Abstract. Long non-coding RNA metastasis-associated urothelial carcinoma associated 1 (UCA1) plays a pivotal role in various human diseases. Its gene expression is regulated by several factors, including transcription factors, chromatin remodeling and epigenetic modification. UCA1 is involved in the regulation of the PI3K/AKT, Wnt/β-catenin, MAPK, NF-κB and JAK/STAT signaling pathways, affecting a series of cellular biological functions, such as cell proliferation, apoptosis, migration, invasion and tumor drug resistance. Furthermore, UCA1 is used as a novel potential biomarker for disease diagnosis and prognosis, as well as a target for clinical gene therapy. The present review systematically summarizes and elucidates the mechanisms of upstream transcriptional regulation of UCA1, the regulatory role of UCA1 in multiple signaling pathways in the occurrence and development of several diseases, and its potential applications in clinical treatment.

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1. Introduction

The whole genome sequencing of eukaryotes has confirmed that ~93% of the DNA in the human genome can be transcribed into RNA (1). Notably, only 2% of mRNAs encode proteins and the remaining 98% are non-coding RNAs (1). Among the different types of non-coding transcripts, long non-coding RNAs (lncRNAs) have attracted great interest. lncRNAs do not contain any extended open reading frames (ORFs) and are >200 nucleotides in length (2). They have been identified as indispensable regulators in a variety of physiological and pathological processes, including epigenetic inheritance, cell cycle, post-transcriptional regulation, translation and chromatin modification (3). In addition, lncRNAs participate in the regulation of cell proliferation, differentiation, apoptosis, invasion, migration and tumor drug resistance (4). lncRNAs play important roles in the occurrence and development of various diseases, particularly malignant tumors (5,6). Previous studies
have demonstrated that IncRNAs function as either oncogenes or tumor suppressors, and are involved in the regulation of tumorigenesis and progression of various tumors (5,6).

Urothelial carcinoma associated 1 (UCA1) was initially identified in bladder cancer by high-throughput RNA sequencing, and is associated with the progression of bladder cancer (7). UCA1 has been demonstrated to be highly expressed in several human tumors, such as gastric cancer (GC) and cholangiocarcinoma, which is closely associated with tumor-node-metastasis (TNM) stage, depth of invasion, vascular invasion, lymph node metastasis, overall survival (OS) and relapse-free survival (RFS) (8-10). In addition, UCA1 is involved in regulating cell proliferation, apoptosis, migration, invasion and drug resistance (11). Several studies have reported that UCA1 participates in the regulation of multiple cellular signaling pathways at transcriptional, post-transcriptional and epigenetic levels (Fig. 1) (12,13). The present review discusses the molecular mechanisms and clinical potential of UCA1 in the regulation of signaling pathways and transcription in human diseases.

2. Overview of UCA1

In 2006, UCA1 was demonstrated to be highly specific and sensitive in the diagnosis of bladder cancer, particularly in patients with superficial G2-G3 (7). Furthermore, UCA1 is considered to be the most specific gene for bladder transitional cell carcinoma (TCC) (7). UCA1 exhibits a notable differential diagnostic function in several urinary tract diseases without TCC (7).

The UCA1 gene contains three exons and two introns, and is located on the positive strand of human chromosome 19p13.12 (7). Notably, the UCA1 sequence contains multiple termination sequences, without any conservative long ORFs (14,15). Initially, the full-length cDNA of UCA1 was identified as 1.4 kb (7). However, recent studies have demonstrated that UCA1 has three different isoforms (1.4, 2.2 and 2.7 kb) (16,17). Currently, the 1.4 kb isoform has attracted great interest (14). In addition to its different isoforms (1.4, 2.2 and 2.7 kb) (16,17). Currently, the 1.4 kb isoform has attracted great interest (14). In addition to its associations with non-cancerous diseases, including systemic lupus erythematosus (SLE), diabetic nephropathy (DN) and Parkinson's disease (PD) (18-20), UCA1 is also involved in the progression of different types of cancer, including bladder cancer, colorectal cancer (CRC) and hepatocellular carcinoma (HCC) (21-23). Furthermore, overexpression of UCA1 is closely associated with clinicopathological characteristics, including poor prognostic factors, such as TNM stage, vascular invasion and lymph node metastasis (8,24,25).

Increasing evidence suggest that UCA1 functions as an oncogene, which plays an important role in the tumorigenesis and development of different types of cancer, including papillary thyroid carcinoma (26), pancreatic cancer (PC) (27) and lung adenocarcinoma (28). UCA1 expression is regulated by several factors, such as transcription factors, chromatin remodeling and epigenetic modification (Fig. 2) (29-31). Furthermore, UCA1 contains microRNA (miRNA/miR) binding sites that regulate the expression of target genes through the sponging of miRNAs (Table 1) (8,11,24).

3. Upstream regulation of UCA1 expression

As presented in Table II, upstream regulators of UCA1 include transcription factors, chromatin remodeling complexes, epigenetic changes and binding proteins (29,31-33). The core promoter of the UCA1 gene can bind with several transcription factors, such as CCAAT/enhancer binding protein α (C/EBPα) (32), C/EBPβ (34), E2F transformation-specific transcription factor 2 (35), specificity protein 1 (36), MYB (37) and E1A binding protein p300 (EP300) (38). These transcription factors interact with the promoter to upregulate UCA1 expression, and SN1 can upregulate UCA1 expression through transcriptional activator MYB and promote 5-fluorouracil (5-FU)-induced apoptosis of HCC cells (37). Similarly, macrophage-derived chemokine CCL18 upregulates UCA1 expression through transcription factor EP300 in osteosarcoma (38). In addition, the combination of hyaluronic acid and CD44 stimulates the signal transduction of PI3K and AKT, resulting in phosphorylation of C/EBPα, which binds to the promoter of the UCA1 gene to induce transcriptional activation of UCA1, resulting in migration and invasion of HSC-3 cells in human head and neck squamous cell cancer (39).

AT-rich interaction domain 1A (ARID1A) is one of the major members of SWItch/Sucrose non-fermentable chromatin remodeling complexes, which is often found to be loss-of-function mutations in different types of cancer, such as non-small cell lung cancer (NSCLC) (40), breast cancer (BC) (41) and pancreatic ductal adenocarcinoma (PDAC) (42). ARID1A inhibits UCA1 expression by regulating chromatin access of transcription factor C/EBPα (30). It has been confirmed that the CPERα/TBX3 complex directly inhibits UCA1 transcription and promotes cancer cell senescence by regulating chromatin structure (43). Furthermore, the AT-rich sequence binding protein 1 suppresses UCA1 expression by closing the chromatin structure of the UCA1 promoter region in BC (29). Notably, epigenetic modification participates in regulating UCA1 expression. S-adenosylmethionine inhibits UCA1 transcription by increasing DNA methyltransferase or decreasing DNA demethylase (31). The stability of UCA1 is notably improved due to the formation of functional ribonucleoprotein complexes between hnRNPI and UCA1 (44). Conversely, UCA1 interacts with insulin-like growth factor 2 mRNA-binding protein 1 and is downregulated due to its reduced stability (45).

Bone morphogenetic protein 9 (BMP9), a member of the BMP family, belongs to the transforming growth factor-β (TGF-β) superfamily. TGF-β is a well-known inducer of epithelial-to-mesenchymal transition (EMT) (33,46). BMP9 or TGF-β can upregulate UCA1 expression to promote invasion and metastasis of cancer cells, including BC and GC cells (33,46). In addition, TGF-β inactivates the Hippo pathway by regulating the complex of transcriptional co-activator with PDZ binding motif/yes-associated protein (YAP) and transcriptional enhancer TEA domain (TEAD), which subsequently upregulates UCA1 expression and promotes the migration and invasion of BC cells (47). Some clinical trials have reported that metformin exhibits anticancer potential and can be used as an adjuvant for cancer prevention or an AMPK activator for cancer treatment (48,49). Metformin can decrease endometrial hyperplasia via the UCA1/miR-144/TGF-β1/AKT signaling pathway (50). In addition, metformin suppresses the migratory ability of trophoblast cells by regulating the signal transduction pathway of UCA1/miR-204/MMP-9 (51). Notably, IncRNA
GAS8-AS1 inhibits migration and invasion of osteosarcoma cells by downregulating UCA1 expression (52). Furthermore, up-frameshift protein 1, palmitic acid, cancer-associated fibroblasts and hepatitis B virus X protein can also regulate UCA1 expression and affect the proliferation of cancer cells, including HCC, GC and CRC cells (53-56).
4. Signaling pathways regulated by UCA1

**PI3K/AKT signaling pathway.** The PI3K/AKT signaling pathway is involved in important physiological activities, including cell proliferation, invasion and metastasis, and is closely associated with cancer (16,35), DN (19), SLE (18), myocardial fibrosis (57) and PD (20). Recently, the regulatory mechanisms of IncRNAs in the PI3K/AKT pathway and their effects on diseases have attracted great interest (58-60).

It has been reported that UCA1 can promote malignant phenotypes of PDAC by activating the AKT signaling pathway (16). This process includes the promotion of cell proliferation, invasion, EMT, inhibition of apoptosis and enhancement of 5-FU resistance (16). In bladder cancer (35) and SLE (18), UCA1 is highly expressed and promotes cell proliferation by mediating the PI3K/AKT signaling pathway. UCA1 knockdown inhibits proliferation and migration of glioma cells through miR-193a-mediated downregulation of cyclin-dependent kinase 6 (CDK6), and inactivates the PI3K/AKT pathway by decreasing the expression levels of phosphorylated PI3K and AKT proteins (61). In acute myeloid leukemia (AML), UCA1 can be used as an endogenous sponge to compete with miR-126, which in turn suppresses activation of the PI3K/AKT signaling pathway by inhibiting the expression of RAS-related C3 botulinum toxin substrate 1 (RAC1) (62).

Recent studies have demonstrated that enhancer of zeste homolog 2 (EZH2) can promote cell cycle progression by affecting the PI3K/AKT pathway or the expression levels of cyclins (63-65). EZH2 can also be post-translationally modified by phosphorylation of AKT (66). UCA1 directly interacts with EZH2 in GC and enhances EZH2 expression, which in turn activates the AKT/GSK3β/cyclin D1 (CCND1) axis to increase cell proliferation (36). However, UCA1 suppresses p27Kip1/CDK2 signal transduction and promotes cell proliferation and tumorigenesis by recruiting EZH2 (56). In PC (67) and BC (44), UCA1 promotes the proliferation of cancer cells by inhibiting p27 expression. UCA1 can also inhibit the level of cAMP response element-binding (CREB) protein, and regulate the cell cycle of bladder cancer cells via the PI3K-dependent pathway (68). A study has reported that UCA1 impairs the binding of brahma-related gene 1 (BRG1) to the p21 promoter and the chromatin remodeling activity of BRG1 to accelerate the proliferation of bladder cancer cells (69). Cisplatin and gemcitabine resistance in bladder cancer cells is mediated by UCA1-CREB-miR-196a-5p paradigm (70).

UCA1 can inhibit PTEN and promote p-AKT expression to induce the proliferation of osteosarcoma cells (71). Notably, p-PTEN is a phosphatase, and PTEN is a negative regulator of PI3K. Dephosphorylation of PTEN can decrease activation of AKT and block its downstream signal transduction (71). In vivo studies have demonstrated that UCA1 functions via the PI3K/AKT signaling pathway (19,48,72). In the Sprague-Dawley rat model of DN, inhibition of UCA1 decreases renal pathological damage, improved renal function and decreased inflammation in DN rats by suppressing the PI3K/AKT signaling pathway (19). In addition, downregulation of UCA1 expression can ameliorate the damage of dopaminergic neurons by inhibiting the PI3K/AKT signaling pathway to decrease oxidative stress and inflammation in PD (20). Thus, UCA1 participates in the regulation of the PI3K/AKT signaling pathway by affecting EZH2, CDK6, RAC1 and PTEN, which promote cell proliferation, invasion, metastasis and drug resistance, and inhibit apoptosis in diseases (36,61,62,71).

Several studies have demonstrated that mammalian target of rapamycin (mTOR) is the core component downstream of the PI3K/AKT pathway (73-75). IncRNAs participate in cell proliferation, apoptosis, invasion and energy metabolism by regulating the mTOR signaling pathway (73). It has been reported that upregulation of UCA1 expression confers tamoxifen resistance in BC cells, partly by activating the mTOR signaling pathway (74). In addition, UCA1 interacts with mTOR to inhibit p27 and miR-143 expression; however, the expression levels of Kirsten rat sarcoma viral oncogene homolog and CCND1 significantly increase, which results in the proliferation, EMT and metastasis of CRC cells (55). Notably, it has been demonstrated that UCA1 increases CREB1 expression by acting as a competitive endogenous RNA (ceRNA) of miR-582, thus promoting EMT via the CREB1-mediated mTOR pathway, which results in osteosarcoma metastasis (72). In cardiomyocytes, UCA1 decreases miR-122 and miR-143 expression, and regulates their downstream mTOR signaling pathway to inhibit oxygen-glucose deprivation (OGD) or hypoxia/reoxygenation (H/R)-induced apoptosis and injury (76,77). UCA1 knockdown can also regulate signal
transduction of mTOR via miR-200c and miR-195, and inhibit the proliferation and invasion of hemangioma cells and microvascular endothelial cells (78). Furthermore, bladder cancer cells preferentially metabolize glucose by aerobic glycolysis, known as the Warburg effect (79). UCA1 promotes glycolysis and upregulates hexokinase 2 expression via the mTOR-STAT3/miR-143 pathway in bladder cancer cells (79). Taken together, these findings suggest that UCA1 can directly or indirectly activate the mTOR signaling pathway by serving as a regulator of miR-582 and miR-195, and affect the expression of proteins, such as CREB1 and CCND1, to promote cell proliferation, drug resistance and inhibit apoptosis.

Wnt/β-catenin signaling pathway. The Wnt/β-catenin signaling pathway is a developmental signal-transduction pathway. Activation of this pathway can result in the proliferation, invasion, metastasis and differentiation of cancer cells, ultimately inducing tumorigenesis (80). The canonical Wnt pathway activates gene transcription through β-catenin accumulation in the cytoplasm and translocation to the nucleus (80).

Several studies have demonstrated that UCA1 promotes cell proliferation and EMT in osteosarcoma (38), glioma (81) and papillary thyroid carcinoma (82) by activating the Wnt/β-catenin signaling pathway. In addition, the Wnt/β-catenin signaling pathway is closely associated with chemoresistance (12,81,83). UCA1 induces chemoresistance to cisplatin and temozolomide in glioma and decreases the sensitivity of BC cells to tamoxifen via the Wnt/β-catenin signaling pathway (81,83). Notably, UCA1 can also increase cisplatin resistance of bladder cancer cells by activating Wnt signaling in a Wnt6-dependent manner (12).

Previous studies have reported that UCA1 regulates the Wnt/β-catenin signaling pathway via miR-200c and miR-185-5p, and affects the proliferation and EMT in hemangioma (78) and melanoma cells (84), respectively. In osteosarcoma, UCA1 knockdown inhibits miR-30a expression and induces the silencing of C-X-C chemokine receptor type 4 (CXCR4), thus decreasing cell proliferation and metastasis (85). In addition, downregulation of miR-30a expression decreases the levels of Wnt3a, Wnt5a and β-catenin proteins, which in turn inhibits the Wnt/β-catenin signaling pathway (85). UCA1 regulates matrix metalloproteinase-9 expression, which is a downstream gene of Wnt/β-catenin (86), via miR-204 and increases trophoblast cells migration (51). Notably, enhanced UCA1 expression upregulates the expression of highly upregulated in liver cancer (HULC) by inhibiting HULC promoter
methylation, and upregulates β-catenin by promoting β-catenin promoter-enhancer chromatin DNA looping formation, which in turn promotes the malignant transformation of hepatocyte-like cells (87). Collectively, these findings suggest that UCA1 is involved in tumorigenesis via the Wnt/β-catenin signaling pathway by regulating miRNAs, such as miR-204 and miR-301a, and lncRNAs, such as HULC.

**MAPK signaling pathway.** The MAPK pathway participates in the regulation of cell proliferation, invasion, metastasis, apoptosis and differentiation, and is closely associated with the occurrence of various diseases such as PDAC (16), melanocytes (13) and acute myocardial infarction (76). Its functional pattern predominantly involves phosphorylating nuclear transcription factors, cytoskeletal proteins and enzymes (88). The MAPK signaling pathway includes four pathways: The ERK, P38, SAPK/JNK and ERK5/BMK1 pathways. As an important regulatory gene, UCA1 can participate in the regulation of the MAPK signaling pathway (88).

A previous study demonstrated that UCA1 promotes the proliferation, migration and invasion of PDAC cells, and decreases apoptosis and increases 5-FU resistance by activating the ERK signaling pathway (16). In addition, UCA1 negatively regulates the CREB/MITF/melanogenesis axis by suppressing the ERK and JNK signaling pathways in melanocytes, thus inhibiting the expression of melanogenesis-related genes in melanocytes (13).

**UCA1 knockdown activates the AMPK signaling pathway by upregulating a series of miRNAs (61,76,78,89). In addition, UCA1 knockdown regulates AMPK signal transduction via miR-200c and suppresses the proliferation, migration and invasion of hemangioma cells (78). Furthermore, in acute myocardial infarction, UCA1 decreases OGD aroused cell apoptosis and injury by downregulating miR-122 expression and suppressing its downstream JNK/p38 MAPK signaling pathway (76). Knockdown of UCA1 inactivates the MAPK signaling pathway by downregulating CDK6 expression mediated by miR-193a, which decreases the proliferation and promotes the apoptosis of glioma cells (61). In cholangiocarcinoma, UCA1 upregulates chloride intracellular channel 1 (CLIC1) expression by inhibiting miR-122 expression and activating the ERK/MAPK signaling pathway to promote the metastasis of malignant cells (89). In addition,
UCA1 promotes the viability and EMT of TPC-1 cells by competing with miR-15a and activating the Hippo and JNK signaling pathways in human thyroid cancer (90). Taken together, these findings suggest that UCA1 activates the MAPK signaling pathways by regulating CLIC1 and CDK6 expression, inducing cell proliferation, migration and drug resistance, and inhibiting apoptosis.

Nuclear factor-kappa B (NF-κB) signaling pathway. NF-κB is an extensively expressed multi effect transcription factor. It is a heterotrimer composed of p50, p65 and IkB (91). The NF-κB signaling pathway can be regulated by UCA1 (85,94). In osteosarcoma, inhibition of UCA1 downregulates miR-301a expression and decreases CXCR4 expression, thus suppressing cell proliferation and metastasis (85). Furthermore, miR-301a positively regulates the phosphorylation of IkB and p65 proteins and activates the NF-κB signaling pathway (85). UCA1 knockdown exerts an anticancer effect on GC cells by rescuing miR-182 expression to activate the NF-κB and PI3K/AKT/ULK1 signaling pathways (94). In HCC, the synergism between UCA1 and inflammatory cytokine IL6 promotes SVV39H1 expression. Notably, methyltransferase-like 3, which binds to SVV39H1 mRNA, is also upregulated. Excessive SVV39H1 expression can increase the expression of tri-methylation of histone 3 lysine 9 trimethylation (H3K9me3) (92). Notably, under inflammatory conditions, H3K9me3 induces phosphorylation of NF-κB, resulting in the malignant transformation of hepatocyte-like stem cells (92). This synergism between UCA1 and IL6 can aggravate the malignant transformation of hepatocyte-like stem cells via the NF-κB signaling pathway (92). In addition, UCA1 regulates the inflammatory responses in epilepsy by regulating the miR-203-mediated myocyte enhancer factor 2C/NF-κB signaling pathway (93).

JAK/STAT signaling pathway. The JAK/STAT signaling pathway is a common pathway for various cytokines and growth factors to transmit signals within cells (95). It mediates several biological responses, including cell proliferation, differentiation, migration, apoptosis and immune regulation (95). Previous studies have demonstrated that IncRNAs play a regulatory role in the JAK/STAT signaling pathway (96,97).

UCA1 promotes the development of cancer cells by activating the JAK/STAT signaling pathway, including multiple myeloma (MM) (98), AML (62) and pre-eclampsia (99). UCA1 activates the JAK2/STAT3 pathway via the miR-331-3p/IL6R axis in MM, and regulates cell proliferation and apoptosis (98). In AML, UCA1 competes with miR-126 as an endogenous sponge. miR-126 suppresses activation of the JAK/STAT signaling pathway by decreasing RAC1 expression, thus inhibiting cell proliferation, migration and invasion (62). Notably, UCA1 exerts opposite effects on the regulation of the JAK/STAT signaling pathway in some non-cancerous cells (99,100). A study has reported that UCA1 expression is upregulated in trophoblast cells of pre-eclampsia pregnancy, and it can inhibit the invasion and proliferation of trophoblast cells by downregulating JAK2 expression (99). In addition, overexpression of UCA1 inhibits activation of the JAK/STAT signaling pathway, which in turn inhibits activation of astrocytes in temporal lobe epilepsy (100). It is suggested that UCA1 promotes IL6R and RAC1 expression to stimulate the JAK/STAT signaling pathway, which increases cell proliferation and invasion in several tumors, while UCA1 exerts opposing effects in some non-cancerous cells (62,98).

TGF-β/SMAD signaling pathway. The TGF-β superfamily is composed of secretory polypeptide molecule TGF-β, activins, inhibins and BMPs, and participates in various biological activities, such as cell invasion and migration (101). The TGF-β superfamily is involved in cartilage and bone formation, inflammation, regulation of endocrine functions, and formation and development of tumors (101). SMADS are important molecules for intracellular TGF-β signal transduction (101).

Previous studies have demonstrated that EMT induced by TGF-β1 is an important reason for the invasion and migration of cancer cells (46,102). The UCA1/miR-124 axis regulates TGF-β1-induced EMT and invasion of tongue cancer cells (46). In addition, UCA1 promotes the proliferation of MM cells by targeting TGF-β1 (102). SMAD4 and SMAD5, two members of SMADs, are important elements involved in the TGF-β pathway (103). It has been confirmed that UCA1 regulates the TGF-β signaling pathway via the miR-145-5p/SMAD5 and miR-124-3p/SMAD4 axes and promotes chondrogenic differentiation of human bone marrow mesenchymal stem cells (103). Notably, UCA1 competitively binds with miR-1 and miR-203a to upregulate the expression of Slug, a downstream effector of TGF-β, and subsequently regulates EMT in glioma cells (104) and BC cells (33).

Other signaling pathways. UCA1 also participates in the regulation of other signaling pathways, including the Notch, Hippo and p53 signaling pathways. In human glioma, UCA1 knockdown inhibits the proliferation and migration of cells through miR-193a-mediated downregulation of CDK6, and blocks the Notch signaling pathway by decreasing the expression levels of phosphorylated Notch1, Notch2 and Notch3 proteins (61). In renal cell carcinoma, UCA1 upregulates Delta-like 4 (DLL4) expression by acting as a ceRNA of miR-182-5p, and induces the EMT process via the DLL4-mediated Notch pathway, which in turn promotes cell proliferation and migration, and inhibits apoptosis (11). Furthermore, UCA1 can form a ribonucleoprotein complex with Mps one binder kinase activator-1, large tumor suppressor 1 and YAP, which decreases the phosphorylation of YAP (105). Dephosphorylated YAP translocates into the nucleus and combines with TEAD protein, inhibiting the key proteins of the Hippo signaling pathway and promoting proliferation, migration and invasion of PC cells (105). Conversely, UCA1 activates the Hippo signaling pathway by downregulating miR-15a expression and increasing cell viability and EMT in human thyroid cancer (90). In cardiomyocytes, UCA1 inhibits H/R-induced apoptosis by decreasing miR-143 expression and suppressing its downstream p53 signaling pathway (77).
Furthermore, \textit{UCA1} can regulate the p53 signaling pathway via miR-143 and MDM2; the Notch signaling pathway via CDK6 and DLL4 or regulate YAP and other signaling pathways, which promotes cell proliferation, EMT, migration and invasion, and inhibits cell apoptosis (11,61,105).

5. Clinical applications of \textit{UCA1}

Several studies have reported that \textit{UCA1} has potential clinical applications (106-109). Currently, there are three common clinical applications of \textit{UCA1}: Acts as a diagnostic biomarker (110,111), prognostic biomarker (112,113) and therapeutic target (87). The use of \textit{UCA1} as a therapeutic target for reversing drug resistance has been extensively investigated (22,83).

\textit{UCA1} as a diagnostic biomarker. Early diagnosis is beneficial to the prognosis of diseases. Poor prognosis is mainly attributed to the metastasis of cancer cells, drug resistance and tumor recurrence, which are closely associated with late diagnosis (114). Thus, it is important to improve the early diagnostic rate of patients. Recently, several studies have demonstrated that lncRNAs have great potential to be used as biomarkers for disease diagnosis, including \textit{UCA1} (115-117).

\textit{UCA1} is highly specific and easy to be detected in serum, plasma and urine. Liquid biopsy is becoming a novel method for disease detection (72,118). In laryngeal squamous cell carcinoma (110), NSCLC (111), osteosarcoma (72) and HCC (118), serum \textit{UCA1} levels of patients are higher than that of the healthy control population. Notably, \textit{UCA1} secreted by exosomes into the serum of patients can promote the development of prostate cancer (PCa) (114). In addition, serum \textit{UCA1} expression is significantly higher in patients with HCC than those with benign liver disease, which helps to distinguish the two groups (119). In non-cancerous diseases, \textit{UCA1} can limit the inflammatory responses in epilepsy (93), and \textit{UCA1} expression is higher in patients with non-refractory epilepsy than those with refractory epilepsy (120). Notably, combined measurement of \textit{UCA1} levels in serum and plasma can increase the sensitivity and specificity for the diagnosis of some malignancies (119). In addition, \textit{UCA1} expression is higher in the urine of patients with PCa compared with healthy controls (114). Taken together, these findings suggest that \textit{UCA1} has the potential to be used as a biomarker for diagnosis and screening of diseases.

Increasing evidence suggests that the combination of \textit{UCA1} and other lncRNAs may exhibit better diagnostic performance. As a predictor of CRC, the combination of \textit{UCA1}, HOXA transcript at the distal tip and plasmacytoma variant translocation 1 has better diagnostic performance compared with \textit{UCA1} alone, and can be used to screen patients with advanced CRC (115). Another study demonstrated that the combination of \textit{UCA1}, gastric cancer high expressed transcript 1, taurine upregulated gene 1 and p21-associated ncRNA DNA damage activated can improve the diagnostic ability and significance of GC (116). Furthermore, when comparing patients with bladder cancer with healthy controls, the combination of \textit{UCA1}, \textit{circFARSA} and \textit{circSHKBP1} has better diagnostic performance compared with \textit{UCA1} alone (117).

Early differential diagnosis of cancer and precancerous lesions is an important method to decrease the risk of recurrence and improve prognosis (121). A study has demonstrated that the combination of \textit{UCA1}, HOX transcript antisense intergenic RNA, hydatidiform mole associated and imprinted metastasis-associated lung adenocarcinoma transcript 1 can distinguish between patients with bladder cancer and patients with urocytis, with a sensitivity and specificity of 95.7% and 94.3%, respectively (121). Collectively, these findings suggest that it is feasible to use \textit{UCA1} as a diagnostic biomarker. However, further studies are required to verify the clinical applications of \textit{UCA1}.

\textit{UCA1} as a prognostic biomarker. With the rapid growth of disease morbidity and mortality, overall prognosis will become the principal determinant of global public health (122). Surgery is one of the routine therapies for cancer; however, its complications and recurrence affect the prognosis of patients (122). Recent studies have demonstrated that \textit{UCA1} is closely associated with clinicopathological characteristics, including vascular invasion, lymph node metastasis and TNM stage, and can be used as a prognostic biomarker of diseases (24,25,123). However, there is no doubt whether further investigation on the role of \textit{UCA1} as a prognostic marker will contribute to the treatment of cancer.

\textit{UCA1} is closely associated with tumor size, histological differentiation, stage of lymph node metastasis, depth of invasion, vascular invasion, OS, RFS and prognostic biomarkers (Table III). It has been reported that in some cancers, such as CRC (24), HCC (23), GC (8), adrenal cortical carcinoma (124) and esophageal cancer (125), survival probability of patients is associated with \textit{UCA1} expression. The Cancer Genome Atlas (https://cancergenome.nih.gov) data for lung adenocarcinoma revealed that the survival probability of patients with NSCLC, with high \textit{UCA1} expression, is unfavorable than those with low \textit{UCA1} expression (Fig. 3). Previous studies have suggested that overexpression of \textit{UCA1} in CRC indicates a large tumor, advanced TNM stage, deeply infiltrated lymph node, positive lymph node metastasis and poor OS (22,24). Other studies have reported that \textit{UCA1} expression in GC tissues and cells is positively associated with TNM stage, lymph node infiltration, lymph node metastasis and OS (8,9). Notably, \textit{UCA1} expression

Figure 3. Association between \textit{UCA1} expression and survival time of patients with non-small cell lung cancer, based on The Cancer Genome Atlas data. \textit{UCA1}, urothelial carcinoma associated 1.
in the plasma of patients with GC significantly decreases following surgery (126). Thus, UCA1 can be used as an index of postoperative prognosis. In addition, UCA1 expression is significantly upregulated in SLE, which is positively associated with SLE disease activity index (18). Collectively, these findings suggest that UCA1 can be used as an independent prognostic factor to monitor the occurrence and development of diseases.

### UCA1 as a therapeutic target.

With a better understanding of the pathogenesis of diseases, several molecules and signal transduction pathways are likely to be suitable for targeted therapy (122). Given that UCA1 exerts carcinogenic effects associated with several molecules and cascade reactions, it has been confirmed as an ideal therapeutic target (22,70,81). Targeted knockout of UCA1 can be used to improve radiosensitivity, inhibit cancer metastasis, prevent cancer growth in vivo, promote apoptosis and reverse drug resistance of cancer cells (21,37,72). Clinical applications of UCA1 as a therapeutic target for reversing drug resistance has attracted great interest (21,127). UCA1 is also known as a cancer upregulated drug resistant gene (87). Previous studies have reported that downregulating UCA1 expression can reverse drug resistance in cancers, and some drugs for chemotherapy exert an anticancer role by mediating UCA1 (Table IV), including cisplatin (70,81), tamoxifen (83), paclitaxel (128), 5-FU (22), Adriamycin (129), temozolomide (81), cetuximab (130), trastuzumab (131), imatinib (132), docetaxel (133) and gemcitabine (70). These drugs provide the possibility of chemotherapy-related clinical applications, and studies have demonstrated that UCA1 knockdown can reverse multidrug resistance in retinoblastoma (127) and bladder cancer (21). In addition, the combination of UCA1-targeted therapy and programmed cell death 1 (PD-1) immune checkpoint blockade has a better synergistic effect following CRISPR-Cas9-mediated UCA1 knockdown (134). However, further studies are required to confirm the therapeutic value of UCA1 for diseases.

| Disease          | Upregulation/ downregulation | Clinical correlation (Refs.) |
|------------------|-------------------------------|-----------------------------|
| Renal cancer     | Upregulation                  | Degree of differentiation, TNM stage and lymph node metastasis (11,107) |
| SLE              | Upregulation                  | SLEDAI (18)                 |
| CRC              | Upregulation                  | Tumor size, tumor stage, lymph node infiltration, lymph node metastasis and OS (22,24) |
| HCC              | Upregulation                  | Tumor stage, TNM stage, Microvascular infiltration and OS (23) |
| GC               | Upregulation                  | TNM stage, tumor stage, lymph node infiltration, lymph node metastasis and OS (8,9) |
| Tongue cancer    | Upregulation                  | TNM staging, lymph node metastasis, lymph node infiltration and OS (46) |
| Osteosarcoma     | Upregulation                  | Tumor stage, tumor size and OS (72) |
| OSCC             | Upregulation                  | TNM stage, lymph node metastasis and OS (108) |
| PTC              | Upregulation                  | Tumor size, tumor stage, lymph node metastasis and OS (26,82) |
| MM               | Upregulation                  | OS (98,102)                 |
| PC               | Upregulation                  | Tumor stage and OS (27,105) |
| LSCC             | Upregulation                  | Lymph node metastasis and OS (110) |
| NSCLC            | Upregulation                  | TNM stage, tumor size and OS (111) |
| PCA              | Upregulation                  | Edmondson-Steiner grade, TNM stage and lymph node metastasis (112,114) |
| Epilepsy         | Upregulation                  | Classification of epilepsy (120) |
| Glioma           | Upregulation                  | TNM stage, tumor size, lymph node metastasis and OS (109) |
| Cholangiocarcinoma | Upregulation              | TNM stage, tumor stage, lymph node infiltration, lymph node metastasis, RFS and OS (10) |
| OC               | Upregulation                  | TNM stage, lymph node metastasis and OS (128) |
| NPC              | Upregulation                  | Tumor stage, lymph node metastasis and OS (113) |
| ACC              | Upregulation                  | TNM stage and lymph node metastasis (124) |
| LUAD             | Upregulation                  | TNM stage, lymph node metastasis, RFS and OS (28) |
| Melanoma         | Upregulation                  | Tumor stage and lymph node metastasis (106) |
| EC               | Upregulation                  | Degree of differentiation, TNM stage, lymph node metastasis and OS (125) |

UCA1, urothelial carcinoma associated 1; ACC, adrenal cortical carcinoma; CRC, colorectal cancer; EC, esophageal cancer; GC, gastric cancer; HCC, hepatocellular carcinoma; LSCC, laryngeal squamous cell carcinoma; LUAD, lung adenocarcinoma; MM, multiple myeloma; NPC, nasopharyngeal carcinoma; NSCLC, non-small cell lung cancer; OC, ovarian cancer; OS, overall survival; OSCC, oral squamous cell carcinoma; PC, pancreatic cancer; PCa, prostate cancer; PTC, papillary thyroid carcinoma; RFS, relapse-free survival; SLEDAI, systemic lupus erythematosus disease activity index; TNM, tumor-node-metastasis.
6. Conclusions and perspective

*UCA1* can regulate a series of signaling pathways by acting as a ceRNA of several miRNAs, and affect epigenetic, transcriptional and post-transcriptional regulation. It plays a regulatory role in several biological functions, including cell proliferation, apoptosis, migration, invasion and drug resistance. In addition, *UCA1* can be used as a potential biomarker for disease diagnosis and treatment. For some diseases, the combination of *UCA1* and other lncRNAs has demonstrated better diagnostic and screening performance. Strategies, such as CRISPR-Cas9 system or siRNA-mediated knockout, and the combination of *UCA1*-targeted therapy and PD-1 immune checkpoint blockade may be used to transform *UCA1* from basic research into clinical practice.

Recently, although great progress has been made in understanding the biology of *UCA1*, even in its therapeutic applications, several unknown areas in *UCA1* research remain. First, the lack of effective methods to investigate RNA secondary and tertiary structures and nuclear ultrastructure of *UCA1* impedes the study on the composition of its isoforms and tissue-specific regulation (4). Secondly, several studies have confirmed that lncRNAs can promote the drug resistance of cancer cells by regulating their stemness feature (27,135,136,104); however, the mechanism by which *UCA1* affects the drug resistance stem cells remains unclear. Some lncRNAs may play important regulatory roles in cellular biological processes via multiple pathways (5,6). However, whether binding miRNAs affects the expression or function of *UCA1* remains unclear. In conclusion, *UCA1*, as a well-known lncRNA with great clinical potential, requires increasing comprehension and in-depth study.

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Availability of data and materials

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Authors' contributions

ZL and YW contributed to drafting the review and figures. SY, FW, and JL revised the manuscript for important intellectual content. JZ and LZ conceived the project and revised the manuscript for important intellectual content. ZL and YW confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.
Long non-coding RNAs (lncRNAs) play a critical role in the regulation of gene expression and the development of various diseases. Among them, lncRNA UCA1 is a well-studied lncRNA that has been implicated in the progression of various cancer types. UCA1 is located on chromosome 3 and is a non-coding RNA that is transcribed from a complex lncRNA gene cluster.

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