Diverse roles of UBE2T in cancer (Review)

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Abstract. As a leading cause of mortalities worldwide, cancer results from accumulation of both genetic and epigenetic alterations. Disruption of epigenetic regulation in cancer, particularly aberrant ubiquitination, has drawn increasing interest in recent years. The present study aimed to review the roles of ubiquitin-conjugating enzyme E2 T (UBE2T) and its associated pathways in the pathogenesis of pan-cancer, and the development of small-molecule modulators to regulate ubiquitination for treatment strategies. The current study comprehensively investigated the expression landscape and functional significance of UBE2T, as well as its correlation with cancer cell sensitivity to chemotherapy/radiotherapy. Multiple levels of evidence suggested that aberrant UBE2T played important roles in pan-cancer. Information was collected from 16 clinical trials on ubiquitin enzymes, and it was found that these molecules had an important role in the ubiquitin-proteasome system. Further studies are necessary to explore their feasibility and effectiveness as diagnostic and prognostic biomarkers, or as up/down-stream and therapeutic targets for cancer treatment.

Contents

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1. Introduction

Ubiquitination, an enzymatic post-translational modification (PTM) process, plays an important role in multiple cellular processes, including proteasome degradation of proteins, cell cycle, transcriptional regulation, DNA repair and signal transduction. The ubiquitin cascade reaction is carried out in three steps: Ubiquitin is activated by ubiquitin activating enzyme (UBE1) through ATP, supplied with energy, and transferred to the cysteine sulfhydryl group of ubiquitin-binding enzyme (UBE2). Next, ubiquitin conjugate is transferred to the target protein via specific recognition by E3 ubiquitin protein ligase. Ubiquitin binding enzymes, also known as UBE2 or ubiquitin carrier enzymes under certain conditions, perform the second step of the ubiquitin reaction.

UBE2 is a polygenic family, and its members are diverse in terms of molecular weight, structure and function, but they all contain a highly conserved ubiquitin domain called UBC domain. According to whether it contains a terminal extension, E2 family members are divided into four categories: i) Class I (containing only catalytic domain and requiring E3 for substrate recognition); ii) class II (containing a N-terminal extension); iii) class III (containing a C-terminal extension); and iv class IV (containing N- and C-terminal extensions).

Ubiquitin-conjugating enzyme E2 T (UBE2T, also known as E2 ubiquitin-conjugating enzyme T, FANCT, PIG50 and HSPC150) belongs to the UBE2 superfamily, which plays a fundamental role in the second step of ubiquitination. Following previous studies that reported that UBE2T was involved in the regulation of DNA repair in Fanconi anaemia (FA), it was recently molecularly identified as a risk factor closely associated with oncogenesis, metastasis, survival and prognosis in human patients or mammal animals with cancer (1-11).

In humans and the majority of mammals UBE2T has been described as exhibiting both oncogene activity and non-oncogene functions. Therefore, it is currently unclear if UBE2T is a

typical oncogene or if it is involved in other functions besides carcinogenesis, and whether it has cancer-inhibitory effects. Similarly, it is not known at present whether UBE2T has any other mechanism of action besides ubiquitin-dependent functions, how it behaves in different cancer types and which is its effect on chemotherapy/radiotherapy sensitivity. To answer these questions, further research on UBE2T is required.

2. UBE2T

Ubiquitination of proteins can change their localization, activity and/or stability. Ubiquitination requires the synergy of ubiquitin-activating enzymes (E1s), ubiquitin-binding enzymes (E2s) and ubiquitin ligases (E3s). E2s, as a central player, contributes to the interaction with an E1 enzyme and ≥1 E3s (12,13). As the main components of the ubiquitin-proteasome system (UPS), E2s and E3s are considered key determinants of substrate recognition and ubiquitination.

To date, ~40 types of UBE2s have been reported, which promote ubiquitin substrate binding, and regulate the stability and binding of cancer promoters, suppressors and regulators (14-16). Increasing evidence has verified that E2s show dysregulation in various cancer types, as they are linked to tumor-promoting processes and self-renewal abilities such as dysregulation in DNA repair, cell cycle, apoptosis and oncogenic signalling (10,17-22). The dysfunctional status of E2 members is considered a potential biomarker for diagnosis, prognosis and therapy in patients with various cancer types (22-31).

The structures of the majority of E2 proteins (full-length or UBC domains) have been confirmed, and the topologies are mainly consistent with this canonical folding. In few cases, including UBE2J, UBE2G, UBE2Q and UBE2R, the UBC domain is decorated with functionally important insertions. UBE2K has additional domains linked to the UBC domains, or forms part of large multidomain proteins such as UBE2O or baculoviral IAP repeat containing 6. In addition, the majority of E2s contain only a single structural UBC domain, the α/β fold, but a large number of them have short N- and/or C-terminal extensions that can confer important E2-specific functions. Thus, E2s have a common fold that may been applied to specific systems (14-16).

UBE2T (UniProt accession no. Q9NPD8) belongs to the superfamily UBE2, which comprises protein-coding genes. Human UBE2T is 22.521 kDa, similar to the majority of members of this family, which have a molecular weight of 20-25 kDa. UBE2T is a protein with 197 amino acids and a basal isoelectric point of 7.78 that is attached covalently to the Lys residues of the substrate during the ubiquitination process (21,32). UBE2T is composed of the core UBC folding and a C-terminal extension (~40 residues). To a large extent, this extension is unstructured, little conserved and has a negligible role in fan-mediated FA group D2 (FANCD2) mono-ubiquitination *in vitro* (33). The conserved Lys91 located near the catalytic site of UBE2T is constitutively monoubiquitinated *in vivo* and has been proposed to negatively regulate E2 (34).

The importance of E2 function in disease is the role of UBE2T in FA. A total of 20 genes, which are classified into two types, are involved in the FA pathway. Certain type I proteins, namely FANCA, -B, -C and -D2, as well as UBE2T together with FA-associated proteins comprise an 'upstream' ubiquitin signalling module. E2 has been recognized as a *bona fide* FA gene and is alternatively named FANCT, and exhibits a strong affinity for the RING domain of FANCL [dissociation constant (K_D) ~450 nM] (33,35). A previous study determined the structure for the E3-E2 pair, the FANCL RING domain (residues 299-373) and UBE2T (residues 1-153) to 2.4 Å resolution, and indicated that not only the conserved hydrophobic residues Ile309 and Trp341, but also the FANCL-specific Tyr311 are important for the FANCL-UBE2T interaction. The authors revealed that residues involved in the electrostatic and hydrogen-bonding network observed in the FANCL-UBE2T interface are highly variable (36).

UBE2T is the primary E2 of the FA pathway, and is required for FANCD2 and FANCI activation. Deficiency of UBE2T, which is necessary for FANCD2 and FANCI ubiquitination, causes the FA-T subtype of FA (37). A previous study carried out genetic engineering on derivatives of red fluorescent protein (RFP), with a His6 tag on the N-terminus and human wild-type ubiquitin (HisRFP ubiquitin) on the C-terminus, and found that RFP with only a small part of the E2 enzymes E2B, E2C, UBC5B, UBC4C, E2D4 and E2T directly ubiquitinated chimera. The authors detected that E2T catalysed ubiquitin polymerization through Lys27 of ubiquitin, which indicated that E2T contained a region that interacted non-covalently with the attacking ubiquitin-ubiquitin molecules to form a Lys-specific linkage, with the ubiquitin binding to the active site through this interaction. The authors also found that the β2-β3 loop of UBE2T contained a unique basic residue that formed a salt bridge with Glu340 of FANCL, while Arg60 in UBE2T was predominantly acidic (Asp/Glu) in other ubiquitin E2s and served as a positive selector for the FANCL RING-UBE2T pairing (33). Large-scale E2-E3 interaction studies have suggested that UBE2T interacts with ≥15 other E3s (33,38-40). UBE2T appears to function with a limited group of homologous to the E6-AP C-terminus E3s, and mainly supports multi-simple ubiquitination. However, the proposed UBE2T binding ring E3s and the FANCL ring domains are less conservative, and only 5 of them may support a β2-β weak interaction of 3 rings (if any) (33). However, when presented with a different set of E2s, FANCL could exclusively form a compound with UBE2T, and only homologous E2-E3 could cause site specific uni-ubiquitination of FANCD2 *in vitro* (36). The specific and stable FANCL-UBE2T interaction provides insights into how uni-ubiquitination events are regulated. Since both loading ubiquitin from E1s and unloading it through E3s require overlapping UBE2T surfaces, low UBE2T closure rates may limit the reload of ubiquitin, thereby inhibiting continuous ubiquitination (33).

In addition, the allosteric 'linchpin' residue (typically Arg) required for all RING/U-box-mediated ubiquitination events are absent from FANCL. Moreover, the allosteric 'linchpin' residue (typically Arg) required for all RING/U-box-mediated ubiquitination events is absent from FANCL (Ser363) (41).

It accepts ubiquitin in the E1 complex and catalyses its covalent attachment to other proteins, thus catalysing ubiquitination, and participates in mitomycin C (MMC)-induced DNA repair. On the other hand, it acts as a specific E2 ubiquitin binding enzyme of the FA complex by binding to the E3 ubiquitin protein ligase FANCL and catalysing the

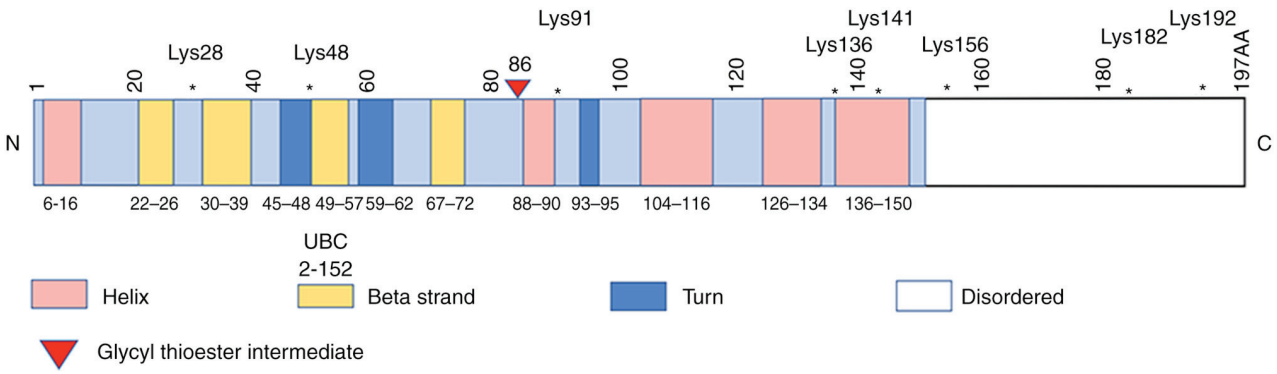

Figure 1. Schematic diagram of human ubiquitin-conjugating enzyme E2 T domains. Pink represents helix, yellow represents beta strand, blue represents turn, white represents distorted and the red triangle represents Glycyl thioester intermediate, which is used to catalyse the covalent connection between ubiquitin and target protein. *represents the ubiquitination site.

mono-ubiquitination of FANCD2 (which is a direct interaction and a key step in the DNA damage pathway), thus mediating the mono-ubiquitination of FANCL and FANCI (42-48). FA is a disease highly associated with UBE2T, and its related pathways include DNA damage and protein metabolism. Genome analysis of patient revealed a paternal 23-kb deletion across the UBE2T locus (49). The Gln2 residue in helix1 of UBE2T is not an integral part of the UBE2T-FANCL interaction surface. However, the binding of Gln2Glu mutation to FANCL was not as efficient, and reduced FANCD2 mono-ubiquitination by UBE2T-FANCL *in vitro* (33). A c.180 + 5G>A splice donor site mutation initiated a frame shift and premature stop codon, resulting in a truncated UBE2T protein with a non-functional UBC domain (49). The gene sequence from a FA patient revealed markedly low frequencies of either AluY-mediated deletions or duplications of UBE2T exons 2-6 (50). It has been suggested that all the identified pathogenic alterations of UBE2T are likely loss-of-function alleles, and the deficiency of UBE2T protein is associated with FA. It has been reported that UBE2T and FANCD2 access this subcellular fraction independently of the FA core complex, and substrates FANCD2/FANCI independently accumulate on chromatin during DNA replication or damage (34). Besides its interaction with essential E2, FANCL also has a highly conserved RWD-like domain (characterised by RING finger and WD repeat containing proteins and DEAD-like helicases) that stimulates the UBE2T-mediated uni-ubiquitination of FANCD2 (51).

Moreover, it has been shown to contribute to the ubiquitination and degradation of breast cancer gene 1 (BRCA1) (28,47,52-54). It interacts with the BRCA1/BRCA1 associated RING domain 1 (BARD1) complex in breast cancer (BrC) cells and causes the degradation of BRCA1. It also impacts BRCA1 ubiquitination but not that of BARD1 (52). Importantly, UBE2N, UBE2C, BE2H, UBE2B, UBE2W and UBE2F are also considered paralogues of that. UBE2T appears to contribute promoting the response by acting at different ubiquitin Lys residues. PTM was found for the UBE2T gene (Fig. 1), including auto-ubiquitination, since it contains 8 Lys sites (namely Lys28, 48, 91, 136, 141, 156, 182 and 192). In addition, it also exhibits two other modifications, namely sites of phosphorylation (Thr72, Ser184 and His194) and acetylation (Lys191). UBE2T has been shown to directly or indirectly interact with numerous proteins involved in a wide range of cellular processes, including cell cycle, cell proliferation, transcription and translation. Bioinformatic analyses using data from the Biological General Repository for Interaction Datasets (https://thebiogrid.org/), Protein Interaction Network Analysis 2 (https://omics.bjcancer.org/pina2012/) and STRING (https://cn.string-db.org/) databases found 73 interacting proteins for human UBE2T (Fig. 2A). Several of them are associated with protein (poly/mono)-ubiquitination, regulation of intracellular transport, regulation of intracellular protein transport and response to radiation (Fig. 2B).

3. Expression of UBE2T in cancer

UBE2T not only regulates numerous biological functions, particularly DNA repair, but also affects the occurrence, development and prognosis of cancer by impacting various cancer pathways characterized by oncogenes in multiple cancer types (8,55,56). Aberrant UBE2T expression is frequently found in cancer tissue samples and cell lines (Fig. 3A-C). UBE2T overexpression promoted cell proliferation, which was inhibited by UBE2T knockdown. Recently, research has focused on the function of UBE2T in tumorigenesis and tumor progression (57). Previous studies on UBE2T included BrC, bladder cancer (BC), cervical cancer, cholangiocarcinoma, colorectal cancer (CRC), esophageal cancer, lung cancer, hepatocellular carcinoma (HCC/liver HCC), melanoma, nasopharyngeal carcinoma, osteosarcoma, ovarian cancer and pancreatic cancer (PCA). The present study confirmed that high expression of UBE2T occurred in multiple types of cancer, and revealed the specific biological function and associated related cell signaling pathways (Table I). Data obtained from The Cancer Genome Atlas (TCGA, https://www.genome.gov/Funded-Programs-Projects/Cancer-Genome-Atlas) database indicated that UBE2T amplification was a common phenomenon in multiple types of cancer, although mutations have also been recognised (Fig. 3D). Additionally, overexpression of UBE2T is associated with poor survival in patients with cancer (Fig. 4).

UBE2T in the digestive system

Liver. HCC is the most common type of primary liver cancer, and UBE2T is upregulated and associated with adverse clinical

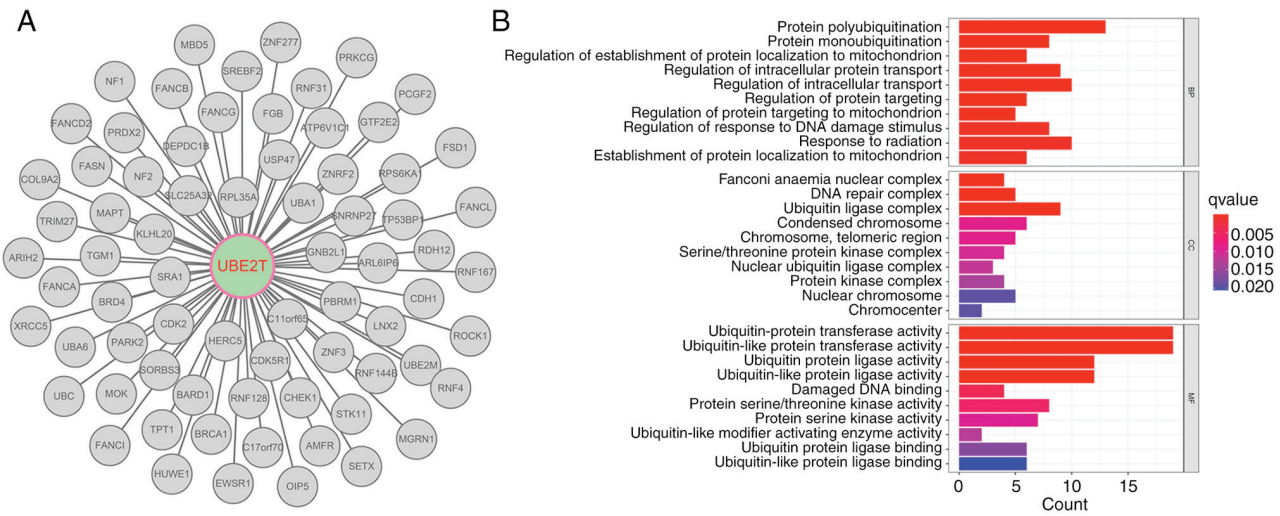

Figure 2. UBE2T interacting proteins and their potential biological functions. (A) The data were obtained from protein interaction network analysis (PINA2, http://omics.bjcancer.org/pina/), STRING (http://string-db.org/), and BioGRID (https://thebiogrid.org/). (B) Potential biological functions that the UBE2T interacting proteins may participate in. UBE2T, human ubiquitin-conjugating enzyme E2 T.

outcomes in patients. Experiments *in vitro* and *in vivo* showed that UBE2T promoted the development of HCC, including apoptosis, invasion, metastasis, metabolism migration and proliferation (58,59).

Circular RNAs (circRNAs) exhibit important regulatory functions in cancer biology. UBE2T is a target of certain circRNAs in cancer. It was suggested that there was a significant negative correlation between microRNA (miR)-1322 and UBE2T, which can directly interact. The overexpression of miR-1322 resulted in a significant decrease in UBE2T protein in HCC cells (59). Targeting UBE2T via miR-1305 disrupted the activation of the Akt signaling pathway, and ultimately inhibited the formation and proliferation of liver cancer stem cells, as well as tumorigenicity (56). Moreover, circ_0090049 regulated the expression of UBE2T by regulating miR-605-5p or miR-548c-3p, thereby promoting the proliferation of HCC cells (3). The expression level of miR-212-5p was observed to be markedly lower in HCC than in adjacent tissues, and was negatively correlated with the expression of UBE2T. miR-212-5p inhibited the malignant phenotype in a UBE2T-dependent manner (30,60).

It was found that cancer susceptibility 1 recruited AlkB homolog 5 to UBE2T mRNA, reduced the m^6A level of UBE2T (a downstream target), enhanced the stability of UBE2T mRNA and inhibited its binding with YTH N6-methyladenosine RNA binding protein 2, thus causing UBE2T upregulation (2). It was found that UBE2T was positively correlated with pyrimidine metabolism, the Akt/β-catenin cell signaling pathway and ubiquitination mediated by Akt Lys63. Liquid chromatography/mass spectrometry metabolomics results showed that the key products of pyrimidine metabolism, which include several key enzymes [namely carbamoyl-phosphate synthetase 2, aspartate transcarbamylase, and dihydroorotase, dihydroorotate dehydrogenase (DHODH) and uridine monophosphate synthetase] in pyrimidine synthesis, were significantly increased in HCC cells overexpressing UBE2T (58). UBE2T regulated β-catenin nuclear translocation, which led to the subsequent induction of the epithelial-mesenchymal transition (EMT) through MAPK/ERK-dependent activation. Overexpression of UBE2T also activated other EMT-related signaling pathways such as Akt/mTOR and Wnt/β-catenin (61). Silencing UBE2T reduced the percentages of CD47-, CD133- and CD90-positive cells, while UBE2T overexpression exhibited increased percentages of these markers (62).

Overexpression of UBE2T was negatively correlated with prognosis and overall survival (OS) time, while it was positively correlated with pathological grade and TNM stage of HCC progression, which showed higher expression at all four stages compared with that of non-cancer control samples (8,30,63). The level of UBE2T was significantly higher in stages II and III than in stage I (30). In addition, it was confirmed to have notable advantages with HCC grade, HCC satellite lesions and vascular invasion (63). miR-543 directly targeted UBE2T, which was downregulated in HCC. Ectopic expression of UBE2T led to the reduction of p53, p21 and Noxa, and promoted the degradation of p53 protein by enhancing its ubiquitination (8).

Abnormal cell cycle progression and inhibition of apoptosis are considered markers of cancer. UBE2T promoted radioresistance, which led to DNA damage response (DDR), and promoted G_2/M arrest by enhancing checkpoint kinase 1 (CHK1) activation. It also enhanced CHK1 activation and promoted G_2/M arrest, while its knockdown impaired the activation of CHK1 (64). Numerous genes are controlled by UBE2T (65). The carcinogenesis of small ubiquitin-like modifier (SUMO) specific peptidase 1 was mediated by the deSUMOylation of UBE2T and the UBE2T/Akt signaling pathway (55). UBE2T regulated G_2/M conversion via regulating CDK1 and cyclin B1. Silencing UBE2T resulted in an increase in the percentage of cells in G_2/M phase and a decrease in the percentage of cells in G_1 phase, indicating G_2/M phase cell cycle arrest. By contrast, the percentage of cells in the G_2/M phase decreased after UBE2T overexpression (66).

Bile duct, gallbladder, stomach, colon and rectum. UBE2T is considered a useful biomarker for the differential diagnosis

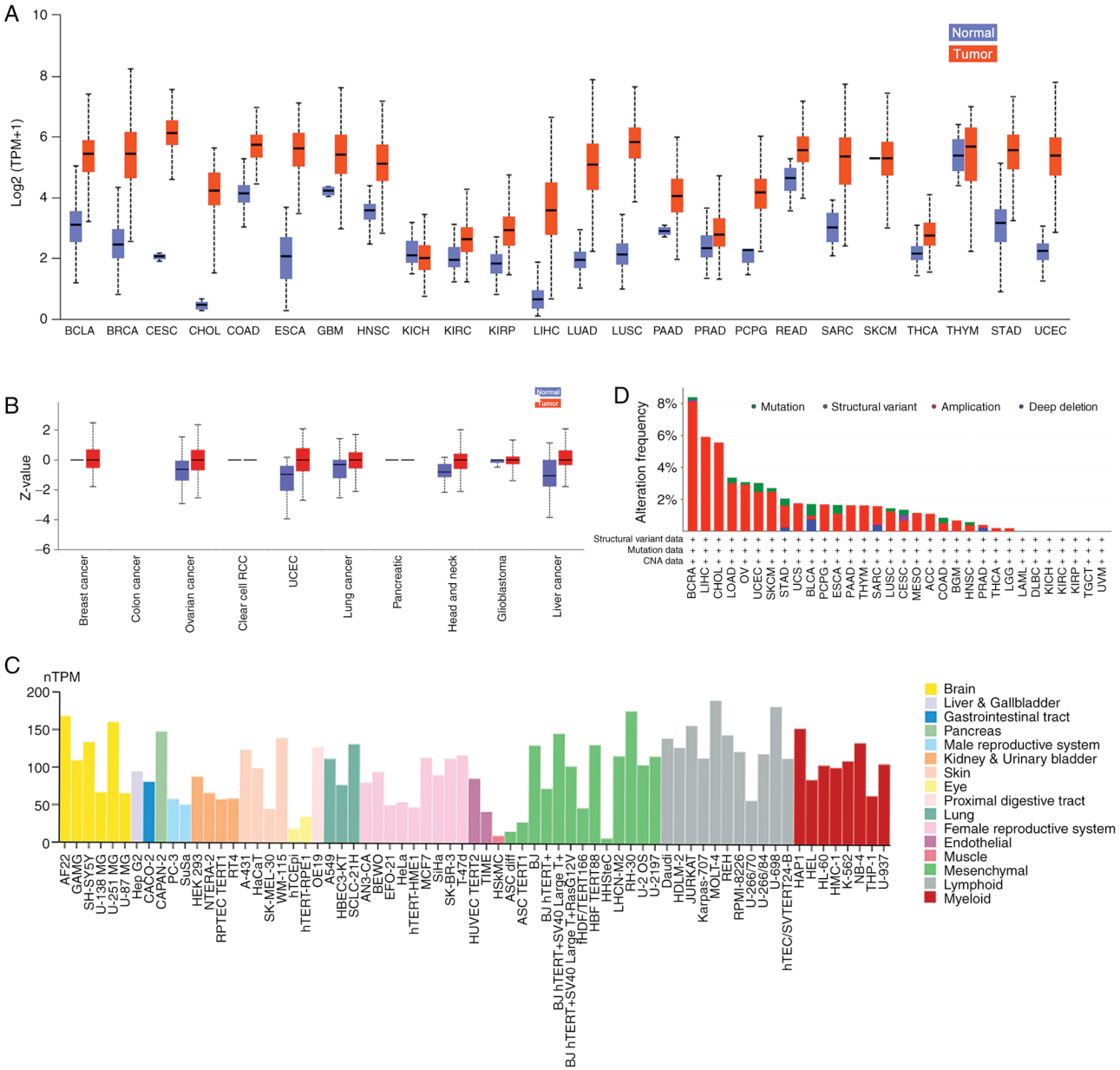

Figure 3. Pan-cancer expression landscape of UBE2T in different samples. (A) The differential expression of UBE2T in pan-cancer from TCGA. (B) Protein expression of UBE2T in several cancers from CPTAC. Blue represents normal, red represents tumor, and shadows represent a differential expression. (C) The expression of UBE2T in differential cell lines. Mutation features of UBE2T in different tumors of TCGA. the mutation features of UBE2T in TCGA tumors were analyzed using the cBioPortal tool. The alteration frequencies with mutation type (D) are displayed. UBE2T, human ubiquitin-conjugating enzyme E2 T; TCGA, The Cancer Genome Atlas.

of intrahepatic cholangiocarcinoma (CAA). High expression of UBE2T can be an independent indicator of poor prognosis, and is associated with shorter recurrence time and OS (67). In gallbladder cancer, high expression of UBE2T is significantly correlated with high risk, which is considered an independent risk factor for patients with gallbladder cancer (68).

Previous studies have shown that E2F family members show an advantageous function in gastric cancer (GC). E2F5 was significantly positively correlated with UBE2T in GC, which promoted malignant progression by promoting UBE2T transcription, while UBE2T overexpression reversed the effect of E2F5 depletion on cell invasion and proliferation (69). Chondroitin polymerizing factor may regulate E2F1 by affecting UBE2T-mediated E2F1 ubiquitination, which may determine the status of GC (70). The level of UBE2T was negatively correlated with the prognosis of patients with GC. High levels of UBE2T were identified, which were associated with risk factors, including early and late stages, lymph nodes, distant metastasis and *Helicobacter pylori*. Overexpression of UBE2T showed that markers of poor prognosis were higher than tubulin tyrosine ligase-like family member 12 in diffuse GC, indicating a shorter life span. In intestinal GC, however, the survival rate of patients overexpressing CDC16 was significantly lower than that of patients overexpressing UBE2T (71).

UBE2T is ubiquitinated by receptor for activated C kinase 1 (RACK1), and its degradation (mediated by the hyperactivation of the Wnt/β-catenin signaling pathway) promotes GC progression, which indicates that UBE2T is the upstream

Table I. The characteristic landscape of aberrant UBE2T in different types of cancer.

Tumor type	Alterations	Affected functions	Pathways	Role	Target validation	(Refs.)
HCC	Elevated	Proliferation, apoptosis, cycle, migration, invasion, chemosensitivity, metastasis, prognosis and metabolism	miR-1322	Downstream target	Circ_0000291 knockdown	Wang *et al* 2022 (59)
			miR-1305/Akt miR-605-5p	Downstream target	UBE2T knockdown	Wei *et al* 2019 (56)
			miR-548c-3p miR-212-5p	Downstream target	circ_0090049 knockdown	Chen *et al* 2022 (3)
				Downstream target	UBE2T knockdown/ overexpress	Ren *et al* 2021 (60)
			CASC11	Downstream target	CASC11 knockdown	Chen *et al* 2021 (2)
			Akt/β-catenin	Critical regulator	UBE2T knockdown/ overexpress	Zhu *et al* 2022 (58)
			MAPK/ERK, AKT/mTOR and Wnt/β-catenin	Critical Regulator	UBE2T knockdown/ overexpress	Lioulia *et al* 2022 (61)
			Mule/β-catenin	Regulator	UBE2T knockdown/ overexpress	Ho *et al* 2021 (62)
			miR-543	Downstream target	UBE2T knockdown/ overexpress	Liu *et al* 2017 (8)
			CHK1	Regulator	UBE2T knockdown/ overexpress	Sun *et al* 2020 (64)
			SENP1	Downstream target	SENP1 knockdown	Tao *et al* 2020 (55)
			cyclin B1, CDK1	Regulator	UBE2T knockdown/ overexpress	Liu *et al* 2019 (66)
ICC	Elevated	Proliferation, migration, invasion, apoptosis and cycle	mTOR	Downstream target	UBE2T knockdown/ overexpress	Liu *et al* 2020 (110)
GC	Elevated	Proliferation, migration, invasion, apoptosis, prognosis, cycle and metastasis	E2F5	Downstream target	E2F5 knockdown	Li *et al* 2022 (69)
			CHPF	Regulator	E2F1 knockdown	Lin *et al* 2021 (70)
			MYC	Biomarker	MYC knockdown	Heitor da Silva Maues *et al* 2020 (71)
			Wnt/β-catenin	Upstream regulator	UBE2T knockdown / inhibitor M435-1279	Yu *et al* 2021 (72)
			EMT and Wnt/β-catenin	Biomarker/ target	UBE2T knockdown	Luo *et al* 2017 (9)
			EMT	Biomarker	UBE2T knockdown/ overexpress	Yu *et al* 2016 (73)
CRC	Elevated	Proliferation, apoptosis, migration and invasion	P53	Biomarker/ target	UBE2T knockdown/ overexpress	Wu *et al* 2020 (75)

Table I. Continued.

Tumor type	Alterations	Affected functions	Pathways	Role	Target validation	(Refs.)
PCA	Elevated	Proliferation, apoptosis, migration and invasion	EMT	Biomarker/ target	UBE2T knockdown/ overexpress	Zheng *et al* 2020 (76)
LUAD	Elevated	Proliferation, prognosis, migration, invasion, apoptosis, autophagy and cycle	EMT	Regulator	UBE2T knockdown/ overexpress	Zhang *et al* 2022 (77)
			FBLN5, ERK/GSK3β	Biomarker/ target	UBE2T knockdown	Li *et al* 2022 (78)
			Wnt/β-catenin	Regulator/ target	UBE2T knockdown	Liu *et al* 2017 (85)
			PI3K/AKT	Biomarker/ target	NEDD4L knockdown	Chen *et al* 2021 (86)
			P53/AMPK/ mTOR	Regulator	UBE2T knockdown/ overexpress	Zhu *et al* 2021 (87)
NPC	Elevated	Proliferation, metastasis, invasion	AKT/GSK3β/ β-catenin	Biomarker/ target	UBE2T knockdown	Hu *et al* 2016 (6)
Osteosarcoma	Elevated	Proliferation, migration, invasion, apoptosis, cell cycle and radiosensitivity	Cell cycle	Regulator	UBE2T knockdown	Shen *et al* 2019 (89)
			PI3K/AKT	Regulator/ target	UBE2T knockdown	Wang *et al* 2016 (90)
MM	Elevated	Proliferation, migration, invasion, apoptosis and prognosis	miR-498	Regulator/ target	Not yet	Cao *et al* 2022 (91)
BrC	Elevated	Proliferation, migration, glycolysis and invasion	miR-543	Target	miR-543 overexpress	Li and Li 2021 (95)
			PI3K/AKT	Target	UBE2T knockdown/ overexpress	Qiao *et al* 2022 (97)
OV	Elevated	Proliferation, autophagy, invasion and prognosis	AKT/mTOR	Biomarker/ target	UBE2T knockdown	Huang *et al* 2022 (7)
Cervical cancer	Elevated	Proliferation, migration, invasion and prognosis	GRP78/FAK	Regulator	UBE2T knockdown/ overexpress	Liu *et al* 2021 (18)
PC	Elevated	Proliferation, migration, metastasis and invasion	EMT	Target	UBE2T knockdown/ overexpress	Wen *et al* 2015 (99)
BC	Elevated	Proliferation, migration, cell cycle and apoptosis	Cell cycle	Biomarker/ target	UBE2T knockdown	Gong *et al* 2016 (101)
RCC	Elevated	Proliferation, migration, metastasis invasion, cycle and apoptosis	miR-182-5p	Target	UBE2T knockdown/ overexpress	Wu *et al* 2022 (103)
			PI3K/Akt/mTOR	Regulator	UBE2T	Hao *et al* 2019 (5)
MuM	Elevated	Proliferation, cycle and chemosensitivity	Homologous recombination	Target	UBE2T knockdown knockdown	Alagpulinsa *et al* 2019 (1)

Table I. Continued.

Tumor type	Alterations	Affected functions	Pathways	Role	Target validation	(Refs.)
DLBC	Elevated	Proliferation	PI3K	Not yet	UBE2T knockdown	Derenzini *et al* 2018 (106)
RB	Elevated	Proliferation, immune infiltration, prognosis cell cycle and apoptosis	Anaplasia	Biomarker	UBE2T knockdown	Wang *et al* 2022 (107)
GBM	Elevated	Invasion, and migration	GRP78/EMT	Target	UBE2T knockdown	Huang *et al* 2020 (108)

HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; GC, gastric cancer; CRC, colorectal cancer; PCA, pancreatic cancer; LUAD, lung adenocarcinoma; NPC, nasopharyngeal carcinoma; MM, malignant melanoma; BrC, breast cancer; OV, ovarian cancer; PC, prostate cancer; BC, bladder cancer; MuM, multiple myeloma; DLBCL, diffuse large B cell lymphoma; RB, retinoblastoma; GBM, glioblastoma; CASC11, cancer susceptibility candidate 11; CHK1, checkpoint kinase 1; SENP1, SUMO-specific proteases1; CHPF, chondroitin polymerizing factor; EMT, epithelial-mesenchymal transition; FBLN5, fibulin-5; NEDD4, Neural precursor cell expressed, developmentally downregulated 4, E3 ubiquitin protein ligase.

regulator of RACK1. M435-1279, an inhibitor of UBE2T, blocks the UBE2T-mediated RACK1 degradation to inhibit the overactivation of Wnt/β-catenin, thereby inhibiting the proliferation and progression of GC (72). Similarly, in HCC, UBE2T inhibition mediated by small interfering (si)RNA inhibits the proliferation and colony formation of GC cells by promoting G_2/M phase cell cycle arrest and increasing apoptosis (9,73). Bioinformatics analysis of clinical samples found that cell cycle, DNA replication, mitotic M-M/G_1 phases and the ataxia-telangiectasia-mutated signaling pathway were involved in CRC progression. The finding was consistent with a previous study, which reported that higher UBE2T expression levels were associated with poorer prognosis, and silencing UBE2T could inhibit CRC cell proliferation (74). UBE2T is not only associated with prognosis and clinical TNM stage, but also with N classification and histological grade in CRC (75). Overexpression of UBE2T could promote the proliferation, migration and invasion of CRC cells through the ubiquitination of p53 (8). UBE2T has been shown to promote the invasion of PCA and GC, which may be regulated by EMT (73,76).

UBE2T in the respiratory system

Lung and larynx. Silencing UBE2T may regulate the stability of FANCI by binding to FANCI, since upon silencing UBE2T, the FANCI protein levels decreased without significant changes in its mRNA levels. The ubiquitin content in A549 and H1299 cells were downregulated after silencing UBE2T, which was also involved in FANCD2 (a paralogue of FANCI) ubiquitination. Knockdown of UBE2T decreased the mono-ubiquitination of FANCD2, while overexpression of UBE2T increased it (77). Cell proliferation, migration and invasion abilities decreased after knocking down of UBE2T, while silencing UBE2T increased fibulin 5, and inhibited the activation of phosphorylated (p)-ERK, p-GSK3β and β-catenin (78).

According to the expression profile of non-small cell lung cancer (NSCLC) obtained from the National Center for Biotechnology Information-Gene Expression Omnibus database (https://www.ncbi.nlm.nih.gov/geo/), UBE2T is one of the differential genes, and its prognosis risk ratio is the most remarkable. Its increase was identified as a potential risk factor for pathological stage I lung adenocarcinoma (LUAD) (79). Certain differential genes, particularly UBE2T, showed similar survival risks (80). Elevated expression of these genes, including UBE2T, was associated with poorer OS in patients with NSCLC (81). The expression of UBE2T in LUAD was correlated with late clinicopathological factors (age, sex, clinical stage, and T and M classification). Survival analysis also revealed a similar trend, where high expression of UBE2T was associated with poor prognosis (82). UBE2T exhibited the strongest protein-protein interaction with other 7 protein types based on protein-protein interaction networks (83). According to data from cBioPortal (https://www.cbioportal.org/), UBE2T was amplified in ~7% of cases of NSCLC and was associated with disease recurrence after surgical resection. No significant molecular alterations or clear trends in clinical outcomes were observed in these genes (84).

UBE2T impacts certain downstream genes of the β-catenin and Wnt/β-catenin signalling pathways. In NSCLC cells transfected with si-UBE2T, the protein levels of β-catenin, c-Myc and cyclin D1 were significantly decreased, while the expression of E-cadherin was significantly increased (85). UBE2T, a novel physiological substrate of the E3 ubiquitin ligase NEDD4 like E3 ubiquitin protein ligase (NEDD4L), targets the ubiquitination and degradation of UBE2T, and leads to the inhibition of PI3K-Akt signalling, thereby inhibiting LUAD progression (86). UBE2T stimulated autophagy, and silencing it eliminated autophagy in LUAD cells. Blockade of p53 counteracted the inhibitory effect of UBE2T depletion on autophagy. In addition, the AMPK/mTOR axis was activated during UBE2T-mediated autophagy, while UBE2T promoted autophagy through the p53/AMPK/mTOR signaling pathway (87).

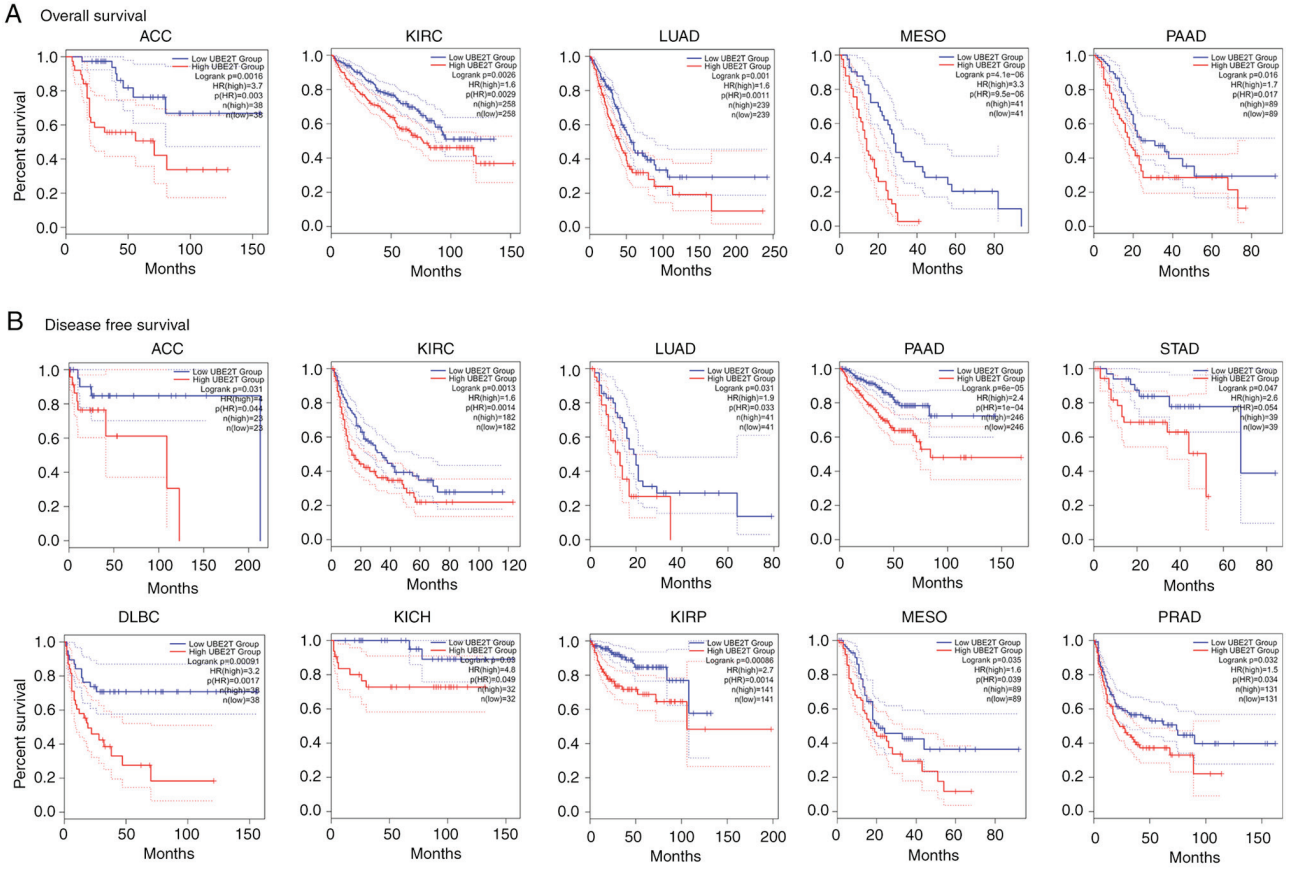

Figure 4. Correlation between UBE2T expression and survival prognosis of cancer in TCGA. The GEPIA2 tool was used to perform (A) overall survival and (B) disease-free survival analyses of different tumors in TCGA by UBE2T expression. The Log-rank test was used for the survival analysis. Only TCGA cancers with statistically significant differences between cohorts are presented. UBE2T, human ubiquitin-conjugating enzyme E2 T; TCGA, The Cancer Genome Atlas; ACC, adrenocortical cancer; DLBC, large B-cell lymphoma; KICH, kidney chromophobe; KIRC, kidney clear cell carcinoma; KIRP, kidney papillary cell carcinoma; LUAD, lung adenocarcinoma; MESO, mesothelioma; PAAD, pancreatic adenocarcinoma; PRAD, prostate adenocarcinoma; STAD, stomach adenocarcinoma.

UBE2T in pharynx, bones and skin. UBE2T overexpression increased β-catenin expression, enhanced p-Akt and p-GSK3β, and promoted β-catenin nuclear translocation (6). Transcription and DNA copy number of UBE2T were significantly increased in esophageal squamous cell carcinoma (ESCC). ESCC is usually caused by base excision repair, cell cycle, DNA replication, FA, mismatch repair or the p53 signaling pathway. The protein level of UBE2T was significantly associated with disease-free survival, but not with OS, in ESCC (88).

UBE2T is also highly expressed in human osteosarcoma. Silencing UBE2T inhibited the proliferation of osteosarcoma cells and induced cell arrest in the G_2/M phase (89). The effect of UBE2T knockdown on the activity of the PI3K/Akt signaling pathway was investigated. The protein levels of p-PI3K and p-Akt were significantly downregulated in UBE2T-silenced MG63 cells compared with those in the corresponding control cells. However, the total protein levels of PI3K and Akt were hardly affected (90).

UBE2T is a novel target gene of miR-498, which can directly bind to the 3'-untranslated region of UBE2T and inhibit the level of UBE2T. Overexpression of UBE2T could reverse the inhibitory effect of miR-498 on the progression of malignant melanoma (MM) cells. High levels of UBE2T were associated with poor prognosis in MM (91), and showed a significant association with mitosis (92).

UBE2T in the breast and genital system. The hormone positive (HR^+) subtype (also named luminal type) is the most common type of BrC. UBE2T is associated with the survival rate, but HR^+ BrC cells showed dependence on UBE2C (93). UBE2T was highly expressed in BrC, particularly in triple-negative BrC (TNBC) and human epidermal growth factor receptor 2-positive BrC. It was also significantly positively correlated with T helper (Th)2 in all BrC subtypes. Its upregulation in different subtypes led to Th1/Th2 imbalance, while polarization towards Th2 cells may lead to disease progression (94). miR-543 directly targeted UBE2T, and a negative correlation between miR-543 and UBE2T was observed in BrC tissues. In addition, overexpression of miR-543 disrupted the cancer-promoting effects of UBE2T by inhibiting the activity of the ERK/MAPK signaling pathway, thus inhibiting the viability, proliferation, migration and invasion of BrC (95).

Various genes, including UBE2T, were found to be associated with an unfavourable prognosis in each BrC subtype (54). High expression of UBE2T indicated a lower pathological complete remission rate in patients with TNBC after neoadjuvant chemotherapy, and in patients with luminal BrC with tumor recurrence within 5 years after endocrine therapy or chemotherapy (96). Compared with that in the normal breast epithelial cell line MCF-10A, the expression of UBE2T was upregulated in BrC cells. Overexpression of UBE2T promoted

cell proliferation, migration, invasion and glycolysis, while UBE2T knockdown showed the opposite results (97).

In total, 8 highly connected hub genes, were selected for further study (98). UBE2T was significantly associated with BrC, and was involved in cell cycle, DNA replication, p53 signaling pathway, prognosis of patients with BrC and aggressive degrees (98). UBE2T was amplified in ~12% of breast tumors, while in ovarian serous cystadenocarcinoma, no significant molecular alterations or clear trends in clinical outcomes were observed (84). Upon UBE2T knockdown, Akt/mTOR inactivation activated autophagy in ovarian cancer (OV) cells, causing UBE2T depletion and inhibiting EMT. UBE2T upregulation could predict poor prognosis and promote the malignant progression of OV (7). UBE2T upregulation also showed a strong correlation with poor OS in OV. Moreover, UBE2T was closely associated to specific immune cells, which were mainly involved in cell cycle-related events, and in Titin and p53 mutations. UBE2T copy number amplification and hypomethylation may be responsible for its upregulation in OV (57). UBE2T overexpression of contributed to the proliferation and metastasis of cervical cancer cells, and UBE2T-overexpressing cervical cancer cells exhibited enhanced self-renewal ability. UBE2T promoted cervical cancer stem cell characteristics and exerted carcinogenic effects by activating the glucose regulated protein 78 (GRP78)/focal adhesion kinase signaling pathway (18).

UBE2T in the urinary system. The expression of UBE2T and vimentin was positively correlated with the metastatic ability of prostate cancer (PC). Overexpression of UBE2T induced EMT, and promoted PC proliferation and metastasis. It acted as an oncogene, at least in part through cooperation with vimentin (99). In addition, UBE2T and the LASSO regression analysis were used to calculate the autophagy score of each patient in a previous study (100).

UBE2T could be detected in the nucleus and cytoplasm of cancer cells, but showed stronger expression in the nucleus. UBE2T knockdown significantly decreased the proliferation ability of BC cells. Moreover, silencing UBE2T induced cell cycle arrest at the G_2/M phase and increased apoptosis; thus, it may be considered a potential biomarker and therapeutic target for BC (101). Univariate Cox regression results showed that it was potential ubiquitination-related prognostic molecule, and it was verified to be associated with OS (102). High expression of UBE2T was positively correlated with advanced pathological stage, distant metastasis, histological grade and maximum tumor diameter. miR-182-5p exhibited inhibitory effects on the development, proliferation, migration and invasion of clear cell renal cell carcinoma (ccRCC) by targeting UBE2T (103). Gao *et al* (104) analyzed and screened 5 hypoxia gene subsets by using the Gene Set Enrichment Analysis. UBE2T was one of the genes, and the genomic characteristics were significantly correlated with the survival rate of ccRCC. UBE2T was significantly correlated with advanced tumor stage and high grade in RCC, and the prognosis was poor with its high expression. Vimentin and N-cadherin, which are markers of mesenchymal cells, were decreased with UBE2T knockdown, while the levels of E-cadherin and fibronectin were enhanced, indicating that the EMT process was blocked (5).

UBE2T in miscellaneous systems

Myeloma and leukemia. UBE2T is often amplified, and this is frequently found in multiple myeloma (MuM), where its increased copy number and expression are associated with low survival. This indicated that UBE2T was required for efficient DNA repair by homologous recombination (1). UBE2T is a meaningful indicator of MuM staging, particularly in the early stage. Its expression increased with the deterioration of MuM compared with stages I and II, while the expression of UBE2T in stage III was significantly higher, as well as in patients with relapse. UBE2T overexpression was associated with poor prognosis, and amplification of 1q21 indicated poor results, revealing that the UBE2T level increased with the increase of amplification (11). Its strong association with homologous recombination and the abundance of UBE2T in subgroups of MuM suggest a central role for gain of chromosome 1q and upregulation of UBE2T as potential drivers of MuM aggressiveness (105). Clustered regularly interspaced short palindromic repeats single guide RNA determined the specific dependence of UBE2T on the ubiquitination mechanism involved in acute myeloid leukaemia (46) Downregulation of UBE2T induced by bromodomain and extra-terminal protein family inhibitor (BETi) enhanced the levels of GSK3β S9 phosphorylation and β-catenin. BETi decreased UBE2T levels and increased the phosphorylation of GSK3β S9; however, combined depletion of UBE2T and UBE2C strengthened the anti-proliferative effect of a PI3K inhibitor (106).

Eye, brain and nervous system. As one of the core genes, UBE2T was closely associated with anaplastic grade, and its level was significantly different in retinoblastoma cells (107). UBE2T and GRP78 have a dominant association. UBE2T enhanced glioblastoma invasion and migration abilities via GRP78. UBE2T could maintain the stability of GRP78, but the level of EMT biomarkers alterations was significantly different upon silencing UBE2T, which led to significant overexpression of E-cadherin, and downregulation of N-cadherin and vimentin (108). DEP domain containing 1B affected baculoviral IAP repeat containing 5 ubiquitination via UBE2T, causing its deregulation and thus regulating the progression of chordoma (109).

4. UBE2T-mediated signaling pathways in cancer

EMT is an important biological process in which malignant tumor cells derived from epithelial cells acquire the abilities of migration and invasion. The related proteins mainly involved in UBE2T research include β-catenin and E-cadherin, which participate in the EMT-related Wnt/β-catenin signaling pathway (5). For example, RACK1 inhibited the degradation of UBE2T and decreased the stability of Wnt after increasing the expression of UBE2T/β-catenin, promoted the EMT process, and led to the infiltration and migration of cancer cells (72). Ubiquitination of mutator-like elements via UBE2T inhibited the degradation of β-catenin protein and promoted the EMT process (62). Moreover, mTOR and p-Wnt could also be activated by β-catenin, and promoted the EMT process (61).

Cell cycle regulation is common in cancer research focused on UBE2T. UBE2T-mediated overexpression of ubiquitinated p53 activated mouse double minute 2 homolog

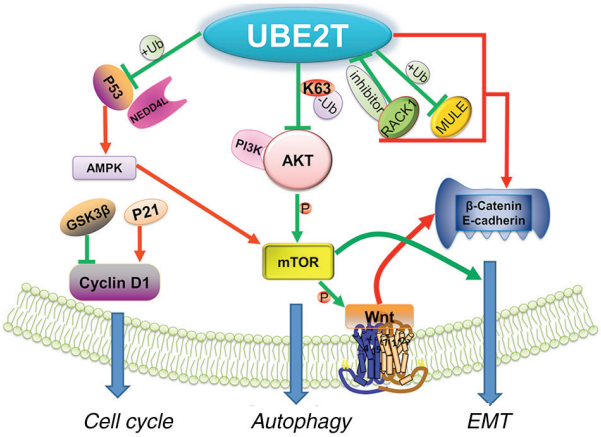

Figure 5. The major proteins, their ubiquitination, and the biological processes that UBE2T regulates. +Ub represents ubiquitination, P represents phosphorylation, red solid arrow indicates activation, green T-shaped solid line indicates inhibition, and blue bold arrow represents cell type. UBE2T, human ubiquitin-conjugating enzyme E2 T.

(MDM2), and both PI3K/protein tyrosine phosphatase 3 and MDM2 could activate Akt, and inhibit GSK3β and p21 (6,8). GSK3β could inhibit cyclin D1 to increase the risk of carcinogenesis, and p21 could activate cyclin D1 to regulate the cell cycle (9). It has been reported that β-catenin, after activating c-Myc, can activate cyclin D1 to control the cell cycle, and NEDD4L can inhibit the PI3K-Akt signaling pathway by targeting the ubiquitination and degradation of UBE2T, thus inhibiting the progression of cancer cells (86). UBE2T-related pathways usually lead to changes in cell number in the G_2/M phase (66,89).

In the autophagic phenotype, UBE2T could inhibit Akt after deubiquitination of Lys63, and activate the mTOR signaling pathway upon phosphorylation of Akt after inhibition, thus activating cell autophagy (58). In addition, UBE2T downregulated the p53 level, and activated the AMPK/mTOR axis, suggesting that it promoted autophagy through p53/AMPK/mTOR signaling (87).

The aforementioned are the three common phenotypes and related pathways described in the current study, but are not limited to the aforementioned mechanisms (Fig. 5) (108), since there are also complex regulatory associations and cross-links between different pathways, which must be further evaluated in future studies (10).

5. Cancer therapies involving UBE2T

Chemosensitivity. Surgery remains the best treatment for localized cancer, and is often combined with conventional radiotherapy and chemotherapy. Previous evidence confirmed that palbociclib and ribosciclib, two CDK4/6 inhibitors, suppressed the expression of the ubiquitin-conjugating enzyme UBE2T in luminal BrC (93). Leflunomide, a DHODH inhibitor that has been approved by the USA Food and Drug Administration for the treatment of rheumatoid arthritis, decreased DHODH levels and attenuated the DHODH upregulation induced by UBE2T, and reduced the proliferation ability of UBE2T-overexpressing cells (58). Rapamycin (RAPA), a specific mTOR inhibitor, was used to further investigate the UBE2T effect via the EMT process and mTOR signaling in HuCCT1 and QBC939 cells. The application of RAPA suppressed the proliferation, migration and invasion abilities of cells, and effectively attenuated the effects induced by UBE2T overexpression in CAA cells, namely EMT process activation and mTOR downstream effectors enhancement (110).

Certain common chemotherapeutic drugs, including cisplatin, paclitaxel, gemcitabine and docetaxel, were more sensitive to cisplatin and gemcitabine in patients with ESCC in a low-risk group based on TCGA-ESCC cohort analysis (88). Cisplatin stimulated autophagy in GC (A549) cells, and overexpression of UBE2T further exacerbated autophagy, involving cisplatin-induced protective autophagy. Moreover, UBE2T overexpression counteracted the chemosensitivity of A549 cells to cisplatin treatment, while inhibiting autophagy by chloroquine reversed the UBE2T-induced cisplatin resistance (87). Currently, treating tumors such as NSCLC is becoming difficult because chemotherapeutic drugs are ineffective due to resistance. It was found that the hsa_circ_0092887-mediated miR-490-5p/UBE2T signaling axis may contribute to paclitaxel-resistance intervention in NSCLC (111).

MOLM-13 cells treated with 5-azacytidine were also significantly less sensitive to UBE2T inactivation (46). A previous study evaluated the effect of UBE2T alteration on the chemoresistance of HCC by using annexin V (62). UBE2T-silenced HCC cells (MHCC-97L and PLC/PRF/5) exhibited enhanced cell death after doxorubicin, sorafenib and lenvatinib treatment. By contrast, UBE2T-overexpressing Huh7 cells exhibited reduced cell death when treated with doxorubicin (62).

It has been found that M435-1279, a novel UBE2T small molecule inhibitor, significantly inhibited the proliferation of HGC27, AGS and MKN45 cells, while the small molecule AG-690/12244866 significantly supressed HGC27 cell proliferation but not AGS or MKN45 cell proliferation. M435-1279 exerted lower cytotoxicity in GES-1 cells than AG-690/12244866, indicating that M435-1279 may be a potential drug for the treatment of GC (72). UBE2T promoted the proliferation and metastasis of nasopharyngeal carcinoma cells via modulating the Akt/GSK3β/β-catenin axis. MK-2206 2HCl, as a specific inhibitor of Akt, could block the pro-migration and -invasion effects of UBE2T (6).

UBE2T knockdown not only decreased the viability of MM1S and U266 cells *in vitro* (in MuM), but also apparently reinforced the cytotoxicity of the DNA-damaging agents camptothecin (0-40 nM), MMC (0-80 nM) and melphalan (0-20 μM). The IC_{50} of these three agents in UBE2T-silenced MuM cell lines was 2.7-11-fold lower than that in control cells (1). Wortmannin is an Akt inhibitor that could significantly enhance the proliferation and invasion abilities of MG63 cells when UBE2T was knocked out (90). Similarly, it could reverse the increased phosphorylation of PI3K, Akt and mTOR induced by UBE2T overexpression, and even attenuate the UBE2T overexpression-mediated induced proliferation of 786-O cells (5). In the bortezomib and dexamethasone groups, there was no marked alteration in UBE2T in MuM in either of the treatment responses, although triple drug therapy (vincristine, adriamycin and dexamethasone) showed favourable partial response as induction therapy followed by autologous stem cell

transplant as a maintenance therapy (11). Hydroxyurea and aphidicolin produced more potent inhibiting effects in a concentration-dependent manner on the proliferation of BrC cells transfected with UBE2T small hairpin RNA. In addition, UBE2T suppression enhanced the therapeutic benefits of drugs that functioned by inducing DNA replication stress (4). BETi enhanced lymphoma vulnerability to PI3K inhibitors by downregulating UBE2T, which further enhanced the negative feedback regulation of the PI3K signaling pathway (106).

It was found that several cell lines (HT29, DU145, MCF-7, MDA-MD-468, U373, HCT116, HeLa and ME180) exposed to a hypoxic environment (<0.02% O_2) for 24 or 48 h were more sensitive to treatment with 1 μg/ml MMC (112). Notably, the activation of the FA pathway has been linked to chemotherapy resistance in several types of cancer. A previous study identified a small-molecule inhibitor of UBE2T/FANCL-mediated FANCD2 mono-ubiquitylation that sensitizes cancer cell lines to the DNA cross-linking agent. Two compounds, CU1 and CU2, were identified to sensitize osteosarcoma cells to a more clinically relevant chemotherapeutic agent. However, CU1 exhibited strong cytotoxicity, while CU2 exhibited promising selectivity in biochemical ubiquitylation assays and demonstrated activity against the FA pathway in U2OS cells. Thus, it could be used in clinical applications to sensitize cancer cells to DNA cross-linking agents such as carboplatin or MMC (44).

Radiosensitivity. DDR is closely associated with radioresistance in cancer cell lines. The survival fraction, as well as the volume and weight of HCC tumors (xenografts originating from MHCC-97H cells), were longer, larger and heavier after radiotherapy. In UBE2T-overexpressing cells, there were fewer cells with >10 γH2AX foci, lower γH2AX levels after irradiation (IR), and improved recovery back to the basal levels, compared with those in control cells, which was indicative of a stronger DDR (64). Cantharidin is an inhibitor of protein phosphatase 2 A, and has been demonstrated to be able to arrest the cell cycle in the G_2/M phase. It could sensitize PC cells to radiotherapy, involving cell cycle modulation, increased DNA damage and DDR suppression (113).

NSCLC (H1299) and osteosarcoma (U-2OS and MG-63) cells with UBE2T knockdown were more sensitive to IR than control cells, and A549 cells overexpressing UBE2T were more resistant to radiotherapy (10,89). Radiation resistance could affect prognosis in NSCLC, and UBE2T promoted radiation resistance *in vitro* (0-10 Gy) and *in vivo* (10 Gy) via accelerating the G_2/M transition and inhibiting apoptosis. UBE2T could contribute to radiation resistance via the ubiquitination of forkhead box protein O1, and it could reverse radiation resistance in NSCLC cells (10).

Osteosarcoma cell lines (simultaneously transfected with siRNA-UBE2T or siRNA-control) were irradiated with 0, 2, 4, 6, 8 or 10 Gy and then incubated for 1-2 weeks. Silencing UBE2T could significantly strengthen the effect of radiation in osteosarcoma. UBE2T knockdown combined with X-ray IR could significantly reduce the proliferation of osteosarcoma cells and the growth of osteosarcoma (6 Gy), as well as inhibit metastasis, stimulate the production of reactive oxygen species, and promote apoptosis (89).

6. Conclusion

A growing number of studies have revealed that UBE2T expression is upregulated in human pan-cancer. Recent evidence has indicated the importance of UBE2T in tumorigenesis, proliferation, migration, metastasis, drug resistance, radioresistance and poor prognosis in cancer patients. The articles included in the present review were focused on different tumor types, pathways and factors. The purpose was to summarize the research gaps and identify topics for further research. In the present review, it was discussed that UBE2T activates the mono-ubiquitination of FANCD2 and has been reported to be involved in cancer development. The roles of UBE2T and associated enzymes in pan-cancer pathogenesis involving DNA repair, cell cycle, apoptosis and oncogenic signaling were reviewed. In addition, the roles of UBE2T in tumorigenesis, progression and treatment, as well as the development of small molecule modulators to regulate ubiquitination therapeutic strategies were also discussed.

Increased transcription and translation of UBE2T has been widely linked to pan-cancer. Numerous studies show serious limitations, since despite the fact that numerous studies are available, a considerable part of them derive from bioinformatics analysis, and lack experiments to verify the screening information from the datasets.

UBE2T-associated genes or pathways have not been clearly recognized as drug targets or prognostic biomarkers, including TPX2, CDC20, CDC20, CDC45, ANLN, ASPM, PRC1, CCNB2, CCNB2, MELK, PRC1, TOP2A and KIAA0101. Regulating these genes/proteins in cancer cell lines or mouse/rat models via silencing, overexpression, inhibitor, chemosensitivity or radiosensitivity may clarify their therapeutic value in cancer.

The majority of studies have focused on the mechanism of UBE2T in the occurrence, development and prognosis of cancer. Overexpression of UBE2T results in tumour growth and deterioration, and by knocking out or overexpressing UBE2T, cancer-suppressing functions can be activated or inactivated in pan-cancer. However, the current data suggest that this modulation may be specific, and exactly which genes/pathways are affected by EMT, cell cycle and autophagy should be identified. Additionally, chemosensitivity and radiosensitivity can regulate cancer cell fate and status, and affect their functions in the pathological process. Once these target mechanisms are elucidated, more precise and efficient treatment therapies can be expected.

UBE2T is a typical oncogene that is involved in chromosome instability syndromes and immunological disorder besides carcinogenesis. It does not exhibit cancer-inhibitory effects. As a disease-associated E2-conjugating enzyme, UBE2T, has been reported to be more than just an intermediary of the ubiquitin signaling pathway, by playing multifaceted roles in human pathology. UBE2T insufficiency in tumors is expected to enhance the tumor growth inhibitory effect of IR/chemical components.

Notably, a considerable part of the current data on UBE2T in cancer are preclinical data from major databases and clinical tissue samples. Limited experimental studies suggested numerous potential roles for UBE2T, which remain to be elucidated. Clinical data have highlighted the role of the

UPS. Unexpectedly, it was found that there were 16 clinical trials on ubiquitin enzymes, which involved the inhibitor of ubiquitin-activating enzyme MLN7243 (ClinicalTrials.gov Identifier NCT02045095) and the ubiquitin-binding protein p62 (ClinicalTrials.gov Identifier NCT03925753). Novel E2s therapies for cancer should be investigated in clinical trials, and the identification of novel E2s as potential cancer drug targets, as well as the development of new specific chemical probes of UBE2T should be explored in future studies.

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Availability of data and materials

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Authors' contributions

NM and XL proposed the concept and design. NM and ZL acquired the data. JY and RX analyzed and interpreted the data (e.g., statistical analysis, computational analysis). NM and XL wrote the manuscript. LH supported administrative, technical, or material support (i.e., reporting or organizing data, constructing databases). XL supervised the study. All authors read and approved the final manuscript.

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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