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Ubiquitination-Binding Enzyme 2C is Associated with Cancer Development and Prognosis and is a Potential Therapeutic Target

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Abstract: UBE2C (Ubiquitination-binding enzyme 2C), one of the E2 enzymes encoded in the human genome, is a component of the ubiquitin proteasome system and plays a pivotal role in regulating cell cycle progression. Moreover, UBE2C is highly expressed and may play a pivotal role in both high-incidence and high-mortality malignancies, including lung cancers, breast cancers, and esophageal cancers. UBE2C influences a number of key processes, including cell cycle progression, tumor invasion and metastasis, proliferation, and drug resistance. However, few articles have systematically summarized the role of UBE2C in cancer. The aim of this review is to describe the structure and function of UBE2C, focusing on the current status of UBE2C research in malignant tumors. Furthermore, this review presents the potential of UBE2C as a new therapeutic target and a diagnostic and prognostic biomarker. Finally, future research directions for UBE2C are proposed. It is of great value to explore the mechanism of action of UBE2C in the tumor microenvironment (TME). A comprehensive and coherent comprehension of UBE2C will undoubtedly facilitate its transition from fundamental research to clinical applications.

Keywords: UBE2C, Biomarker, Therapeutic target, Prognosis, Invasion

Introduction

UBE2C, one of the E2 enzymes in the human genome, functions as a crucial component of the ubiquitin proteasome system,[1] Protein degradation commences with the ubiquitination of damaged proteins, an ATP-dependent process involving three enzyme types: ubiquitin-activating enzymes (E1), ubiquitin-conjugating enzymes (E2), and ubiquitin ligases (E3). First, a ubiquitin-activating enzyme E1 hydrolyses the ATP and then adenylates one ubiquitin molecule. Later, this ubiquitin is translocated to the cysteine active site of E1. Finally, adenylated ubiquitin is translocated to the second enzyme, cysteine, the ubiquitin conjugated enzyme E2. An enzyme called ubiquitin ligase E3 recognizes the targeted protein and catalyses the translocation of the ubiquitin from E2 to the protein.[2] These enzymes act systematically to polyubiquitinate substrates, targeting them for recognition and subsequent degradation by the proteasome. The ubiquitin proteasome system (UPS) plays a critical role in protein homeostasis and the elimination of damaged proteins.[2,3] UPS dysregulation leads to the accumulation of damaged proteins that play key roles in DNA damage repair, cell differentiation, cell cycle control, apoptosis and other vital functions. This dysregulation is associated with a variety of tumors.[2]

UBE2C is highly conserved, and its human homolog (also known as UbcH10) was cloned in 1997.[4] UBE2C consists of a conserved core domain containing the catalytic cysteine residue and an N-terminal extension. UBE2C is indispensable for disrupting mitotic cell cycle proteins and securin, crucial elements for the spindle assembly checkpoint and

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mitotic exit.[5] There are four classes of E2 enzymes; class I comprises solely the core domain and necessitates the presence of E3 for ubiquitin conjugation. Class II and III possess C-terminal and N-terminal extensions from the core domain, respectively. These extensions may aid in targeting proteins, facilitating the recognition and regulation of ubiquitin attachment to them. Class IV contains both N- and C-terminal extensions.[6] UBE2C belongs to the class III of E2 enzymes. The UBE2C gene in humans is situated at 20q13.12. There are eight transcript variants resulting from selective splicing. The UBE2C protein discussed here is derived from splice variant 1, characterized by the longest reading frame. The full-length UBE2C protein consists of 179 amino acids and has a molecular weight of 19.65 kDa.[7] UBE2C is able to interact with 3–4 different proteins, ie ubiquitin, E1, E3, and possibly target proteins.[8,9]

UBE2C Regulates Cell Cycle Progression

The cell cycle is a pervasive, complex, and highly regulated process, involving successive events during which a cell replicates its genetic material, grows, and divides into two daughter cells. Numerous cellular proteins participate in controlling the progression of the four cell cycle phases: G1, S, G2, and M. Studies over the past few decades have shown that cell cycle phase transitions are primarily driven by the phosphorylation of numerous target proteins through the cell cycle protein-dependent kinase (CDK)-cycle protein complex.[9–11] Post-translational modification (PTM) of cell cycle-associated proteins is mainly achieved by two types of protein modifications: phosphorylation and ubiquitination, which are used for qualitative and quantitative control, respectively.[12] UBE2C is required for disrupting mitotic cell cycle proteins and other mitosis-related substrates.[12] The Anaphase Promoting Complex/Cyclosome (APC/C) is an evolutionarily conserved multisubunit E3 ubiquitin ligase, and APC/C is controlled by two major activators, Cdc20 and Cdh1, each of which targets APC/C to a specific substrate at precise times during the cell cycle. At mid-cycle, UBE2C degrades securin and cyclin B via APC/CCDC20, facilitating progression to the late stage.[13] Securin is a protease that degrades the adhesin ring, which holds two sister chromatids together. Through the degradation of securin and the subsequent activation of separase, the sister chromatids are separated, and thus UBE2C directly contributes to the onset of the late stage[14.] Cyclin B forms a complex with Cdk1 and the Cyclin B/Cdk1 complex remains active throughout the cell cycle. Until mitosis, UBE2C-APC/CCDC20 induces degradation of cell cycle protein B, leading to inactivation of Cdk1, which replaces Cdc20 by Cdh1 in the APC/C-UBE2C complex, promoting sequential ubiquitination and degradation of key regulators. This causes mitosis to exit and progress into the G1 and S phases.[5,15] Once UBE2C functions, it is degraded by self-ubiquitination together with APC/CCdh1, and its expression is, therefore, controlled by a positive autoregulatory feedback loop dependent on the concentration of APC/C substrates competing with UBE2C. When APC/C is inactivated by cell cycle protein A, UBE2C levels gradually increase during the S and G2 phases, allowing UBE2C to reaccumulate.[16–18] UBE2C overexpression triggers whole chromosome instability, leading to missegregation and aneuploidy. Its accumulation also stimulates cell proliferation, suggesting that UBE2C overexpression may play an important role in tumorigenesis and tumor progression (Figure 1).[19]

The Research of UBE2C in Cancer

Overexpression of UBE2C has been described in many human cancers, namely lung, breast, colorectal, esophageal, gastric, liver, prostate, bladder, thyroid, and brain cancers. (Table 1) presents the data from the most relevant papers regarding the role and clinical impact of UBE2C expression on different types of malignancies.

Lung Cancer

UBE2C expression has predominantly been investigated in non-small cell lung cancer (NSCLC). Recent bioinformatics studies have identified UBE2C as a prognostic factor in lung adenocarcinoma (LUAD).[20] However, further comprehensive studies are necessary to translate these findings into clinical applications. Interestingly, one study reported that overexpression of UBE2C and angiogenic factor with G patch and FHA domains 1(AGGF1) correlates with angiogenesis and poor prognosis, potentially aiding in predicting NSCLC invasion, metastasis, and prognosis.[21] Furthermore, an increase in the UBE2C+ cancer cell subpopulation has been observed during LUAD invasion, which correlates with a significantly higher incidence of invasive adenocarcinoma located peripherally within the tumor, indicating a more aggressive phenotype.[22] This suggests that UBE2C may be involved throughout the development of LUAD. However,

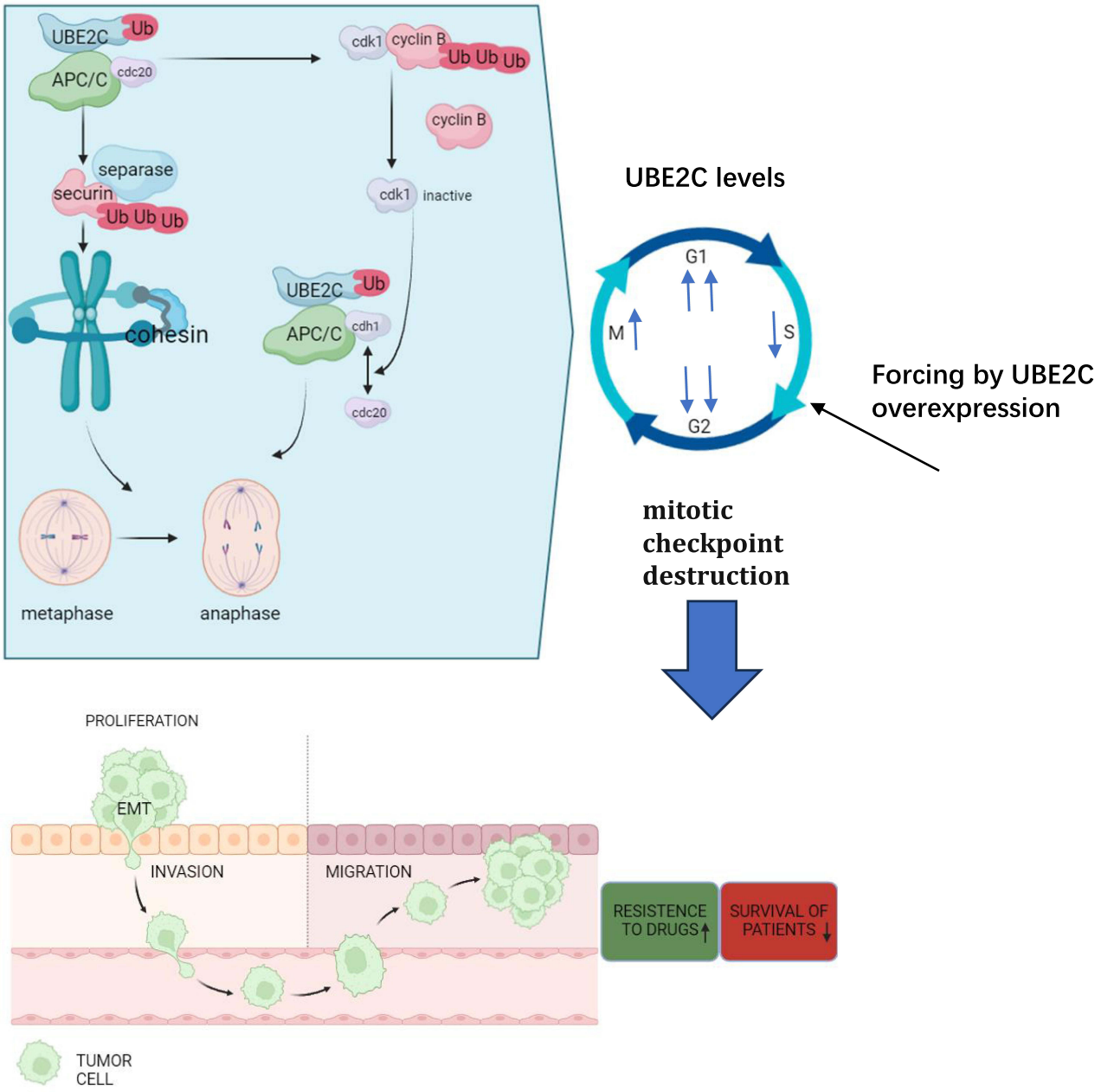

Figure 1 UBE2C induces the mid-to-late cell cycle transition by degradation of securin and cyclin B by APC/CCDC20.UBE2C-induced degradation of cyclin B inactivates Cdk1, which is activated by the replacement of Cdc20 by Cdh1 in the APC/C-UBE2C complex. The activated complex degrades securin, which in turn activates the separase enzyme and degrades the sister chromatid adhesion protein ring. This leads to the start of prophase and the end of mitosis. Overexpression of UBE2C leads to chromosome missegregation and tumor formation. High expression of UBE2C is closely associated with malignant tumor proliferation, invasion, metastasis, EMT (epithelial-mesenchymal transition), increased drug resistance, and decreased patient survival.

the precise mechanism of UBE2C remains unclear. Recently, one study identified the UBE2C/CDH1/DEPTOR axis as forming an oncogenic cascade that regulates cell cycle progression and autophagy. It further validated UBE2C as a promising target in Kras-mutated lung cancers.[23]

Breast Cancer

Initially, UBE2C was integrated into a highly sensitive and specific multi-marker assay for detecting circulating tumor cells (CTCs) in breast cancer patients. Researchers used high-throughput membrane arrays to detect a set of mRNA

Table 1 Summarizing the Role and Impact of UBE2C in Different Types of Malignant Tumors

Lung cancer	UBE2C as a prognostic factor in lung adenocarcinoma	[20]
	Overexpression of UBE2C and AGGF1 is associated with angiogenesis and poor prognosis	[21]
	UBE2C+ cancer cell subpopulations are increasing during LUAD invasion	[22]
	The UBE2C/CDH1/DEPTOR axis forms an oncogene and tumor suppressor cascade that regulates cell cycle progression and autophagy	[23]
Breast cancer	UBE2C Protein May Serve as a Prognostic Marker in N+ Breast Cancer	[26]
	UBE2C may serve as a prognostic marker for breast cancer	[28]
	UBE2S and UBE2C downregulate Numb and enhance breast cancer malignancy	[29]
	UBE2C can promote BC proliferation by activating the AKT/mTOR signaling pathway	[30]
	ALKBH5 promotes stemness, growth and metastasis of triple negative breast cancer (TNBC) cells by regulating m6A modification of UBE2C to upregulate UBE2C expression and decrease p53 expression	[31]
Colorectal cancer	UBE2C overexpression enhances cell proliferation and UBE2C depletion inhibits cell proliferation in colon cancer cells	[33, 34]
	UBE2C inhibits colorectal cancer cell growth in vitro and in vivo	[35]
	UBE2C promotes rectal carcinoma via miR-381	[39]
Esophageal cancer	High levels of UBE2C are significantly associated with prognosis in patients with esophageal squamous cell carcinoma	[40]
	This suggests that ECRG4 down-regulates the expression of UBE2C in ESCC cells through NF-κB signaling, and UBE2C is involved in the anti-proliferative and pro-apoptotic functions of ECRG4 in ESCC cells.	[41]
	FOXM1 binds to and transcriptionally activates the UBE2C promoter region in ESCC cell lines, resulting in upregulation of UBE2C	[42]
	UBE2C and UBE2C + CD8 + T cells are poor prognostic factors for esophageal cancer, and UBE2C and UBE2C + CD8 + T cells can be used as biomarkers for patient stratification and response to treatment.	[43]
Gastric cancer	Inhibition of UBE2C expression inhibits cell proliferation	[44]
	UBE2C-deficient cell cycle G2/M phase arrest and subsequent Knockdown of UBE2C reduces the level of phosphorylated AURKA (p-AURKA) through the Wnt/β-catenin and PI3K/Akt signaling pathways, which inhibits gastric cancer development and progression	[45]
	Overexpression of UBE2C promotes growth and invasion of gastric cancer cells through activation of ERK1/2 signaling pathway	[46]
Liver cancer	UBE2C is highly expressed in hepatocellular carcinoma tumor specimens and cells, and silencing of UBE2C inhibits the value-adding capacity of hepatocellular carcinoma cells	[47]
	Knockdown of UBE2C significantly inhibits cell proliferation and colony forming ability and cell migration and invasion ability	[48]
	UBE2C expression is negatively regulated by hsa-miR-193b-3p in hepatocellular carcinoma	[49]
Prostate cancer	Higher levels of H3K4 methylation and FoxA1 binding on the UBE2C enhancer lead to UBE2C protein overexpression	[50]
	MED1 phosphorylation leads to UBE2C motif cyclisation, UBE2C gene expression and cell growth	[51]
	UBE2C overexpression is associated with worse prognosis in prostate cancer	[53]
Bladder cancer	Positive UBE2C was significantly associated with higher tumor stage and lymphovascular invasion. In addition, positivity was significantly associated with shorter cancer-specific survival after cystectomy	[54]
	Positive UBE2C in blood and urine samples from normal patients is significantly associated with higher tumor stage, lymphovascular invasion and shorter cancer-specific survival after cystectomy	[55]
Thyroid cancer	UBE2C overexpression may be associated with thyroid tumor progression	[56]
	UBE2C quantitative RT-PCR analysis contributes to improved detection of malignancy in thyroid fine needle aspiration (FNA) samples compared to non-immunohistochemistry	[58]

(*Continued*)

Table 1 (Continued).

Brain tumor	Expression levels of UBE2C mRNA were elevated in high-grade astrocytomas compared with low-grade astrocytomas or normal controls	[60,61]
	UBE2C plays an important role in cell proliferation, apoptosis and cell cycle progression in glial cells	[61]
	UBE2C expression is an independent prognostic factor	[62]
	FoxM1 triggers UBE2C transcription by binding to the promoter region and is associated with poor prognosis in gliomas	[63]
	Combined upregulation of UBE2C and AURKB is associated with poor prognosis, treatment resistance and reduced overall survival in glioma patients	[64]
	In meningiomas, UBE2C overexpression is associated with higher histological grade, increased proliferation and poor prognosis	[65]
	RIZ1 regulates UBE2C in a c-Myc-dependent manner	[66]
	UBE2C increases leptomeningeal dissemination in vivo.	[67]

markers for circulating tumor cell (CTC) expression in the peripheral blood of female breast cancer patients. Peripheral blood was collected from 92 breast cancer patients and 100 normal subjects, and membrane arrays were used to detect CTCs with markers such as pituitary tumor transforming gene 1, Survivin, UbcH10, and thymidine kinase 1, and the sensitivity and specificity were increased to 86% and 86%, respectively, for four mRNA marker groups. For the group of 4 mRNA markers, the sensitivity and specificity were increased to 86% and 88%, respectively. In addition, patients' clinicopathological characteristics tumor size ($p = 0.006$), histological grade ($p = 0.012$), lymph node metastasis ($p = 0.001$), and TNM staging ($p = 0.006$) were also found to be significantly correlated with the rate of positive detection of the multiple markers.[24] Using cDNA nylon microarrays containing 8032 cDNA unique sequences representing 5776 different genes to analyze the gene expression profiles of the tumors, the investigators found that UBE2C was most relevant to patients with lymph node-positive breast cancer.[25] Subsequently validated the utility of UBE2C protein as a prognostic marker in N+ breast cancer via immunohistochemistry (IHC). Using paraffin-embedded blocks from 92 consecutive women with primary lymph node-positive breast tumors, the investigators assessed the effect of UBE2C IHC values on metastasis-free survival (MFS) and overall survival (OS) and compared them with the performance of Ki-67 and the Nottingham Prognostic Index (NPI). The results found a significant effect of UBE2C IHC on both MFS and OS (risk ratio = 6.79 - P = 0.002; risk ratio = 7.14 - P = 0.009). Akaike information criterion proved that the prognostic power of UBE2C IHC was stronger than that of Ki-67 (and close to that of NPI). Furthermore, multivariate analyses with NPI showed that, contrary to Ki-67 IHC, UBE2C IHC remained an independent factor, both for MFS (adjusted P=0.02) and OS (adjusted P=0.04).[26] However, the predictive value of UBE2C as a marker of proteasome activity requires further investigation. Interestingly, inhibition of UBE2C sensitized breast cancer cells to radiation, Adriamycin, and hormone blockers. Thus, UBE2C represents a promising therapeutic target for enhancing sensitivity to radiation and chemotherapy.[27] Recent bioinformatics studies have identified UBE2C as a prognostic marker for breast cancer, highlighting its functional enrichment in the cell cycle, oocyte meiosis, and p53 signaling pathway.[28] However, several studies have offered varying insights into the specific mechanisms. Studies have demonstrated that UBE2S and UBE2C downregulate Numb and promote breast cancer malignancy.[29] Additionally, UBE2C has been shown to promote breast cancer proliferation by activating the AKT/mTOR signaling pathway.[30] Interestingly, AlkB homolog 5(ALKBH5) has been shown to enhance stemness, growth, and metastasis in triple negative breast cancer (TNBC) cells by regulating m6A modification of UBE2C, resulting in increased UBE2C expression and decreased p53 expression.[31] This gives an additional direction to the therapeutic outlook for TNBC.

Colorectal Cancer

In 2006, a DNA microarray study analyzed the expression profiles of 1700 genes in primary tumors, liver metastases, and paired normal tissues from nine patients with advanced colorectal cancer. The study identified abnormalities in UBE2C gene expression levels and motif copy numbers, indicating a potential role in the progression of colon cancer to liver metastases.[32] Subsequent studies screened DLD-1 and HT-29 colon cancer cell lines, confirming that UBE2C

overexpression promoted cell proliferation while UBE2C depletion inhibited proliferation in colon cancer cells.[33,34] Analysis of 150 patients with colon tumors regarding age, gender, tumor size, lymph node status (N0-2), histological grade (G1-3), and histological type revealed that elevated UBE2C levels correlated with high-grade histological tumors. This association suggests aggressive cellular behavior and a potential poor prognosis in colon cancer patients.[33] Furthermore, studies have confirmed that RNA interference (RNAi)-mediated silencing of the UBE2C gene inhibits the growth of colorectal cancer (CRC) cells both in vitro and in vivo, suggesting potential antitumor activity.[35] Treatment of colorectal cancer cells with the proteasome inhibitor bortezomib resulted in UBE2C down-regulation and accumulation of cytosolic protein A and cytosolic protein B1,[36] N-acetyl-leu-leu-norleucinal (ALLN) treatment has shown potential as an effective drug for colorectal cancer by reducing UBE2C expression,[37] Inhibition of UBE2C reduced CRC cell growth rates and enhanced sensitivity to irinotecan, SN-38, and cetuximab treatment,[38] These studies collectively contribute to the development of new therapeutic strategies involving drug combinations for colorectal cancer treatment. In vitro and in vivo studies have demonstrated that UBE2C is overexpressed in rectal cancer and regulated by miR-381, which promotes cell proliferation, invasion and inhibits apoptosis.[39] Since 2018, most research on colorectal cancer has centered around bioinformatics, with fewer studies investigating specific molecular mechanisms.

Esophageal Cancer

The UBE2C protein was detected in esophageal squamous cell carcinoma cancerous lesion tissues and some dysplastic lesions surrounding the cancerous tissues, but not in normal tissues. Furthermore, in patients with esophageal squamous cell carcinoma, high levels of UBE2C were significantly correlated with prognosis.[40] Esophageal cancer related gene 4 (ECRG4) is down-regulated in esophageal squamous-cell carcinoma (ESCC) and inhibits the tumorigenicity of ESCC cells. The mRNA levels of ECRG4 and UBE2C were found to be negatively correlated in esophageal squamous cell carcinoma tissues. The nuclear factor κB (NF-κB) inhibitor pyrrolidine dithiocarbamate (PDTC) was found to inhibit NF-κB p65 nuclear translocation and UBE2C expression. Furthermore, ECRG4 silencing was found to partially reverse this process. Moreover, UBE2C knockdown in TE-1 cells significantly inhibited cell proliferation and induced apoptosis, while ECRG4 knockdown partially reversed this process. This suggests that ECRG4 down-regulates the expression of UBE2C in ESCC cells through NF-κB signaling, and UBE2C is involved in the anti-proliferative and pro-apoptotic functions of ECRG4 in ESCC cells.[41] FOXM1 (forkhead box protein M1) is a transcription factor that participates in all stages of tumor development, mainly through the control of cell cycle and proliferation, regulating the expression of genes involved in G1/S and G2/M transition and M phase progression. It was found that FOXM1 binds to and transcriptionally activates the UBE2C promoter region in esophageal cancer squamous cell lines, resulting in the upregulation of UBE2C. This suggests that FOXM1 transcriptionally regulates UBE2C expression in ESCC.[42] A recent study identified UBE2C and UBE2C + CD8 + T cells were identified as poor prognostic factors for esophageal cancer by bulk-RNA seq and scRNA-seq analyses, and this was verified by immunological analysis of specimens from patients with locally advanced esophageal cancer who underwent radical surgery after neoadjuvant ICB plus chemotherapy. This exemplifies the potential of UBE2C and UBE2C + CD8 + T cells as potential biomarkers for patient stratification and response to treatment.[43]

Gastric Cancer

Relatively high expression levels of UBE2C were observed in KATO III, SGC-7901, GAXC-023 and GAXC-031 gastric cancer cell lines, while lower expression was observed in NCI-N87, HS-746T and NCI-SNU-1 gastric cancer cell lines. Inhibition of UbcH10 expression inhibited cell proliferation and made cells more sensitive to apoptosis with cell cycle changes and attenuated cell survival signaling in SGC-7901 and KATO III gastric cancer cell lines, and overexpression of UBE2C promoted cell proliferation and resistance to cisplatin-induced apoptosis in NCI-N87 and HS-746T gastric cancer cell lines. UBE2C expression was found to be significant in gastric cancer tissues from most patients and correlated with their low differentiation.[44] UBE2C-deficient cell cycle G2/M phase arrest and subsequent reduction of gastric adenocarcinoma tumorigenesis were found in MGC-803 and SGC-7901 gastric cancer cells. Knockdown of UBE2C using siRNA significantly reduced the level of phosphorylated AURKA (p-AURKA) through the Wnt/β-catenin and PI3K/Akt signaling pathways, which inhibited gastric carcinogenesis and progression. Knockdown of UBE2C

resulted in the up-regulation of the expression of E-calmodulin and down-regulation of N-calmodulin, and inhibited epithelial mesenchymal transition (EMT).[45] In the BGC-823 intestinal-type gastric cancer cell line with high expression of UBE2C, it was confirmed that down-regulation of UBE2C inhibited the growth of cancer cells in vitro, and in the intestinal-type gastric cancer cells with low expression of UBE2C, it was confirmed that overexpression of UBE2C promoted the invasive ability of gastric cancer cells in vitro. Overexpression of UBE2C accelerated the growth and invasiveness of gastric cancer cells through activation of the ERK1/2 signaling pathway UBE2C overexpression accelerated the cell cycle process and promoted the growth and invasion of gastric cancer cells by activating the ERK1/2 signaling pathway. The increased expression of UBE2C in gastric cancer of intestinal type was confirmed in a large number of gastric cancer tissues in Shanghai, China.[46]

Liver Cancer

As early as 2007, a study was conducted to evaluate the expression of UBE2C in tumor and non-tumor samples and three HCC cell lines, HuH-7, Hep-G2, and Hep-3B, from 65 hCC patients. The results showed that all three cell lines tested highly expressed UBE2CmRNA. 62 out of 65 tumor samples from hepatocellular carcinoma patients had higher UBE2CmRNA expression levels in cancerous tissues than in non-cancerous tissues. And UBE2C protein expression in tumor and normal tissues of representative hepatocellular carcinoma patients was verified by protein blotting. Strong UBE2C protein expression was observed in cancerous tissues. And in Hep-3B cell line, it was verified that silencing of UBE2C inhibited the proliferative capacity of HCC cells by at the mRNA level and at the protein level.[47] Then a study found that UBE2C was abnormally overexpressed in hepatocellular carcinoma patients by bioinformatics, which may serve as a new prognostic biomarker for hepatocellular carcinoma. And by knocking down endogenous UBE2C in SK-Hep-1 and SMMC-7721 cells using lentiviral particles expressing UBE2C shRNA (shUBE2C), it was found that the protein expression level of UBE2C in the cells was significantly reduced, and significantly inhibited the cell proliferation and colony formation ability as well as cell migration and invasion ability. It was also found that UBE2C knockdown enhanced the sensitivity of SK-Hep-1 and SMMC-7721 to Adriamycin and 5-fluorouracil, and that UBE2C decreased the sensitivity of hepatocellular carcinoma cells to sorafenib treatment.[48] Recently, two potential dysregulation mechanisms of UBE2C have been identified. Correlation analysis of UBE2C promoter methylation levels with UBE2C mRNA expression levels in TCGA hepatocellular carcinoma samples by cBioPortal database revealed that hypomethylation of the UBE2C promoter may be responsible for its high expression in hepatocellular carcinoma. The potential binding miRNAs of UBE2C were predicted by miRNet database, and the expression changes of UBE2C after overexpression of 10 potential upstream miRNAs in HepG2 and Huh7 cell lines revealed that UBE2C expression in hepatocellular carcinoma was negatively regulated by hsa-miR-193b-3p.[49] It has also recently been found that UBE2C has a prognostic role in hepatoblastoma and that the ubiquitin pathway is a therapeutic target for this disease.[48]

Prostate Cancer

In prostate cancer, UBE2C is thought to play a key role in the evolution of prostate cancer from an androgen-dependent state to an androgen-independent state, and higher levels of H3K4 methylation and FoxA1 binding on the UBE2C enhancer led to UBE2C protein overexpression in cases of androgen-dependent prostate cancer.[50] The mRNA expression of UBE2C in the androgen receptor(AR)-positive denudation-resistant prostate cancer cell line, LNCaP, and the AR-negative denudation-resistant prostate cancer cell line, PC-3, was compared by quantitative RT-PCR, and overexpression of UBE2C was found to have an important role in the growth of AR-negative denudation-resistant cells. In PC-3 cell line, silencing of FoxA1 and MED1 was found to impair long-range interactions of the UBE2C motif by 3C assay of the UBE2C motif. Analysis by protein blotting showed that siFoxA1 and siMED1 correspondingly reduced the protein expression level, and the silencing effect of MED1 on loop formation was greater than that of FoxA1, suggesting that MED1 is an important player in AR MED1 has a greater effect on loop formation than FoxA1, indicating that MED1 is a key mediator of chromatin cycling and gene expression in UBE2C motifs in AR-negative castration-resistant prostate cancer(CRPC) cells. A stable PC-3 cell line expressing FLAG/HA epitope-tagged wild-type (WT) MED1 (PC-3/WT MED1) and FLAG/HA epitope-tagged double-phosphate mutant (T1032A/T1457A) MED1 (PC-3/DM MED1) were constructed and analyzed by a series of immunoprecipitation/protein blotting analyses, which revealed that AR-negative

phosphorylation of MED1 in CRPC cells has a causal role in UBE2C motif cycling, UBE2C gene expression and cell growth. This was followed by a similar finding in the AR-positive CRPC cell model LNCaP-abl. The general importance of MED1 and phosphorylated MED1 in UBE2C locus cycling, UBE2C gene expression and CRPC growth was demonstrated.[51] A follow-up study found that G1/S cell cycle inhibitor-779 (CCI-779), an mTOR inhibitor, inhibited UBE2C mRNA and protein expression in the AR-positive CRPC cell models abl and C4-2B. However, its clinical use value still needs further validation.[52] Recently, it has also been demonstrated that UBE2C overexpression is associated with a worsening prognosis in prostate cancer, as evidenced by protein expression analysis, immunohistochemical staining evaluation, and correlation analysis of clinical variables using 497 PCa samples and 52 benign prostate tissue samples from the TCGA database, and specimens from 90 patients with prostate cancer taken from the Toufi Biotechnology Co[53].

Bladder Cancer

UBE2C positivity was observed in 62% of 82 cases of urothelial carcinoma of the bladder treated by radical cystectomy by immunohistochemistry, whereas no UBE2C was detected in 14 cases of non-tumorigenic urothelial carcinoma. UBE2C was not detected in any of the 14 non-neoplastic urothelial cases examined, and a clinicopathological correlation analysis of these 82 cases showed that UBE2C positivity was significantly associated with higher tumor stage and lymphovascular invasion. In addition, positivity was significantly associated with shorter cancer-specific survival after cystectomy. Inhibition of UBE2C synthesis using siRNA in bladder cancer cell line UM-UC-3 was found to inhibit bladder cancer cell growth.[54] A study examining urine samples from 212 bladder cancer patients and 106 normal controls (64 healthy individuals and 42 patients with hematuria) found that UB22C cell-free RNA(ctRNA) levels were significantly higher in bladder cancer patients than in normal samples and hematuria control samples, and that UBE2C positivity was significantly correlated with higher tumor stage and lymphovascular invasion. In addition, positivity was significantly associated with shorter cancer-specific survival after cystectomy.[55]

Thyroid Cancer

Thyroid tumors are excellent models for studying the process of tumor cell transformation because they contain a wide range of histotypes displaying different degrees of malignancy. By examining the expression of UBE2C in the following thyroid tumor cell lines (TPC-1, WRO, NPA, ARO, FRO, NIM 1, B-CPAP, FB-1, FB-2, Kat-4 Kat −18), it was found that it was abundantly expressed in all cell lines of goiter cancer origin, whereas it was hardly expressed in normal thyroid cells. The high expression of UBE2C was observed in undifferentiated human thyroid carcinomas and experimental undifferentiated thyroid tumors, while only weak expression was observed in follicular and papillary human thyroid carcinomas, suggesting that the overexpression of UBE2C may be related to the progression of thyroid tumors.[56] In two novel anaplastic thyroid cancer (ATC) lines (HTh 104 and HTh 112) and six commonly used ATC lines further characterized (HTh 7, HTh 74, HTh 83, C 643, KAT-4, and SW 1736), several non-random breakpoints were identified by spectral karyotyping (SKY) and G-banding in these cell lines including UBE2C gene in 20q13.12.[57] The UBE2C quantitative RT-PCR assay helps improve the detection of malignancy in thyroid fine needle aspiration (FNA) samples compared to non-immunohistochemistry. UBE2C can be added as a component to quantitative RT-PCR-based assays.[58]

Brain Tumor

Brain tumors have a lower incidence compared to the above cancers, but the role of UBE2C in brain tumors such as gliomas, meningiomas, and brain metastases has been investigated. The expression of UBE2C in astrocytic tumors was directly correlated with tumor grade, and expression was not observed in normal tissues or in glial cells. The expression level of UBE2C mRNA was elevated in high-grade astrocytomas compared with low-grade astrocytomas or normal controls.[59,60] Furthermore, it was shown that RNA interference (RNAi) against UBE2C induced growth inhibition, apoptosis, and cell cycle arrest in the U-251 glioblastoma cell line, demonstrating the important role of UBE2C in the proliferation, apoptosis, and cell cycle progression of glioblast cells.[61] Next, a study examined the expression levels of UBE2C in 220 human glioma tissues and 5 non-cancerous brain tissue specimens. It was found that UBE2C expression level was low in non-cancerous and low-grade glioma tissues, while it was elevated in high-grade gliomas. And by

multifactorial analysis of 80 patients with glioblastoma, UBE2C expression was found to be an independent prognostic factor.[62] Furthermore, it has been found that Forkhead box transcription factor M1 (FoxM1) triggers UBE2C transcription by binding to the promoter region and is associated with poor prognosis in gliomas.[63] Combined upregulation of UBE2C and Aurora kinase B (AURKB) is associated with poor prognosis, treatment resistance, and reduced overall survival in glioma patients.[64] In meningiomas, UBE2C overexpression is associated with higher histologic grade, increased proliferation and poor prognosis.[65] In addition, it has been found that in primary meningioma cells, UBE2C plays an important role in cell proliferation, metastasis and apoptosis, and by constructing a reporter plasmid with a mutation in the promoter region of UBE2C, it has been verified that RIZ1 regulates UBE2C in a c-Myc-dependent manner.[66] For brain metastases, a recent study identified the upregulation of UBE2C by RNA sequencing of 30 human brain metastases and found that UBE2C was highly expressed in human brain metastases from different primary tumors compared to normal tissue. In patients with brain metastases, high levels of UBE2C were associated with reduced survival. Overexpression of UBE2C increased migration and invasion of breast cancer cells (MDA) and lung cancer cells (A549). UBE2C increases leptomeningeal dissemination in vivo, an aggressive phenotype of metastatic brain disease, resulting in reduced survival in vivo.[67]

Clinical Significance of UBE2C in Human Cancer

UBE2C as a Potential Biomarker for Human Cancer

In summary, current research indicates that UBE2C shows promise as a significant cancer biomarker across a broad spectrum of human tumors. It is notably overexpressed in lung, breast, esophageal, and hepatocellular carcinomas, which are associated with high incidence and mortality rates. Moreover, numerous studies have highlighted that increased UBE2C expression correlates with diverse malignant behaviors such as invasiveness, lymph node metastasis, and distant metastasis. Pan-cancer analysis identified UBE2C as a common differentially expressed gene in almost all types of cancers, associated with poor prognosis and of significant diagnostic value in many cancer types.[68] We conclude that UBE2C is a therapeutic diagnostic gene that can be used as a reliable biomarker for diagnosing cancer, improving response to therapy, and increasing overall survival of cancer patients.

Inhibition of UBE2C as a Potential Therapeutic Target

To enhance selectivity and minimize toxicity, targeting E2 enzymes or E3 ligases represents the most effective strategy for modulating the UPS.[69] Inhibitors targeting E3 ligases are presently under clinical investigation for their potential in cancer therapy.[70] Extensive research has demonstrated the impact of UBE2C in cancer therapy. In breast cancer, In vitro study reveals that inhibition of UBE2C sensitizes breast cancer cells to radiation, Adriamycin, and hormone blockers, and that UBE2C may serve as a potential therapeutic target for inducing sensitization by radiation and chemotherapy.[27] Researchers have found that the cysteine protease inhibitor ALLN effectively reduces the expression of UBE2C through in vivo and in vitro experiments, providing a potential therapeutic approach for the treatment of colorectal cancer.[37] In vitro studies have shown that UBE2C inhibition may sensitize colorectal cancer cells to irinotecan, SN-38, and cetuximab, in part through downregulation of AKT.[38] In gastric cancer, researchers found that overexpression of UBE2C promoted resistance to cisplatin-induced apoptosis by in vitro experiments.[44] Another study found that depletion of UBE2C in gastric cancer cells impaired the ERK1/2 signaling pathway in vitro while reducing tumor volume in vivo. In hepatocellular carcinoma, researchers found that UBE2C knockdown enhanced the sensitivity of hepatocellular carcinoma cells to Adriamycin and 5-fluorouracil, as well as to sorafenib treatment, by in vitro experiments.[48] A recent study found that dactolisib (PI3K/mTOR inhibitor) was effective in the treatment of UBE2C-driven breast and lung cancer brain metastases (BM) in situ mouse xenografts by in vitro experiments. Moreover, early oral administration of dactolisib prevented molluscum contagiosum dissemination in vivo.[67] UBE2C is additionally implicated in DNA repair and the restart of damaged DNA replication forks, critical for preserving genome integrity and mitigating cancer risk,[71] Enhanced expression and activation of DNA damage response signaling and repair genes contribute to cancer resistance against radiation therapy.[72] Due to the limited effectiveness of radiotherapy and the emergence of chemotherapy resistance, there is an urgent need to develop inhibitors targeting DNA damage repair

signaling. Combining these inhibitors with radiotherapy and chemotherapy drugs shows potential for enhancing cancer treatment efficacy. Therefore, the development of UBE2C inhibitors is crucial for the treatment of cancer patients. However, inhibitors of the E2 enzyme are still in preclinical studies, CC0651 is an allosteric inhibitor for CDC34, which is a common E2 enzyme for cullin–ligase complexes. The fact that CC0651 causes tumour suppressors to aggregate and results in cell proliferation inhibition shows that it can become an efficient inhibitor in clinical applications.[73] However, for pharmacokinetic reasons, its development faces many problems.[74] Another potential target of cancer therapy is UBC13 (encoded by UEV1A), an E2 enzyme regulating the NF-kB pathway induction by forming chains depending on the ubiquitin K63. It has been shown that the NSC697923 inhibitor can inhibit the formation of K63 chains by UBC13 and also can affect the proliferation and survival of the larger B cells in lymphoma.[75] BAY-11-7082 is a well-known inhibitor of the NF-kB pathway and can inhibit IkB kinase. However, it can also inhibit UBC13 because it can prevent the binding of ubiquitin to UBC13; hence, it can inhibit the formation of the K63 chain in a similar way to the action of NSC697923 (a cell-permeable and selective inhibitor of E2)[76] and there is still a long way to go in the development of UBE2C inhibitors.

Discussion

UBE2C is a crucial enzyme in the cell cycle and is frequently utilized by researchers as a cancer biomarker. The overexpression of UBE2C is observed in almost all common cancers and correlates with histological grade, poor prognosis, resistance to treatment, and recurrence. Moreover, numerous studies have demonstrated that UBE2C plays a pivotal role in the proliferation, epithelial-mesenchymal transition, invasion, and migration of malignant tumors. Nevertheless, further in-depth mechanistic studies are still required, particularly in the TME, which is closely related to tumor development. This approach represents the optimal methodology for elucidating the mechanisms underlying UBE2C development in a diverse array of malignant neoplasms. One may investigate the interrelationship between UBE2C and the TME by examining its association with immune cells, tumor-associated fibroblasts, endothelial cells, and extracellular matrix. Moreover, epithelial-mesenchymal transition represents a pivotal element within the TME. In gastric cancer, it has been demonstrated that UBE2C knockdown results in upregulation of E-calmodulin expression and downregulation of N-calmodulin expression, as well as inhibition of epithelial-mesenchymal transition. Further research is necessary to determine the relationship between UBE2C and EMT and to elucidate the precise mechanisms by which UBE2C facilitates cancer cell phenotypic transformation towards local invasion. This approach allows us to investigate the specific mechanisms by which UBE2C contributes to tumor development.

The expression of UBE2C has been demonstrated to be a potential factor in the development of resistance to certain chemotherapeutic agents and proteasome inhibitory treatments. Nevertheless, further studies and testing of UBE2C-specific inhibitors are still required.

The utilization of UBE2C as a diagnostic and prognostic biomarker is promising. Currently, in conjunction with the growing utilization of ctRNA and cell-free DNA (ctDNA) in liquid biopsies, novel tumor biomarkers are useful for early tumor screening, optimization of therapeutic choices, and monitoring of disease dynamics. It is anticipated that further research will demonstrate the potential of UBE2C as a key diagnostic and prognostic biomarker in cancer.

Conclusion

In conclusion, although the relevance of UBE2C to cancer has been demonstrated, there is still a lack of specific mechanistic studies in a variety of common tumors, and better and more rigorous research data are needed to assess its true value as a diagnostic and prognostic marker and potential therapeutic target.

List of Abbreviations

CDK, Cell cycle protein-dependent kinase; PTM, Post-translational modification; APC/C, Anaphase Promoting Complex/Cyclosome; UBE2C, Ubiquitination-binding enzyme 2C; NSCLC, Non-small cell lung cancer; LUAD AGGF1, Lung adenocarcinoma angiogenic factor with G patch and FHA domains 1; CTCs, circulating tumor cells; IHC, Immunohistochemistry; MFS, metastasis-free survival; OS, overall survival; TNBC, triple negative breast cancer; ALKBH5, AlkB homolog 5; RNAi, RNA interference; ALLN, N-acetyl-leu-leu-norleucinal; CRC, colorectal cancer;

PDTC, pyrrolidine dithiocarbamate; ECRG4, Esophageal cancer related gene 4; FOXM1, forkhead box protein M1; CRPC, castration-resistant prostate cancer; AR, androgen receptor; ctRNA, cell-free RNA; SKY, spectral karyotyping; ATC, anaplastic thyroid cancer; FNA, fine needle aspiration; UPS, ubiquitin proteasome system; E1, Enzyme 1; E2, Enzyme 2; E3, Enzyme 3; TME, tumor microenvironment; EMT, epithelial mesenchymal transition; ctDNA, cell-free DNA.

Disclosure

The authors report no conflicts of interest in this work.

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