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REVIEW

Ubiquitin proteasome system research in gastrointestinal cancer

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Abstract

The ubiquitin proteasome system (UPS) is important for the degradation of proteins in eukaryotic cells. It is involved in nearly every cellular process and plays an important role in maintaining body homeostasis. An increasing body of evidence has linked alterations in the UPS to gastrointestinal malignancies, including esophageal, gastric and colorectal cancers. Here, we summarize the current literature detailing the involvement of the UPS in gastrointestinal cancer, highlighting its role in tumor occurrence and development, providing information for therapeutic targets research and anti-gastrointestinal tumor drug design.

Key words: Ubiquitin proteasome system; Gastrointestinal cancer

Core tip: The ubiquitin proteasome system (UPS) is involved in almost every cellular process, playing an important role in maintaining body homeostasis. Increasing evidence indicates that alterations in the UPS are correlated with gastrointestinal malignancies. Here, we review current information describing UPS members involved in gastrointestinal cancer, providing a resource for further study and clinical application.

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INTRODUCTION

The ubiquitin proteasome system (UPS) is important for the degradation of proteins in eukaryotic cells. Approximately 80%-90% of intracellular proteins involved in every cellular function are degraded though the UPS[1]. Compared with the lysosomal system, the UPS is highly selective. It can regulate the proteins that it degrades *via* the ubiquitination-proteasome-deubiquitination mechanism to maintain homeostasis in the body. When regulatory proteins are stabilized by a decrease in degradation or are lost due to accelerated degradation, an imbalance is generated and diseases such as cancer occur.

Gastrointestinal cancer is a cancer of different organs of the digestive system, the most frequently occurring cancers of which are esophageal, gastric and colorectal. Despite improvements in diagnostic and therapeutic methods, gastrointestinal cancers remain a significant threat to patients[2]. Recently, growing evidence has indicated that the UPS is linked to the development of gastrointestinal cancer. In this review, we discuss the members of the UPS thought to be involved in gastrointestinal cancer and highlight their roles in tumor occurrence and development.

The UPS is an important pathway for intracellular protein degradation

In cells, there are two main systems utilized for protein degradation: The autophagy-lysosome system and the UPS[3,4]. The lysosomal pathway degrades extracellular proteins imported into the cell by endocytosis or pinocytosis, while the UPS controls the degradation of intracellular proteins[5,6].

The UPS is composed of ubiquitin, ubiquitination enzymes, deubiquitination enzymes (DUBs), and proteasomes.

Ubiquitin is a highly conserved 76 amino acid protein, wild-expressed in eukaryotic cells[7]. During the ubiquitination process, multiple ubiquitin proteins can be covalently attached to a target protein by ubiquitination enzymes[8]. These ubiquitination enzymes include ubiquitin activating enzyme (E1), ubiquitin carrier protein (E2), and ubiquitin protein ligase (E3). Initially, E1 activates ubiquitin in an ATP-dependent manner, forming a thioester linkage between the carboxy-terminal glycine residue of ubiquitin and a cysteine in the active site of the E1 enzyme. Activated ubiquitin is then transferred from an E1 enzyme to a cysteine residue of an E2 enzyme. E3 then catalyzes the final step of the ubiquitination process by transferring ubiquitin to lysine residues of targeted proteins, forming a polyubiquitin chain that earmarks the targeted proteins[8-10]. Humans possess two E1 enzymes (UBA1 and UBA6), several dozen E2 enzymes, and several hundred E3 enzymes[11-13]. The specificity of the E3 enzymes determines the specific recognition of target proteins, providing selectivity in which proteins are targeted to the proteasome for degradation[10,14,15].

Upon ubiquitination, targeted protein is degraded by the 26S proteasome in an ATP-dependent manner[16,17]. The 26S proteasome is a complex consisting of a proteolytic core particle (20S proteasome) that is capped at both ends by 19S regulatory particles (19S regulatory complex). The 20S proteasome is a barrel-shaped complex comprised of four stacked rings and contains multiple catalytic centers in the chamber. The 19S proteasome recognizes a polyubiquitinated protein, unfolds it, liberates it from the polyubiquitin chain, and translocates the protein into the proteasome chamber for degradation. The ubiquitin molecules are recycled, and the peptides generated are used for antigen presentation or are degraded into amino acids that are recycled for new protein synthesis[9,10,17].

DUBs are a cluster of enzymes that oppose the action of the E3 ligases by cleaving the isopeptide bonds between lysine residues of targeted proteins and the C-terminal glycine of ubiquitin. They play important roles in maintaining the balance of the UPS. Analysis of the human genome has indicated the presence of - 100 functional DUBs[18-20].

Tumorigenesis consists of several steps, including self-sufficiency in growth signals, insensitivity to growth inhibitor signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis[21-24]. The UPS is an important regulator of protein degradation that is involved in every cellular function, including cell proliferation, apoptosis, migration and invasion. Thus, deregulation of this system may lead to tumorigenesis.

The UPS in esophageal cancer

Esophageal cancer (EC) is the eighth most common type of cancer, and ranks as the sixth leading cause of cancer-related mortality worldwide. The incidence of EC varies internationally, with the highest rates found in Eastern Asia and in Eastern and Southern Africa[2,25].

Several E2 enzymes, including ubiquitin-conjugating enzyme H10 (UBCH10, also known as UBE2C), ubiquitin-conjugating enzyme E2L3 (UBE2L3, also known as UBCH7), E2-EPF ubiquitin carrier protein (UCP), and ubiquitin-conjugating enzyme E2D3 (UBE2D3) have been shown to be involved in the development of EC. UBCH10 is expressed in cancerous and dysplastic esophageal lesions, but not in normal tissue. Its expression is positively correlated with lymph nodes metastasis (LNM), TNM classification, and clinical stages, and negatively correlated with relapse-free survival period. Down-regulation of UBCH10 can inhibit cell proliferation and induce the sensibility to the treatment of MG-262[26,27]. Knockdown of UBE2L3 expression can reduce the anoikis resistance of EC cells[28]. Higher level of UCP has been linked to a greater tumor burden, poor response to neoadjuvant therapy, and worse overall survival for EC patients. Furthermore, UCP down-regulation can inhibit the proliferation, migration and invasion of EC cells, probably through the VHL/HIF-1α-TGF-β1 pathway[29]. UBE2D3 expression is significantly lower in EC tissues and is correlated with histological grade, N stage, and

recurrence, suggesting that it acts as a tumor suppressor in EC. UBE2D3 may be involved the hTERT signal pathway, which can promote the development of invasive esophageal squamous cell cancer by interacting with the epidermal growth factor receptor and p53[30,31].

Numerous E3 enzymes participate in the development of EC, some of which promotes tumor development. C-terminal Hsp-interacting protein (CHIP) exhibits a higher expression level in metastatic lymph nodes and is positively correlated with a poor survival rate in stage Ⅲ EC patients[32]. F-box protein 31 (FBXO31) is an ubiquitin ligase whose cytoplasmic expression is concordant with the nuclear expression of cyclin D1. In EC tissues, higher FBXO31 expression level is significantly correlated with depth of tumor invasion, clinical stage, and poorer prognosis[33]. p53-associated cellular protein-testes derived (PACT) is highly up-regulated in EC. Experimental studies have revealed that knockdown of PACT significantly attenuates the p53-Hdm2 interaction, reduces p53 polyubiquitination, and enhances p53 accumulation, leading to both apoptosis and cell growth retardation[34]. SMAD specific E3 ubiquitin protein ligase 2 (Smurf2) targets TGF pathway-restricted Smad2. In EC, high expression of Smurf2 is correlated with depth of invasion, LNM, and poor survival rate. High expression of Smurf2 can down-regulate Smad2, which in turn regulates the TGF signaling pathway[35]. S-phase kinase-interacting protein 2 (Skp2) can interact with the S-phase kinase Cdk2/cyclinA and is involved in the ubiquitin-dependent degradation of p27. Skp2 expression is closely correlated with TNM stage. High expression of Skp2 is associated with poor overall survival in resectable EC. Further study reveals that knockdown of Skp2 inhibits cell migration and invasion and sensitizes cancer cells to anoikis, at least in part through the phosphoinositidyl 3-kinase-Akt pathway[36,37]. Ubiquitin-like with PHD and ring finger domains 1 (UHRF1) is overexpressed in EC tissues. Its expression is correlated with the T-stage and N-stage as well as with differentiation. Down-regulation of UHRF1 can enhance the radio-sensitivity of TE-1 cells by altering cell cycle progression, increasing apoptosis and decreasing DNA damage repair capacity[38].

Some E3 enzymes act as tumor suppressors in EC. F-box protein 4 (FBX4) is a ubiquitin ligase that directs the ubiquitylation of cyclin D1. Increased FBX4 function can enhance the normal activity of EC cells, and 14-3-3ε is involved in regulating its function[39]. F-box and leucine-rich repeat protein 19 (FBXL19) functions as an antagonist of Rac3 by regulating its stability, and it also regulates the TGFβ1-induced down-regulation of E-cadherin. Over-expression of FBXL19 attenuates TGFβ1-induced E-cadherin down-regulation and the elongation phenotype of EC cells[40,41]. F-box and WD repeat domain containing 7 (FBXW7, E3 ubiquitin protein ligase) can induce the degradation of positive cell cycle regulators, such as Myc, cyclin E and Jun. In EC tissues, a decrease in FBXW7 copy number regulates FBXW7 mRNA expression, and reduced expression of FBXW7 is an independent prognostic factor in EC[42].

Besides, there are still some E3 enzymes play controversial roles in EC. MDM2 (MDM2 proto-oncogene) is a key negative regulator of P53, but its expression state and clinicopathological parameters in esophageal squamous cell carcinoma are controversial. This may be due to a lack of sufficient case numbers in each study or the use of different methods to detect MDM2 expression. Meta-analysis suggests that MDM2 acts as a potent marker of early primary tumor stages but poses a high risk of regional LNM in EC. Notably, the MDM2 309GG genotype may be associated with an increased risk of EC among Asians[43,44].

DBUs, including ubiquitin specific peptidase 7 (USP7), ubiquitin specific protease-9X (USP9X), Ubiquitin-specific protease 22 (USP22), ubiquitin carboxyl-terminal hydrolase 37 (UCH37), and ubiquitin carboxyl-terminal hydrolase1 (UCHL1) are correlated with EC development. USP7 can deubiquitylate p53 and protect it from proteasome-mediated degradation. EC cells can be protected against metformin-induced growth inhibition by siRNA against USP7[45]. Up-regulation of USP9X in EC tissues plays an important role in the formation and progression of precancerous lesions, and its increased expression is significantly correlated with poorer survival rate in EC patients[46]. High expression of the USP22 protein is significantly associated with tumor progression, relapse and poor prognosis[47]. The expression of UCH37 is higher in EC tissues and is associated with outcome and recurrence. UCHL1 is silenced by promoter region hypermethylation in EC, and the restoration of its expression suppresses EC cell colony formation[48,49].

The UPS in gastric cancer

Gastric cancer (GC) is the second most common cause of cancer-related death, and its incidence rates are highest in Eastern Asia[2].

The E2 enzyme UBCH10 is known to be involved in GC. UBCH10 is expressed at higher levels in primary stomach tumors compared with corresponding normal tissues[50].

The oncogenic E3 ubiquitin ligases involved in GC are discussed in detail below. Autocrine motility factor receptor (AMFR) expression is significantly increased in GC tissues and is associated with invasion depth and LNM. Its expression is correlated with poor overall survival and an increased risk of recurrence in GC cases. AMFR is thought to participate in the EMT pathway because its expression is negatively correlated with E-cadherin expression and is positively correlated with N-cadherin[51]. Cullin 1 (CUL1) overexpression is significantly correlated with GC TNM stage, depth of invasion, LNM, worse overall survival rate, and 3-year survival rate in GC patients. Experimental studies have demonstrated that CUL1 knockdown inhibits cell growth by up-regulating p27 expression and decreases cell adhesion by suppressing the expression of Src family kinases and focal adhesion kinase[52]. MDM2 protein level is significantly up-regulated in GC and is significantly correlated with clinicopathologic

characteristics and a shorter overall survival of GC patients. Similar to its role in EC, the MDM2 309GG genotype may be significantly associated with an increased risk of GC[43,53]. Makorin ring finger protein 1 (MKRN1) can simultaneously induce p53 and p21 ubiquitination as well as proteasome-dependent degradation. In GC cells, MKRN1 could affect gastric tumorigenesis by repressing cellular senescence and tumor-suppressive effects through the down-regulation of p14ARF in either a p53-dependent or -independent manner[54]. RING box protein-1 (RBX1) exhibits a higher expression level in GC tissues, and silencing it significantly inhibits the proliferation of GC cells *in vitro*[55].

E3 ubiquitin ligases with tumor suppressor activity in GC are discussed in detail below. checkpoint with forkhead and ring finger domains (CHFR) is reported to promote the ubiquitination and degradation of oncogenic proteins such as Aurora A and polo-like kinase 1[56]. It is frequently down-regulated in GC as a result of CHFR promoter methylation, suggesting that it acts as a tumor suppressor in GC. Methylation of the CHFR promoter is correlated with tumor differentiation. CHFR methylation is significantly higher in poorly differentiated GC samples[57]. Moreover, CHFR promoter methylation is a sensitive marker of the effect of docetaxel in GC patients[58]. CHIP expression is significantly lower in GC tissues. CHIP down-regulation is correlated with LNM and tumor differentiation. Further study has demonstrated that CHIP down-regulation results in increased angiogenesis and contributes to GC progression and a poor prognosis, probably through the NF-κB signaling pathway[59-61]. FBXO31 expression is dramatically decreased in GC tissue and is significantly associated with tumor size, infiltration, clinical grade and patient prognosis. *In vitro*, FBXO31 overexpression significantly decreases colony formation, induces a G1-phase arrest, and inhibits the expression of CyclinD1 in GC cells. *In vivo*, ectopic expression of FBXO31 dramatically inhibits xenograft tumor growth in nude mice[62]. FBXW7 mRNA expression in GC samples is markedly decreased, and its deregulation is associated with the presence of LNM and GC stage Ⅲ-Ⅳ, as well as poor prognosis. Reduced FBXW7 expression is associated with MYC overexpression and a more invasive phenotype in GC cells[63]. Neural precursor cell expressed, developmentally down-regulated 4-like (NEDD4L) is strongly related to the invasion and metastasis of GC. Tumors lacking NEDD4L expression exhibit a greater extent of LNM, lymphatic invasion, and venous invasion, and present poor clinical outcomes for GC patients[64]. RNF180 (Ring finger protein 180) acts as a tumor suppressor in GC, and the methylated CpG site count of the RNF180 DNA promoter is highly associated with patient survival[65]. Zinc and ring finger 3 (ZNRF3) is down-regulated in gastric adenocarcinoma tissues. There is also a correlation between the down-regulation of ZNRF3 and poor tissue differentiation. Further study has revealed that ZNRF3 inhibits GC cell growth and promotes cell apoptosis by affecting the Wnt/beta-catenin/TCF signaling pathway[66].

E3 ubiquitin ligases with controversial functions in GC are discussed in detail below. Cbl proto-oncogene B (CBLB) is highly expressed in GC tissue with EGFR, and their expression levels have been linked to the invasion and development of GC. However, some studies have revealed that CBLB represses IGF-I-induced EMT, likely by targeting IGF-IR for degradation and further inhibiting the Akt/ERK-miR-200c-ZEB2 axis in GC cells[67,68]. Constitutive photomorphogenic 1 (COP1, also known as RFWD2) has been shown to regulate c-Jun and p53. One study found that COP1 mRNA was significantly decreased in GC tissues, and knockdown of COP1 in GC cells promoted cell proliferation and the expression of MMP1, MMP7 and MMP10[69]. However, another study showed that COP1 overexpression was associated with poor prognosis in primary GC[70]. Neural precursor cell expressed, developmentally down-regulated 4 (NEDD4) is a regulator of PTEN and plays a complicated role in GC. One study revealed that overexpression of NEDD4 was tightly associated with TNM stage and a lower GC survival rate. And knockdown of NEDD4 dramatically inhibited GC cell migration and invasion[71]. However, another study demonstrated that NEDD4 increased in intestinal metaplasia compared to normal gastric mucosa and decreased in gastric carcinoma compared to dysplasia[72].

The DUBs involved in GC are discussed in detail below. UCHL1 is frequently methylated in primary GCs and has been found to be more frequently methylated in diffuse-type GCs than in intestinal-type GCs. Moreover, UCHL1 is involved in galangin-induced apoptosis in human GC cells[49,73]. Ubiquitin-specific protease 10 (USP10) is expressed at lower levels in GC tissues and cells compared to their wild-type equivalents. A lack of USP10 expression results in a marked propensity toward gastric wall invasion, LNM, highly malignant biological behavior, and poor survival[74].

The UPS in colorectal cancer

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and the second in females. The highest incidence rates are in Australia and New Zealand, Europe, and Northern America.

The E2 enzymes related to CRC are discussed in detail below. UBCH10 is highly expressed in CRC. The depletion of UBCH10 hinders tumorigenesis both *in vitro* and *in vivo*, probably by regulating the expression of cell cycle proteins such as cyclin A and cyclin B1. Furthermore, n-acetyl-leu-leu-norleucinal (ALLN) treatment is more effective in tumors with lower UBCH10 expression[75]. Ubiquitin-conjugating enzyme E2Q family member 2 (UBE2Q2) expression is increased in 65.11% colorectal carcinoma tissues compared with their corresponding normal tissues[76]. Ubiquitin-conjugating enzyme E2I (UBE2I) RNAi suppresses the 3D growth of KRAS mutant CRC cells *in vitro* and attenuates tumor growth *in vivo*[77].

The oncogenic E3 ubiquitin ligases in CRC are discussed in detail below. F-box and leucine-rich repeat

protein 20 (FBXL20) is overexpressed in human colorectal adenocarcinoma. Moreover, the inhibition of FBXL20 expression can effectively suppress cell proliferation and promote apoptosis in CRC cells, while the overexpression of FBXL20 promotes the invasive ability of CRC cells, possibly by inducing the degradation of SET and E-cadherin through caspase activation[78,79]. HECT, UBA and WWE domain containing 1 (HUWE1) is required for the growth of CRC cells in culture and in orthotopic xenograft models. HUWE1 shRNA suppresses the clonogenic growth of CRC cells, and small molecule inhibitors of HUWE1 can inhibit MYC-dependent transactivation in CRC cells but not in stem and normal colon epithelial cells[80]. UHRF1 expression is up-regulated in approximately two-thirds of CRC specimens and is particularly expressed in right compared with left hemicolon cancer. High UHRF1 expression tends to be associated with the depth of invasion and with E2F-1 expression. Knockdown of UHRF1 suppresses cellular growth in colon cancer cell lines[81-83]. ubiquitin-like with PHD and ring finger domains 2 (UHRF2) is up-regulated at both the transcriptional and translational levels in tumor tissues. Overexpression of UHRF2 is highly linked to clinical stage, depth of invasion, nodal involvement, tumor histologic grade and the presence of metastases. Patients with UHRF2-positive tumors have a much lower disease-free survival and overall survival[84]. Skp2-siRNA effectively inhibits proliferation, increases the level of apoptosis, and induces G0/G1 phase arrest of colon cancer cells, along with increasing p27 and p16 protein levels. Tumorigenicity experiments show that the inhibition of Skp2 significantly increases the survival Skp2 is associated with a poor therapeutic response and adverse outcomes in rectal cancer patients treated with neoadjuvant chemoradiotherapy[87].

E3 ubiquitin ligases exhibiting tumor suppressor activity in CRC are discussed in detail below. CHIP is down-regulated, predominantly in the late stages of CRC, and the CHIP promoter is hypermethylated in CRC specimens. Overexpression of CHIP results in impaired tumor growth in nude mice and decreased migration and invasion abilities of tumor cells. Further study reveals that CHIP negatively regulates NF-κB signaling by promoting the ubiquitination and degradation of p65. The suppressive effect of CHIP leads to decreases in the expression of NF-κB-targeted oncogenes, including Cyclin D1, c-Myc, MMP-2, VEGF and IL-8[88]. Neural precursor cell expressed, developmentally down-regulated 4-like (NEDD4L) mRNA is significantly down-regulated in all CRCs. NEDD4L protein is significantly decreased in CRC compared to adjacent normal mucosa. Moreover, NEDD4L inhibits canonical Wnt signaling at or below the level of β-catenin *in vitro*[89]. Neuregulin receptor degradation protein-1 (NRDP1) is significantly decreased in CRC tissues. Knockdown of NRDP1 enhances the proliferation of CRC cells, while the overexpression of NRDP1 inhibits the proliferation of CRC cells. Further analysis shows that NRDP1 may induce the degradation of its target ErbB3 to inhibit the activation of both the ERK/MAPK and PI3K/Akt pathways in CRC cells, which seems to affect cell proliferation *via* the nuclear retention of a major cell-cycle inhibitor, p27. In addition, NRPD1 inhibits the expression of MMP7, which is required for cell invasion[90,91]. Ring finger protein 43 (RNF43) can negatively regulate Wnt signaling, and its gene mutations in this gene has been found in over 18% of colorectal adenocarcinomas. Truncating mutations of RNF43 are more prevalent in microsatellite-unstable tumors and show mutual exclusivity with inactivating APC mutations in colorectal adenocarcinomas. These results indicate that RNF43 is one of the most commonly mutated genes in CRC[92].

FBXW7 plays a controversial role in CRC. On one hand, FBXW7 mRNA expression is significantly lower in tumor tissues, an expression pattern correlated with poorer prognosis. *In vitro*, FBXW7-specific siRNA enhances the expression of c-MYC and cyclin E and promotes cell proliferation[93]. Moreover, studies have found that the FBXW7 mutation is correlated with colorectal tumorigenesis[94]. On the other hand, a large-scale study has revealed that there is no strong association between patient prognosis and FBXW7 mutation[95].

The DUBs involved in CRC are discussed in detail below. OTU deubiquitinase, ubiquitin aldehyde binding 1 (OTUB1) is overexpressed in CRC tissues, and its expression level is associated with metastasis. A high OTUB1 expression level is also associated with poor survival, and OTUB1 serves as an independent prognostic factor in multivariate analysis. Further study has revealed that OTUB1 promotes the metastasis of CRC cell lines *in vitro* and *in vivo* by regulating EMT[96]. Ubiquitin specific peptidase 11 (USP11) overexpression is frequently observed in CRC tissues and is correlated with poor survival. CRC cell lines expressing high levels of USP11 exhibit strong resistance to Smac mimetic-induced cIAP2 degradation. Furthermore, USP11 down-regulation sensitizes these cells to apoptosis induced by TRAIL and BV6, and suppresses tumor growth in a xenograft model[97]. Ubiquitin-specific protease 22 (USP22) expression is significantly higher in primary CRCs than in the paired non-cancerous tissues at both the mRNA and protein levels. Higher USP22 expression is significantly associated with shorter periods of disease-specific survival and shorter disease-free survival. In addition, USP22 expression is significantly correlated with BMI-1, c-Myc and cyclin D2 and is a novel regulator of the SIRT1-STAT3 signaling pathway[98-100]. Ubiquitin-specific protease 28 (USP28) deletion results the fewer intestinal tumors of the murine model in CRC. And in established tumors, USP28 deletion reduces tumor size and dramatically increases lifespan[101]. Ubiquitin-specific protease 33 (USP33) expression is down-regulated in CRC samples, and a reduced USP33 mRNA level is correlated with increased tumor grade, LNM and poor patient survival. USP33 acts as a tumor suppressor in CRC by mediating the inhibitory function of Slit-Robo signaling on CRC cell migration[102]. USP44

Table 1 The roles of ubiquitin proteasome system members in gastrointestinal cancer

Enzyme	Esophageal cancer			Gastric cancer			Colorectal cancer		
	P[1]	S[2]	C[3]	P[1]	S[2]	C[3]	P[1]	S[2]	C[3]
E2 enzyme	UBCH10 UBE2L3 UCP	UBE2D3		UBCH10			UBCH10 UBE2Q2 UBE2I		
E3 enzyme	CHIP FBXO31 PACT Smurf2 Skp2 UHRF1	FBX4 FBXL19 FBXW7	MDM2	AMFR CUL1 MDM2 MKRN1 RBX1	CHFR CHIP FBXO31 FBXW7 NEDD4L RNF180 ZNRF3	CBLB COP1 NEDD4	FBXL20 HUWE1 UHRF1 UHRF2 Skp2	CHIP NEDD4L NRDP1 RNF43	FBXW7
DUBs	UCH37 USP9X USP22	UCHL1 USP7			UCHL1 USP10		OTUB1 USP11 USP22 USP28	USP33 USP44	UCHL1

[1]Tumor promoter role; [2]Tumor suppressor role; [3]Controversial role. AMFR: Autocrine motility factor receptor; CBLB: Cbl proto-oncogene B; CHFR: Checkpoint with forkhead and ring finger domains; CHIP: C-terminal Hsp-interacting protein; COP1: Constitutive photomorphogenic 1; CUL1: Cullin 1; DUB: Deubiquitination enzymes; FBXO31: F-box protein 31; FBX4: F-box protein 4; FBXL: F-box and leucine-rich repeat protein; FBXW7: F-box and WD repeat domain containing 7; HUWE1: HECT, UBA and WWE domain containing 1; MDM2: MDM2 proto-oncogene; MKRN1: Makorin ring finger protein 1; NEDD4: Neural precursor cell expressed, developmentally down-regulated 4; NEDD4L: Neural precursor cell expressed, developmentally down-regulated 4-like; NRDP1: Neuregulin receptor degradation protein-1; OTUB1: OTU deubiquitinase, ubiquitin aldehyde binding 1; PACT: p53-associated cellular protein-testes derived; RBX1: RING box protein-1; RNF: Ring finger protein; Smurf2: SMAD specific E3 ubiquitin protein ligase 2; Skp2: S-phase kinase-interacting protein 2; UBCH10: Ubiquitin-conjugating enzyme H10; UBE2L3: Ubiquitin-conjugating enzyme E2L3; UBE2D3: Ubiquitin-conjugating enzyme E2D3; UCP: E2-EPF ubiquitin carrier protein; UHRF: Ubiquitin-like with PHD and ring finger domains; UCH37: Ubiquitin carboxyl-terminal hydrolase 37; USP: Ubiquitin specific protease; UCHL1: Ubiquitin carboxyl-terminal hydrolase1; UBE2Q2: Ubiquitin-conjugating enzyme E2Q family member 2; UBE2I: Ubiquitin-conjugating enzyme E2I; ZNRF3: Zinc and ring finger 3.

is hypermethylated in all CRC cell lines and in most colorectal adenomas, but rarely in normal mucosa samples[103]. UCHL1 plays a controversial role in CRC. Some investigations have shown that UCHL1 is more frequently methylated in CRC tissues than in normal colorectal tissues, whereas other studies have indicated that high UCHL1 expression is related to colorectal tumor progression, invasion, LNM, and poor clinical outcome[104].

CONCLUSION

The UPS plays an essential role in controlling every cellular process and in maintaining the homeostasis of the body. In this review, we discussed the members of the UPS known to be involved in gastrointestinal cancer. Among the UPS, the dysregulation of the enzymes E2, E3 and DUBs play the most prominent role in tumorigenesis and development. As shown in Table 1, some enzymes may be just involved in one type cancer, while others may be involved in two or three types. Moreover, a single enzyme may play different roles in different cancers, as is the case for CHIP and UCHL1. This suggests that these enzymes may exhibit tissue specificity or may function through different mechanisms in different situation. Further study is necessary to better understand the biological function of the UPS and for the development of new therapeutic targets and anti-tumor drugs.

REFERENCES

1 **Chen D**, Dou QP. The ubiquitin-proteasome system as a prospective molecular target for cancer treatment and prevention. *Curr Protein Pept Sci* 2010; **11**: 459-470 [PMID: 20491623]

2 **Torre LA**, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; **65**: 87-108 [PMID: 25651787 DOI: 10.3322/caac.21262]

3 **Laney JD**, Hochstrasser M. Analysis of protein ubiquitination. *Curr Protoc Protein Sci* 2002; Chapter **14**: Unit 14.5 [PMID: 18429222 DOI: 10.1002/0471140864.ps1405s29]

4 **Haas KF**, Broadie K. Roles of ubiquitination at the synapse. *Biochim Biophys Acta* 2008; **1779**: 495-506 [PMID: 18222124 DOI: 10.1016/j.bbagrm.2007.12.010]

5 **Hochstrasser M**. Ubiquitin, proteasomes, and the regulation of intracellular protein degradation. *Curr Opin Cell Biol* 1995; **7**: 215-223 [PMID: 7612274]

6 **Goldberg AL**. Functions of the proteasome: the lysis at the end of the tunnel. *Science* 1995; **268**: 522-523 [PMID: 7725095]

7 **Goldknopf IL**, Busch H. Isopeptide linkage between nonhistone and histone 2A polypeptides of chromosomal conjugate-protein A24. *Proc Natl Acad Sci USA* 1977; **74**: 864-868 [PMID: 265581]

8 **Hershko A**, Heller H, Elias S, Ciechanover A. Components of ubiquitin-protein ligase system. Resolution, affinity purification, and role in protein breakdown. *J Biol Chem* 1983; **258**: 8206-8214 [PMID: 6305978]

9 **Hochstrasser M**. Ubiquitin-dependent protein degradation. *Annu Rev Genet* 1996; **30**: 405-439 [PMID: 8982460 DOI: 10.1146/annurev.genet.30.1.405]

10 **Nalepa G**, Rolfe M, Harper JW. Drug discovery in the ubiquitin-proteasome system. *Nat Rev Drug Discov* 2006; **5**: 596-613 [PMID: 16816840 DOI: 10.1038/nrd2056]

11 **Groettrup M**, Pelzer C, Schmidtke G, Hofmann K. Activating the ubiquitin family: UBA6 challenges the field. *Trends Biochem Sci* 2008; **33**: 230-237 [PMID: 18353650 DOI: 10.1016/j.tibs.2008.01.005]

12 **Marblestone JG**, Butt S, McKelvey DM, Sterner DE, Mattern MR, Nicholson B, Eddins MJ. Comprehensive ubiquitin E2 profiling of ten ubiquitin E3 ligases. *Cell Biochem Biophys* 2013; **67**: 161-167 [PMID: 23695783 DOI: 10.1007/s12013-013-9627-3]

13 **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 DOI: 10.1371/journal.pone.0001487]

14 **Scheffner M**, Nuber U, Huibregtse JM. Protein ubiquitination involving an E1-E2-E3 enzyme ubiquitin thioester cascade. *Nature* 1995; **373**: 81-83 [PMID: 7800044 DOI: 10.1038/373081a0]

15 **Hou YC**, Deng JY. Role of E3 ubiquitin ligases in gastric cancer. *World J Gastroenterol* 2015; **21**: 786-793 [PMID: 25624711 DOI: 10.3748/wjg.v21.i3.786]

16 **Geng F**, Wenzel S, Tansey WP. Ubiquitin and proteasomes in transcription. *Annu Rev Biochem* 2012; **81**: 177-201 [PMID: 22404630 DOI: 10.1146/annurev-biochem-052110-120012]

17 **Konstantinova IM**, Tsimokha AS, Mittenberg AG. Role of proteasomes in cellular regulation. *Int Rev Cell Mol Biol* 2008; **267**: 59-124 [PMID: 18544497 DOI: 10.1016/S1937-6448(08)00602-3]

18 **Komander D**, Clague MJ, Urbé S. Breaking the chains: structure and function of the deubiquitinases. *Nat Rev Mol Cell Biol* 2009; **10**: 550-563 [PMID: 19626045 DOI: 10.1038/nrm2731]

19 **Tsou WL**, Sheedlo MJ, Morrow ME, Blount JR, McGregor KM, Das C, Todi SV. Systematic analysis of the physiological importance of deubiquitinating enzymes. *PLoS One* 2012; **7**: e43112 [PMID: 22937016 DOI: 10.1371/journal.pone.0043112]

20 **Fraile JM**, Quesada V, Rodríguez D, Freije JM, López-Otín C. Deubiquitinases in cancer: new functions and therapeutic options. *Oncogene* 2012; **31**: 2373-2388 [PMID: 21996736 DOI: 10.1038/onc.2011.443]

21 **Hanahan D**, Weinberg RA. The hallmarks of cancer. *Cell* 2000; **100**: 57-70 [PMID: 10647931]

22 **Hanahan D**, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011; **144**: 646-674 [PMID: 21376230 DOI: 10.1016/j.cell.2011.02.013]

23 **Martin GS**. Cell signaling and cancer. *Cancer Cell* 2003; **4**: 167-174 [PMID: 14522250]

24 **Weinberg RA**. Oncogenes, antioncogenes, and the molecular bases of multistep carcinogenesis. *Cancer Res* 1989; **49**: 3713-3721 [PMID: 2660980]

25 **Mao WM**, Zheng WH, Ling ZQ. Epidemiologic risk factors for esophageal cancer development. *Asian Pac J Cancer Prev* 2011; **12**: 2461-2466 [PMID: 22320939]

26 **Matsumoto A**, Ishibashi Y, Urashima M, Omura N, Nakada K, Nishikawa K, Shida A, Takada K, Kashiwagi H, Yanaga K. High UBCH10 protein expression as a marker of poor prognosis in esophageal squamous cell carcinoma. *Anticancer Res* 2014; **34**: 955-961 [PMID: 24511039]

27 **Lin J**, Raoof DA, Wang Z, Lin MY, Thomas DG, Greenson JK, Giordano TJ, Orringer MB, Chang AC, Beer DG, Lin L. Expression and effect of inhibition of the ubiquitin-conjugating enzyme E2C on esophageal adenocarcinoma. *Neoplasia* 2006; **8**: 1062-1071 [PMID: 17217624 DOI: 10.1593/neo.05832]

28 **Yang Y**, Wang BS, Wang XM, Zhang Y, Wang MR, Jia XM. [Screening and identification of anoikis-resistant gene UBCH7 in esophageal cancer cells]. *Yi Chuan* 2012; **34**: 190-197 [PMID: 22382060]

29 **Chen MF**, Lee KD, Lu MS, Chen CC, Hsieh MJ, Liu YH, Lin PY, Chen WC. The predictive role of E2-EPF ubiquitin carrier protein in esophageal squamous cell carcinoma. *J Mol Med* (Berl) 2009; **87**: 307-320 [PMID: 19083192 DOI: 10.1007/s00109-008-0430-3]

30 **Guan GG**, Wang WB, Lei BX, Wang QL, Wu L, Fu ZM, Zhou FX,Zhou YF. UBE2D3 is a positive prognostic factor and is negatively correlated with hTERT expression in esophageal cancer. *Oncol Lett* 2015; **9**: 1567-1574 [PMID: 25789002 DOI: 10.3892/ol.2015.2926]

31 **Okawa T**, Michaylira CZ, Kalabis J, Stairs DB, Nakagawa H, Andl CD, Johnstone CN, Klein-Szanto AJ, El-Deiry WS, Cukierman E, Herlyn M, Rustgi AK. The functional interplay between EGFR overexpression, hTERT activation, and p53 mutation in esophageal epithelial cells with activation of stromal fibroblasts induces tumor development, invasion, and differentiation. *Genes Dev* 2007; **21**: 2788-2803 [PMID: 17974918 DOI: 10.1101/gad.1544507]

32 **Wen J**, Luo KJ, Hu Y, Yang H, Fu JH. Metastatic lymph node CHIP expression is a potential prognostic marker for resected esophageal squamous cell carcinoma patients. *Ann Surg Oncol* 2013; **20**: 1668-1675 [PMID: 23429937 DOI: 10.1245/s10434-012-2733-4]

33 **Kogo R**, Mimori K, Tanaka F, Komune S, Mori M. FBXO31 determines poor prognosis in esophageal squamous cell carcinoma. *Int J Oncol* 2011; **39**: 155-159 [PMID: 21537837 DOI: 10.3892/ijo.2011.1018]

34 **Li L**, Deng B, Xing G, Teng Y, Tian C, Cheng X, Yin X, Yang J, Gao X, Zhu Y, Sun Q, Zhang L, Yang X, He F. PACT is a negative regulator of p53 and essential for cell growth and embryonic development. *Proc Natl Acad Sci USA* 2007; **104**: 7951-7956 [PMID: 17470788 DOI: 10.1073/pnas.0701916104]

35 **Fukuchi M**, Fukai Y, Masuda N, Miyazaki T, Nakajima M, Sohda M, Manda R, Tsukada K, Kato H, Kuwano H. High-level expression of the Smad ubiquitin ligase Smurf2 correlates with poor prognosis in patients with esophageal squamous cell carcinoma. *Cancer Res* 2002; **62**: 7162-7165 [PMID: 12499250]

36 **Liang Y**, Hou X, Cui Q, Kang TB, Fu JH, Zhang LJ, Luo RZ, He JH, Zeng YX, Yang HX. Skp2 expression unfavorably impacts survival in resectable esophageal squamous cell carcinoma. *J Transl Med* 2012; **10**: 73 [PMID: 22533738 DOI: 10.1186/1479-5876-10-73]

37 **Wang XC**, Wu YP, Ye B, Lin DC, Feng YB, Zhang ZQ, Xu X, Han YL, Cai Y, Dong JT, Zhan QM, Wu M, Wang MR. Suppression of anoikis by SKP2 amplification and overexpression promotes metastasis of esophageal squamous cell carcinoma. *Mol Cancer Res* 2009; **7**: 12-22 [PMID: 19147533 DOI: 10.1158/1541-7786.MCR-08-0092]

38 **Yang C**, Wang Y, Zhang F, Sun G, Li C, Jing S, Liu Q, Cheng Y. Inhibiting UHRF1 expression enhances radiosensitivity in human esophageal squamous cell carcinoma. *Mol Biol Rep* 2013; **40**: 5225-5235 [PMID: 23943380 DOI: 10.1007/s11033-013-2559-6]

39 **Barbash O**, Lee EK, Diehl JA. Phosphorylation-dependent regulation of SCF (Fbx4) dimerization and activity involves a novel component, 14-3-3ε. *Oncogene* 2011; **30**: 1995-2002 [PMID: 21242966 DOI: 10.1038/onc.2010.584]

40 **Dong S**, Zhao J, Wei J, Bowser RK, Khoo A, Liu Z, Luketich JD, Pennathur A, Ma H, Zhao Y. F-box protein complex FBXL19 regulates TGFβ1-induced E-cadherin down-regulation by mediating Rac3 ubiquitination and degradation. *Mol Cancer* 2014; **13**: 76 [PMID: 24684802 DOI: 10.1186/1476-4598-13-76]

41 **Wei J**, Mialki RK, Dong S, Khoo A, Mallampalli RK, Zhao Y, Zhao J. A new mechanism of RhoA ubiquitination and degradation: roles of SCF (FBXL19) E3 ligase and Erk2. *Biochim Biophys Acta* 2013; **1833**: 2757-2764 [PMID: 23871831 DOI: 10.1016/j.bbamcr.2013.07.005]

42 **Yokobori T**, Mimori K, Iwatsuki M, Ishii H, Tanaka F, Sato T, Toh H, Sudo T, Iwaya T, Tanaka Y, Onoyama I, Kuwano H, Nakayama KI, Mori M. Copy number loss of FBXW7 is related to gene expression and poor prognosis in esophageal squamous cell carcinoma. *Int J Oncol* 2012; **41**: 253-259 [PMID: 22576686 DOI: 10.3892/ijo.2012.1436]

43 **Shen W**, Hu P, Cao JQ, Liu XX, Shao JH. MDM2 oncogene, E3 ubiquitin protein ligase T309G polymorphism and risk of oesophageal or gastric cancer: meta-analysis of 15 studies. *J Int Med Res* 2014; **42**: 1065-1076 [PMID: 25070969 DOI: 10.1177/0300060514527910]

44 **Chen JY**, Yang H, Wen J, Luo KJ, Liu QW, Lei JY, Zhen YZ,Fu JH. Association between positive murine double minute 2 expression and clinicopathological characteristics of esophageal squamous cell carcinoma: a meta-analysis. *Dis Esophagus* 2015; Epub ahead of print [PMID: 25873358 DOI: 10.1111/dote.12361]

45 **Xu Y**, Lu S. Metformin inhibits esophagus cancer proliferation through upregulation of USP7. *Cell Physiol Biochem* 2013; **32**: 1178-1186 [PMID: 24335168 DOI: 10.1159/000354517]

46 **Peng J**, Hu Q, Liu W, He X, Cui L, Chen X, Yang M, Liu H, Wei W, Liu S, Wang H. USP9X expression correlates with tumor progression and poor prognosis in esophageal squamous cell carcinoma. *Diagn Pathol* 2013; **8**: 177 [PMID: 24152793 DOI: 10.1186/1746-1596-8-177]

47 **Li J**, Wang Z, Li Y. USP22 nuclear expression is significantly associated with progression and unfavorable clinical outcome in human esophageal squamous cell carcinoma. *J Cancer Res Clin Oncol* 2012; **138**: 1291-1297 [PMID: 22447106 DOI: 10.1007/s00432-012-1191-5]

48 **Chen Y**, Fu D, Xi J, Ji Z, Liu T, Ma Y, Zhao Y, Dong L, Wang Q, Shen X. Expression and clinical significance of UCH37 in human esophageal squamous cell carcinoma. *Dig Dis Sci* 2012; **57**: 2310-2317 [PMID: 22615012 DOI: 10.1007/s10620-012-2181-9]

49 **Yu J**, Tao Q, Cheung KF, Jin H, Poon FF, Wang X, Li H, Cheng YY, Röcken C, Ebert MP, Chan AT, Sung JJ. Epigenetic identification of ubiquitin carboxyl-terminal hydrolase L1 as a functional tumor suppressor and biomarker for hepatocellular carcinoma and other digestive tumors. *Hepatology* 2008; **48**: 508-518 [PMID: 18666234 DOI: 10.1002/hep.22343]

50 **Okamoto Y**, Ozaki T, Miyazaki K, Aoyama M, Miyazaki M, Nakagawara A. UbcH10 is the cancer-related E2 ubiquitin-conjugating enzyme. *Cancer Res* 2003; **63**: 4167-4173 [PMID: 12874022]

51 **Huang Z**, Zhang N, Zha L, Mao HC, Chen X, Xiang JF, Zhang H, Wang ZW. Aberrant expression of the autocrine motility factor receptor correlates with poor prognosis and promotes metastasis in gastric carcinoma. *Asian Pac J Cancer Prev* 2014; **15**: 989-997 [PMID: 24568530]

52 **Bai J**, Zhou Y, Chen G, Zeng J, Ding J, Tan Y, Zhou J, Li G. Overexpression of Cullin1 is associated with poor prognosis of patients with gastric cancer. *Hum Pathol* 2011; **42**: 375-383 [PMID: 21190721 DOI: 10.1016/j.humpath.2010.09.003]

53 **Ye Y**, Li X, Yang J, Miao S, Wang S, Chen Y, Xia X, Wu X, Zhang J, Zhou Y, He S, Tan Y, Qiang F, Li G, Røe OD, Zhou J. MDM2 is a useful prognostic biomarker for resectable gastric cancer. *Cancer Sci* 2013; **104**: 590-598 [PMID: 23347235 DOI: 10.1111/cas.12111]

54 **Ko A**, Shin JY, Seo J, Lee KD, Lee EW, Lee MS, Lee HW, Choi IJ, Jeong JS, Chun KH, Song J. Acceleration of gastric tumorigenesis through MKRN1-mediated posttranslational regulation of p14ARF. *J Natl Cancer Inst* 2012; **104**: 1660-1672 [PMID: 23104211 DOI: 10.1093/jnci/djs424]

55 **Migita K**, Takayama T, Matsumoto S, Wakatsuki K, Tanaka T, Ito M, Nishiwada S, Nakajima Y. Prognostic impact of RING box protein-1 (RBX1) expression in gastric cancer. *Gastric Cancer* 2014; **17**: 601-609 [PMID: 24292229 DOI: 10.1007/s10120-013-0318-y]

56 **Fukuda T**, Kondo Y, Nakagama H. The anti-proliferative effects of the CHFR depend on the forkhead associated domain, but not E3 ligase activity mediated by ring finger domain. *PLoS One* 2008; **3**: e1776 [PMID: 18335050 DOI: 10.1371/journal.pone.0001776]

57 **Gao YJ**, Xin Y, Zhang JJ, Zhou J. Mechanism and pathobiologic implications of CHFR promoter methylation in gastric carcinoma. *World J Gastroenterol* 2008; **14**: 5000-5007 [PMID: 18763281]

58 **Li Y**, Yang Y, Lu Y, Herman JG, Brock MV, Zhao P, Guo M. Predictive value of CHFR and MLH1 methylation in human gastric cancer. *Gastric Cancer* 2015; **18**: 280-287 [PMID: 24748501 DOI: 10.1007/s10120-014-0370-2]

59 **Liu F**, Zhou J, Zhou P, Chen W, Guo F. The ubiquitin ligase CHIP inactivates NF-κB signaling and impairs the ability of migration and invasion in gastric cancer cells. *Int J Oncol* 2015; **46**: 2096-2106 [PMID: 25672477 DOI: 10.3892/ijo.2015.2893]

60 **Gan L**, Liu DB, Lu HF, Long GX, Mei Q, Hu GY, Qiu H, Hu GQ. Decreased expression of the carboxyl terminus of heat shock cognate 70 interacting protein in human gastric cancer and its clinical significance. *Oncol Rep* 2012; **28**: 1392-1398 [PMID: 22895543 DOI: 10.3892/or.2012.1957]

61 **Wang S**, Wu X, Zhang J, Chen Y, Xu J, Xia X, He S, Qiang F, Li A, Shu Y, Røe OD, Li G, Zhou JW. CHIP functions as a novel suppressor of tumour angiogenesis with prognostic significance in human gastric cancer. *Gut* 2013; **62**: 496-508 [PMID: 22535373 DOI: 10.1136/gutjnl-2011-301522]

62 **Zhang X**, Kong Y, Xu X, Xing H, Zhang Y, Han F, Li W, Yang Q, Zeng J, Jia J, Liu Z. F-box protein FBXO31 is down-regulated in gastric cancer and negatively regulated by miR-17 and miR-20a. *Oncotarget* 2014; **5**: 6178-6190 [PMID: 25115392]

63 **Calcagno DQ**, Freitas VM, Leal MF, de Souza CR, Demachki S, Montenegro R, Assumpção PP, Khayat AS, Smith Mde A, dos Santos AK, Burbano RR. MYC, FBXW7 and TP53 copy number variation and expression in gastric cancer. *BMC Gastroenterol* 2013; **13**: 141 [PMID: 24053468 DOI: 10.1186/1471-230X-13-141]

64 **Gao C**, Pang L, Ren C, Ma T. Decreased expression of Nedd4L correlates with poor prognosis in gastric cancer patient. *Med Oncol* 2012; **29**: 1733-1738 [PMID: 21909941 DOI: 10.1007/s12032-011-0061-3]

65 **Xie XM**, Deng JY, Hou YC, Cui JL, Wu WP, Ying GG, Dong QP, Hao XS, Liang H. Evaluating the clinical feasibility: The direct bisulfite genomic sequencing for examination of methylated status of E3 ubiquitin ligase RNF180 DNA promoter to predict the survival of gastric cancer. *Cancer Biomark* 2015; **15**: 259-265 [PMID: 25769451 DOI: 10.3233/CBM-150466]

66 **Zhou Y**, Lan J, Wang W, Shi Q, Lan Y, Cheng Z, Guan H. ZNRF3 acts as a tumour suppressor by the Wnt signalling pathway in human gastric adenocarcinoma. *J Mol Histol* 2013; **44**: 555-563 [PMID: 23504200 DOI: 10.1007/s10735-013-9504-9]

67 **Dong Q**, Liu YP, Qu XJ, Hou KZ, Li LL. [Expression of c-Cbl, Cbl-b, and epidermal growth factor receptor in gastric carcinoma and their clinical significance]. *Chin J Cancer* 2010; **29**: 59-64 [PMID: 20038312]

68 **Li H**, Xu L, Li C, Zhao L, Ma Y, Zheng H, Li Z, Zhang Y, Wang R, Liu Y, Qu X. Ubiquitin ligase Cbl-b represses IGF-I-induced epithelial mesenchymal transition via ZEB2 and microRNA-200c regulation in gastric cancer cells. *Mol Cancer* 2014; **13**: 136 [PMID: 24885194 DOI: 10.1186/1476-4598-13-136]

69 **Sawada G**, Ueo H, Matsumura T, Uchi R, Ishibashi M, Mima K, Kurashige J, Takahashi Y, Akiyoshi S, Sudo T, Sugimachi K, Doki Y, Mori M, Mimori K. Loss of COP1 expression determines poor prognosisin patients with gastric cancer. *Oncol Rep* 2013; **30**: 1971-1975 [PMID: 23933908 DOI: 10.3892/or.2013.2664]

70 **Li YF**, Wang DD, Zhao BW, Wang W, Huang CY, Chen YM, Zheng Y, Keshari RP, Xia JC, Zhou ZW. High level of COP1 expression is associated with poor prognosis in primary gastric cancer. *Int J Biol Sci* 2012; **8**: 1168-1177 [PMID: 23091414 DOI: 10.7150/ijbs.4778]

71 **Sun A**, Yu G, Dou X, Yan X, Yang W, Lin Q. Nedd4-1 is an exceptional prognostic biomarker for gastric cardia adenocarcinoma and functionally associated with metastasis. *Mol Cancer* 2014; **13**: 248 [PMID: 25395181 DOI: 10.1186/1476-4598-13-248]

72 **Yang Z**, Yuan XG, Chen J, Lu NH. Is NEDD4-1 a negative regulator of phosphatase and tensin homolog in gastric carcinogenesis? *World J Gastroenterol* 2012; **18**: 6345-6348 [PMID: 23180960 DOI: 10.3748/wjg.v18.i43.6345]

73 **Yamashita K**, Park HL, Kim MS, Osada M, Tokumaru Y, Inoue H, Mori M, Sidransky D. PGP9.5 methylation in diffuse-type gastric cancer. *Cancer Res* 2006; **66**: 3921-3927 [PMID: 16585221 DOI: 10.1158/0008-5472.CAN-05-1511]

74 **Zeng Z**, Wu HX, Zhan N, Huang YB, Wang ZS, Yang GF, Wang P, Fu GH. Prognostic significance of USP10 as a tumor-associated marker in gastric carcinoma. *Tumour Biol* 2014; **35**: 3845-3853 [PMID: 24343337 DOI: 10.1007/s13277-013-1509-1]

75 **Li SZ**, Song Y, Zhang HH, Jin BX, Liu Y, Liu WB, Zhang XD, Du RL. UbcH10 overexpression increases carcinogenesis and blocks ALLN susceptibility in colorectal cancer. *Sci Rep* 2014; **4**: 6910 [PMID: 25376843 DOI: 10.1038/srep06910]

76 **Shafiee SM**, Seghatoleslam A, Nikseresht M, Hosseini SV, Alizadeh-Naeeni M, Safaei A, Owji AA. Expression Status of UBE2Q2 in Colorectal Primary Tumors and Cell Lines. *Iran J Med Sci* 2014; **39**: 196-202 [PMID: 24753643]

77 **Yu B**, Swatkoski S, Holly A, Lee LC, Giroux V, Lee CS, Hsu D, Smith JL, Yuen G, Yue J, Ann DK, Simpson RM, Creighton CJ, Figg WD, Gucek M, Luo J. Oncogenesis driven by the Ras/Raf pathway requires the SUMO E2 ligase Ubc9. *Proc Natl Acad Sci USA* 2015; **112**: E1724-E1733 [PMID: 25805818 DOI: 10.1073/pnas.1415569112]

78 **Zhu J**, Li K, Dong L, Chen Y. Role of FBXL20 in human colorectal adenocarcinoma. *Oncol Rep* 2012; **28**: 2290-2298 [PMID: 23023584 DOI: 10.3892/or.2012.2065]

79 **Zhu J**, Deng S, Duan J, Xie X, Xu S, Ran M, Dai X, Pu Y,Zhang X. FBXL20 acts as an invasion inducer and mediates E-cadherin in colorectal adenocarcinoma. *Oncol Lett* 2014; **7**: 2185-2191 [PMID: 24932313 DOI: 10.3892/ol.2014.2031]

80 **Peter S**, Bultinck J, Myant K, Jaenicke LA, Walz S, Müller J, Gmachl M, Treu M, Boehmelt G, Ade CP, Schmitz W, Wiegering A, Otto C, Popov N, Sansom O, Kraut N, Eilers M. Tumor cell-specific inhibition of MYC function using small molecule inhibitors of the HUWE1 ubiquitin ligase. *EMBO Mol Med* 2014; **6**: 1525-1541 [PMID: 25253726 DOI: 10.15252/emmm.201403927]

81 **Kofunato Y**, Kumamoto K, Saitou K, Hayase S, Okayama H, Miyamoto K, Sato Y, Katakura K, Nakamura I, Ohki S, Koyama Y, Unoki M, Takenoshita S. UHRF1 expression is upregulated and associated with cellular proliferation in colorectal cancer. *Oncol Rep* 2012; **28**: 1997-2002 [PMID: 23023523 DOI: 10.3892/or.2012.2064]

82 **Sabatino L**, Fucci A, Pancione M, Carafa V, Nebbioso A, Pistore C, Babbio F, Votino C, Laudanna C, Ceccarelli M, Altucci L, Bonapace IM, Colantuoni V. UHRF1 coordinates peroxisome proliferator activated receptor gamma (PPARG) epigenetic silencing and mediates colorectal cancer progression. *Oncogene* 2012; **31**: 5061-5072 [PMID: 22286757 DOI: 10.1038/onc.2012.3]

83 **Wang F**, Yang YZ, Shi CZ, Zhang P, Moyer MP, Zhang HZ, Zou Y, Qin HL. UHRF1 promotes cell growth and metastasis through repression of p16(ink^{4}a) in colorectal cancer. *Ann Surg Oncol* 2012; **19**: 2753-2762 [PMID: 22219067 DOI: 10.1245/s10434-011-2194-1]

84 **Lu S**, Yan D, Wu Z, Jiang T, Chen J, Yuan L, Lin J, Peng Z, Tang H. Ubiquitin-like with PHD and ring finger domains 2 is a predictor of survival and a potential therapeutic target in colon cancer. *Oncol Rep* 2014; **31**: 1802-1810 [PMID: 24573556 DOI: 10.3892/or.2014.3035]

85 **Chen H**, Mo X, Yu J, Huang S, Huang Z, Gao L. Interference of Skp2 effectively inhibits the development and metastasis of colon carcinoma. *Mol Med Rep* 2014; **10**: 1129-1135 [PMID: 24913024 DOI: 10.3892/mmr.2014.2308]

86 **Xu SY**, Wang F, Wei G, Wang B, Yang JY, Huang YZ, Zhang L, Zheng F, Guo LY, Wang JN, Tang JM. S-phase kinase-associated protein 2 knockdown blocks colorectal cancer growth via regulation of both p27 and p16 expression. *Cancer Gene Ther* 2013; **20**: 690-694 [PMID: 24336114 DOI: 10.1038/cgt.2013.70]

87 **Tian YF**, Chen TJ, Lin CY, Chen LT, Lin LC, Hsing CH, Lee SW, Sheu MJ, Lee HH, Shiue YL, Huang HY, Pan HY, Li CF, Chen SH. SKP2 overexpression is associated with a poor prognosis of rectal cancer treated with chemoradiotherapy and represents a therapeutic target with high potential. *Tumour Biol* 2013; **34**: 1107-1117 [PMID: 23328995 DOI: 10.1007/s13277-013-0652-z]

88 **Wang Y**, Ren F, Wang Y, Feng Y, Wang D, Jia B, Qiu Y, Wang S, Yu J, Sung JJ, Xu J, Zeps N, Chang Z. CHIP/Stub1 functions as a tumor suppressor and represses NF-κB-mediated signaling in colorectal cancer. *Carcinogenesis* 2014; **35**: 983-991 [PMID: 24302614 DOI: 10.1093/carcin/bgt393]

89 **Tanksley JP**, Chen X, Coffey RJ. NEDD4L is downregulated in colorectal cancer and inhibits canonical WNT signaling. *PLoS One* 2013; **8**: e81514 [PMID: 24312311 DOI: 10.1371/journal.pone.0081514]

90 **Jiang Y**, Sun S, Liu G, Yan B, Niu J. Nrdp1 inhibits metastasis of colorectal cancer cells by EGFR signaling-dependent MMP7 modulation. *Tumour Biol* 2015; **36**: 1129-1133 [PMID: 25330950 DOI: 10.1007/s13277-014-2726-y]

91 **Lu H**, Li H, Mao D, Zhu Z, Sun H. Nrdp1 inhibits growth of colorectal cancer cells by nuclear retention of p27. *Tumour Biol* 2014; **35**: 8639-8643 [PMID: 24867101 DOI: 10.1007/s13277-014-2132-5]

92 **Giannakis M**, Hodis E, Jasmine Mu X, Yamauchi M, Rosenbluh J, Cibulskis K, Saksena G, Lawrence MS, Qian ZR, Nishihara R, Van Allen EM, Hahn WC, Gabriel SB, Lander ES, Getz G, Ogino S, Fuchs CS, Garraway LA. RNF43 is frequently mutated in colorectal and endometrial cancers. *Nat Genet* 2014; **46**: 1264-1266 [PMID: 25344691 DOI: 10.1038/ng.3127]

93 **Iwatsuki M**, Mimori K, Ishii H, Yokobori T, Takatsuno Y, Sato T, Toh H, Onoyama I, Nakayama KI, Baba H, Mori M. Loss of FBXW7, a cell cycle regulating gene, in colorectal cancer: clinical significance. *Int J Cancer* 2010; **126**: 1828-1837 [PMID: 19739118 DOI: 10.1002/ijc.24879]

94 **Davis H**, Lewis A, Behrens A, Tomlinson I. Investigation of the atypical FBXW7 mutation spectrum in human tumours by conditional expression of a heterozygous propellor tip missense allele in the mouse intestines. *Gut* 2014; **63**: 792-799 [PMID: 23676439 DOI: 10.1136/gutjnl-2013-304719]

95 **Chang CC**, Lin HH, Lin JK, Lin CC, Lan YT, Wang HS, Yang SH, Chen WS, Lin TC, Jiang JK, Chang SC. FBXW7 mutation analysis and its correlation with clinicopathological features and prognosis in colorectal cancer patients. *Int J Biol Markers* 2015; **30**: e88-e95 [PMID: 25450649 DOI: 10.5301/jbm.5000125]

96 **Zhou Y**, Wu J, Fu X, Du W, Zhou L, Meng X, Yu H, Lin J, Ye W, Liu J, Peng H, Liu RY, Pan C, Huang W. OTUB1 promotes metastasis and serves as a marker of poor prognosis in colorectal cancer. *Mol Cancer* 2014; **13**: 258 [PMID: 25431208 DOI: 10.1186/1476-4598-13-258]

97 **Lee EW**, Seong D, Seo J, Jeong M, Lee HK, Song J. USP11-dependent selective cIAP2 deubiquitylation and stabilization determine sensitivity to Smac mimetics. *Cell Death Differ* 2015; **22**: 1463-1476 [PMID: 25613375 DOI: 10.1038/cdd.2014.234]

98 **Liu YL**, Yang YM, Xu H, Dong XS. Aberrant expression of USP22 is associated with liver metastasis and poor prognosis of colorectal cancer. *J Surg Oncol* 2011; **103**: 283-289 [PMID: 21337558 DOI: 10.1002/jso.21802]

99 **Liu Y**, Yang Y, Xu H, Dong X. Implication of USP22 in the regulation of BMI-1, c-Myc, p16INK4a, p14ARF, and cyclin D2 expression in primary colorectal carcinomas. *Diagn Mol Pathol* 2010; **19**: 194-200 [PMID: 21052002 DOI: 10.1097/PDM.0b013e3181e202f2]

100 **Ao N**, Liu Y, Feng H, Bian X, Li Z, Gu B, Zhao X, Liu Y. Ubiquitin-specific peptidase USP22 negatively regulates the STAT signaling pathway by deubiquitinating SIRT1. *Cell Physiol Biochem* 2014; **33**: 1863-1875 [PMID: 24969755 DOI: 10.1159/000362964]

101 **Diefenbacher ME**, Popov N, Blake SM, Schülein-Völk C, Nye E, Spencer-Dene B, Jaenicke LA, Eilers M, Behrens A. The deubiquitinase USP28 controls intestinal homeostasis and promotes colorectal cancer. *J Clin Invest* 2014; **124**: 3407-3418 [PMID: 24960159 DOI: 10.1172/JCI73733]

102 **Huang Z**, Wen P, Kong R, Cheng H, Zhang B, Quan C, Bian Z, Chen M, Zhang Z, Chen X, Du X, Liu J, Zhu L, Fushimi K, Hua D, Wu JY. USP33 mediates Slit-Robo signaling in inhibiting colorectal cancer cell migration. *Int J Cancer* 2015; **136**: 1792-1802 [PMID: 25242263 DOI: 10.1002/ijc.29226]

103 **Sloane MA**, Wong JW, Perera D, Nunez AC, Pimanda JE, Hawkins NJ, Sieber OM, Bourke MJ, Hesson LB, Ward RL. Epigenetic inactivation of the candidate tumor suppressor USP44 is a frequent and early event in colorectal neoplasia. *Epigenetics* 2014; **9**: 1092-1100 [PMID: 24837038 DOI: 10.4161/epi.29222]

104 **Zhong J**, Zhao M, Ma Y, Luo Q, Liu J, Wang J, Yuan X, Sang J, Huang C. UCHL1 acts as a colorectal cancer oncogene via activation of the β-catenin/TCF pathway through its deubiquitinating activity. *Int J Mol Med* 2012; **30**: 430-436 [PMID: 22641175 DOI: 10.3892/ijmm.2012.1012]

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