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Ubiquitin-conjugating enzymes as potential biomarkers and therapeutic targets for digestive system cancers (Review)

XIANGXIANG LEI[1*], XIAOGE HU[2*], QILIANG LU[3], WEN FU[3], WEN SUN[4], QIANCHENG MA[5], DONGSHENG HUANG[2] and QIURAN XU[2]

[1]Institute of Basic Medical Sciences and Forensic Medicine, Hangzhou Medical College, Hangzhou, Zhejiang 310053; [2]The Key Laboratory of Tumor Molecular Diagnosis and Individualized Medicine of Zhejiang Province, Zhejiang Provincial People's Hospital, Affiliated People's Hospital, Hangzhou Medical College, Hangzhou, Zhejiang 310014; [3]Qingdao Medical College, Qingdao University, Qingdao, Shandong 266000; [4]Second Clinical Medical Institute, Zhejiang Chinese Medical University, Hangzhou, Zhejiang 310053; [5]Institute of Bioengineering, Zhejiang University of Technology, Hangzhou, Zhejiang 310014, P.R. China

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Abstract. Digestive system cancers are the leading cause of cancer-related death worldwide due to their high morbidity and mortality rates. The current treatment methods include surgical treatment, chemotherapy, radiotherapy and endoscopic treatment, and the precisely targeted therapy of digestive system cancers requires to be further studied. The ubiquitin-proteasome system is the main pathway for protein degradation in cells and the ubiquitin-conjugating enzymes (E2s) have a decisive role in the specific selection of target proteins for degradation. The E2s have an important physiological role in digestive system cancers, which is related to the clinical tumor stage, differentiation degree and poor prognosis. Furthermore, they are involved in the physiological processes of digestive system tumor cell proliferation, migration, invasion, stemness, drug resistance and autophagy. In the present article, the progress and achievements of the E2s in gastric cancer, hepatocellular carcinoma, pancreatic cancer, colorectal cancer, intrahepatic cholangiocarcinoma, gallbladder cancer and esophageal squamous cell carcinoma were reviewed, which may provide early screening indicators and reliable therapeutic targets for digestive system cancers.

Correspondence to: Dr Dongsheng Huang or Dr Qiuran Xu, The Key Laboratory of Tumor Molecular Diagnosis and Individualized Medicine of Zhejiang Province, Zhejiang Provincial People's Hospital, Affiliated People's Hospital, Hangzhou Medical College, 158 Shangtang Road, Gongshu, Hangzhou, Zhejiang 310014, P.R. China
E-mail: dshuang@hmc.edu.cn
E-mail: windway626@sina.com

[*]Contributed equally

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Contents

1. Introduction

Digestive system cancers are the leading cause of cancer-related death worldwide and represent a global health challenge, with cancer cells participating in the occurrence and progression of cancer by altering cellular molecular and cellular biological processes (1). A variety of treatments for gastric cancer (GC), including chemotherapy, radiotherapy, surgery, immunotherapy and targeted therapy, have been clinically proven to be effective against GC, but poorly differentiated gastric adenocarcinoma and gastric adenocarcinoma without immunotherapy active marker subtypes still require effective treatment (2). Systemic therapies for hepatocellular carcinoma (HCC) are currently in clinical use, while checkpoint inhibitors and tyrosine kinase inhibitors or anti-VEGF therapies are still being tested (3). Screening for pancreatic cancer (PC) is difficult; as a result, numerous patients are diagnosed with advanced or metastatic cancer. Surgically assisted chemotherapy and chemotherapy may be used for early-stage patients, while multidrug radiotherapy may be used for advanced and metastatic patients to improve patient survival (4,5). Colorectal cancer (CRC) is the fourth most deadly cancer in the world and is closely related to poor lifestyle habits. The most current

treatment regimens may only improve patient survival due to patients not exhibiting clinical symptoms until the later stages (6). Therefore, the early screening and diagnosis of CRC urgently require breakthroughs. Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver cancer and its high lethality and increasing incidence year by year are of increasing concern (7). Gallbladder cancer (GBC) is a common malignancy in the biliary system and current treatment modalities include surgical resection, chemotherapy and radiotherapy. Immunotherapy, targeted therapy and nanoparticle therapy are advancing in clinical trials (8). Esophageal squamous cell carcinoma (ESCC) is the most common form of esophageal cancer and despite innovations and changes in clinical treatment, its five-year survival rate remains low (9).

Ubiquitination is a post-translational modification that is involved in the degradation of proteins and regulates a variety of cellular physiological processes. Ubiquitination has a specific role in neurodegenerative diseases, including Parkinson's disease, Alzheimer's disease and Huntington's disease. These neurodegenerative disorders are immunoreactive for anti-ubiquitin antibodies (10). In addition, ubiquitination is involved in regulating the tumor necrosis factor signaling pathway, IL-1β and Toll-like receptor signaling (11). Ubiquitination also has a surprising relationship with cellular autophagy. Ubiquitination degrades the associated proteasome and regulates the expression of autophagy-related factors (12).

The ubiquitin-proteasome system is the main pathway for protein degradation. The ubiquitin-proteasome system is a combination of ubiquitin, ubiquitin-activating enzyme (E1), ubiquitin-conjugating enzyme (E2) and ubiquitin-ligase enzyme (E3) to complete the degradation of target proteins (13). In the ubiquitin-proteasome pathway, E1 transfers the activated ubiquitin molecules to the Cys residues of E2. Subsequently, an E2 may mark different types of E3 to catalyze specific substrate ubiquitination. In this process, E3 is responsible for the transfer of ubiquitin molecules from E2 to the substrate protein (14-16). The ubiquitin-proteasome pathway is presented in Fig. 1. The ubiquitin-proteasome system has a role in a variety of tumors and multiple small molecule inhibitors targeting the ubiquitin-proteasome pathway are already in clinical trials (17). Prior to this, the function of E2s in different cancers has been previously reviewed in corresponding articles (18). In addition, the regulation of autophagic degradation pathways by E2s and their possible use as potential therapeutic targets in cancers have also been summarized (12,19). However, E2s also have multiple roles in digestive system cancers. The present article provides a detailed review of the expression and roles of E2s in digestive system cancers, which may provide a reference for E2s to become molecular therapeutic targets in digestive system cancers.

2. E2s

E2s belong to a multi-gene family with different numbers of members in different species. There are nearly 40 E2s in humans, which are divided into four categories according to the highly conserved ubiquitin-binding catalytic (UBC) folding structural domain and the presence or absence of N-terminal and C-terminal, of which the class I E2s consists of the catalytic folding structural domain only. Class II E2s consist of the catalytic folding domain and the N terminal. Class III E2s consist of the catalytic folding domain and the C-terminal. Class IV E2s consist of the catalytic folding structural domain, N-terminal and C-terminal together (18,20), as presented in Fig. 2.

E2s are involved in a variety of physiological functions in cells. E2s and the ubiquitin ligase Parkin protein mediate the mitochondrial autophagic pathway in cells. Furthermore, E2s containing *Baculovirus* IAP repeats may inhibit the expression of autophagic fluxes (12). The ratio of charged to uncharged E2s and the concentration of free ubiquitin determine whether the OTU deubiquitinase, ubiquitin aldehyde binding 1-E2 complex can function as a deubiquitinating enzymes or polyubiquitination inhibitor (21). Of note, E2s may themselves be ubiquitinated and their ubiquitination levels may be regulated by their protein levels (22). E2s also have a non-negligible role in digestive system cancers, and importantly, molecular inhibitors targeting E2s are currently under investigation, while molecular inhibitors applied to immune strategy therapy of cancer are still waiting to be developed, and E2s, as important platforms in the ubiquitin system, have an incalculable role as targets for clinical treatment (19,23).

3. Class I E2s in digestive system cancers

Class I E2s in GC. Initial studies showed that intron 6 and exon 7 of ubiquitin-conjugating enzyme D1 (UBE2D1) are highly homologous to the sequence of SFT, a membrane protein for iron transport. Compared to normal control tissue, the liver of patients with hereditary hemochromatosis expressed higher levels of UBE2D1 (24). UBE2D1 is highly expressed in GC tissues and UBE2D1 is involved in gastric carcinogenesis; as a target of microRNA (miR)-144-3p, it is negatively correlated with miR-144-3p and its expression is closely related to the resistance of patients with GC to cisplatin therapy (25). Xie *et al* (26) used lentivirus to transfect GC cells and found that silencing UBE2D1 downregulated the expression of epithelial-mesenchymal transition (EMT) proteins MMP2 and MMP9, thereby inhibiting the migratory ability of GC cells. *In vivo* experiments also demonstrated that the knockdown of UBE2D1 inhibited the metastasis of xenograft tumors in mice. In addition, UBE2D1 regulates the TGF-β/SMAD4 signaling pathway through the ubiquitination of SMAD4, which modulates the development of GC (26).

Class I E2s in HCC. UBE2A is the first class of E2s and previous studies have indicated its involvement in the DNA damage repair pathway (27). UBE2A was not only highly expressed in HCC tissues but also elevated in 6 HCC cell lines, and its expression was mainly located in the cytoplasmic sites of HCC cells. UBE2A was significantly associated with tumor stage, vascular invasion and patient survival in HCC (28). However, the potential mechanism of UBE2A affecting HCC requires to be further studied. UBE2D1 belongs to the UBE2D family of E2s. It has been experimentally proven to ubiquitinate and degrade p53 *in vivo* and *in vitro* (29,30). UBE2D1 is highly expressed in HCC tissues and HCC cells, which may reduce the survival time of patients with HCC. High expression of UBE2D1 promotes the proliferation of HCC cells and also exacerbates the progression of HCC through

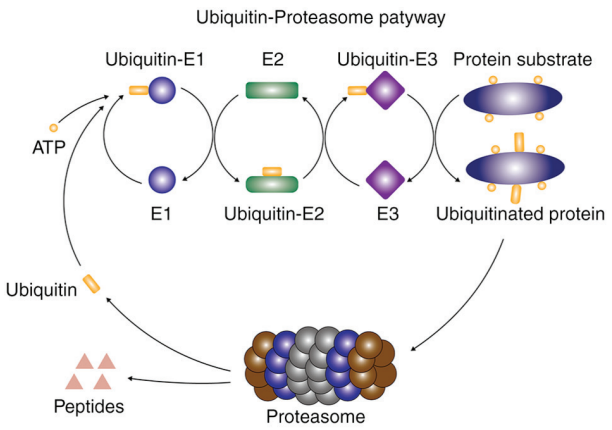

Figure 1. The ubiquitin proteasome pathway. Under ATP-supplied conditions, E1s capture free ubiquitin molecules and provide them to E2s, which act as transfer platforms for ubiquitin to E3s, E3s interact with E2s to transfer ubiquitin to substrate proteins, which degrade and release ubiquitin molecules, and ubiquitin re-engages in the ubiquitin proteasome pathway.

ubiquitination and degradation of p53 (31). UBE2I is essential for positive selection and the late maturation process of thymocytes. In addition, UBE2I-mediated sumoylation has a beneficial effect on cardiac function in transgenic mice after cardiac damage (32,33). UBE2I is upregulated in numerous cancers, including breast cancer, as well as glioma (34,35). Fang *et al* (36) examined the expression levels of UBC9 (UBE2I) in HCC tissues and HCC cells and determined that UBC9 expression was increased in HCC tissues and also in HCC cells. In addition, UBC9 exhibited higher sensitivity to adriamycin in HCC. Of note, UBC9 is able to bind to HDAC4 and be acetylated. The expression level of acetylated UBC9 is negatively correlated with HDAC4 and targeting this pathway increases radiation-induced mortality of HCC cells (37). Cell functional experiments demonstrated that UBE2I promoted the proliferation, migration and invasion of HCC cells, which is regulated by the upstream gene miR-195-3p. UBE2I may regulate the expression of autophagy-related proteins, including microtubule associated protein 1 light chain 3 α/β, Beclin-1 and autophagy-related 16 like 1. Of note, high UBE2I expression reduces overall survival (OS) and relapse-free survival in patients as analyzed by the The Cancer Genome Atlas (TCGA) database. Therefore, UBE2I may promote the occurrence and malignant progression of HCC through the autophagy pathway (38,39). However, the specific autophagy pathway has not been studied and confirmed. UBE2L3 regulates the proportion of cells in S-phase and regulates the proliferation of HeLa cells. UBE2L3 may ubiquitously degrade p53, thereby reducing the p53 damage response to DNA (40,41). Furthermore, UBE2L3 regulates the proliferation of HCC cells by regulating the activation of p65 through an ubiquitin-mediated proteasome degradation pathway. At the same time, *in situ* tumorigenesis was performed in mice and it was found that tumor growth was inhibited by knocking down UBE2L3. Of note, analysis of liver cancer and normal tissue samples revealed that high UBE2L3 expression shortened the OS time and disease-free survival (DFS) time of patients (42). UBE2N is a cancer-associated E2, which is known to promote the growth of melanoma (43). UBE2N mRNA expression levels are upregulated in HCC tissues and HCC lines. MiR-147b regulates UBE2N to promote the proliferation of HCC cells. Whether it may be used as a therapeutic target for liver cancer still requires to be proven (44).

Class I E2 in PC. UBE2N was highly expressed in pancreatic ductal carcinoma and elevated in 4 types of PC cells, including SW1990. Tripartite motif containing 11 (TRIM11) is an important protein that may regulate ferritin phagocytosis and sensitivity to gemcitabine in pancreatic ductal carcinoma. Of note, UBE2N has a similar role to TRIM11 in regulating the autophagic pathway. It was demonstrated that UBE2N interacts with TRIM11, thereby promoting TRIM11-mediated ferritin phagocytosis and resistance to gemcitabine in PC (45).

Class I E2 in CRC. It has been demonstrated that UBE2B ubiquitinates β-catenin in MCF10A breast cancer cells and that ubiquitination of β-catenin is reduced by inhibition of UBE2B expression (46). Of note, UBE2B is highly expressed in CRC cells with ionizing radiation resistance. The use of the UBE2B inhibitor significantly reduced the resistance of CRC cells to ionizing radiation. In addition, the expression of UBE2B in patients with CRC was closely associated with certain clinical indicators, such as vascular invasion and tumor regression grade (47).

4. Class II E2s in digestive system cancers

Class II E2 in GC. Okamoto *et al* (48) used real-time reverse transcription-quantitative PCR to detect the expression of 17 E2s in nearly 30 tumors and their normal tissues. The results revealed that UBE2C expression was significantly elevated in most tumors, including GC, suggesting that UBE2C may be involved in the development and progression of GC (48). Zhang *et al* (49) found that the expression of UBE2C mRNA and protein in GC tissues was higher than that in adjacent tissues and its expression was correlated with the Lauren classification, serous infiltration, lymphatic metastasis and TNM staging of GC. In addition, patients with UBE2C-positive expression of GC have lower five-year survival rates relative to negative patients and survival times are lower than median survival times (49). Furthermore, UBE2C is regulated by miR-300 and RNA-binding protein HuR to promote GC growth, DNA synthesis and cell migration (50). In addition, as a functional target, it is regulated by miR-17/20a and positively correlated with the expression of miR-17/20a. Inhibition of its expression was observed to inhibit the proliferation of GC cells *in vitro* (51). *In vivo* experiments have demonstrated that UBE2C inhibits the development of gastric adenocarcinoma through the Wnt/β-catenin and PI3K/Akt signaling pathways (52). UBCH10 (UBE2C) may also inhibit the apoptosis of GC cells, contributing to the proliferation of GC cells (53). Tissue sample data and results from *in vivo* and *in vitro* experiments suggest that UBE2C may be a potential therapeutic target for GC.

Class II E2s in HCC. Ieta *et al* (54) identified that UBE2C expression in HCC was higher than that in adjacent tissues and was significantly associated with tumor grade and poor clinical prognosis. In addition, analysis of liver cancer tissues revealed

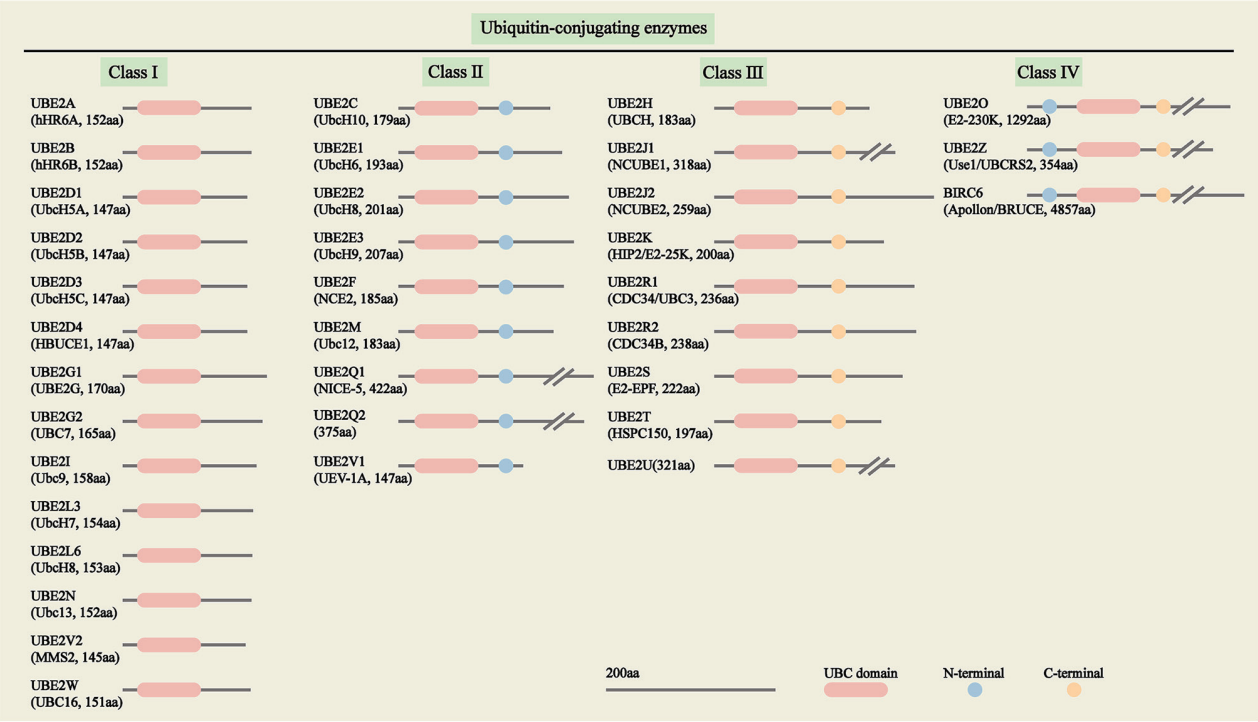

Figure 2. Classification of UBEs. The UBEs are classified into four types based on their N-terminal, C-terminal and UBC domains. Class I consists of UBC domains only. Class II consists of the UBC domains and the N-terminal. Class III consists of the UBC domains and the C-terminal. Class IV consists of the UBC domains, N-terminal and C-terminal together. UBC, ubiquitin-binding catalytic; UBE, ubiquitin-conjugating enzyme.

a lower DFS rate in patients with high UBE2C expression (54). In addition, UBE2C overexpression was reported to seriously shorten the survival time of patients with HCC. UBE2C may worsen the progression of HCC by ubiquitination and degradation of p53. UBE2C is regulated by DNA primase subunit 1 to mediate the ubiquitination of p53 (55,56). UBE2C is associated with proliferation, migration and invasion of HCC. In addition, patients with low expression of UBE2C had higher sensitivity to adriamycin and low expression of UBE2C was also sensitive to 5-fluorouracil and sorafenib (57). UBE2M is an E2 that may ubiquitinate and degrade UBE2F to inhibit lung cancer cell growth. In addition, UBE2M may activate ubiquitin ligases to regulate the ubiquitination pathway (58). UBE2M regulates the proliferation of HCC cells by regulating the G1- to S-phase transition of the cell cycle and high UBE2M expression shows significantly lower OS and DFS time in HCC patients (59). UBE2Q1 expression is upregulated in HCC and the upregulation mechanism is attributed to the increased copy of the UBE2Q1 gene repeated on chromosome 1q21. In addition, UBE2Q1 may regulate cell proliferation, migration, invasion, cell cycle and the expression levels of p21 and p53 proteins, and regulate the progression of HCC by regulating β-catenin-EGFR-PI3K-Akt-mTOR signaling pathway (60,61). Patients with high UBE2Q1 expression have a shorter survival time after surgery (61). In HBV-associated HCC, the UBE2Q1 gene is in a hypomethylated state, which is significantly negatively correlated with the TNM stage. Whether this state may be used to assess the progression of the disease remains to be confirmed (62).

Class II E2 in PC. UBE2C expression was upregulated in pancreatic ductal carcinoma tissue, as well as in pancreatic ductal carcinoma cells, and the OS time was shorter in patients with high levels of UBE2C expression. It promotes the progression of pancreatic ductal carcinoma by regulating the cell cycle, cell proliferation and EMT. In addition, knockdown of UBE2C inhibited tumor growth in nude mice, which may suggest UBE2C as a new target for PC therapy (63). Recent studies have indicated that UBE2C is a potential therapeutic target for PC. The small molecule inhibitor DHPO, a sesquiterpene lactone compound, has been reported to inhibit the proliferation and migration of PC cells *in vitro* and inhibit the growth and metastasis of pancreatic tumors *in vivo*. DHPO inhibits the malignant progression of PC. DHPO provides a new candidate for the precise treatment of PC (64).

Class II E2s in CRC. Chen *et al* (65) and Fujita *et al* (66) determined that UBCH10 (UBE2C) expression was elevated in CRC tissue samples and that high levels of UBCH10 expression were associated with high-grade histological tumors by analyzing CRC tissue samples (65,66). Cacciola *et al* (67) reported that UBCH10 expression was elevated in CRC cells. They then analyzed the correlation between mutations in the KRAS gene and UBCH10 protein expression in CRC samples and found that UBCH10 expression was correlated with the type of KRAS codon 12 mutations (67). Genetic inactivation of UBCH10 stabilizes the expression of the cell cycle proteins Cyclin A and Cyclin B1 and regulated the growth of CRC cells *in vitro* and even in nude mice (68). Chen *et al* (69) inhibited UBCH10 expression by RNA interference and found that a decrease in UBCH10 reduced the growth rate of CRC cells, causing more cells to stagnate in the G2-M phase. UBE2C may be targeted by miR-381 to regulate cell viability, proliferation, colony

formation, invasion and apoptosis (70). In addition, UBE2C expression affects the sensitivity of CRC cells to bortezomib and oxaliplatin (71). Shafiee *et al* (72) examined the expression of UBE2Q1 in CRC tissues as well as cells; they found that UBE2Q1 was highly expressed in both CRC tissues and cells compared to normal tissues and cells. Fahmidehkar *et al* (73) constructed a CRC cell line with stable overexpression of UBE2Q1 and examined the effect of UBE2Q1 overexpression on cell proliferation by *in vitro* assays. The results indicated that UBE2Q1 overexpression regulated the cell cycle of CRC cells and thus the growth rate of CRC cells *in vitro* (73). UBE2Q2 was overexpressed in CRC tissue samples as well as in CRC cells (74). Mokarram *et al* (75) found that UBE2Q2 was more unmethylated than UBE2Q1 by detecting the methylation level of the UBE2Q gene promoter in CRC tissues. This may indicate that the unmethylated status of UBE2Q2 is associated with the progression of CRC (75). Furthermore, UBE2V1 expression was reported to be enhanced in CRC tissues and cells and is associated with poor clinical prognosis. UBE2V1 inhibits the autophagy process and promotes EMT and CRC cell metastasis in an autophagy-dependent mode *in vitro* and *in vivo*. Rapamycin and trehalose regulate UBE2V1-mediated lung metastasis in a mouse xenograft model (76).

Class II E2s in GBC and ICC. Washiro *et al* (77) screened for the differentially expressed cell cycle gene UBE2C in advanced GBC tissues and normal gallbladder tissues by DNA microarray technology, and the results suggested that UBE2C may be involved in the development of gallbladder carcinogenesis. Zhao *et al* (78) indicated that UBE2M was highly expressed in ICC compared to non-tumor tissues. Patients with high UBE2M expression in ICC had a shorter OS time as well as a shorter recurrence-free survival time. Knockdown of UBE2M suppressed the proliferation of ICC cells *in vitro*, as well as inhibited the growth of xenograft tumors in nude mice. Knockdown of UBE2M induced the upregulation of apoptosis-related proteins, such as PARP, cPARP, caspase-3 and caspase-9, in ICC cells and induced apoptosis in cancer cells to regulate the progression of ICC (78).

Class II E2 in ESCC. Wang *et al* (79) identified through the ESCC microarray dataset that UBE2C may have a non-negligible role in the development and progression of ESCC. By analyzing data from the TCGA and Gene-Tissue Expression databases, Dastsooz *et al* (80) indicated that UBE2C was overexpressed in a variety of cancers and was associated with a shorter OS time. In ESCC, UBE2C expression was increased. They then analyzed the relationship between UBE2C and clinicopathological staging through the TCGA database and they found that UBE2C expression was higher in the early stages of ESCC, which may imply that UBE2C is involved in tumor development and progression. Li *et al* (81) showed by a bioinformatics analysis that UBE2C expression was upregulated in patients with esophageal cancer and that the OS time was shorter in patients with high UBE2C expression. In addition, the immunohistochemical staining results confirmed various results of Dastsooz *et al* (80), as UBE2C expression was elevated in ESCC but not in normal tissue (82). Li *et al* (83) collected extensive protein and mRNA expression data and confirmed that UBE2C is highly expressed in ESCC and is more expressed in males than in females. Of note, they predicted the upstream molecules that may regulate UBE2C and their hypothesis of a competing endogenous RNA axis consisting of long noncoding RNA HLA complex P5/hsa-miR-1395p/UBE2C regulating ESCC, providing an idea for further exploring the molecular mechanisms of the regulation of UBE2C in ESCC. ECRG4 augurin precursor (ECRG4) is a gene that inhibits the oncogenicity of ESCC cells. In ESCC, the expression of UBE2C was negatively correlated with ECRG4, which promoted the proliferation of ESCC and inhibited the apoptosis of cancer cells (84).

5. Class III E2s in digestive system cancers

Class III E2s in GC. Relative to GES1 in gastric epithelial cells, Huntingtin-interacting protein 2 (HIP2) was highly expressed at the mRNA and protein level in AGS and other six GC cell lines. Furthermore, the expression of HIP2 was also higher in GC tissues than in paracancerous tissues. In addition, the OS rate was higher in the HIP2 low-expression patient group. The results of *in vivo* experiments indicated that high expression of HIP2 promoted the proliferation, migration and invasion of GC (85). UBE2T has a proliferative effect in cells, as it may monoubiquitinate Fanconi anemia (FA) complementation group D2 and participate in the regulation of the FA pathway (86). UBE2T was highly expressed in GC tissues, as well as in the 9 GC cells tested, and associated with the OS of patients with GC. It promotes the proliferation of GC cells *in vitro* and participates in the regulation of the cell cycle, as well as the process of EMT of GC cells (87). In addition, the knockdown of UBE2T inhibits the growth of xenograft tumors in nude mice. UBE2T may activate the Wnt/β-catenin pathway, inhibit c-Myc expression and promote GC progression (88). Of note, Yu *et al* (89) found that UBE2T regulates the ubiquitination of receptor for activated C kinase 1 as an upstream gene independently of ubiquitin ligase, thereby activating the Wnt/β-catenin pathway to promote the progression of GC. By contrast, the UBE2T inhibitor M435-1279 blocks the Wnt/β-catenin pathway to inhibit the progression of GC (89). In conclusion, Wnt/β-catenin and PI3K/Akt signaling pathways are involved in the progression of G; these E2s and their related miRNAs have important roles in the carcinogenesis and progression of GC.

Class III E2s in HCC. UBE2S has an essential role in mitosis. Studies have indicated that it works with the ubiquitin ligase APC/C to promote the ubiquitination of substrates (90). Both UBE2S and UBE2T belong to the third class of E2s, both of which have a larger role in HCC. By bioinformatics analysis, Zhang and Yang (91) found that UBE2S, UBE2T and UBE2C are associated with HCC progression. UBE2C is highly expressed in patients with TP53-mutated HCC, as are UBE2S and UBE2T. The results of this analysis of clinical patient data were confirmed by other experiments (91). Expression of UBE2S is associated with survival, metastasis and recurrence in patients with HCC and analysis of TCGA data indicated that the OS and DFS time were shorter in patients with high UBE2S expression. By contrast, *in vivo* experiments have indicated that UBE2S regulates the p53 signaling pathway

through ubiquitination to affect cell cycle, proliferation and migration (92,93). Furthermore, UBE2S may also be transcriptionally activated by forkhead box M1, facilitate ubiquitination of phosphatase and tensin homolog and phosphorylates AKT, thereby enhancing the resistance of HCC cells to 5-fluorouracil and oxaliplatin (94). The effect of UBE2S on other chemotherapeutic drugs remains elusive. UBE2T is widely regulated in HCC and its expression is significantly associated with the grade of HCC, vascular invasion and poor clinical prognosis of patients with HCC. UBE2T may regulate the cell cycle and apoptosis, which may also be regulated by miRNA to affect the malignant phenotype of HCC cells. For instance, regulation by miR-212-5p affects cell proliferation, migration and invasion. MiR-543 may also regulate UBE2T ubiquitination and degrades p53 protein. MiR-1305 is also able to target it to inhibit the Akt signaling pathway and inhibit the self-renewal and tumorigenesis of liver cancer stem cells (95-100). UBE2T is the sumoylation target of SUMO-specific peptidase 1, which mediates its carcinogenic effects (101). Furthermore, patients with HCC with high UBE2T expression had shorter OS and DFS. UBE2T interacts with ubiquitin ligase ring finger protein 8 to monoubiquitin H2AX, activating phosphorylation of checkpoint kinase 1 and enhancing radioresistance in HCC (102).

Class III E2s in PC. The expression of UBE2S and UBE2T was observed to be elevated in pancreatic ductal carcinoma tissues and cells, and they promoted cell proliferation and migration. In addition, high UBE2S expression was associated with reduced OS time. UBE2S may promote EMT in PC cells. Furthermore, UBE2S is negatively correlated with von Hippel-Lindau tumor suppressor expression, activates hypoxia-inducible factor 1α, regulates the levels of phosphorylated STAT3 and promotes the malignant progression of PC under hypoxic conditions. UBE2T regulates protein expression during EMT in PC cells (103,104). The roles of E2s in PC with high mortality remain largely elusive.

Class III E2s in CRC. UBE2S regulates the proliferation and migration of CRC cells. The Wnt/β-catenin signaling pathway is involved in several key cellular processes. Furthermore, studies suggest that UBE2S and β-catenin may have a common interaction molecule, SOX2. Experimental results demonstrated that UBE2S ubiquitinated β-catenin at the position of the K19 residue, thus stabilizing its protein expression. Therefore, UBE2S may be an emerging target for CRC treatment (105). Luo and Zhou (106) and Wu *et al* (107) demonstrated that UBE2T expression was elevated in CRC tissues and samples and that elevated UBE2T was associated with reduced OS time in clinical patients. It promotes the proliferation, migration and invasion of CRC cells and inhibits apoptosis. *In vivo* experiments suggested that knockdown of UBE2T inhibits the growth of transplanted tumors (108). These studies suggest that UBE2S and UBE2T have carcinogenic effects in CRC and they may be used as a screening index for early-onset CRC.

Class III E2 in GBC and ICC. UBE2T is considered to be a biomarker associated with the pathological features, clinical staging and survival prognosis of GBC (109). UBE2T has a pro-cancer function in a variety of cancers. Yu *et al* (110) investigated the expression levels of UBE2T in normal intrahepatic ductal tissue and ICC tissue and assessed their clinical prognosis. The results of the survival analysis indicated that high UBE2T expression was an independent risk factor for time to tumor recurrence and OS (110). Similarly, Liu *et al* (111) demonstrated that the expression of UBE2T was higher in cholangiocarcinoma tissue samples than in paracancerous tissues. *In vitro* experiments suggested that the expression of UBE2T was higher in HuCCT1, QBC939 and RBE, 3 cholangiocarcinoma cell lines, than in the normal human intrahepatic bile duct epithelial cell line HIBEpiC. Furthermore, *in vitro* experiments suggested that UBE2T regulates the proliferation, cell cycle and EMT process of cholangiocarcinoma. Of note, the mTOR inhibitor rapamycin suppressed the malignant behavior of UBE2T, promoting cholangiocarcinoma by inhibiting mTOR (111).

Class III E2 in ESCC. Wang *et al* (112) hypothesized through a bioinformatics analysis that UBE2T may promote the progression of ESCC through the cell cycle and p53 signaling pathway, but there is no evidence from *in vivo* and *in vitro* experiments to confirm this conclusion.

6. Class IV E2s in digestive system cancers

Class IV E2s in HCC. The expression of UBE2O is higher in HCC than in paracancerous tissues. The follow-up results are consistent with the TCGA data suggesting longer OS in patients with HCC with low levels of UBE2O. Its influence on the proliferation, migration and invasion of HCC cells is not negligible. In addition, UBE2O negatively regulates protein kinase adenosine monophosphate-activated catalytic subunit α2 and modulates the mTOR signaling pathway to promote malignant progression of HCC (113). Shi *et al* (114) analyzed data from patients with HCC and found that high UBE2Z expression was associated with decreased OS and DFS time. It was negatively correlated with the expression of MMP2 and MMP9 proteins, thus regulating the proliferation and migration of HCC cells. In addition, UBE2Z may regulate the ERK and STAT3 signaling pathways to promote HCC progression (114). The existing evidence suggests that E2s have a carcinogenic role in HCC and promote its malignant progression.

7. Summary and perspectives

In summary, class II and class III E2 have been more studied in digestive system tumors than class I and IV E2, especially in regulating digestive system tumors signaling pathways. Among them, the inhibitors of UBE2C and UBE2T have been studied experimentally. Class I E2s and class IV E2s are less maturely studied in digestive system tumors and additional experimental results are required as proof. However, there is a non-negligible role of E2s in digestive system tumors. The present study describes a number of E2s in tumors with poor clinical prognoses. The upregulation of E2 expression and its involvement in the mechanistic and physiological processes of digestive system cancers is summarized in Table I.

Table I. Expression, clinical significance and physiological roles of four classes of UBEs in digestive system cancers.

A, Class I

Name	Cancer type	Direction of alteration	Clinical significance	Biological roles	(Refs.)
UBE2A	HCC	↑	-	Association with poor clinical prognosis	(28)
UBE2B	CRC	↑	-	Increasing ionizing radiation resistance	(47)
UBE2D1	GC	↓	OS↑	Inhibiting cell migration and ubiquitination of SMAD4	(25,26)
	HCC	↑	OS↓	Ubiquitination of p53, promotion of HCC cell growth	(29-31)
UBE2I	HCC	↓	OS↑ RFS↑	Inhibition of cell proliferation, migration and invasion; up-regulation of autophagy proteins	(38,39)
UBE2L3	HCC	↓	OS↑ DFS↑	Upregulation of p65, inhibition of cell proliferation	(42)
UBE2N	PC	↑	-	Regulation of the phagocytosis of ferritin and the sensitivity to gemcitabine	(45)
	HCC	↑	-	Promotion of cell proliferation	(44)

B, Class II

Name	Cancer type	Direction of alteration	Clinical significance	Biological roles	(Refs.)
UBE2C	GC	↓	OS↑	Inhibition of cell proliferation and promotion of apoptosis Regulation of Wnt/β-catenin and PI3K/Akt pathways	(49-52)
	HCC	↓	OS↑ DFS↑	Inhibition of cell proliferation, migration and invasion, ubiquitination of p53	(54-56)
	PC	↓	OS↑	Inhibition of cell proliferation and EMT	(63)
	CRC	↓	-	Inhibition of cell proliferation, regulation of the cell cycle	(69,70)
	GBC	↑	-	-	(77)
	ESCC	↑	OS↓ DFS↓	Association with poor clinical prognosis	(81,82)
UBE2M	HCC	↓	OS↑ DFS↑	Inhibition of cell proliferation	(59)
	ICC	↓	OS↑ RFS↑	Inhibition of cell proliferation and promotion of apoptosis	(78)
UBE2Q1	HCC	↓	OS↑	Inhibition of cell cycle, migration, invasion, β-catenin-EGFR-PI3K-Akt-mTOR	(60,61)
	CRC	↑	-	Promotion of cell proliferation	(73)
UBE2Q2	CRC	↑	-	-	(74)
UBE2V1	CRC	↓	DFS↑	Promotion of apoptosis, inhibition of EMT	(76)

C, Class III

Name	Cancer type	Direction of alteration	Clinical significance	Biological roles	(Refs.)
UBE2S	HCC	↑	OS↓ DFS↓	Promotion of ubiquitination of p53 and PTEN	(92-94)
	PC	↑	OS↓	Promotion of EMT	(104)
	CRC	↑	-	Promotion of ubiquitination of β-catenin	(105)
UBE2T	GC	↓	OS↑	Inhibition of cell proliferation, migration and EMT	(87,88)
	HCC	↓	OS↑ DFS↑	Inhibition of cell proliferation and ubiquitination of p53, promotion of apoptosis	(98-100,102)
	PC	↑	-	Promotion of cell proliferation and migration, EMT	(103)
	CRC	↑	OS↓	Promotion of cell proliferation and ubiquitination of p53, inhibition of apoptosis	(106-108)
	GBC	↑	-	Association with poor clinical prognosis	(109)
	ICC	↑	OS↓	Promotion of cell proliferation and migration, EMT	(110,111)
	ESCC	↑	-	-	(112)

Table I. Continued.

D, Class IV

Name	Cancer type	Direction of alteration	Clinical significance	Biological roles	(Refs.)
UBE2O	HCC	↓	OS↑	Inhibition of cell proliferation, migration and the mTOR pathway	(113)
UBE2Z	HCC	↓	OS↑ DFS↑	Inhibition of cell proliferation, migration, Erk and Stat3 pathways	(114)

UBE, ubiquitin-conjugating enzyme; OS, overall survival; DFS, disease-free survival; HCC, hepatocellular carcinoma; GC, gastric cancer; CRC, colorectal cancer; PC, pancreatic cancer; ESCC, esophageal squamous cell carcinoma; ICC, intrahepatic cholangiocarcinoma; GBC, gallbladder cancer; EMT, epithelial to mesenchymal transition; PTEN, phosphatase and tensin homolog.

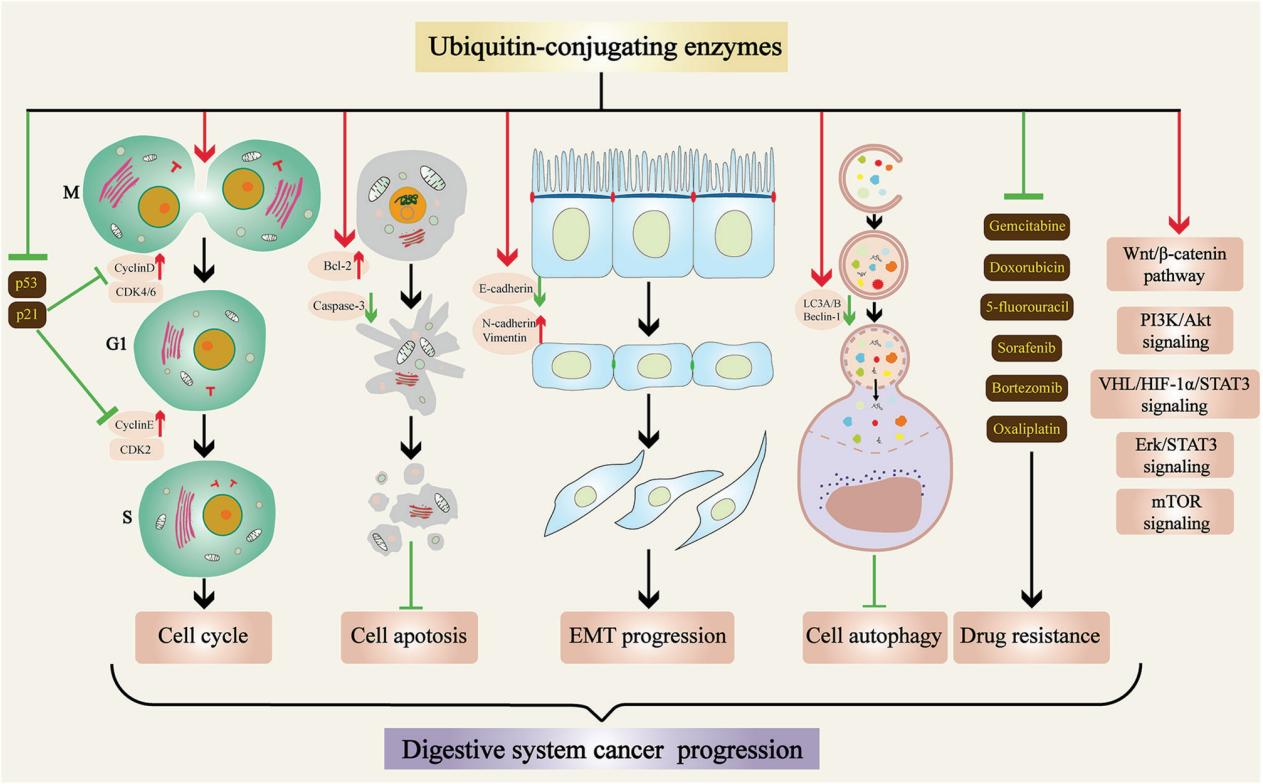

Figure 3. Roles of UBEs in digestive tract tumor cells. UBEs regulate cell cycle, apoptosis, EMT and autophagy protein expression, modulating the processes of tumor cell cycle, apoptosis, EMT and autophagy, and promoting the progression of digestive system cancers. In addition, UBEs may contribute to tumor-cell resistance to certain drugs and regulate the progression of digestive system tumors. UBEs may also promote the malignant progression of digestive system cancers by participating in tumor cell signaling pathways. UBE, ubiquitin-conjugating enzyme; EMT, epithelial to mesenchymal transition; M, mitosis; CDK, cyclin-dependent kinase; LC3A, microtubule associated protein 1 light chain 3 α; HIF, hypoxia-inducible factor; VHL, von Hippel-Lindau tumor suppressor.

The roles of E2s in various physiological processes of tumor cells are presented in Fig. 3. E2s may increase Cyclin D and Cyclin E expression and inhibit p21, as well as p53 expression. Thus, they regulate the cell cycle, promote the proliferation of tumor cells and regulate the development of digestive system cancers. E2s inhibit tumor cell death and promote tumor cell multiplication by regulating apoptosis and autophagy protein expression. In the EMT pathway, E2s inhibit E-cadherin and upregulate N-cadherin, as well as Vimentin expression, increasing the ability of tumor cells to migrate. As a result of E2 upregulation, tumor cells may resist sorafenib, bortezomib and other drugs, increasing their viability. E2s are also involved in the signaling pathways that promote tumor progression in digestive system cancers. In conclusion, E2s are involved in proliferation, migration, invasion, apoptosis, cycling, autophagy, drug resistance and cell signaling pathways of digestive system cancer cells.

Therefore, E2s may potentially be used as part of a molecular therapeutics strategy to treat digestive system cancers. Targeting E2s to inhibit their expression, thereby attenuating their involvement in multiple physiological processes in tumor cells, may be achieved to suppress the malignant progression of digestive system cancers. There is certainly more work to be done to explore the feasibility of E2s as potential targets, as well as their sensitivity. E2s require to be more effective, sensitive and safe as therapeutic targets for digestive system cancers.

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Authors' contributions

XL and XH: Conception of the review and writing of the manuscript. QL and WF: Charting. WS and QM: Literature search. DH and QX: Review of manuscript. All authors have read and agreed to the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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