28:111-4; PMID:16637514

[45] Zou Y, Mi J, Cui J, Lu D, Zhang X, Guo C, Gao G, Liu Q, Chen B, Shao C, et al. Characterization of nuclear localization signal in the N terminus of CUL4B and its essential role in cyclin E degradation and cell cycle progression. J Biol Chem 2009; 284:33320-32; PMID:19801544; http://dx.doi.org/10.1074/jbc.M109.050427

[46] Higa LA, Yang X, Zheng J, Banks D, Wu M, Ghosh P, Sun H, Zhang H. Involvement of CUL4 ubiquitin E3 ligases in regulating CDK inhibitors Dacapo/p27Kip1 and cyclin E degradation. Cell Cycle 2006; 5:71-7; PMID:16322693; http://dx.doi.org/10.4161/cc.5.1.2266

[47] Wang C, Chen Z, Ge Q, Hu J, Li F, Hu J, Xu H, Ye Z, Li LC. Up-regulation of p21(WAF1/CIP1) by miRNAs and its implications in bladder cancer cells. FEBS Lett 2014; 588:4654-64; PMID:25447520; http://dx.doi.org/10.1016/j.febslet.2014.10.037

[48] Nishitani H, Shiomi Y, Iida H, Michishita M, Takami T, Tsurimoto T. CDK inhibitor p21 is degraded by a proliferating cell nuclear antigen-coupled Cul4-DDB1Cdt2 pathway during S phase and after UV irradiation. J Biol Chem 2008; 283:29045-52; PMID:18703516; http://dx.doi.org/10.1074/jbc.M806045200

[49] Cang Y, Zhang J, Nicholas SA, Bastien J, Li B, Zhou P, Goff SP. Deletion of DDB1 in mouse brain and lens leads to p53-dependent elimination of proliferating cells. Cell 2006; 127:929-40; PMID:17129780; http://dx.doi.org/10.1016/j.cell.2006.09.045

[50] Li B, Jia N, Kapur R, Chun KT. Cul4A targets p27 for degradation and regulates proliferation, cell cycle exit, and differentiation during erythropoiesis. Blood 2006; 107:4291-9; PMID:16467204; http://dx.doi.org/10.1182/blood-2005-08-3349

[51] Bondar T, Kalinina A, Khair L, Kopanja D, Nag A, Bagchi S, Raychaudhuri P. Cul4A and DDB1 associate with Skp2 to target p27Kip1 for proteolysis involving the COP9 signalosome. Mol Cell Biol 2006; 26:2531-9; PMID:16537899; http://dx.doi.org/10.1128/MCB.26.7.2531-2539.2006

[52] Frescas D, Pagano M. Deregulated proteolysis by the F-box proteins SKP2 and beta-TrCP: tipping the scales of cancer. Nat Rev Cancer 2008; 8:438-49; PMID:18500245; http://dx.doi.org/10.1038/nrc2396

[53] Guardavaccaro D, Kudo Y, Boulaire J, Barchi M, Busino L, Donzelli M, Margottin-Goguet F, Jackson PK, Yamasaki L, Pagano M. Control of meiotic and mitotic progression by the F box protein beta-Trcp1 in vivo. Dev Cell 2003; 4:799-812; PMID:12791266; http://dx.doi.org/10.1016/S1534-5807(03)00154-0

[54] Margottin-Goguet F, Hsu JY, Loktev A, Hsieh HM, Reimann JD, Jackson PK. Prophase destruction of Emi1 by the SCF(betaTrCP/Slimb) ubiquitin ligase activates the anaphase promoting complex to allow progression beyond prometaphase. Dev Cell 2003; 4:813-26; PMID:12791267; http://dx.doi.org/10.1016/S1534-5807(03)00153-9

[55] Watanabe N, Arai H, Nishihara Y, Taniguchi M, Watanabe N, Hunter T, Osada H. M-phase kinases induce phospho-dependent ubiquitination of somatic Wee1 by SCFbeta-TrCP. Proc Natl Acad Sci U S A 2004; 101:4419-24; PMID:15070733; http://dx.doi.org/10.1073/pnas.0307700101

[56] Jin J, Shirogane T, Xu L, Nalepa G, Qin J, Elledge SJ, Harper JW. SCFbeta-TRCP links Chk1 signaling to degradation of the Cdc25A protein phosphatase. Genes Dev 2003; 17:3062-74; PMID:14681206; http://dx.doi.org/10.1101/gad.1157503

[57] Busino L, Donzelli M, Chiesa M, Guardavaccaro D, Ganoth D, Dorrello NV, Hershko A, Pagano M, Draetta GF. Degradation of Cdc25A by beta-TrCP during S phase and in response to DNA damage. Nature 2003; 426:87-91; PMID:14603323; http://dx.doi.org/10.1038/nature02082

[58] Sasajima H, Nakagawa K, Kashiwayanagi M, Yokosawa H. Polyubiquitination of the B-cell translocation gene 1 and 2 proteins is promoted by the SCF ubiquitin ligase complex containing betaTrCP. Biol Pharm Bull 2012; 35:1539-45; PMID:22975506; http://dx.doi.org/10.1248/bpb.b12-00330

[59] Cunha-Ferreira I, Rodrigues-Martins A, Bento I, Riparbelli M, Zhang W, Laue E, Callaini G, Glover DM, Bettencourt-Dias M. The SCF/Slimb ubiquitin ligase limits centrosome amplification through degradation of SAK/PLK4. Curr Biol 2009; 19:43-9; PMID:19084407; http://dx.doi.org/10.1016/j.cub.2008.11.037

[60] Guderian G, Westendorf J, Uldschmid A, Nigg EA. Plk4 trans-autophosphorylation regulates centriole number by controlling betaTrCP-mediated degradation. J Cell Sci 2010; 123:2163-9; PMID:20516151; http://dx.doi.org/10.1242/jcs.068502

[61] Seki A, Coppinger JA, Du H, Jang CY, Yates JR, 3rd, Fang G. Plk1- and beta-TrCP-dependent degradation of Bora controls mitotic progression. J Cell Biol 2008; 181:65-78; PMID:18378770; http://dx.doi.org/10.1083/jcb.200712027

[62] Pagan JK, Marzio A, Jones MJ, Saraf A, Jallepalli PV, Florens L, Washburn MP, Pagano M. Degradation of Cep68 and PCNT cleavage mediate Cep215 removal from the PCM to allow centriole separation, disengagement and licensing. Nat Cell Biol 2015; 17:31-43; PMID:25503564; http://dx.doi.org/10.1038/ncb3076

[63] Limon-Mortes MC, Mora-Santos M, Espina A, Pintor-Toro JA, Lopez-Roman A, Tortolero M, Romero F. UV-induced degradation of securin is mediated by SKP1-CUL1-beta TrCP E3 ubiquitin ligase. J Cell Sci 2008; 121:1825-31; PMID:18460583; http://dx.doi.org/10.1242/jcs.020552

[64] Guardavaccaro D, Frescas D, Dorrello NV, Peschiaroli A, Multani AS, Cardozo T, Lasorella A, Iavarone A, Chang S, Hernando E, et al. Control of chromosome stability by the beta-TrCP-REST-Mad2 axis.

Nature 2008; 452:365-9; PMID:18354482; http://dx.doi.org/10.1038/nature06641

[65] Peschiaroli A, Dorrello NV, Guardavaccaro D, Venere M, Halazonetis T, Sherman NE, Pagano M. SCFbetaTrCP-mediated degradation of Claspin regulates recovery from the DNA replication checkpoint response. Mol Cell 2006; 23:319-29; PMID:16885022; http://dx.doi.org/10.1016/j.molcel.2006.06.013

[66] Ougolkov A, Zhang B, Yamashita K, Bilim V, Mai M, Fuchs SY, Minamoto T. Associations among beta-TrCP, an E3 ubiquitin ligase receptor, beta-catenin, and NF-kappaB in colorectal cancer. J Natl Cancer Inst 2004; 96:1161-70; PMID:15292388; http://dx.doi.org/10.1093/jnci/djh219

[67] Koch A, Waha A, Hartmann W, Hrychyk A, Schuller U, Waha A, Wharton KA, Jr., Fuchs SY, von Schweinitz D, Pietsch T. Elevated expression of Wnt antagonists is a common event in hepatoblastomas. Clin Cancer Res 2005; 11:4295-304; PMID:15958610; http://dx.doi.org/10.1158/1078-0432.CCR-04-1162

[68] Muerkoster S, Arlt A, Sipos B, Witt M, Grossmann M, Kloppel G, Kalthoff H, Folsch UR, Schafer H. Increased expression of the E3-ubiquitin ligase receptor subunit betaTRCP1 relates to constitutive nuclear factor-kappaB activation and chemoresistance in pancreatic carcinoma cells. Cancer Res 2005; 65:1316-24; PMID:15735017; http://dx.doi.org/10.1158/0008-5472.CAN-04-1626

[69] Liu H, Cheng EH, Hsieh JJ. Bimodal degradation of MLL by SCFSkp2 and APCCdc20 assures cell cycle execution: a critical regulatory circuit lost in leukemogenic MLL fusions. Genes & development 2007; 21:2385-98; PMID:17908926; http://dx.doi.org/10.1101/gad.1574507

[70] Kudo Y, Guardavaccaro D, Santamaria PG, Koyama-Nasu R, Latres E, Bronson R, Yamasaki L, Pagano M. Role of F-box protein betaTrcp1 in mammary gland development and tumorigenesis. Mol Cell Biol 2004; 24:8184-94; PMID:15340078; http://dx.doi.org/10.1128/MCB.24.18.8184-8194.2004

[71] Belaidouni N, Peuchmaur M, Perret C, Florentin A, Benarous R, Besnard-Guerin C. Overexpression of human beta TrCP1 deleted of its F box induces tumorigenesis in transgenic mice. Oncogene 2005; 24:2271-6; PMID:15735746; http://dx.doi.org/10.1038/sj.onc.1208418

[72] Saitoh T, Katoh M. Expression profiles of betaTRCP1 and betaTRCP2, and mutation analysis of betaTRCP2 in gastric cancer. Int J Oncol 2001; 18:959-64; PMID:11295041

[73] Kim CJ, Song JH, Cho YG, Kim YS, Kim SY, Nam SW, Yoo NJ, Lee JY, Park WS. Somatic mutations of the beta-TrCP gene in gastric cancer. APMIS 2007; 115:127-33; PMID:17295679; http://dx.doi.org/10.1111/j.1600-0463.2007.apm_562.x

[74] Gerstein AV, Almeida TA, Zhao G, Chess E, Shih Ie M, Buhler K, Pienta K, Rubin MA, Vessella R, Papadopoulos N. APC/CTNNB1 (beta-catenin) pathway alterations in human prostate cancers. Genes Chromosomes Cancer 2002; 34:9-16; PMID:11921277; http://dx.doi.org/10.1002/gcc.10037

[75] Wood LD, Parsons DW, Jones S, Lin J, Sjoblom T, Leary RJ, Shen D, Boca SM, Barber T, Ptak J, et al. The genomic landscapes of human breast and colorectal cancers. Science 2007; 318:1108-13; PMID:17932254; http://dx.doi.org/10.1126/science.1145720

[76] Jorgensen S, Eskildsen M, Fugger K, Hansen L, Larsen MS, Kousholt AN, Syljuasen RG, Trelle MB, Jensen ON, Helin K, et al. SET8 is degraded via PCNA-coupled CRL4(CDT2) ubiquitylation in S phase and after UV irradiation. J Cell Biol 2011; 192:43-54; PMID:21220508; http://dx.doi.org/10.1083/jcb.201009076

[77] Abbas T, Mueller AC, Shibata E, Keaton M, Rossi M, Dutta A. CRL1-FBXO11 promotes Cdt2 ubiquitylation and degradation and regulates Pr-Set7/Set8-mediated cellular migration. Mol Cell 2013; 49:1147-58; PMID:23478445; http://dx.doi.org/10.1016/j.molcel.2013.02.003

[78] Benamar M, Guessous F, Du K, Corbett P, Obeid J, Gioeli D, Slingluff CL, Jr., Abbas T. Inactivation of the CRL4-CDT2-SET8/p21 ubiquitylation and degradation axis underlies the therapeutic efficacy of pevonedistat in melanoma. EBioMedicine 2016; 10:85-100; PMID:27333051; http://dx.doi.org/10.1016/j.ebiom.2016.06.023

[79] Wang Z, Dai X, Zhong J, Inuzuka H, Wan L, Li X, Wang L, Ye X, Sun L, Gao D, et al. SCF(beta-TRCP) promotes cell growth by targeting PR-Set7/Set8 for degradation. Nat Commun 2015; 6:10185; PMID:26666832; http://dx.doi.org/10.1038/ncomms10185

[80] Wang Z, Liu P, Inuzuka H, Wei W. Roles of F-box proteins in cancer. Nat Rev Cancer 2014; 14:233-47; PMID:24658274; http://dx.doi.org/10.1038/nrc3700

[81] Serrano M, Lin AW, McCurrach ME, Beach D, Lowe SW. Oncogenic ras provokes premature cell senescence associated with accumulation of p53 and p16INK4a. Cell 1997; 88:593-602; PMID:9054499; http://dx.doi.org/10.1016/S0092-8674(00)81902-9

[82] Xu Y, Li N, Xiang R, Sun P. Emerging roles of the p38 MAPK and PI3K/AKT/mTOR pathways in oncogene-induced senescence. Trends Biochem Sci 2014; 39:268-76; PMID:24818748; http://dx.doi.org/10.1016/j.tibs.2014.04.004

[83] Astle MV, Hannan KM, Ng PY, Lee RS, George AJ, Hsu AK, Haupt Y, Hannan RD, Pearson RB. AKT induces senescence in human cells via mTORC1 and p53 in the absence of DNA damage: implications for targeting mTOR during malignancy. Oncogene 2012; 31:1949-62; PMID:21909130; http://dx.doi.org/10.1038/onc.2011.394

[84] Cao J, Wan L, Hacker E, Dai X, Lenna S, Jimenez-Cervantes C, Wang Y, Leslie NR, Xu GX, Widlund HR, et al. MC1R is a potent regulator of PTEN after UV exposure in melanocytes. Mol Cell 2013; 51:409-22; PMID:23973372; http://dx.doi.org/10.1016/j.molcel.2013.08.010

[85] Vredeveld LC, Possik PA, Smit MA, Meissl K, Michaloglou C, Horlings HM, Ajouaou A, Kortman PC, Dankort D, McMahon M, et al. Abrogation of BRAFV600E-induced senescence by PI3K pathway activation contributes to melanomagenesis. Genes Dev 2012; 26:1055-69; PMID:22549727; http://dx.doi.org/10.1101/gad.187252.112

[86] Kilic Eren M, Tabor V. The role of hypoxia inducible factor-1 alpha in bypassing oncogene-induced senescence. PLoS One 2014; 9:e101064; PMID:24984035; http://dx.doi.org/10.1371/journal.pone.0101064

[87] Chen Z, Trotman LC, Shaffer D, Lin HK, Dotan ZA, Niki M, Koutcher JA, Scher HI, Ludwig T, Gerald W, et al. Crucial role of p53-dependent cellular senescence in suppression of Pten-deficient tumorigenesis. Nature 2005; 436:725-30; PMID:16079851; http://dx.doi.org/10.1038/nature03918

[88] Nardella C, Chen Z, Salmena L, Carracedo A, Alimonti A, Egia A, Carver B, Gerald W, Cordon-Cardo C, Pandolfi PP. Aberrant Rheb-mediated mTORC1 activation and Pten haploinsufficiency are cooperative oncogenic events. Genes Dev 2008; 22:2172-7; PMID:18708577; http://dx.doi.org/10.1101/gad.1699608

[89] Young AP, Schlisio S, Minamishima YA, Zhang Q, Li L, Grisanzio C, Signoretti S, Kaelin WG, Jr. VHL loss actuates a HIF-independent senescence programme mediated by Rb and p400. Nat Cell Biol 2008; 10:361-9; PMID:18297059; http://dx.doi.org/10.1038/ncb1699

[90] Hayes L, Weening A, Morey LM. Differential Effects of Estradiol and Bisphenol A on SET8 and SIRT1 Expression in Ovarian Cancer Cells. Dose Response 2016; 14:1559325816640682; PMID:27114721; http://dx.doi.org/10.1177/1559325816640682

[91] Ma J, Fang B, Zeng F, Pang H, Zhang J, Shi Y, Wu X, Cheng L, Ma C, Xia J, et al. Curcumin inhibits cell growth and invasion through up-regulation of miR-7 in pancreatic cancer cells. Toxicol Lett 2014; 231:82-91; PMID:25256401; http://dx.doi.org/10.1016/j.toxlet.2014.09.014