Long non-coding RNA UCA1 relieves cardiomyocytes H9c2 injury aroused by oxygen-glucose deprivation via declining miR-122

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ABSTRACT
Background: Many IncRNAs have been recognized as critical regulatory factors in acute myocardial infarction (AMI). Herein, we further tested the influence of long non-coding RNA urothelial carcinoma associated 1 (UCA1) on cardiomyocytes injury in AMI, along with the role of microRNA-122 (miR-122) in this influence.

Methods: Cardiomyocytes H9c2 was subjected to oxygen-glucose deprivation (OGD) stimulation. Cell viability and apoptosis were assessed. The UCA1 and miR-122 expressions were measured by qRT-PCR. Plasmids and miRNAs transfection were utilized to elevate UCA1 and miR-122 expressions. Subsequently, the influences of UCA1 and/or miR-122 overexpression on OGD-aroused H9c2 cell viability inhibition and apoptosis were probed. The AKT/mTOR and JNK/p38MAPK pathways in cells were analyzed.

Results: OGD aroused H9c2 cell injury by suppressing cell viability and elevating cell apoptosis. Followed by OGD stimulation, the UCA1 expression was lowered in H9c2 cells. Overexpression of UCA1 weakened H9c2 cell injury aroused by OGD and declined miR-122 expression. Moreover, miR-122 attended to the influence of UCA1 overexpression on OGD-aroused H9c2 cell injury. Overexpression of UCA1 weakened OGD-aroused AKT/mTOR pathway inactivation and JNK/p38MAPK pathway activation by declining miR-122.

Conclusion: UCA1-relieved OGD-aroused H9c2 cell injury might be achieved via declining miR-122 and then promoting AKT/mTOR pathway and suppressing JNK/p38MAPK pathway.

Introduction
Acute myocardial infarction (AMI) is myocardial necrosis aroused by insufficient oxygen and nutrient supply of coronary arteries [1]. It is one of the most major cardiovascular diseases and one of the most common reasons for death worldwide [2]. Clinically, patients with AMI usually have severe and persistent post-sternal pain, arrhythmia, progressive electrocardiogram change, increased serum myocardial enzyme activity, shock, even heart failure [3,4]. Due to the molecular mechanism related to myocardial necrosis during AMI is very complex and mysterious [5,6], it is considered that studying the biological mechanism of cardiomyocytes injury after insufficient oxygen and nutrient supply is of great significance for the prevention and treatment of AMI.

Long non-coding RNAs (IncRNAs) are RNA transcripts in cells that have no apparent protein-coding capabilities, but exhibit outstanding gene regulatory activities [7]. Earlier studies reported that IncRNAs engaged in the modulation of numerous biological processes, as well as the initiation and development of many human diseases, including AMI [8–10]. Urothelial carcinoma associated 1 (UCA1) located on human chromosome 19p13.12 positive strand is an IncRNA first identified from bladder cancer BLZ-211 cells [11]. Yan et al. indicated that UCA1 was specifically expressed in the heart of adult under normal states [12]. Moreover, they proved that UCA1 was down-regulated in plasma at the early state of AMI patients and up-regulated at day 3 after AMI [12]. Chen et al. and Wang et al. pointed out that UCA1 could protect cardiomyocytes from ischemia/reperfusion-aroused apoptosis [13,14]. More experimental researches are still demanded to further probe the critical role of UCA1 in cardiomyocytes injury during the insufficient supply of oxygen and nutrient.

Apart from IncRNAs, microRNAs (miRNAs), another type of regulatory RNAs in cells also attend to the modulation of many cellular biological processes and the initiation of human diseases, including AMI [15,16]. Among them, miRNA-122 (miR-122) has been discovered to be up-regulated in the...
plasma of patients with AMI and contribute to AMI development [17]. Furthermore, previous literatures reported that UCA1 could bind to miR-122 and regulate miR-122 expression in cells [18,19].

Herein, rat embryonic ventricular cardiomyocytes-derived H9c2 cells were subjected to the stimulation of oxygen-glucose deprivation (OGD). Subsequently, the UCA1 and miR-122 expression in H9c2 cells were tested. The influences of UCA1 overexpression and miR-122 up-regulation on OGD-roused H9c2 injury were probed. The outcomes of our research will offer experimental basis for further comprehending the molecular mechanism concerning myocardial injury during AMI and provide potential targets for AMI prevention and treatment.

Materials and methods

Cell line and OGD stimulation

H9c2 cells (CL-0089, Procell Life Science & Technology Co., Ltd, Wuhan, China) were grown in Dulbcco’s Modified Eagle’s Medium (DMEM, PM150210A, Procell Life Science & Technology Co., Ltd) including 10% fetal bovine serum (FBS, 164210-500, Procell Life Science & Technology Co., Ltd) at 37 °C with 5% CO2 and 95% air. For OGD stimulation, H9c2 cells were grown in glucose-free DMEM (PM150270, Procell Life Science & Technology Co., Ltd) at 37 °C with 5% CO2 and 95% N2.

Quantitative reverse transcription PCR (qRT-PCR)

The UCA1 and miR-122 expressions in H9c2 cells were tested by qRT-PCR. Total RNAs were separated by RNAiso Plus (9108, Takara Biomedical Technology, Beijing, China). The miR-122 expression was measured by mirVana™ qRT-PCR miRNA Detection kit (AM1558, Invitrogen, CA, USA) and compared with U6 snRNA expression. cDNA was synthesized using High-Capacity cDNA Reverse Transcription kit (4368814, Applied Biosystems, CA, USA). The UCA1 expression was measured with the help of TaqMan™ Non-coding RNA Assay (4426961, Applied Biosystems) and compared with β-actin expression. Primers for UCA1 were 5'-CGGGATCCTGACATTCTCTCTGGA CAATGAG-3' (Forward) and 5'-CCGGAATTCATATAGCCTT AATGATAATTGGC-3' (Reverse). Primers for β-actin were 5'-TGCTTGCTGATCCACATCTG-3' (Forward) and 5'-TGCTTGCT GATCCACATCTG-3' (Reverse). Primers for miR-122 were 5'- GGTTGAGTGTGGAATG-3' (Forward) and 5'-CAGTGCGT GTCGCGGAGT-3' (Reverse). Primers for U6 snRNA were 5'-GGCT CGGCAGCACAT ATACTAAAT-3' (Forward) and 5'-GGCT CGGCAGCACATATAAAT-3' (Reverse). Results were calculated using 2-ΔΔCt method [20].

Plasmids or miRNAs transfection

The full sequence of UCA1 was inserted into pEX-2 plasmid (BioVector NTCC Inc., Beijing, China) to form pEX-UCA1. Empty pEX-2 plasmid was utilized as negative control (NC). miR-122 mimic and NC mimic were received from GenePharma Corporation (China, China). The sequences of miR-122 mimic were 5'-UGGAGUGUGACAAUGGUUUUG-3' (sense) and 5'-AACACAAUUGUCACACUU-3' (antisense). The sequence of NC mimic was 5'-UCACAACCUCCUA GAAAGAGUAGA-3'. Plasmids or miRNAs were transfected into H9c2 cells with the help of Lipofectamine 3000 reagent (L3000-150, Invitrogen, CA, USA).

Cell viability detection

Cell counting kit-8 (CCK-8) assay (HK-K0301, MedChem Express, NJ, USA) was utilized for testing H9c2 cell viability. Cells were cultivated into 96-well plate (1 × 104 cells/well) and subjected to OGD stimulation. Subsequently, 10 μl solution was mixed into the culture medium for 1 h at 37 °C. The absorbance of each well was tested using Microplate Reader (Packard Instrument Company, CT, USA) at 450 nm. Results were externalized as the percentage of control.

Cell apoptosis assessment

Annexin V-FITC/PE apoptosis kit (C1065, Beyotime Biotechnology, Shanghai, China) was utilized for assessing H9c2 cell apoptosis. Cells were cultivated into 6-well plate (1 × 105 cells/well) and subjected to OGD stimulation. Subsequently, cells were gathered in line with the experimental group, rinsed using kit buffer and mixed with 5 μl Annexin V-PE solution for 20 min at room temperature (20–25 °C) in the dark. The rate of apoptotic H9c2 cells was tested by flow cytometer (Attune Nxt, Thermo Fisher Scientific, MA, USA).

Western blotting

Total proteins were separated from H9c2 cells using Cell Lysis Buffers (635656, Takara Biomedical Technology) including Protease Inhibitor Cocktail-ProteoGuard (635672, Takara Biomedical Technology). Western blotting was carried out as earlier described [21]. Anti-Cyclin D1 antibody (sc-8396), anti-p53 antibody (sc-71820), anti-Bax antibody (sc-2005, 1:10000 dilution, Santa Cruz Biotechnology) for 1 h incubated with goat anti-Rabbit (or mouse) IgG-HRP (sc-2004 and sc-2007, 1:10000 dilution, Santa Cruz Biotechnology) at room temperature (20 °C) in the dark. Subsequently, the PVDF membranes were placed into the Bio-Rad ChemiDoc™ XRS system (Bio-Rad Laboratories, CA, USA) and coated with Pierce™ ECL Western Blotting (32209, Thermo Fisher Scientific). The signals of proteins were recorded and
the intensities of bands were calculated with the help of Image Lab™ software (Bio-Rad Laboratories).

**Statistical analysis**

Graphpad 6.0 software was utilized for statistical analysis. Results of multiple experiments were expressed as mean ± standard deviation (SD). *p* Values were computed using Student’s *t*-test or one-way analysis of variance (ANOVA) with Tukey’s test. Significant difference was set at *p* < .05.

**Results**

**OGD aroused H9c2 cell injury**

Firstly, H9c2 cells were subjected to OGD stimulation for 24 h. Data in Figure 1(A) show that OGD stimulation dramatically declined H9c2 cell viability (*p* < .01). The Cyclin D1 protein level was reduced, while the p53 protein level was elevated in H9c2 cells after OGD stimulation (Figure 1(B), *p* < .01). Moreover, Figure 1(C) displayed that OGD stimulation notably promoted H9c2 cell apoptosis (*p* < .01), which was accompanied with the raised expressions of pro-apoptotic proteins, Bax and c/p-Caspase 3 in H9c2 cells (Figure 1(D), *p* < .01). These above-mentioned outcomes illustrated that OGD could arouse H9c2 cell injury.

**OGD lowered UCA1 expression in H9c2 cells**

The UCA1 expression in H9c2 cells after OGD stimulation was tested. As presented in Figure 2, OGD stimulation remarkably lowered the UCA1 expression in H9c2 cells (*p* < .05), which hinted that the lowered expression of UCA1 might take part in the OGD-aroused H9c2 cell injury.

**Overexpression of UCA1 weakened H9c2 cell injury aroused by OGD**

In order to probe the influence of UCA1 up-regulation on OGD-aroused H9c2 cell injury, pEX-UCA1 was transfected into H9c2 cells. Figure 3(A) showed that the UCA1 expression in H9c2 cells was dramatically raised by pEX-UCA1 transfection (*p* < .01). Data in Figure 3(B) pointed out that OGD-aroused H9c2 cell viability decrease was notably weakened by pEX-UCA1 transfection (*p* < .05). Contrast to the OGD + pEX-2 group, the Cyclin D1 protein level was elevated, while the p53 protein level was reduced in the OGD + pEX-UCA1 group (Figure 3(C), *p* < .05 or *p* < .01). In addition, Figure 3(D) displayed that OGD-aroused H9c2 cell apoptosis was also dramatically weakened by pEX-UCA1 transfection (*p* < .05), which was accompanied with the lowered expressions of Bax and c/p-Caspase 3 in H9c2 cells (Figure 3(E), *p* < .05 or *p* < .01). These above-mentioned outcomes illustrated that

![Figure 1](image1.png)

![Figure 2](image2.png)

![Figure 3](image3.png)
overexpression of UCA1 could weaken H9c2 cell injury aroused by OGD.

**Overexpression of UCA1 declined miR-122 expression in OGD-stimulated H9c2 cells**

Followed by OGD stimulation and/or pEX-UCA1 transfection, the miR-122 expression in H9c2 cells was tested. As displayed in Figure 4, OGD stimulation significantly elevated the miR-122 expression in H9c2 cells (p < .01), while pEX-UCA1 transfection notably mitigated the OGD-aroused miR-122 expression elevation in H9c2 cells (p < .01). These outcomes hinted that UCA1 took part in the OGD-aroused H9c2 cell injury through modulating miR-122.

**miR-122 attended to the influence of UCA1 overexpression on H9c2 cell injury aroused by OGD**

Further experiments were carried out to explore whether miR-122 attended to the influence of UCA1 on OGD-aroused H9c2 cell injury. To increase miR-122 expression in H9c2 cells, miR-122 mimic was transfected into H9c2 cells. Figure 5(A) shows that the miR-122 expression in H9c2 cells was notably raised by miR-122 mimic transfection (p < .01). Data in Figure 5(B) display that miR-122 mimic transfection significantly mitigated the influence of pEX-UCA1 transfection on OGD-aroused H9c2 cell viability (p < .05). In contrast to the OGD + pEX-UCA1 + NC mimic group, the Cyclin D1 protein level was reduced, while the p53 protein level was elevated in the OGD + pEX-UCA1 + miR-122 mimic group (Figure 5(C), p < .05). Besides, Figure 5(D) presented that the influence of pEX-UCA1 transfection on OGD-aroused H9c2 cell apoptosis...
was notably reversed by miR-122 mimic transfection \((p < .05)\), which was accompanied with the raised expressions of Bax and \(c/p\)-Caspase 3 in H9c2 cells (Figure 5(E), \(p < .05\)). Taken together, these above-mentioned outcomes illustrated that overexpression of UCA1 relieved H9c2 injury aroused by OGD achieved by declining miR-122.

Overexpression of UCA1 weakened OGD-aroused AKT/mTOR pathway inactivation and JNK/p38MAPK pathway activation in H9c2 cells via declining miR-122

Finally, the AKT/mTOR and JNK/p38MAPK pathways in H9c2 cells after different stimulation were tested. Figure 6(A,B) pointed out that OGD stimulation noticeably suppressed AKT/mTOR pathway via declining \(p/t\)-AKT and \(p/t\)-mTOR expression rates, but dramatically promoted JNK/p38MAPK pathway via elevating \(p/t\)-JNK and \(p/t\)-p38 expression rates \((p < .01)\). pEX-UCA1 transfection dramatically weakened OGD-aroused AKT/mTOR pathway inactivation and JNK/p38MAPK pathway activation in H9c2 cells through raising \(p/t\)-AKT and \(p/t\)-mTOR expression rates, along with reducing \(p/t\)-JNK and \(p/t\)-p38 expression rates \((p < .05 \text{ or } p < .01)\). Besides, miR-122 mimic transfection significantly mitigated the influences of pEX-UCA1 transfection on OGD-aroused AKT/mTOR pathway inactivation and JNK/p38MAPK pathway activation in H9c2 cells \((p < .05 \text{ or } p < .01)\). These outcomes illustrated that overexpression of UCA1 could weaken OGD-aroused AKT/mTOR pathway inactivation and JNK/p38MAPK pathway activation in H9c2 cells via declining miR-122.

Discussion

A number of lncRNAs have been recognized as important regulatory factors to the initiation and development of AMI \([9,22]\). In the current research, we discovered that UCA1 expression was lowered in cardiomyocytes H9c2 under
OGD stimulation. Overexpression of UCA1 weakened H9c2 cell injury aroused by OGD and declined miR-122 expression in OGD-stimulated H9c2 cells. In addition, we found that miR-122 attended to the influence of UCA1 overexpression on OGD-aroused H9c2 cell injury. Besides, overexpression of UCA1 weakened OGD-aroused AKT/mTOR pathway inactivation and JNK/p38MAPK pathway activation in H9c2 cells via declining miR-122.

Cardiomyocytes injury aroused by insufficient oxygen and nutrient supply is the reason for AMI occurrence [1,23]. Earlier studies reported that cardiomyocytes H9c2 viability inhibition and apoptosis aroused by OGD stimulation was a suitable in vitro cell model for studying the molecular mechanism of AMI and testing the potential targets and medicines for AMI prevention and therapy [24,25]. In this study, followed by OGD stimulation, the H9c2 cell viability was reduced, which was accompanied with the decreased expression of Cyclin D1 and increased expression of p53 in H9c2 cells. Moreover, the H9c2 cell apoptosis was enhanced after OGD stimulation, which was accompanied with the elevated expressions of Bax and c/p-Caspase 3 in H9c2 cells. These outcomes illustrated that OGD-aroused H9c2 cell injury could be utilized for analyzing the function of UCA1 on AMI.

Previous clinical study demonstrated that UCA1 expression was changed in plasma of patients with AMI [12]. Experimental researches reported that UCA1 could exert protective function on cardiomyocytes injury aroused by ischemia/reperfusion [13,14,26]. Herein, we also confirmed that OGD stimulation lowered the UCA1 expression in H9c2 cells. Furthermore, we pointed out that overexpression of UCA1 by pEX-UCA1 transfection notably weakened H9c2 cell viability suppression and apoptosis aroused by OGD, which illustrated that overexpression of UCA1 could relieve cardiomyocytes injury in AMI. Besides, there are also other lncRNAs, such as HOX antisense intergenic RNA (HOTAIR) [27], myocardial infarction associated transcript 1 (Mirt1) [28], metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) [29] and solute carrier family 8 member A1 antisense RNA 1 (SLC8A1-AS1) [30], those are discovered to take part in the modulation of AMI initiation and development. Among them, HOTAIR and SLC8A1-AS1 exhibit protective activities, while Mirt1 and MALAT1 exhibit promoting activities. We proposed that many IncRNAs engage in the regulation of AMI progression, they may form an intricate regulatory network in cardiomyocytes. More experiments are still needed in the future to comprehensive analyze this regulatory network.

Many IncRNAs, including UCA1, typically exert gene expression regulatory activities through modulating miRNAs expressions [31,32]. As a downstream miRNAs of UCA1, miR-122 has been reported to be regulated by UCA1 by binding
to the AGTGTGA sequence of miR-122 [33]. Earlier literature discovered that miR-122 had a higher expression level in plasma of patients with AMI and engaged in the development of AMI [17]. The most critical finding in this research was that miR-122 attended to the influence of UCA1 overexpression on OGD-aroused H9c2 cell injury. We found that OGD stimulation elevated the miR-122 expression in H9c2 cells, while UCA1 overexpression declined the miR-122 expression in OGD-stimulated H9c2 cells. Moreover, overexpression of miR-122 mitigated the influences of UCA1 overexpression on OGD-aroused H9c2 cell viability suppression and apoptosis. These outcomes illustrated that overexpression of UCA1 relieved cardiomyocytes injury in AMI might be through declining miR-122.

AKT/mTOR and JNK/p38MAPK pathways are considered to engage in the modulation of cardiomyocytes injury in AMI [34,35]. The unusual inactivation of AKT/mTOR pathway and activation of JNK/p38MAPK pathway in cardiomyocytes during oxygen and nutrient deprivation have been affirmed in previous literatures [36,37]. Besides, UCA1 has been reported to take part in the regulation of AKT/mTOR and JNK/p38MAPK pathways [38,39]. Herein, we found that OGD stimulation suppressed AKT/mTOR pathway, but promoted JNK/p38MAPK pathway in H9c2 cells. More importantly, we discovered that overexpression of UCA1 weakened OGD-aroused AKT/mTOR pathway inactivation and JNK/p38MAPK pathway activation in H9c2 cells. Besides, overexpression of miR-122 weakened the influences of UCA1 overexpression on OGD-aroused AKT/mTOR pathway inactivation and JNK/p38MAPK pathway activation. Considering the functions of AKT/mTOR and JNK/p38MAPK pathways in cardiomyocytes injury of AMI, these outcomes illustrated that overexpression of UCA1 relieved cardiomyocytes injury in AMI might be through declining miR-122 and then promoting AKT/mTOR pathway and suppressing JNK/p38MAPK pathway. In generally, miRNAs take part in the regulation of cellular biological process through binding to the 3’-untranslated regions (3’UTR) of the mRNAs and then causing post-transcriptional gene silencing [40]. Considering that both AKT/mTOR and JNK/p38MAPK pathways are critical signaling pathways in cells, which join in the modulation of multiple cell functions and are regulated by many intracellular or extracellular molecules [41,42], we suggest that UCA1-miR-122 axis regulates the AKT/mTOR and JNK/p38MAPK pathways in H9c2 cells maybe via binding and changing the expression of upstream factors of AKT/mTOR and JNK/p38MAPK pathways. Further experiments are needed in the future to verify the upstream factors related to these regulatory activities.

Conclusion

To sum up, this research further affirmed the influence of UCA1 on cardiomyocytes injury in AMI and confirmed the critical role of miR-122 in this influence. Overexpression of UCA1 relieved OGD-aroused cardiomyocytes H9c2 injury by declining miR-122 and then promoting AKT/mTOR pathway and suppressing JNK/p38MAPK pathway. We put forward that UCA1 and miR-122 might be used as potential targets for AMI prevention and treatment.

Disclosure statement

No potential conflict of interest was reported by the authors.

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