Crosstalk between the IncRNA UCA1 and microRNAs in cancer

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Long non-coding RNAs (lncRNAs) are a major subset of highly conserved non-coding RNAs (ncRNAs) that consist of at least 200 nucleotides and have limited protein-coding potential. Cumulative data have shown that lncRNAs are deregulated in many types of cancer and may control pathophysiological processes of cancer at various levels, including transcription, post-transcription and translation. Recently, lncRNAs have been demonstrated to interact with microRNAs (miRNAs), another major subset of ncRNAs, which regulate physiological and pathological processes by inhibiting target mRNA translation or promoting mRNA degradation. The IncRNA urothelial carcinoma-associated 1 (UCA1) has recently gained much attention as it is overexpressed in many types of cancer and is involved in carcinogenesis. Here, we review the crosstalk between UCA1 and miRNAs during the pathogenesis of cancer, with a focus on cancer-cell proliferation, invasion, drug resistance, and metabolism.

Keywords: cancer; drug resistance; invasion; metabolism; micro RNA; proliferation; UCA1

Long non-coding RNAs (lncRNAs) are a major component of the highly conserved non-coding RNAs (ncRNAs) that consist of > 200 nucleotides with limited protein-coding potential [1]. LncRNAs exert regulatory functions at different levels including transcription, post-transcription, and translation, or can...
directly modulate protein activity and participate in physiological and pathological processes including embryonic development, cell growth, and carcinogenesis [2]. In the last decade, many studies have shown that lncRNAs are aberrantly regulated in various malignant tumors and play an important role on carcinogenesis [3–7].

Urothelial cancer associated 1 (UCA1) is a lncRNA that has gained attention in recent years due to its aberrant expression in a broad range of cancer tissues and cells. The UCA1 gene is located in chromosome 19p13.12 with two transcripts of 1.4 and 2.2 kb in length [8]. UCA1 is upregulated at 5–10 weeks of gestation; after 28 weeks of gestation, it is highly expressed in bladder, heart, and uterus compared to cervix, kidney, liver, lung, intestine, skin, spleen, and stomach; after birth, it is turned off in most tissues except heart and spleen [9,10]. It was first identified in bladder cancer and reactivated in various malignant tumors [11–19]. It plays an important role in tumor growth, apoptosis, invasion, anti-cancer drug resistance, and metabolism. Thus, it is of great clinical significance to understand the functional mechanism of UCA1 in cancer.

The role of lncRNAs in regulating genes by diverse mechanisms has been largely validated. Recently, crosstalk of lncRNAs with microRNAs (miRNAs) has rapidly emerged, indicating a novel mechanism for lncRNA in regulating cancers [20]. MiRNAs, another class of ncRNAs, repress target gene expression through their partial complementarity with the mRNA sequence [21]. LncRNAs could function as competing endogenous RNAs (ceRNAs) to communicate with miRNAs by competing for shared miRNAs [22]. In contrast, miRNAs also negatively modulate lncRNA expression [23]. In addition, some lnc RNAs could act as the host gene of miRNAs or activate the promoter of miRNAs to upregulate the expression of miRNAs [24,25]. The crosstalk of lncRNAs with miRNAs plays a pivotal role in the pathophysiological processes of cancers.

In this review, we present a comprehensive summary of the roles of the UCA1–miRNA–mRNA axis in regulating the processes of cancer, including proliferation, invasion, drug resistance, and metabolism.

**Regulation of IncRNA UCA1 and miRNAs in cancers**

A remarkable hallmark of various solid tumors is their hypoxia, which regulates expression of genes, including those of lncRNAs [26]. UCA1 is found to be upregulated by the hypoxic microenvironment of bladder cancer [27]. Hypoxia-inducible factor 1α (HIF-1α) is activated under hypoxic tumor microenvironments and can bind to the hypoxia response elements of UCA1 promoter to enhance UCA1 expression in a hypoxia-dependent manner [28]. Thus, there is an interaction between HIF-1α and UCA1 under hypoxic conditions. In addition, UCA1 is regulated by other transcription factors such as special AT-rich sequence binding protein 1 (SATB1), which binds to the upstream region of UCA1 to block its transcription [29]. SATB1 depletion increases the promoter activity of UCA1 [30]. Moreover, the transforming growth factor-β (TGF-β) pathway could induce the expression of UCA1 by recruiting a transcriptional complex composed of TAZ, yes-associated protein (YAP), TEAD and SMAD2/3 in breast cancer cells [31,32]. Notably, these pathways also regulate UCA1-related miRNAs. For example, the HIF-1α signaling pathway regulates the expression of miRNAs such as miR-1 and miR-26, which have been reported to be inhibited by UCA1 [26,33,34]. The TGF-β signaling pathway could also induce the expression of UCA1-related miRNAs such as miR-1 and miR-203a [35]. Thus, the crosstalk of UCA1 and miRNAs may play an important role in tumor genesis.

**Regulatory relationships of UCA1 with miRNAs**

The regulatory networks between lncRNAs and miRNAs have been investigated in many tumors. LncRNAs can function as ceRNAs to communicate with miRNAs through competing for shared miRNAs; on the other hand, miRNAs can also negatively modulate lncRNA expression, and in addition, some lncRNAs can positively regulate the level of miRNAs [36]. Several studies have revealed abnormal expression of UCA1 in various kinds of tumors and regulation of the progress of a tumor through sponging miRNAs such as miR-193a-3p, miR-216b, miR-16, and miR-143 [37–40]. In contrast to sponging miRNAs, UCA1 is negatively modulated by miRNAs. A recent study reported that miR-1 inhibited UCA1 expression, and knockdown of miR-1 resulted in UCA1 up-regulation in bladder cancer cells [26]. In addition, UCA1 also could promote tumor growth by increasing expression of miR-196a-5p, which acts as a potential ‘onco-miR’ and was upregulated in multiple tumors [24,25].

**UCA1–miRNA–mRNA axis in cancer genesis**

Cancer growth is a process in which tumor initiating cells develop into a visible tumor mass, and refers to
cancer cell proliferation, resistance to cell death, and angiogenesis [41]. Cancer metastasis is the key reason for cancer death [42]. In addition, drug resistance is a major obstacle to the effective treatment of cancer patients [43].

Much evidence supports that metabolic change is a key event in tumor progression. Specific metabolic reprogramming sustains cancer growth, invasion, and drug resistance [44]. During tumor metabolism, glucose and glutamine are the main sources used to maintain active essential metabolic pathways and their metabolisms are changed during tumorigenesis [45]. Most cancer cells rely mainly on aerobic glycolysis to generate ATP for cellular processes instead of mitochondrial oxidative phosphorylation for glucose metabolism, a phenomenon known as the Warburg effect, resulting in an accelerated rate of glucose consumption and rapid proliferation and apoptosis resistance [46]. Glutaminolysis is pivotal for cancer cells to maintain the redox balance and to reduce excessive reactive oxygen species (ROS) levels. Glutamine metabolism may generate antioxidants such as NADPH and glutathione to contribute to the redox balance in cancer cells [47]. Mitochondria play an important role in metabolism of cancer with the ability to produce ATP and ROS, provide building blocks for anabolism by anaplerosis, and regulate cell death signaling [48]. Mitochondrial metabolism plays multifaceted roles in cancer progression including cancer initiation, development, apoptosis, and autophagy [48].

Numerous studies have demonstrated that crosstalk between UCA1 and miRNAs participates in tumor growth, invasion (Table 1), drug resistance (Table 2), and metabolism (Table 3) in many types of cancer.

Glioma

Glioma is the most common type of adult primary brain tumor with poor prognosis due to its strong capacity for cell proliferation and migration [49]. UCA1 promoted glioma cell proliferation and migration by inhibition of miR-204. Zinc-finger E-box-binding homeobox 1 (ZEB1) is a downstream target of miR-204 and is associated with invasion of many types of tumor via modulation of epithelial–mesenchymal transition (EMT) [44]. UCA1 has also been found to promote glioma proliferation and migration by inhibition of miR-182 [50]. Inhibitor of apoptosis-stimulating protein of p53 (iASPP) and the heart 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFKFB2) are the targets of miR-182 and were found to inhibit p53-dependent cell apoptosis and facilitate glioma invasion, respectively [50,51]. In addition, PFKFB2 is also regarded as a critical gene in charge of glycolysis [52], and the UCA1–miR-182–PFKFB2 axis plays an important role in glioma glycolysis [51].

UCA1 up-regulated the expression of transcription factor nuclear receptor subfamily 2 group member 2 (NR2C2) to promote glioma proliferation and invasion by sponging miR-627-5p [53]. Furthermore, UCA1 promoted glioma cell proliferation and invasion by sponging miR-122, which is a tumor suppressor in many tumors [54]. UCA1 was significantly increased by TGF-β treatment in glioma cells and had a higher level in glioma tissues than in normal adjacent tissues. Knockdown of UCA1 decreased TGF-β-induced EMT, which was associated with tumor invasion. The molecular mechanism is that UCA1 acts as a ceRNA for slug through competitive binding with miR-1 and miR-203a [55].

Oral cancers

Tongue cancer is an oral cavity malignancy threatening public health worldwide [55]. UCA1 interacted with miR-124, thereby modulating the metastasis of tongue cancer cells through jagged 1 (JAG1) and downstream signaling upon TGF-β1 stimulation [56]. UCA1 knockdown or miR-124 inhibition could partially attenuate the invasion of tongue cancer cells induced by TGF-β1 through Notch signaling [56]. Squamous cell carcinoma is the most common oral cancer and frequently involves the tongue [57]. Higher expression of UCA1 was associated with the proliferation or lymph node metastases of squamous cell carcinoma [15]. In addition, UCA1 promoted cisplatin resistance in oral squamous cell carcinoma via up-regulation of zinc finger gene in MEN1 locus (ZFMI) by sponging miR-184 [58]. ZFMI, also named SF1, was found to promote tumor-genesis of colon cancer and testicular germ cell tumors [59].

Gastrointestinal cancers

Gastrointestinal cancers, including esophageal, gastric, and colon cancer, are a major public health problem with poor prognosis. Esophageal cancer is a common gastrointestinal cancer [60], and UCA1 contributed to the proliferation of esophageal cancer by directly interacting with miR-204, and decreasing the binding of miR-204 to the 3′ untranslated region (3′UTR) of Sox4 [61].

Gastric cancer (GC) is a malignant tumor and has the highest morbidity and mortality in Asian countries; UCA1 is positively associated with GC proliferation and invasion [62]. UCA1 could significantly promote...
cell migration and inhibit apoptosis in GC cell lines SUN-216 and SGC-7091 via inhibition of miR-182, whose downstream target is tissue inhibitors of metalloproteinase 2 (TIMP2) [63]. Similarly, UCA1 enhanced the invasion of GC by directly interacting with miR-203 or miR-7-5p, increasing the release of miR-203-targeted transcripts zinc finger E-box-binding homeobox2 (ZEB2) or miR-7-5p-targeted epidermal growth factor receptor (EGFR), respectively [64,65]. Moreover, UCA1 could also promote the proliferation and invasion of GC through sponging miR-495-3p [30]. SATB1 is a target of miR-495-3p and positively correlated with the advanced tumor node metastasis stage of GC [66]. Furthermore, UCA1 could sponge

| Tumor                      | microRNA | mRNA   | Function                  | Reference |
|----------------------------|----------|--------|---------------------------|-----------|
| Glioma                     | miR-204↓ | ZEB1↑  | Proliferation and invasion (+) | [44]      |
|                            | miR-182↓ | IASPP↑ | Proliferation and invasion (+) | [50]      |
|                            |          | PKF6B2↑ | Invasion (+)               | [51]      |
|                            | miR-627-5p↓ | NR2C2↑ | Proliferation and invasion (+) | [53]      |
|                            | miR-122↓  | —      | Proliferation and invasion (+) | [54]      |
|                            | miR-1↑    | Slug   | Proliferation and invasion (+) | [35]      |
|                            | miR-203a↓ | —      | Proliferation and invasion (+) |          |
| Tongue cancer              | miR-124↓ | JAG1↑  | Invasion (+)               | [56]      |
| Squamous cell carcinoma    | miR-184↓ | ZFM1↑  | Proliferation and invasion (+) | [58]      |
| Esophageal cancer          | miR-204↓ | SOX4↑  | Proliferation (+)           | [61]      |
| GC                         | miR-182↓ | TIMP2↑ | Proliferation and invasion (+) | [63]      |
|                            | miR-203↓ | ZEB2↑  | Invasion (+)               | [64]      |
|                            | miR-495-3p↓ | SATB1↑ | Proliferation and invasion (+) | [30]      |
|                            | miR-590-3p↓ | CREB1↑ | Proliferation (+)           | [67]      |
|                            | miR-7-5p↑ | EGFRI↑ | Invasion (+)               | [65]      |
| Colon cancer               | miR-28-5p↓ | HOXB3↑ | Proliferation and invasion (+) | [71]      |
| Pancreatic cancer          | miR-107↓ | ITGA2↑ | Invasion (+)               | [74]      |
|                            | miR-96↓  | FOXO3↑ | Proliferation and invasion (+) | [75]      |
|                            | miR-135a↓ | Bmi1↑  | Proliferation and invasion (+) | [76,77]  |
| Hepatocellular carcinoma   | miR-218b↓ | FGFR1↑ | Proliferation (+)           | [38]      |
|                            | miR-203↓ | Snail2↑ | Invasion (+)               | [79]      |
|                            | miR-301a↓ | CCR4↑  | Invasion (+)               | [80]      |
| Thyroid cancer             | miR-135a↓ | c-myc↑ | Proliferation and invasion (+) | [84]      |
|                            | miR-204↓ | BRD4↑  | Proliferation (+)           | [85]      |
| Lung cancer                | miR-193a↓ | ERBB4↑ | Proliferation and invasion (+) | [37,87]  |
|                            |          | HMGB1↑ | Proliferation (+)           | [88]      |
|                            | miR-144↓ | PBX3↑  | Proliferation and invasion (+) | [90]      |
|                            | miR-143↓ | MAPK1↑ | Proliferation and invasion (+) | [92]      |
|                            | miR-506-3p↓ | COTL1↑ | Proliferation and invasion (+) | [93]      |
| Bladder cancer             | miR-143↓ | HMGB1↑ | Invasion (+)               | [95]      |
|                            | miR-145↓ | ZEB1↑  | Invasion (+)               | [96]      |
|                            | miR-582-5p↓ | ATG7↑ | Proliferation and invasion (+) | [97]      |
| RCC                        | miR-129-3p↓ | SOX4↑ | Proliferation (+)           | [103]     |
| Breast cancer              | miR-495↓ | EZH2↑  | Proliferation and invasion (+) | [106]     |
| Epithelial ovarian cancer  | miR-485-5p↓ | MMP14↑ | Invasion (+)               | [109]     |
| Cervical cancer            | miR-206↓ | VEGF↑  | Proliferation and invasion (+) | [123]     |
| Prostate cancer            | miR-184↓ | Bcl2↑  | Proliferation (+)           | [127]     |
|                            | miR-204↓ | Sirt1↑ | Proliferation and invasion (+) | [128]     |
|                            |          | ATF2↑  | Proliferation and invasion (+) | [129]     |
| Melanoma                   | miR-185↓ | —      | Proliferation and invasion (+) | [132]     |
|                            | miR-507↓ | FOXM1↑ | Proliferation and invasion (+) | [108]     |
| Osteosarcoma               | miR-182↓ | TIMP2↑ | Proliferation (+)           | [139]     |
| Myeloid leukemia           | miR-126↓ | RAC1↑  | Invasion (+)               | [141]     |
the miR-590-3p targeting cyclic adenosine monophosphate response element-binding protein 1 (CREB1), and knockdown of CREB1 inhibits the growth of human GC in vitro and in vivo [67,68]. Moreover, UCA1 increased multi-drug resistance of GC by down-regulating miR-27b [69].

Colon cancer is one of the most common cancers in the world, characterized by unlimited proliferation and high metastasis [70]. High UCA1 level in colon cancer tissues is positively associated with the tumor size and advanced tumor stages via inhibition of miR-28-5p. Homeobox B3 (HOXB3), a downstream target of miR-28-5p, could mediate the functions of UCA1 in proliferation and migration of colon cancer cells [71]. In addition, UCA1 also enhanced colorectal cancer proliferation and 5-fluorouracil (5-FU) resistance by sponging miR-204-5p, whose downstream target is CREB1 [72].

Pancreatic cancer

Pancreatic cancer is a highly aggressive malignant tumor with the characteristic of hepatic metastasis [73]. UCA1 promoted migration of pancreatic cancer by sponging miR-107 targeting integrin subunit α 2 (ITGA2) [74]. Moreover, UCA1 could promote pancreatic cancer cell multiplication and metastatic ability by down-regulating miR-96 and up-regulating forkhead box O3 (FOXO3). FOXO3, a target of miR-96, could impair pancreatic cancer cell viability and inhibit cell apoptosis [75]. Furthermore, UCA1 promoted growth and metastasis of pancreatic cancer by sponging miR-135a [76]. It was found that miR-135a inhibited the proliferation of pancreatic ductal adenocarcinoma by targeting B-cell-specific moloney murine leukemia virus integration site 1 (Bmi1) [77].

Liver cancer

Hepatocellular carcinoma is the most common type of liver cancer [78]. UCA1 promoted hepatocellular carcinoma cell proliferation and suppressed G0/G1 cell cycle arrest by inhibiting miR-216b [38]. MiR-216b targeted the fibroblast growth factor receptor 1 (FGFR1)–extracellular signal-regulated kinase pathway and played an important role in hepatocellular carcinoma cell invasion [38]. In another study, UCA1 sponged miR-203 targeting transcription factor Snail2 to promote the invasion of hepatocellular carcinoma [79]. Aberrant expression of UCA1 was also found in human liver cancer cell line MHCC97 and was associated with tumor cell invasion through sponging miR-301a and up-regulating the expression of chemokine receptor 4 (CXCR4) [80]. CXCR4 is a target of miR-301a and promoted devolvement of HepG2 cells [81]. MiR-301a could block the tumor-genesis promoting effect of UCA1 via activation of the Wnt–β-catenin pathway [82].
Thyroid cancer
Thyroid cancer is the most common malignancy in thyroid tissue and, based on the pathological features, includes papillary carcinoma, follicular carcinoma, medullary carcinoma, and undifferentiated carcinoma [83]. It was found that UCA1 significantly promoted proliferation and migration of thyroid cancer cells; the underlying mechanism was that UCA1 competed with c-myc proto-oncogene (c-myc) for miR-135a binding [84]. Similarly, UCA1 promoted growth and invasion of papillary thyroid carcinoma by competing with bromodomain containing 4 (BRD4) or insulin-like growth factor-binding protein 5 (IGFBP5) for miR-204 binding [85,86].

Lung cancer
Lung cancer is the leading cause of cancer death among both men and women. High UCA1 level in non-small cell lung cancer tissues remarkably promotes cell growth and metastasis via inhibition of miR-193a [37,87]. Both ERBB4 and high mobility group box 1 (HMG1) are the targets of miR-193a and were up-regulated by UCA1 in lung cancer [87,88] and shown to promote proliferation or invasion, respectively [88,89]. Furthermore, UCA1 up-regulates the expression of pre-B-cell leukemia homeobox 3 (PBX3) to promote lung cancer proliferation and invasion by inhibition of miR-144 [90]. Inhibition of miR-144 also was found to promote the proliferation and invasion of bladder cancer by targeting enhancer of zeste homolog 2 (EZH2) [91]. Moreover, silencing of UCA1 could induce G2/M cell cycle arrest and apoptosis via up-regulation of miR-143. Both UCA1 silencing and miR-143 overexpression could cause a significant decrease of mitogen-activated protein kinase 1 (MAPK1) [92]. Similarly, UCA1 contributed to proliferation and invasion of non-small cell lung cancer by functioning as a ceRNA to miR-506-3p, up-regulating its direct downstream target, coactosin-like protein 1 (COTL1) [93].

Bladder cancer
Bladder cancer is a highly prevalent disease with substantial morbidity and mortality [94]. UCA1 overexpression in bladder cancer significantly repressed miR-143 expression [95]. MiR-143 exerted a tumor suppressive role by targeting the 3’UTR of HMGB1, leading to the up-regulation of EMT, which was associated with invasion of bladder cancer [95]. Similarly, UCA1 up-regulated EMT and promoted the invasion of bladder cancer cells though targeting the miR-145–ZEB1/2–fascin homologue 1 pathway [96]. UCA1 promoted cell growth and metastasis of T24 and 5637 cells via enhancement of autophagy-related gene 7 (ATG7) by inhibiting miR-582-5p [97].

In addition to tumor proliferation and invasion, UCA1 also contributed to resistance to cisplatin and gemcitabine, the preferred drugs for chemotherapy after surgery for muscle-invasive bladder cancer patients, through activation of CREB by p-AKT and subsequent up-regulation of miR-196a-5p [25,98]. Moreover, UCA1 promoted the glycolysis of bladder cancer by sponging miR-143, which targeted hexokinase 2 (HK2), through regulating mechanistic target of rapamycin and signal transducer and activator of transcription 3 [40]. HK2, as the first rate-limiting enzyme of glycolysis, helps couple ATP formation in mitochondria to glucose phosphorylation, and was overexpressed in several malignancies, resulting in cancer cell growth, survival, and metastasis [99]. Furthermore, UCA1 contributed to glutamine metabolism and redox state regulation by sponging miR129-3p targeting glutaminase 2 (GLS2), which acts as an antioxidant defense and represses ROS formation by bladder cancer cells. [39,47]. UCA1 also could promote mitochondrial function of bladder cancer by inhibiting the expression level of miR-195, resulting in elevated expression of ADP ribosylation factor-like protein 2 (ARL2), which is essential for mitochondrial function [100]. Consistently, it has been reported that ARL2 expression was directly regulated by miR-195 in human neural progenitor cells [101].

Renal cell carcinoma
Renal cell carcinoma (RCC) accounts for ~90% of kidney cancers [102]. A recent study indicated that UCA1 promoted proliferation and invasion of RCC by sponging the miR-129-3p targeting SOX4 [103]. Consistently, miR129-3p weakened migration and invasion of RCC cells [104], while SOX4 facilitated migration of RCC cells [105]. In addition, UCA1 promoted proliferation of RCC through sponging miR-495, whose downstream target is EZH2 [106].

Breast cancer
Breast cancer is the second leading cause of cancer death among women after lung cancer [107]. UCA1 promoted the growth of breast cancer via inhibition of miR-122-5p, up-regulating its targets, type 1 insulin-like growth factor receptor (IGF-1R) and pyruvate kinase M2 (PKM2). The binding of miR-122-5p to UCA1 was regulated by insulin-like growth factor II mRNA binding protein-1, which is a multifunctional
RNA-binding protein that contains four KH domains for target RNA recognition [108]. UCA1 promoted the growth of breast cancer through interacting with miR-143, which targets the 3‘UTR of the ERBB3/HER3, a kinase-impaired HER receptor tyrosine kinase family member, thereby suppressing the proliferation and invasion of breast cancer cells [109].

Tamoxifen is one of the major hormone therapies for endoplasmic reticulum positive breast cancer in clinical practice, and acquired resistance to tamoxifen remains a major obstacle in breast cancer treatment [110]. Tamoxifen treatment up-regulated expression of UCA1 in breast cancer cells through a miR-18a–HIF1α feedback loop [110]. The overexpression of UCA1 conferred tamoxifen resistance by increasing the activity of Wnt–β-catenin signaling, which was accompanied by a decrease of miR-18a, an important modulator of cell cycle proteins [111,112]. Knockdown of UCA1 increased apoptosis upon tamoxifen treatment accompanied by an increase of cleaved caspase-3 and reduction in p-AKT and p-mechanistic target of rapamycin [113]. In addition, UCA1 also conferred resistance to trastuzumab, which is a monoclonal antibody for human epidermal growth factor receptor 2 (HER2)-positive breast cancer treatments. The molecular mechanism was that UCA1 sponged miR-18a targeting YAP1, which was associated with trastuzumab resistance [114].

Ovarian cancer

Epithelial ovarian cancer is the fifth most common cause of cancer death in women worldwide [115]. The overexpression of UCA1 was involved in the development of epithelial ovarian cancer via inhibition of miR-485-5p [116]. The downstream target of miR-485-5p is matrix metallopeptidase 14 (MMP14), which is the first membrane type matrix metalloproteinase involved in pathological invasion [116]. Thus, the UCA1–miR-485-5p–MMP14 axis plays an important role in development of ovarian cancer.

In addition, UCA1 also conferred cisplatin resistance in ovarian cancer through up-regulation of serine/arginine-rich protein-specific kinase 1 [11], a target of miR-216b [117–119]. Consistently, miR-216b increases cisplatin sensitivity in ovarian cancer cells [120] and could be sponged by UCA1 [34]. Furthermore, UCA1 could sponge miR-129 to enhance resistance to paclitaxel, which is used for chemotherapeutic treatment of many cancers including ovarian cancer [121]. ATP-binding cassette subfamily B member 1 transporter (ABCB1) was a direct target of miR-129 and associated with cisplatin and paclitaxel resistance in ovarian cancer [121].

Cervical cancer

Cervical cancer has the second highest incidence rate among cancers in females, accounting for the majority of cancer-related deaths globally [122]. UCA1 also could promote the proliferation and invasion of cervical cancer cells through inhibiting miR-206 expression. Vascular endothelial growth factor (VEGF) is a target of miR-206, and up-regulated by UCA1 [123]. In addition, UCA1 was found to promote glycolysis of cervical cancer by sponging miR-493-5p targeting HK2, which was proposed as a metabolic target for cancer therapeutic development [124,125].

Prostate cancer

Prostate cancer is one of the main causes of cancer-related death and morbidity in men [126]. UCA1 protected prostate cancer against apoptosis by sponging miR-184, leading to up-regulation of B-cell lymphoma/leukemia 2 [127]. It was also found that UCA1 promoted prostate cancer cell proliferation and invasion via inhibition of miR-204. Silent mating type information regulation 2 homologue 1 (Sirt1) and activating transcription factor-2 (ATF2) are the downstream targets of miR-204 [128–130]. Sirt1 and ATF2 when up-regulated by UCA1 facilitate metastasis and proliferation of prostate cancer, respectively [128–130]. In addition, the UCA1–miR-204–Sirt1 axis also contributed to resistance to docetaxel, which is a standard chemotherapy for patients with metastatic prostate cancer [128,131].

Melanoma

Melanoma is an aggressive skin carcinoma with poor prognosis. UCA1 could inhibit miR-185-5p to promote the growth or invasion of melanoma via regulation of the Wnt–β-catenin signaling pathway [132]. Consistently, miR-185 was also demonstrated to inhibit the proliferation and migration of melanoma [133]. In addition, UCA1 also sponged miR-507 to promote the proliferation of melanoma accompanied by up-regulation of mammalian transcription factor forkhead box protein M1 (FOXM1) [108]. FOXM1, a target of miR-507, is an essential effector of G2/M phase and miR-507 has been defined as a tumor suppressor in many types of cancer [134–136].

Osteosarcoma and myeloid leukemia

Osteosarcoma is the most common form of primary bone cancer and UCA1 is associated with its growth
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[137,138]. UCA1 played oncogenic roles by inhibiting miR-182 and up-regulating TIMP2 accompanied by activation of the phosphoinositide 3-kinase–AKT–glycogen synthase kinase 3 β and nuclear factor κB signaling pathways in osteosarcoma cells [139]. TIMP2, a target of miR-182, could suppress MMP activation, thus facilitating the invasion of multiple cancer cells [139]. Consistently, down-regulation of miR-182 could inhibit the growth of osteosarcoma [140].

Acute myeloid leukemia is a bone marrow malignancy. UCA1 knockdown could promote apoptosis and inhibit proliferation of myelogenous leukemia (ML) cell lines K562 and HL60, respectively [141]. The underlying mechanism is that UCA1 functions as an endogenous sponge for miR-126, thus up-regulating the expression of Ras-related C3 botulinum toxin substrate 1 (RAC1) [141]. Consistently, RAC1 overexpression could alleviate the anti-growth and anti-metastasis actions of miR-126 in ML cells [141]. Additionally, UCA1 conferred imatinib resistance in chronic ML as a ceRNA of multidrug resistance protein-1 (MDR1), which induced imatinib resistance by sequestering miR-16 [142]. Other evidences also favored that imatinib resistance was associated with overexpression of the MDR1 gene in tumor cells [143, 144]. In addition, UCA1 also conferred the resistance of adriamycin, a chemotherapy drug used for the treatment of AML, by sponging the miR-125a targeting HK2 to promote glycolysis [145]. Consistently, miR-125a/HK2 axis was found to regulate the energy metabolism of hepatocellular carcinoma or squamous cell carcinoma [146, 147].

Conclusion and perspective

UCA1 is unregulated in many types of tumor and plays an important role in tumor genesis via regulation of miRNAs. Crosstalk by way of UCA1 with miRNA is diverse, but usually, UCA1 as a ceRNA can sponge miRNAs, up-regulating their target genes. The UCA1–miRNA–mRNA axis participates in diverse biological functions including cancer growth, invasion, drug resistance, and metabolism. Understanding the molecular mechanism is of benefit for exploring the potential applications of UCA1 as a therapeutic target for human cancers.

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