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LncRNA NEAT1/MiR-103a-3p/ATF7 Axis Facilitates Cervical Cancer Cell Viabilities

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ABSTRACT Long noncoding RNAs (lncRNAs) participate in the development of cervical cancer (CC). Hence, impacts of lncRNA NEAT1 on CC cell progression were explored. LncRNA NEAT1, miR-103a-3p and ATF7 RNA expressions were examined using RT-qPCR. CC cell viabilities were detected by CCK-8. ENCORI was used to predict underlying binding spots of miR-103a-3p with lncRNA NEAT1 or ATF7. Fluorescence was examined using a luciferase reporter test. Knockdown of lncRNA NEAT1 was suppressed in Hela cells and inhibited cell viabilities while lncRNA NEAT1 overexpression was upregulated in SiHa cells with facilitating cell viabilities. MiR-103a-3p was confirmed to be targeted and sponged by lncRNA NEAT1. Thereafter, ATF7 was targeted and negatively modulated by miR-103a-3p, which has positive interaction with lncRNA NEAT1. Moreover, upregulated miR-103a-3p suppressed CC cell viabilities while ATF7 upregulation facilitated CC cell viabilities. lncRNA NEAT1 upregulated ATF7 through sponging miR-103a-3p, resulting in accelerated CC cell viabilities.

INTRODUCTION

Cervical cancer (CC) is one malignancy in females with approximately 604,100 new cases and 341,800 deaths in 2020 (Volkova et al. 2021). Despite improvements in diagnosing and treating cervical cancer, the prognosis of patients with CC in the middle and advanced stages remains unsatisfactory (Park et al. 2019). Nearly all kinds of CC are induced by human papillomavirus (HPV) and approximately ninety percent of CC cases occurred in less developed countries lacking systematic screen and vaccination (Cohen et al. 2019; Kessler 2017). Recently, impacts of noncoding RNAs on CC development have been widely investigated, in which long noncoding RNAs (lncRNAs) participate in CC progressions (He et al. 2020; Laengsri et al. 2018).

LncRNAs are over 200 nucleotides long without protein coding property (Bridges et al. 2021). Accumulated proof has showed that lncRNAs played roles in treating cancers and other diseases (Bhan et al. 2017; Lorenzi et al. 2019). LncRNA nuclear-enriched abundant transcript 1 (NEAT1) modulated the growth of tumour cells positively and promoted migration, invasiveness and neovascularisation in gynaecological tumours including endometrial cancer (Wang et al. 2017; Zhang et al. 2017). Suppression of lncRNA NEAT1 enhanced 5-fluorouracil sensitivity in CC cells via miR-34a/Lactate Dehydrogenase A axis (Shao et al. 2021). LncRNA NEAT1 elevated SRY-Box Transcription Factor 4 via sponging miR-133a, resulting in facilitated proliferation, invasiveness, and migration but inhibited apoptosis in CC cells (Yuan et al. 2019). LncRNA NEAT1 has also been detected to accelerate cervical cancer cell progression as a sponge of miR-9-5p (Xie et al. 2019). To further explore impacts of lncRNA NEAT1 on cervical cancer cell progression, other downstream factors should be investigated.

MicroRNAs are critical in existence, diagnosis, prognosis, and treatment of CC (Peralta-Zaragoza et al. 2016). MiRNAs have been verified to

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regulate invasion, occurrence, and migration of tumour cells via targeting mRNAs (Li et al. 2017). Previous research has disclosed that miR-103a-3p served as a novel oncogene or a promising suppressor in various kinds of cancers (Sun et al. 2020). Another research indicated that miR-103a-3p decreased the prostate cancer cell proliferation, and mobility but enhanced apoptosis (Ge et al. 2021). Moreover, miR-103a-3p was spawned by LINC00662, causing upregulation of pyruvate dehydrogenase kinase 4, thereby facilitating CC cell proliferation and decreasing cell apoptosis (Liu et al. 2021). Moreover, ENCORI (https://starbase.sysu.edu.cn/) predicted underlying binding spots about miR-103a-3p with lncRNA NEAT1. Therefore, researchers hypothesised that lncRNA NEAT1 might interact with miR-103a-3p to modulate CC cell progression.

Objectives

This study aimed at investigating lncRNA NAEAT1, miR-103a-3p and ATF7 expressions in CC cells and effects of them on modulating CC cell viabilities.

Experimental

Main Reagents

The reagents used in the study include DMEM (Gibco, USA), foetal bovine serum (Gibco), penicillin (Gibco), Lipofectamine 3000 (Invitrogen, USA), CCK-8 assay kit (Abcam, MA, USA), TRIzol (Beyotime, China), PrimeScript RT Master Kit (Takara Bio, Japan), and Q5® Site-Directed Mutagenesis Kit (BioLabs, USA).

METHODOLOGY

Cell Culture

Hela and SiHa cells were purchased from Biocompare (CA, USA). Incubation of cells were carried out in DMEM with ten percent foetal bovine serum (Gibco,USA) and one percent penicillin (Gibco) at five percent CO_2, 37D.

Cell Transfection

The negative control, NEAT1 small interfering RNA (si-NEAT1), NEAT1 overexpression plasmids (pc-DNA 3.1 NEAT1) and ATF7 overexpression plasmids (pc-DNA 3.1 ATF7) were provided by GenePharma (Suzhou, China). MiR-103a-3p mimics and miR-103a-3p were offered by Sigma Aldrich (VA, USA). Transfections of CC cells with these plasmids were conducted with the use of Lipofectamine 3000 (Invitrogen, USA) based on instructions.

CCK-8 Assay

CCK-8 assay kit (Abcam, MA, USA) was applied for measuring viabilities of CC cells. 96-well plates were used to incubate the cells in logarithmic phase in each group by adding cell suspension (100 μL) into each well. CCK-8 solution (10 μL) was mixed at 24 hours, 48 hours and 72 hours followed by the cultivation for 4 hours at 37^0C. Then, Infinite F50 (Tecan, Switzerland) was applied for checking absorbances at 450 nm. The experiment was run in triplicate.

RT-qPCR

TRIzol was used for total RNA extraction. Purification and concentrations of RNA were assessed. PrimeScript RT Master Mix was applied for reverse transcribing RNA into cDNA and primer design. The $2^{-\Delta\Delta Ct}$ method was performed to examine RNA expression levels. The primer sequences are listed in Table 1.

Table 1: Primer sequences for RT-qPCR

miRNA	*Primer*	*Sequence*
NE	Forward	TCGGGTATGCTGTTGTGAAA
NEAT1	Backward	CGTAACAGAATTAGTTCTTAC
miR-103a-3p	Forward	AGCAGCAUUGUACAGGGCUAUGA
miR-103a-3p	Backward	AUAGCCCUGUACAAUGCUGCUUU
ATF7	Forward	CCAACAGGCAAATGGGGTCT
ATF7	Backward	TAACTGGTGGGCCAGGGATA
GAPDH	Forward	GCACCACCAACTGCTTAGCA
GAPDH	Backward	GTCTTCTGGGTGGCAGTGATG

Bioinformatic Analysis

To investigate underlying miRNAs that interacted with lncRNA NEAT1, ENCORI (https://starbase.sysu.edu.cn/) was applied. Using miRNA-Target (miRNA-lncRNA), potential targeted miRNAs were examined. Moreover, mRNAs that interplayed with lncRNA NEAT1-sponged miRNA were detected using miRNA-Target (miRNA-mRNA).

Luciferase Reporter Assay

The luciferase plasmid was applied for the insertion of predicted binding fragments of miR-103a-3p to construct NEAT1-wt and ATF7-wt, respectively. Meanwhile, NEAT1-mt and ATF7-mt created by Q5® Site-Directed Mutagenesis Kit (BioLabs, USA) are mutated types. Co-transfection of miR-103a-3p mimics/NC into the cervical cancer cells with NEAT-wt/mt and ATF7-wt/mt were carried out with Lipofectamine 3000 (Invitrogen, USA). Luciferase reporter assay (BioVision, CA, USA) was applied for analysing luciferase activities.

Statistical Methods

One-way ANOVA method and student's t-test were chosen for difference evaluation among groups. GraphPad Prism 7.0 (USA) and SPSS 19.0 (IBM, MA, USA) software were used for analyses. $P \leq 0.05$ was statistically meaningful.

RESULTS

LncRNA NEAT1 Modulated CC Cell Viability

LncRNA NEAT1 expression was assessed after the transfection with siRNA. RT-qPCR results showed that lncRNA NEAT1 expressions were reduced in Hela cells (Fig. 1A, $^{**}P<0.05$). Beyond that, Hela cell viability was detected after transfection, showing that downregulated lncRNA NEAT1 decreased viabilities of Hela cells (Fig. 1B, $^{**}P<0.05$). RT-qPCR was also applied for examining lncRNA NEAT1 expression in SiHa cells after overexpression, indicating that lncRNA NEAT1 expressions were elevated (Fig. 1C, $^{**}P<0.05$). Moreover, up-regulation of lncRNA NEAT1 expressions enhanced viabilities of SiHa cells (Fig. 1D, $^{**}P<0.05$).

MiRNA Screening and Verification

Based on data in ENCORI (https://starbase.sysu.edu.cn), expressions of four miRNAs (miR-107, miR-15a, miR-424 and miR-103a-3p) that bound NEAT1 were checked through RT-qPCR. Results revealed that miR-103a-3p expression was elevated the most by NEAT1 downregulation in Hela cells (Fig. 2A, $^{**}P<0.05$). After the transfection of pcDNA3.1-NEAT1 in SiHa cells, expression of miR-103a-3p was reduced the most (Fig. 2B, $^{**}P<0.05$). ENCORI (https://starbase.sysu.edu.cn) also offered underlying binding spots of miR-103a-3p with lncRNA NEAT1 (Fig. 2C). Furthermore, a luciferase reporter test evaluated bindings, showing that miR-103a-3p mimics with NEAT1-wt caused the lowest fluorescence (Fig. 2D, E, $^{**}P<0.05$). Hence, miR-103a-3p was sponged and negatively modulated by lncRNA NEAT1.

ATF7 Acted as a Target of miR-103a-3p

ENCORI also demonstrated that ATF7 had binding spots with miR-103a-3p (Fig. 3A). Additionally, fluorescence was lower in ATF-wt with miR-103a-3p mimics than other groups (Fig. 3B, C, $^{**}P<0.05$). Moreover, ATF7 expressions were decreased by miR-103-3p overexpression (Fig. 3D, E, $^{**}P<0.05$). Beyond that, ATF7 expression was downregulated lncRNA NEAT1 suppression but ATF7 expression was elevated after the transfection of lncRNA NEAT1 overexpression (Fig. 3F, G, $^{**}P<0.05$).

Impacts of miR-103a-3p and ATF7 on Modulating CC Cell Viabilities

After interactions among NEAT1, ATF7 and miR-103a-3p were examined, impacts of miR-103a-3p and ATF7 on viabilities of CC cells were explored. CCK-8 results indicated that miR-103a-3p upregulation inhibited CC cell viabilities (Fig. 4A, B, $^{**}P<0.05$). In contrast, ATF7 overexpression facilitated viabilities of CC cells (Fig. 4C, D, $^{**}P<0.05$).

DISCUSSION

Malignancies are multi-staged due to metastasis-related genes, various oncogenes, and

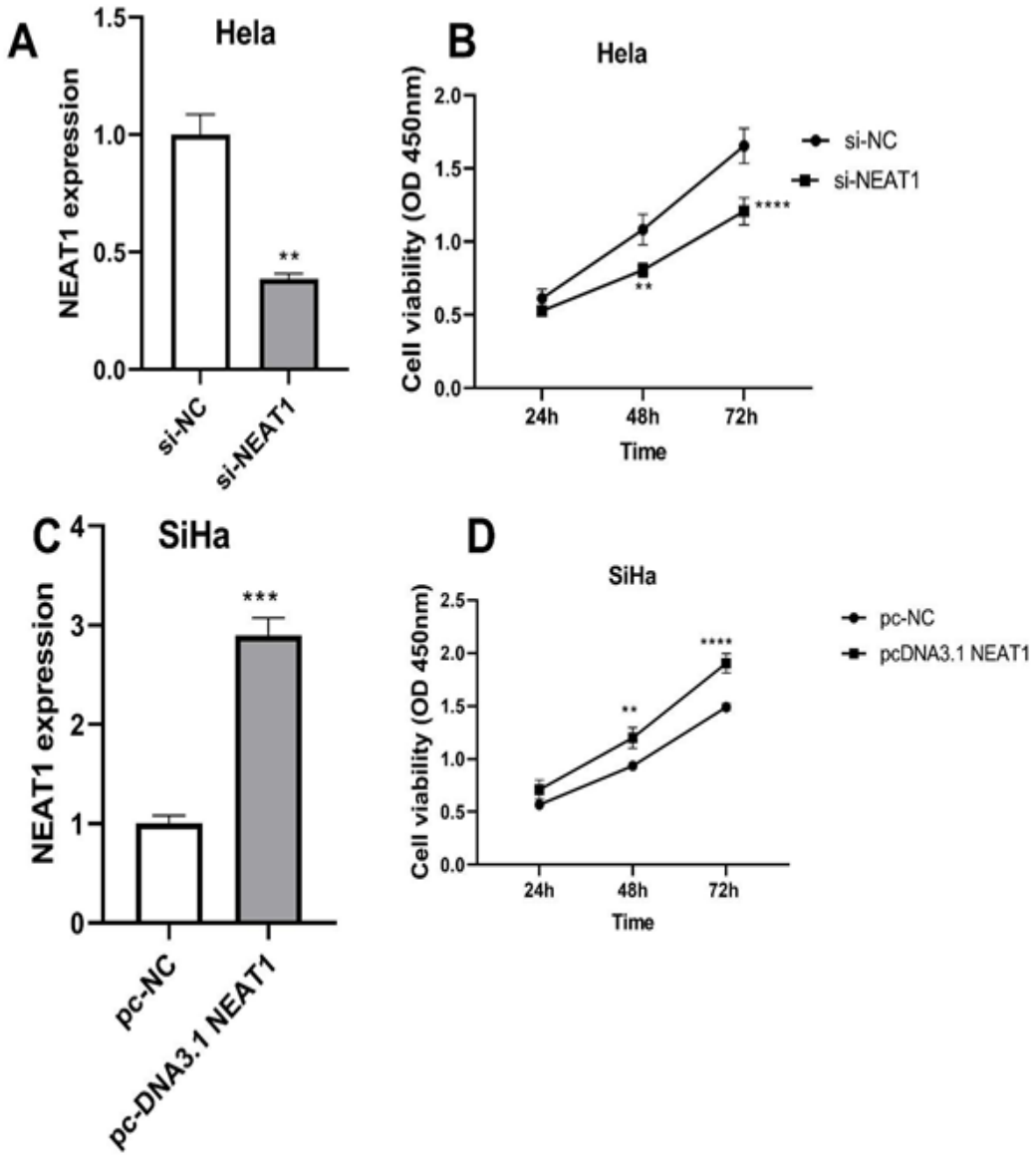

Fig. 1. LncRNA NEAT1 expressions in CC cells and its impacts on cell viabilities: A) RT-qPCR measured lncRNA NEAT1 expressions in Hela cells. B) Cell viability in HeLa cells with siNEAT1 was evaluated through CCK-8 assay. C) LncRNA NEAT1 expressions in SiHa cells were measured by RT-qPCR. D) CCK-8 evaluated the SiHa cell viability with lncRNA NEAT1 overexpression. **P . 0.05

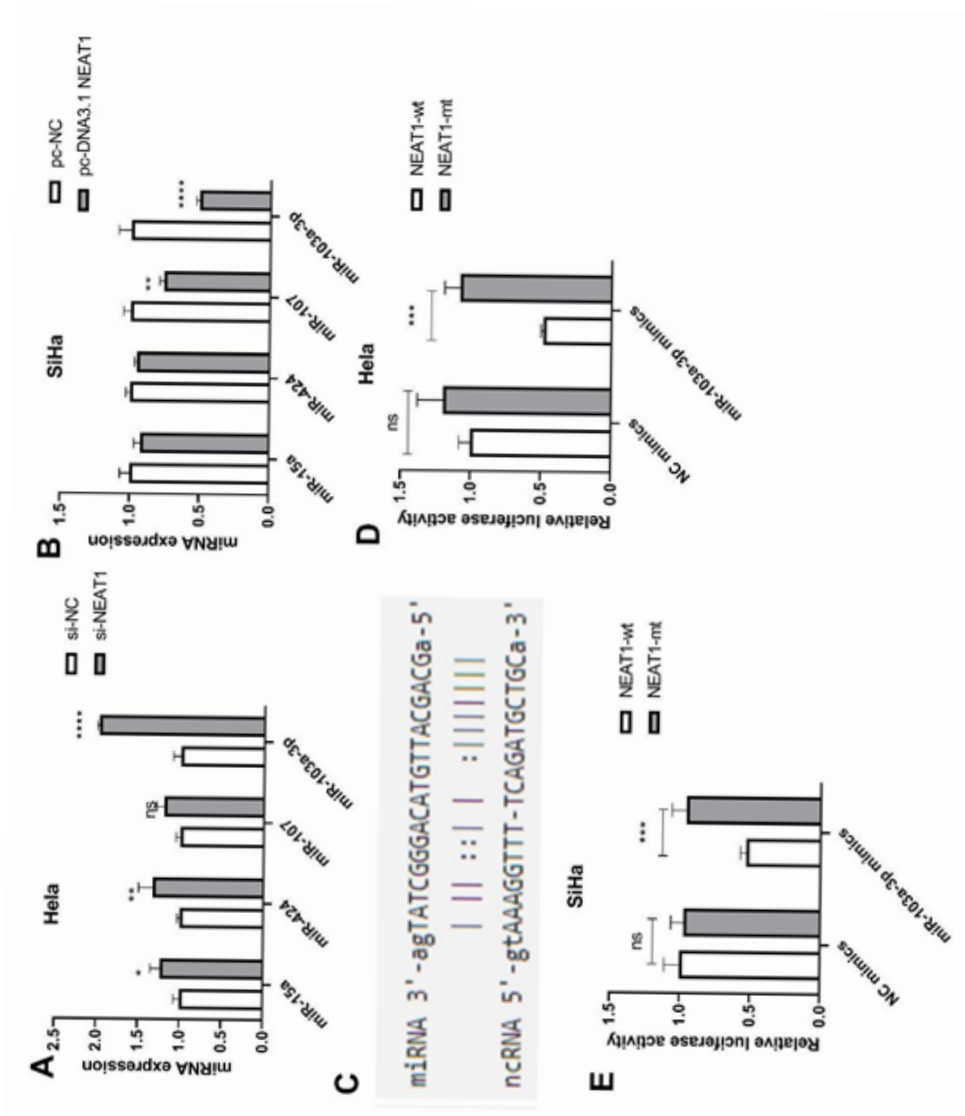

Fig. 2. MiRNA screening and verification: A, B) MiR-15a, miR-424, miR-107 and miR-103a-3p expressions were examined using RT-qPCR. C) Binding spots of miR-103a-3p with lncRNA NEAT1 were acquired from ENCORI (https://starbase.sysu.edu.cn). D, E) Luciferase reporter test evaluated fluorescence. $^{**}P < 0.05$

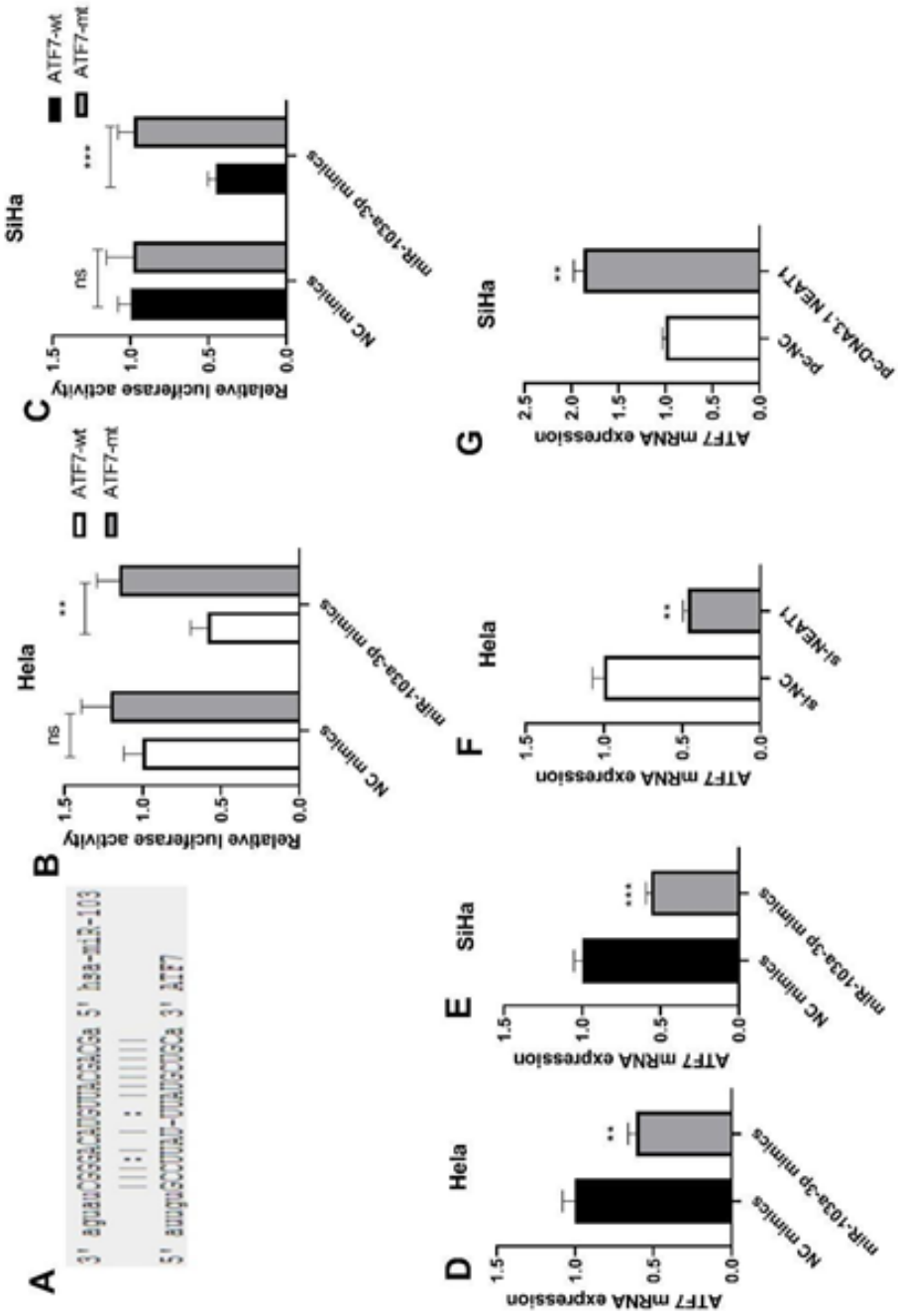

Fig. 3. ATF7 acted as a target of miR-103a-3p: A) ENCORI provided binding spots of miR-103a-3p with ATF7. B, C) Bindings about ATF7 and miR-103a-3p were validated using luciferase reporter test. D, E) ATF7 expressions with miR-103a-3p were examined using RT-qPCR. F, G) ATF7 expressions with lncRNA NEAT1 suppression and upregulation were analyzed through RT-qPCR. **P ≤0.05

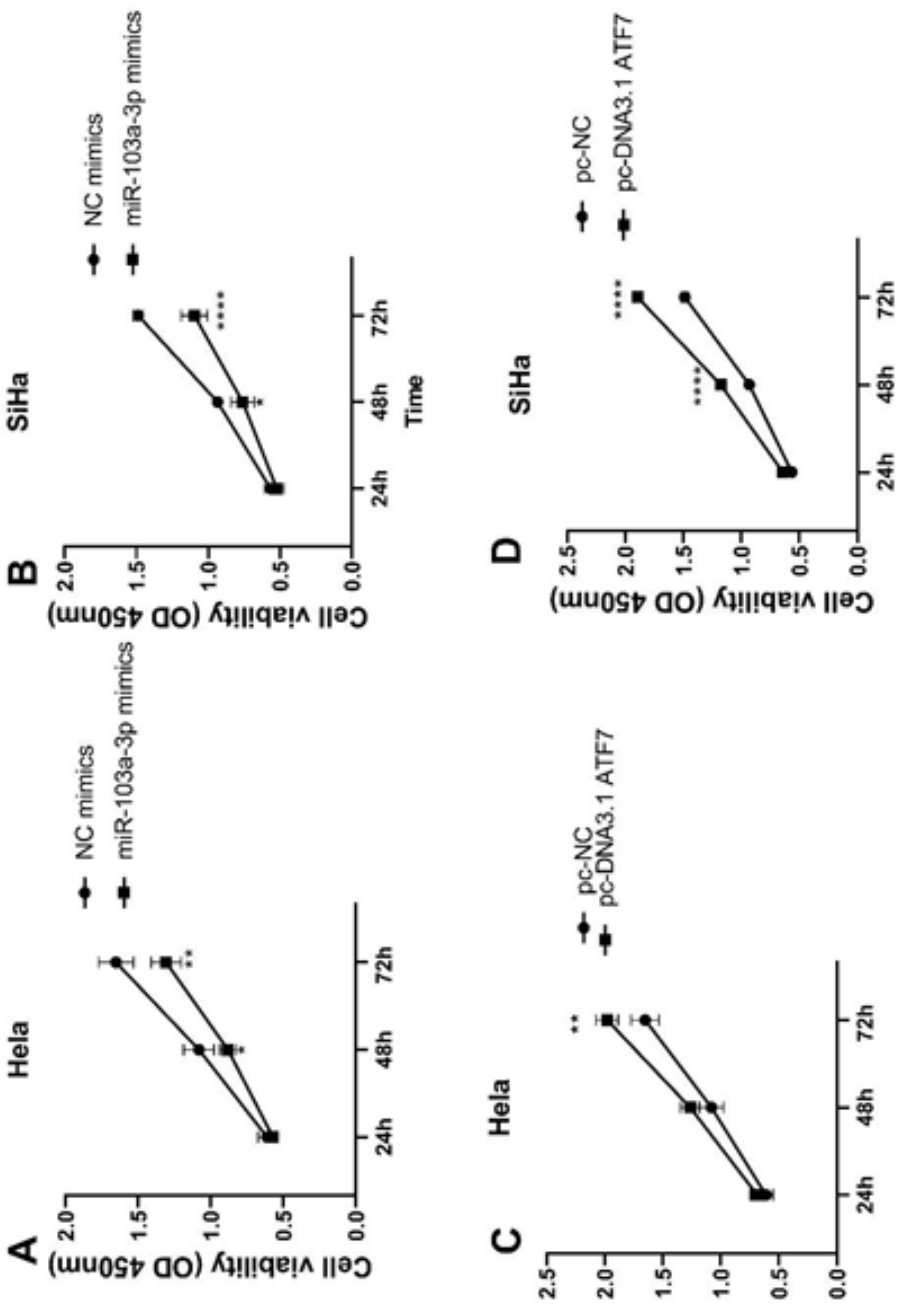

Fig. 4. Impacts of miR-103a-3p and ATF7 on regulating Hela and SiHa cell viabilities: A) CCK-8 examined viabilities of CC cells with miR-103a-3p overexpression. B) ATF7 overexpression-regulated viabilities of CC cells were validated using CCK-8. $^{**}P \leq 0.05$

tumour-suppressor genes (Kontomanolis et al. 2020). These gene expressions were regulated at both transcriptional as well as post-transcriptional level (Li et al. 2018). Growing evidence revealed the dysregulation of lncRNAs in human neoplasm participated in modulating cancer development (Chan and Tay 2018). Although functions of many lncRNAs in human diseases have been reported, several lncRNAs remain poorly investigated. In the present study, lncRNA NEAT1 overexpression accelerated the CC cell viabilities while downregulation of lncRNA NEAT1 reduced cell viabilities, indicating that lncRNA NEAT1 facilitated CC cell progression by promoting the cell viability.

LncRNAs played critically by modulating protein levels and mRNA levels of target genes and their biological processes (Dykes and Emanueli 2017; Qiu et al. 2013), which have been discovered to be involved in almost all kinds of cancers (Dong et al. 2015). LncRNA NEAT1 might be used as a predictor for prognosis of the tumour that was involved in developments of many tumours (Wang et al. 2017). LncRNA NEAT1 has been reported as an oncogene in malignancies including hepatocellular carcinoma (Fang et al. 2017), lung cancer (Li et al. 2018), and breast cancer (Li et al. 2017) and so on. Moreover, lncRNA NEAT1 promoted tumour cell proliferation and invasiveness and hampered apoptosis in CC cells (Guo et al. 2018). The results showed that downregulated NEAT1 inhibited CC cell viabilities, but overexpressed lncRNA NEAT1 accelerated CC cell viabilities. To clarify the mechanism of lncRNA NEAT1, bioinformatic tools were used for the prediction of miRNAs that interplayed with lncRNA NEAT1. Previous research has demonstrated that miR-103a-3p was elevated in neoplasms, such as lung cancer (Wang et al. 2021), colorectal cancer (Chen et al. 2012) and gastric cancer (Hu et al. 2018). Herein, researchers used ENCORI to predict underlying binding spots between lncRNA NEAT1 and miR-103a-3p. Results of the luciferase reporter test revealed that miR-103a-3p was sponged by lncRNA NEAT1. Moreover, miR-103a-3p expressions were negatively regulated by lncRNA NEAT1. Hence, lncRNA NEAT1 might modulate CC cell progression via sponging miR-103a-3p.

Activating transcription factor 7 (ATF7) is a protein coding gene that could form heterodimers and homo-dimers with c-fos or c-jun through its c terminal region and play a regulatory function in apoptosis and proliferation in various diseases (Chen et al. 2022). Inhibition of ATF7 stimulated the onset of Eì-Myc induction but desensitised apoptosis in lymphoma cells after induced by stress (Juilland et al. 2016; Walczynski et al. 2014). Another study revealed that ATF7 improved overall survival of colorectal cancer patients (Guo et al. 2015). However, impacts of ATF7 on cervical cancer were still unknown. Researchers investigated its roles on cellular models of cervical cancer. ATF7 was targeted by miR-103a-3p. Besides that, ATF7 expression was positively regulated by lncRNA NEAT1 while negatively regulated by miR-103a-3p, suggesting that lncRNA NEAT1, miR-103a-3p and ATF7 might have a therapeutic network among each other. Furthermore, CCK-8 assay was applied to examine CC cell viabilities with miR-103a-3p overexpression and ATF7 upregulation, showing that overexpressed miR-103a-3p restrained CC cell viabilities while ATF7 overexpression accelerated CC cell viabilities. Therefore, lncRNA NEAT1 regulated viabilities of CC cells via modulating miR-103a-3p/ATF7 axis.

CONCLUSION

In summary, lncRNA NEAT1 sponged miR-103a-3p to upregulate ATF7, resulting in facilitated viabilities of CC cells, suggesting that lncRNA NEAT1/miR-103a-3p/ATF7 axis might be potential biomarkers for treating CC. Nevertheless, further studies *in vivo* and clinical stages are needed to acquire more knowledge about them.

RECOMMENDATIONS

In this study, lncRNA NEAT1 downregulation suppressed its expressions and inhibited CC cell viabilities while NEAT1 overexpression elevated its expressions and accelerated viabilities of CC cells. Additionally, miR-103a-3p was sponged and negatively modulated by lncRNAs NEAT1. ATF7 was targeted and inhibited by miR-103a-3p, which has positive interaction with lncRNA NEAT1. Moreover, miR-103a-3p restrained

CC cell viabilities but elevated ATF7 facilitated CC cell viabilities. Researchers have provided a novel lncRNA NEAT1/miR-103a-3p/ATF7 axis in modulating CC cell viabilities. Nevertheless, biological functions about these three are needed to be investigated.

ABBREVIATION LIST

CC: Cervical Cancer
lncRNA: long noncoding RNA
NEA1: Nuclear Enriched Abundant Transcript 1
ATF7: Activating Transcription Factor 7
DMEM: Dulbecco's Modified Eagle Medium
ANOVA: Analysis of Variance

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