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Role of Ubiquitin-Conjugating Enzyme UBE2C in Gastrointestinal Cancers

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Abstract: Ubiquitin-conjugating enzyme UBE2C is one of the important members of ubiquitin-proteasome pathway (UPP). Amplification and/or overexpression of UBE2C have been reported in many malignancies, and a high expression of UBE2C is associated with poor clinical outcomes. In this review, the pathological role of dysregulated UBE2C in gastrointestinal cancers and its potential role as a diagnostic and/or a prognostic marker as well as a therapeutic target in these cancers are discussed.

Keywords: UBE2C; Digestive tract; Gastrointestinal cancers

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1. Introduction

Ubiquitination is an essential post-translational modification of proteins with diverse cellular functions. As a catalytic cascade, ubiquitination is accomplished sequentially, involving ubiquitin-activating enzymes (E1), ubiquitin-conjugating enzymes (E2), and ubiquitin ligases (E3) [1,2]. The human genome encodes two E1 enzymes, 38 E2 enzymes, and over 600 E3 enzymes, constituting a multiplex ubiquitination machinery to proceed the large variety of ubiquitin modifications [3-6]. Central in this catalytic cascade is the family of ubiquitin-conjugating enzymes (E2), which is characterized by the presence of a highly conserved ubiquitin-conjugating (UBC) domain [7]. By coupling activation of the ubiquitin molecule to downstream conjugation events, E2 determines the ubiquitination type of the downstream substrate, either with a single molecule or as a chain. Furthermore, while E3 is responsible for substrate specificity, E2 is the critical determinant for selection of the lysine site to construct ubiquitin chains, which thereby directly determines the cellular fate of the substrate [8]. E2 enzymes can be classified into four classes based on the existence of additional extensions to the catalytic UBC-fold. Class I E2s consist only of the UBC-fold, class II and class III E2s have either N- or C-terminal extensions, whereas class IV E2s have extensions at both terminals [9]. These extensions endow distinct E2s with important functions, such as subcellular localization, stabilization of the interaction with E1s, or modulation of activity of the interacting E3s.

UBE2C, belonging to class II E2 enzymes, is known to interact with the anaphase-promoting complex/cyclosome (APC/C) E3 ligase to promote cell cycle through mitosis. It contains a highly conserved N-terminal extension, which is essential in the regulation of APC/C E3 activity and the site of lysine residue to be modified on the substrate [10]. As an APC/C specific E2, UBE2C has a direct role in

regulating the spindle assembly checkpoint by catalyzing multi-ubiquitination of one or more components of the APC–Cdc20–checkpoint protein complex [11]. Cells that overexpress UBE2C would fail to maintain spindle checkpoint activity after entering mitosis, resulting in chromosome missegregation and aneuploidy, which may eventually lead to tumor formation [11,12].

Amplification and/or overexpression of UBE2C have been reported in many malignancies, and a high expression of UBE2C is associated with poor clinical outcomes. In this review, the pathological role of dysregulated UBE2C in gastrointestinal cancers and its potential role as a diagnostic and/or a prognostic marker as well as a therapeutic target in these cancers are discussed.

2. Molecular biology of UBE2C and its role in cell cycle regulation

UBE2C has eight homologs and contains 179 amino acids with the molecular weight of 19652 Da [13]. Although small in size, it provides three to four binding sites to interact with other proteins simultaneously, including ubiquitin molecule, E1 enzyme, E3 enzyme, and the targeting substrate [14]. This is attributed to the unique spatial structure of the UBE2C protein that is featured with a four-stranded antiparallel β-sheet, a 3^{10}-helix, and four α-helices.

The ubiquitin-conjugating enzyme 2C (UBE2C) is essential for cell cycle progression as demonstrated by observations that mutation of the active site (position 114) inhibits the targeted destruction of mitotic cyclins. The influence of UBE2C on cell cycle progression is exerted during multiple phases of the cycle, during which the expression levels of the enzyme fluctuate. The major effect of UBE2C is to mediate the specific ubiquitination of ubiquitin ligase E3 enzyme known as anaphase-promoting complex/cyclosome (APC/C), that is involved in the completion of the cell cycle. Research has demonstrated that UBE2C promotes cell cycle progression from metaphase to anaphase through the regulation of mitotic spindle assessment checkpoints (SACs) and sister chromatid separation in an enzymatic cascade reaction [15]. During the mitotic (M) phase, cell division cycle protein 20 (Cdc20) is inhibited by SAC proteins, including Mad2, Bub3, and $BubR_1$. When UBE2C is highly expressed, APC/C and UBE2C can degrade SAC by ubiquitination. The Cdc20 protein is dissociated by the SAC and forms APC/C-Cdc20 complexes [16,17]. The degradation of securin, a key substrate of APC/C, is enhanced by UBE2C through ubiquitination, releasing separase. Separase subsequently promotes the separation of sister chromatids and the onset of anaphase. Conversely, UBE2C can also inhibit the cell cycle via complexing with cyclin B, which activates Cdk1, a major inhibitory protein for cells to withdraw from mitosis and enter S phase (**Figure 1**).

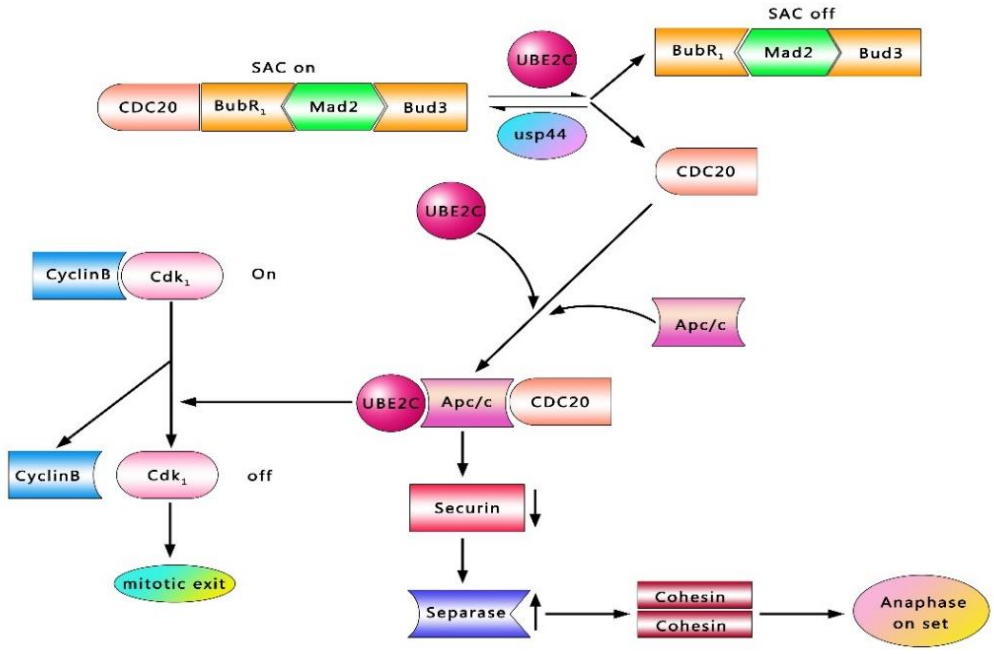

Figure 1. In M phase, Cdc20 is inhibited by SAC proteins, including Mad2, Bub3, and $BubR_1$. APC/C and UBE2C can degrade SAC by ubiquitination, whereas USP44 antagonizes this process. The Cdc20 complexes with APC/C and UBE2C, thus enhancing the degradation of securin by ubiquitination, releasing separase. Separase promotes the separation of the sister chromatids and the onset of anaphase. The APC/C also degrades cyclin B resulting in the inhibition of Cdk1 and mitotic exit. SAC: spindle assembly checkpoint; APC/C: anaphase-promoting complex/cyclosome.

In 2003, Okamoto [18] compared the expression of RNA in 25 normal human tissue samples with 24 tumor cell lines and tumor cell samples using reverse transcription polymerase chain reaction (RT-PCR). The results showed that 17 types of E2 genes were overexpressed among the samples and UBE2C protein was highly expressed in the majority of tumor cells but not in normal tissue samples. The expression of UBE2C can thus be considered as a tumor marker, and a high (relative) expression of the enzyme in cancer patients has been associated with a poor prognosis. A number of other studies have also implicated UBE2C in the pathogenesis of a range of different cancers. Pallante [19] found that the levels of UBE2C protein in thyroid cancer cell line were 150 times those found in healthy cells; the transfection of NPA and TPC1 cell lines by SiRNA significantly reduced the growth of thyroid cancer cells. Furthermore, Rawat's breast cancer cell line experiments have shown that cell proliferation and cell adhesion-independent growth were significantly lower in a UBE2C-inhibited group than in a UBE2C-transfected cell line [20]. By observing a group of transgenic mice that express high levels of UBE2C, Van Ree [12] established a model of UBE2C transgenic mice and found that this high expression of UBE2C could lead to the production of chromosome lag and aneuploid cells in mitosis. In a model of lung cancer induced by dimethylbenz(α)anthracene (DMBA), UBE2C mice were not only more likely to develop lung cancer, but also more serious forms of lung cancer.

The mitotic spindle checkpoint is inhibited by UBE2C and loses its monitoring functional capability. Uncontrolled activation of APC/C leads to chromosome misclassification and the production of aneuploidy cells. The expression of UBE2C is thus an important marker of chromosomal instability and is associated with malignant growth of tissues.

The UBE2C enzyme also plays a role in DNA damage. Cells expressing human papillomavirus type 16 (HPV-16) E6 and E7 proteins have the ability to enter as well as exit mitosis. It has been demonstrated that UBE2C plays an important role in this process by regulating Cdc20 and APC/C [21].

3. Possible regulatory mechanisms and treatment of UBE2C

Recent research has identified UBE2C as an important and complex regulatory factor in the ubiquitin-proteasome system. Its role in the regulation of tumor growth has become a research hotspot, attracting significant attention across a range of different types of cancer due to its potential as a therapeutic target. The current scientific evidence in this area is summarized below.

In gastric cancer research, it has been shown that the inhibition of miR-17/20a expression in gastric cancer cells can cause the inhibition of cell proliferation. Results of quantitative real-time polymerase chain reaction (qRT-PCR) and western blot analysis have shown that UBE2C is a direct target of miR-17/20a, thus implicating UBE2C as a factor in the progression of gastric tumor growth. Further research has shown that the expression of UBE2C mRNA and protein is positively regulated by miR-17/20a [22]. A study conducted by Yang [23] has suggested that gastric cancer cell lines can increase cisplatin-mediated apoptosis after UBE2C knockdown by siRNA. Other studies have shown that the inhibition of UBE2C by wild-type p53 is p21-E2F4-dependent, while the activation of UBE2C by mutant p53 is dependent on nuclear factor (nuclear factor Y, NF-Y) [24].

Colon cancer studies [25] have shown that the inhibition of UBE2C reduces the growth rate of colon cancer cells (in-part through downregulation of cyclin B and ERK1) and increases the efficacy of chemotherapy drugs, such as irinotecan, SN-38, and cetuximab (partially down-regulated by protein kinase B (AKT)). Furthermore, experiments on colorectal cancer cells conducted by Prashant confirmed that the protease-inhibitor drug, bortezomib, mediates the increased expression of cyclin A and cyclin B by downregulating UBE2C; bortezomib-treated nude mice exhibited a significant increase in cyclin A and cyclin B expression compared to untreated mice, and downregulation of UBE2C increased the sensitivity of colon cancer cells to apoptosis mediated by bortezomib and the chemotherapeutic drug, oxaliplatin [26]. Cyclin A and cyclin B play important roles in the regulation of cell mitosis. The same research further showed that bortezomib can stabilize cyclin A and cyclin B expression at both translation and transcriptional levels.

Another colorectal cancer study [27] suggested that a high expression of UBE2C protein in tumor cells is correlated with tumor cell resistance to apoptosis, which is mediated by N-acetyl-leu-leu-norleucinal (ALLN), and that the inhibition of UBE2C is likely to lead to cell apoptosis. The suggested mechanism for this effect is that the low level of UBE2C increases the activity of caspase 8 and caspase 3 in the presence of ALLN, thus impairing the survival of tumor cells.

In another research [28], it has been shown that the inhibition of UBE2C expression can increase the sensitivity to both radiation therapy and chemotherapy. In addition, small molecule inhibitors for UBE2C are being studied in this field using docking studies.

Studies of other cancer types have shown that the knockdown of UBE2C reduces osteosarcoma proliferation and invasion by inhibiting Ki67, matrix metalloproteinase-3, and matrix metalloproteinase-9 [29]. In lung cancer studies [30], UBE2C was found to be negatively correlated with mutant p53 and epidermal growth factor receptor (EGFR), which are involved in tumorigenesis. Further, in a study of castration-resistant prostate cancer (CRPC) cell lines – abl and C4-2B, it has been found that a cell cycle inhibitor, CCI-779, inhibited the expression of UBE2C mRNA and protein as well as interfered with cell growth.

4. UBE2C and gastrointestinal cancers

In recent years, research on the involvement of UBE2C in gastrointestinal cancers have confirmed that it is highly expressed in esophageal, colon, gastric, liver, and pancreatic cancers. Furthermore, correlation studies have suggested that UBE2C expression is associated with the development of tumor cells. These studies are reviewed below.

Lin [31] found that the transfection of Seg-1 cell line with plasmids that failed to express UBE2C resulted in a reduction in the proliferation of esophageal cancer cells and the suspension of these cells in the mitotic phase. After the transfection of cells with RNAi, the cell cycle was disturbed, cell proliferation was inhibited and the number of G2 phase cells peaked after 72 hours. The cell proliferation of Seg-1 cell line reduced after treating with protease inhibitor.

Fujita [32] found that UBE2C is not usually expressed in normal colonic tissues but markedly expressed in colon cancer tissues. In that study, the authors reported that there was an overexpression of UBE2C in the DLD1 cell line and the culture doubling time of tumor cells in the overexpressed group was markedly lower compared to the control group. In addition, similar results have been observed in agarose growth experiments. The opposite effect was noted in colon cancer cell lines where the UBE2C gene had been knocked out. The study found that there is an association between the number of mitotic cells and the level UBE2C expression. A separate study by Chen [33] similarly found that the expression of UBE2C in normal colon cells *in vitro* is essentially negative. The authors studied cell proliferation and invasion in a HT-29 cell line transfected with UBE2C plasmid (HT-29/UbcH10). The results showed that UBE2C overexpression promoted the proliferation and invasion of tumor cells compared to the control group. However, UBE2C expression was significantly lower in HT-29/UbcH10-RNAi cells that had been transfected with siRNA to block UBE2C. The same study performed a basement membrane invasion test, and the authors reported a significant difference in the number of passing through the basement membrane between the transfected group and the control group. Collectively, these findings indicate that UBE2C expression increases the generation of colon cancer cells and accelerates tumor progression.

A number of clinical studies have shown that UBE2C protein expression is raised in colon cancer tissues [23-25]. Yang confirmed that the expression of UBE2C is raised in gastric cancer cell lines compared to normal gastric tissues and observed that the proliferation of gastric cancer cells decreased following a knockdown of UBE2C expression. Immunohistochemistry analysis further revealed that UBE2C protein is highly expressed in the majority of gastric cancer tissue samples, whilst its expression levels are low in adjacent interstitial tissues [23]. Okamoto [18] used qRT-PCR to measure UBE2C mRNA expression and reported it to be high in gastric cancer tissues but low or absent in normal tissues. Furthermore, it was found that the overexpression of UBE2C in NIH3T3 cells, that had been transfected with appropriate expression plasmids, increased the binding of bromodeoxyuridine, promoted cell proliferation, and accelerated colony formation in the agarose assay. The study concluded that UBE2C promotes gastric cancer cell proliferation and the transformation of normal cells into malignant cells.

In a study about liver cancer [34], the expression levels of UBE2C mRNA as measured by qRT-PCR were reported to be significantly higher in a range of cancer cell lines compared to normal liver tissue. The expression of UBE2C mRNA in hepatocarcinoma cell line was found to be significantly higher than that in a normal liver cell line and the difference was significant.

Pancreatic ductal adenocarcinoma (PDA) accounts for more than 90% of pancreatic cancers. A research on UBE2C expression in 94 PDA tumor tissues and adjacent normal pancreatic tissues showed that the expression of UBE2C protein in ductal carcinoma tissues was higher than that in paracancerous tissue [35].

5. UBE2C and clinicopathological characteristics of gastrointestinal cancers

Evidence from available studies indicates that UBE2C expression may be a potential prognostic marker or therapeutic target in gastrointestinal cancers. Clinical studies have shown that UBE2C expression is correlated with a variety of clinical and pathological parameters as well as the prognosis in patients with gastrointestinal tumors. These studies are summarized below.

In a study about esophageal cancer [36], significant differences in lymphatic invasion, lymph node

metastasis, and TNM staging were reported between patients with high UBE2C expression and those with low expression of the protein. The 50% survival rate of these two groups also differed significantly.

Chen [33] measured the expression of UBE2C in 45 cases of colorectal cancer and in corresponding adjacent normal tissue samples. The study reported that the expression was 10 times higher in the former compared with the latter. There were no statistically significant differences in UBE2C protein expression with age, sex, or tumor size among the samples, but there was an association with lymph node metastasis and pathological differentiation. Studies by Fujita [32] and Cacciola [25] have confirmed these findings and further identified an association between UBE2C expression and mutations in KRAS oncogene. Studies have also identified that UBE2C expression and cancer cell proliferation in colon cancer tissues are lower in older patients than in younger ones; in addition, distant metastases is rare in older patients [26]. This suggests that UBE2C expression is associated with the proliferation of tumors at adjacent tissue sites.

In 2013, Zhao [35] reported that UBE2C protein expression is related to pancreatic ductal adenocarcinoma differentiation, clinical stage, and lymph node metastasis. Zhao hypothesized that UBE2C plays an important role in the progression of pancreatic cancer and proposed that it could be used as a prognostic indicator.

In 2011, a study [34] about liver cancer investigated the associations between UBE2C mRNA expression and various factors, such as age, sex, tumor size, tumor size, portal vein invasion, histopathological differentiation, TNM staging, envelope formation, alpha-fetoprotein, hepatitis B surface antigen (HBsAg), and other clinical pathological parameters. The expression of UBE2C mRNA was found to be significantly correlated to histopathological differentiation, tumor size, TNM staging, and portal vein invasion. The authors concluded that the overexpression of UBE2C in hepatocellular carcinoma may be indicative of a poor prognosis and is therefore of clinical significance.

In gastric cancer, the expression of UBE2C was found to have correlation with lymphatic metastasis, serosa invasion, TNM staging, and Lauren's classification. Univariate analysis showed that the overexpression of UBE2C has associations with poor prognosis. The multivariate analysis demonstrated that the expression of UBE2C, lymphatic metastasis, and TNM staging are independent prognostic indicators [37].

6. Conclusion and perspectives

The collective body of currently available evidence suggests that UBE2C plays an important role in the initiation, development, as well as proliferation of gastrointestinal tumors and may represent a novel therapeutic target and/or prognostic marker for gastrointestinal cancers.

Table 1. Studies of UBE2C expression in human gastrointestinal cancers

Type of gastrointestinal cancer	Findings	References
Esophageal cancer	After transfection of RNAi, cell proliferation is inhibited.	[31]
Colon cancer	High expression levels in colon cancer tissues. UBE2C overexpression promotes the proliferation and invasion of the tumor.	[22,31,33]
Gastric cancer	Gastric cancer cell lines have higher expression of UBE2C compared with normal gastric tissues. Gastric cancer cell proliferation decreases after UBE2C expression has been knocked down.	[18,23]
Liver cancer	Expression of UBE2C mRNA in adjacent normal tissues is much lower than that in hepatocellular carcinoma tissues.	[34]
Pancreatic ductal adenocarcinoma	Expression of UBE2C protein in ductal carcinoma tissues is higher than that in para-cancerous tissues.	[35]

Table 2. UBE2C and clinicopathological characteristics of gastrointestinal cancers

Type of gastrointestinal cancer	Findings	References
Esophageal cancer	Its expression correlates with lymphatic invasion, lymph node metastasis, and TNM staging. Overexpression of UBE2C is associated with poor prognosis.	[36]
Colon cancer	Its expression is associated with lymph node metastasis and pathological differentiation. Its expression is lower in elderly patients compared to younger patients.	[25,32,33]
Liver cancer	Its expression significantly correlates with histopathological differentiation, tumor size, TNM staging, and portal vein invasion.	[34]
Pancreatic ductal adenocarcinoma	Its expression is related to pancreatic ductal adenocarcinoma differentiation, clinical stage, and lymph node metastasis. UBE2C can be used as an independent predictor of prognosis.	[35]
Gastric cancer	Its expression correlates with lymphatic metastasis, serosa invasion, TNM staging, and Lauren's classification. UBE2C can be used as an independent predictor of prognosis.	[37]

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Disclosure statement

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