

# Long non-coding RNA UCA1 promotes glycolysis by upregulating hexokinase 2 through the mTOR–STAT3/microRNA143 pathway

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## Key words

Aerobic glycolysis, cancer metabolism, lncRNA, UCA1, Warburg effect

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Cancer cells preferentially metabolize glucose through aerobic glycolysis, a phenomenon known as the Warburg effect. Emerging evidence has shown that long non-coding RNAs (lncRNAs) act as key regulators of multiple cancers. However, it remains largely unexplored whether and how lncRNA regulates glucose metabolism in cancer cells. In this study, we show that lncRNA UCA1 promotes glycolysis in bladder cancer cells, and that UCA1-induced hexokinase 2 (HK2) functions as an important mediator in this process. We further show that UCA1 activates mTOR to regulate HK2 through both activation of STAT3 and repression of microRNA143. Taken together, these findings provide the first evidence that UCA1 plays a positive role in cancer cell glucose metabolism through the cascade of mTOR–STAT3/microRNA143–HK2, and reveal a novel link between lncRNA and the altered glucose metabolism in cancer cells.

One of the most distinguishing characteristics between normal and tumorigenic cells is altered glucose metabolism. Most cancer cells rely mainly on aerobic glycolysis to generate the energy needed for cellular processes instead of more efficient mitochondrial oxidative phosphorylation, a phenomenon known as the Warburg effect, resulting in an accelerated rate of glucose consumption with enhanced lactate production regardless of oxygen availability.<sup>(1,2)</sup> In addition to being a striking feature of cancer cell metabolism, the Warburg effect confers advantages to cancer cells, providing conditions favoring rapid proliferation and apoptosis resistance.<sup>(3,4)</sup> Indeed, the Warburg effect, or the reprogramming of cellular energy metabolism, was recently added as an emerging hallmark of cancer.<sup>(5)</sup>

Long non-coding RNAs (lncRNAs) constitute a novel class of mRNA-like transcripts with no protein-coding capacity, which are larger than 200 nucleotides.<sup>(6)</sup> Long non-coding RNAs exert their function in a wide range of processes and can regulate gene expression by various mechanisms.<sup>(7,8)</sup> More evidence has suggested that lncRNAs play a role in the processes of cell growth, differentiation, apoptosis, and cancer metastasis.<sup>(9,10)</sup> However, there have been few studies focusing on the involvement of lncRNAs in cancer metabolism, especially in the Warburg effect. We previously screened and cloned lncRNA urothelial cancer-associated 1 (UCA1) by using subtractive suppression hybridization technique from two human bladder transitional cell carcinoma cell lines, BLS-211

and BLZ-211, which were derived from the same patient's sample but with different biological characteristics.<sup>(11)</sup> Studies from our and other laboratories have indicated that UCA1 is highly expressed in bladder carcinoma and enhances tumorigenic behavior of bladder cancer cells *in vitro* and *in vivo*, which strongly suggested that UCA1 has oncogenic functions in bladder cancer progression.<sup>(12–14)</sup>

In the present study, we discovered that UCA1 promotes glucose consumption and lactate production in bladder cancer cells. Metabolic change is a key event in understanding tumor progression and UCA1 is involved in glucose metabolic processes, however, the precise mechanism for direct regulation of glycolysis by UCA1 has not been elucidated. Thus, we investigated the mechanism for the UCA1-regulated metabolic switch in bladder cancer cells.

## Materials and Methods

**Cell culture and treatment.** All human bladder cancer cell lines were cultured in RPMI-1640 (Gibco, Grand Island, NY, USA) supplemented with 10% heat inactivated bovine calf serum at 37°C in a humidified atmosphere with 5% CO<sub>2</sub>. To inhibit the activity of mammalian target of rapamycin (mTOR), rapamycin (Cell Signaling Technology, Danvers, MA, USA) was used to treat cells. Cells were transfected with siRNA (Genepharma, Shanghai, China) using XtremeGENE siRNA Transfection Reagent (Roche, Nutley, NJ, USA) according to the manufac-

turer's instructions. Plasmids, microRNA (miRNA) mimics, and inhibitors (RiboBio, China) were transfected into cells with FuGENE HD Transfection Reagent (Roche) following the manufacturer's specifications. Stable UCA1 knocked-down 5637 cells and control cells, transfected with pRNAT-U6.1/Neo-shUCA and pRNAT-U6.1/Neo-Nc plasmid, respectively, were designated as pRNAT-U and pRNAT-N.<sup>(13)</sup> Stable cell lines with overexpression of UCA1 in UMUC-2 cells, designated as pcDNA-U and pcDNA-M (integrated with pcDNA3.1/UCA1 and pcDNA3.1/Mock respectively), were kindly provided by our colleague Chen Yang and Yu Wang, from Center for Translational Medicine, The First Affiliated Hospital, School of Medicine, Xi'an Jiaotong University, Xi'an, China.<sup>(14)</sup>

**Real-time quantitative PCR analysis.** The total RNA was extracted from cells by TRIzol Reagent (Invitrogen, Carlsbad, CA, USA). RNA was subjected to reverse transcription reactions using the PrimeScript RT reagent Kit (Invitrogen, Carlsbad, CA, USA). Real-time quantitative PCR assay was carried out with SYBR Premix Ex Taq II (TaKaRa, China) and monitored with the CFX96 Touch Real-Time PCR Detection System (Bio-Rad, Hercules, CA, USA). Cycling conditions were as follows: initial denaturation at 95°C for 10 s, followed by 40 cycles of 95°C for 5 s, 60°C for 15 s, and 72°C for 31 s, and no template controls were included for each assay. Comparative cycle threshold method was used to calculate fold change in gene expression by Bio-Rad CFX Manager 2.1 software (Bio-Rad). The mRNA expression was normalized with  $\beta$ -actin, and the miRNA expression was normalized with U6. All experiments were carried out in triplicate.

**Western blot analysis.** Treated cells were pelleted and then lysed by RIPA buffer (Thermo Scientific, Waltham, MA, USA) containing protease inhibitors (Roche). After SDS-PAGE resolution and membrane transfer, the target proteins were probed with primary antibody against HK2, phospho-signal transducer and transcription activator 3 (STAT3), or  $\beta$ -actin (Cell Signaling Technology) followed by incubation with HRP-conjugated secondary antibodies. Finally, the bands were visualized using a chemiluminescence detection kit (Pierce, Rockford, IL, USA) and the specific bands were recorded on X-ray film.

**Glucose consumption and lactate production assay.** To determine the levels of glucose and lactate, the supernatants of cell culture media were collected and detected using a glucose and lactate assay kit (BioVision, Milpitas, CA, USA) according to the manufacturer's instructions. The values at different time

periods were analyzed by the optical density values. Glucose consumption and lactate production were calculated based on the standard curve, and normalized to the cell number.

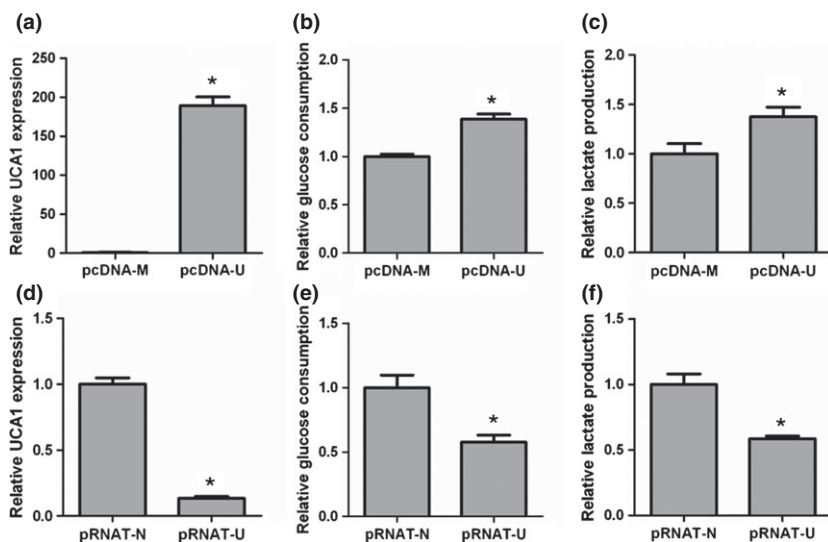
**Statistical analysis.** All statistical analyses were carried out using the spss standard version 13.0 software (SPSS, Chicago, IL, USA). Results were presented as mean  $\pm$  SD from at least three independent determinations. Comparisons between groups were evaluated by a Student's *t*-test. *P*-values < 0.05 was considered statistically significant.

## Results

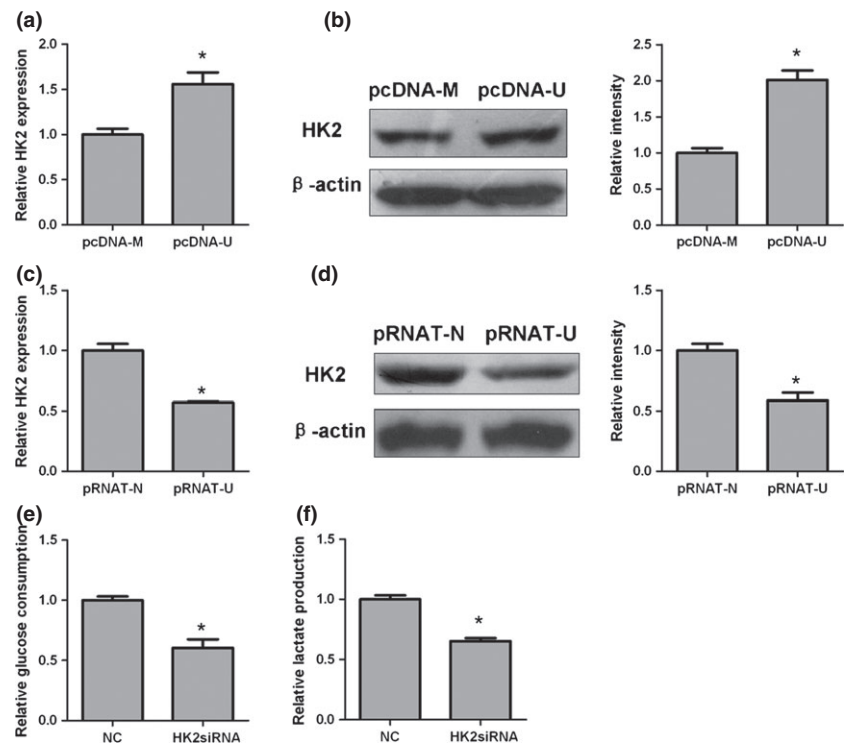
**UCA1 promotes glycolysis in bladder cancer cells.** Given that UCA1 promotes tumor initiation and malignant progression,<sup>(11)</sup> and that the reprogramming of energy metabolism is critical to the survival and proliferation of cancer cells,<sup>(15)</sup> we asked whether UCA1 potentiates cancer cell energy metabolism. To this end, we first examined the effect of UCA1 on glucose metabolism in bladder cancer cells. The results showed that overexpression of UCA1 dramatically increased the rates of glucose consumption and lactate production in UM-UC-2 cells (Fig. 1a–c). We also knocked down UCA1 in 5637 cells, which have high endogenous UCA1 expression, and found that the rates of glucose consumption and lactate production were significantly decreased in these cells (Fig. 1d–f). Collectively, these results indicate that UCA1 enhances glycolysis in bladder cancer cells.

**UCA1 regulates glycolysis through hexokinase 2.** Hexokinases catalyze the first and irreversible step of glucose metabolism, the ATP-dependent phosphorylation of glucose to yield glucose-6-phosphate.<sup>(16)</sup> Hexokinase 2 (HK2) is the major isozyme that is overexpressed in tumors and contributes to aerobic glycolysis, and thus it is documented as a pivotal player in the Warburg effect and is proposed as a metabolic target for cancer therapeutic development.<sup>(17)</sup>

To probe the potential mechanism by which UCA1 regulates glycolysis in bladder cancer cells, we examined the effects of UCA1 on the expression of HK2. Quantitative PCR analyses showed that HK2 mRNA levels were upregulated by UCA1 (Fig. 2a). In line with these results, Western blot assays showed that UCA1 enhanced HK2 protein expression (Fig. 2b). Moreover, both HK2 mRNA and protein levels were significantly reduced by knockdown of UCA1 (Fig. 2c,d). Given that HK2 is a critical enzyme catalyzing the first and



**Fig. 1.** Long non-coding RNA UCA1 promotes glycolysis in bladder cancer cells. (a, d) Quantitative PCR analysis of UCA1 expression in stable cell lines. UMUC-2 cells were transfected with pcDNA3.1/UCA1 (pcDNA-U) and pcDNA3.1/Mock (pcDNA-M) plasmids (a); 5637 cells were transfected with pRNAT-U6.1/Neo-shUCA (pRNAT-U) and pRNAT-U6.1/Neo-Nc (pRNAT-N) plasmids (d). (b, c, e, f) Glucose consumption and lactate production were analyzed in stable cell lines with overexpression of UCA1 (b, c) and knockdown of UCA1 (e, f). The average values  $\pm$  SD of three separate experiments were plotted. \**P* < 0.05.



**Fig. 2.** Long non-coding RNA UCA1 regulates glycolysis through hexokinase 2 (HK2) in stable bladder cancer cells. (a, c) Quantitative PCR analysis of HK2 mRNA levels in UMUC-2 cells transfected with pcDNA3.1/UCA1 (pcDNA-U) or pcDNA3.1/Mock (pcDNA-M) plasmids and 5637 cells transfected with pRNAT-U6.1/Neo-shUCA (pRNAT-U) and pRNAT-U6.1/Neo-Nc (pRNAT-N) plasmids. (a) Overexpression of UCA1. (c) Knockdown of UCA1. (b, d) Western blot analysis of HK2 protein level in stable cell lines with overexpression of UCA1 (b) or knockdown of UCA1 (d). (e, f) Glucose consumption (e) and lactate production (f) analysis in pcDNA-U cells transfected with HK2 siRNA or negative control (NC). The average values  $\pm$  SD of three separate experiments were plotted. \* $P < 0.05$ .

irreversible step of glycolysis,<sup>(16)</sup> and that its expression is most significantly regulated by UCA1, we reasoned that HK2 upregulation likely plays a major role in the enhancement of glucose consumption and lactate production under such conditions. Indeed, knockdown of HK2 significantly attenuated the effect of UCA1 on glucose consumption and lactate production (Fig. 2e,f). We thus focused on the regulation of HK2 for further mechanistic studies.

**UCA1 induces HK2 mRNA expression through the mTOR–STAT3 pathway.** The phosphatidylinositol-3-kinase (PI3K)–protein kinase B (Akt)–mTOR signaling pathway plays a crucial role in regulating cell growth, survival, and metabolism.<sup>(18)</sup> Various alterations of the proto-oncogenes and tumor suppressors along this pathway mark this network as one of the most frequently dysregulated signaling cascades in cancers.<sup>(19,20)</sup>

Our previous studies showed that UCA1 played a pivotal role in bladder cancer progression by activating the PI3K–Akt–mTOR pathway.<sup>(13)</sup> In addition, a recent study showed that STAT3 is a direct transcriptional activator for HK2.<sup>(21)</sup> Taking into account that STAT3 is a known downstream effector of mTOR,<sup>(22,23)</sup> we speculated that the UCA1 upregulated HK2 through activation of mTOR–STAT3 signaling. As expected, we found that the phosphorylation of STAT3 was positively related to UCA1 in stable cell lines (Fig. 3a,b). Furthermore, HK2 mRNA levels were reduced by rapamycin (Fig. 3c), whereas knockdown of STAT3 completely abolished the induction of HK2 transcript levels (Fig. 3f). Consistent with an important role of the mTOR–STAT3 pathway in mediating the upregulation of HK2 transcription by UCA1, we found that the rates of glucose consumption and lactate production were significantly decreased by rapamycin or STAT3 siRNA (Fig. 3d,e,g,h). Collectively, these results reveal that UCA1 promotes HK2 mRNA transcription through activation of the mTOR–STAT3 pathway.

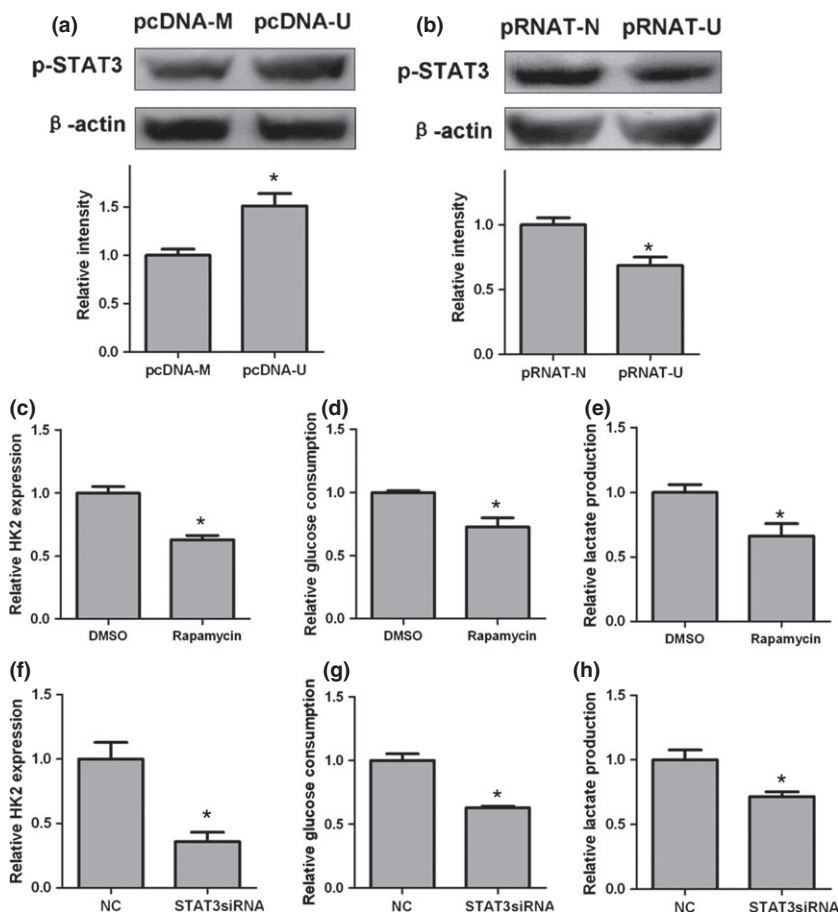
**UCA1 suppresses microRNA143 to elevate HK2 protein level.** MicroRNAs are small non-coding RNA sequences that regulate gene expression by targeting mRNAs for cleavage or translational inhibition.<sup>(24)</sup> Since the discovery that miRNAs are

aberrantly expressed in cancer, accumulating evidence suggests that miRNAs contribute to tumor growth by modulating levels of oncogenes and tumor suppressors.<sup>(25)</sup> Not surprisingly, some miRNAs have been shown to regulate cancer metabolism.<sup>(26)</sup>

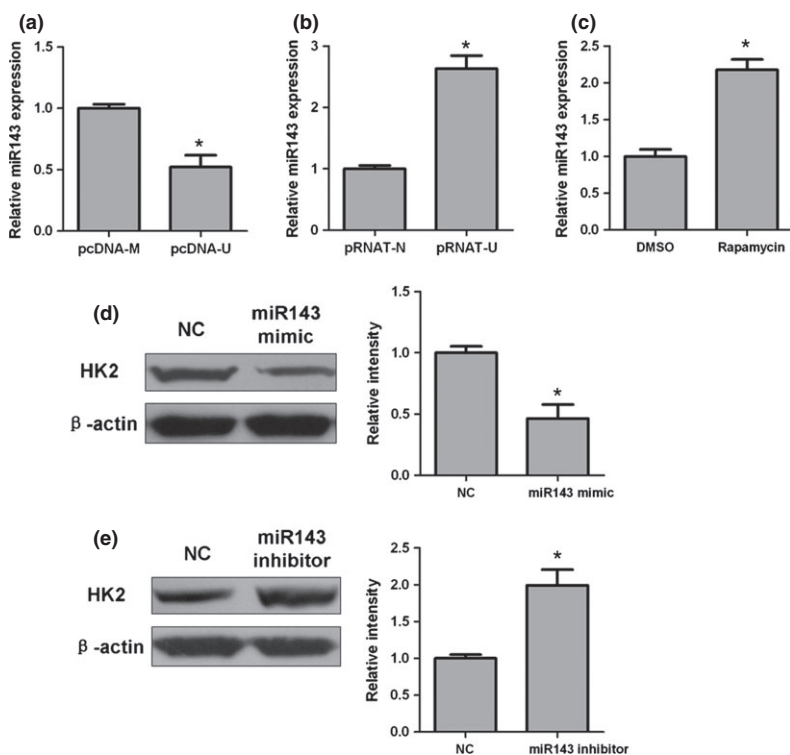
As recent findings suggested that miRNA143 (miR143), which is downregulated by mTOR activation, reduced glucose metabolism and inhibited cancer cell proliferation and tumor formation through targeting HK2,<sup>(21,27)</sup> we tested whether this regulation also extends to UCA1. Indeed, we found that miR143 expression was inversely correlated with UCA1 in stable cell lines (Fig. 4a,b), whereas rapamycin increased miR143 levels suppressed by UCA1 (Fig. 4c). We also found that the miR143 mimic significantly reduced the protein levels of HK2 (Fig. 4d), whereas miR143 inhibitor led to enhanced HK2 expression (Fig. 4e). These results suggested that UCA1 uses an additional mechanism to positively regulate HK2 protein expression at the post-transcriptional level.

## Discussion

Although only a small number of functional lncRNAs have been well characterized to date, they have been shown to be involved in a variety of biological processes that include, but are not limited to, X-chromosome inactivation, genomic imprinting, cell differentiation and development, and small RNA processing, as well as an association with a number of human diseases.<sup>(8)</sup> The importance of lncRNA in tumor initiation and malignant progression is well documented, as is the Warburg effect on survival and proliferation of cancer cells in the tumor microenvironment.<sup>(15)</sup> Although the latest reports suggest that lncRNAs lincRNA-p21 and CRNDE contribute to the Warburg effect,<sup>(28,29)</sup> whether and how other lncRNAs regulate the cancer cell glucose metabolism remains largely unexplored. In this study, we found that UCA1 significantly accelerates glycolysis in bladder cancer cells, providing direct evidence that lncRNA potentiates glucose metabolism in cancer cells.



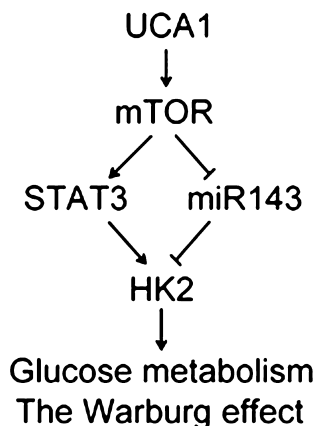
**Fig. 3.** (a, b) Long non-coding RNA UCA1 induces hexokinase 2 (HK2) mRNA expression through the mTOR–STAT3 pathway in stable bladder cancer cells. Western blot analysis of p-STAT3 protein levels in UMUC-2 cells transfected with pcDNA3.1/UCA1 (pcDNA-U) or pcDNA3.1/Mock (pcDNA-M) plasmids and 5637 cells transfected with pRNAT-U6.1/Neo-shUCA (pRNAT-U) and pRNAT-U6.1/Neo-Nc (pRNAT-N) plasmids. (a) Overexpression of UCA1. (b) Knockdown of UCA1. (c, f) Quantitative PCR analysis of HK2 mRNA levels in pcDNA-U cells. (c) Cells were treated with rapamycin or DMSO. (f) Cells were transfected with STAT3 siRNA or negative control (NC). (d, e, g, h) Glucose consumption and lactate production analysis in pcDNA-U cells. (d, e) Cells were treated with rapamycin or DMSO. (g, h) Cells were transfected with STAT3 siRNA or NC. The average values  $\pm$  SD of three separate experiments were plotted. \* $P < 0.05$ .



**Fig. 4.** Long non-coding RNA UCA1 suppresses microRNA143 (miR143) to elevate hexokinase 2 (HK2) protein level in stable bladder cancer cells. (a, b, c) Quantitative PCR analysis of miR143 expression in UMUC-2 cells transfected with pcDNA3.1/UCA1 (pcDNA-U) or pcDNA3.1/Mock (pcDNA-M) plasmids and 5637 cells transfected with pRNAT-U6.1/Neo-shUCA (pRNAT-U) and pRNAT-U6.1/Neo-Nc (pRNAT-N) plasmids. (a) Overexpression of UCA1. (b) Knockdown of UCA1. (c) pcDNA-U cells were treated with rapamycin or DMSO. (d, e) Western blot analysis of HK2 protein level in stable cell lines. (d) pcDNA-U cells were transfected with miR143 mimic or negative control (NC). (e) pRNAT-U cells were transfected with miR143 inhibitor or NC. The average values  $\pm$  SD of three separate experiments were plotted. \* $P < 0.05$ .

*UCA1* is well documented as an oncogene in bladder cancers.<sup>(11)</sup> Through positively regulating the PI3K–Akt–mTOR pathway, *UCA1* promotes malignant transformation and cancer

progression of bladder cancer.<sup>(13)</sup> For the first time, our data here show that *UCA1* contributes to glycolysis in bladder cancer cells. This finding, along with our recent study that hypoxic conditions



**Fig. 5.** Schematic representation of the mechanism for UCA1-regulated metabolic switch. HK2, hexokinase 2; miR143, microRNA143.

induce UCA1 expression in bladder cancer cells, suggests a novel function of UCA1 in regulating cancer cell glucose metabolism.

Mechanistically, UCA1 exerts its role in glycolysis by upregulation of HK2, a key glycolytic enzyme and pivotal player in the Warburg effect.<sup>(17)</sup> We then showed that inactivation of mTOR by rapamycin fully attenuated the effect of UCA1 on glycolysis in bladder cancer cells. We found that two signals control the regulation of HK2 by UCA1 through the mTOR pathway. First, UCA1 facilitates the activation of STAT3, which promotes the transcription of HK2. Second,

UCA1 represses miR143 and subsequently restores HK2 expression at the post-transcriptional level. Without the activation of STAT3, there is insufficient HK2 mRNA; however, without repression of miR143, increased mRNA levels of HK2 by UCA1/mTOR/STAT3 do not result in more HK2 proteins. The importance of this dual-control system is reflected by the results that both activation of STAT3 and repression of miR143 are required for UCA1 to accelerate glycolysis in bladder cancer cells. Thus, our findings reveal a novel UCA1–mTOR–STAT3/miR143–HK2 axis that links lncRNA and glucose metabolism in cancer cells (Fig. 5).

In summary, our study here provides the first evidence that UCA1 plays a positive role in cancer cell glucose metabolism through the cascade of mTOR–STAT3/miR143–HK2. Although the other mechanisms involved in cancer cell glucose metabolism by UCA1 still remain to be further explored, our data hopefully improve current understanding of the regulatory network of cancer metabolism and provide potential targets for the development of cancer therapeutic strategies.

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### Disclosure Statement

The authors have no conflict of interest.

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