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Original Research Article

Long intergenic non-protein coding RNA 00174 promotes cardiac hypertrophy by targeting miR-150-5p

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Abstract

Purpose: *miR-150-5p is associated with several diseases but its relation with cardiac hypertrophy (CH) is yet to be unveiled. However, long intergenic non-protein coding RNA 174 (LINC00174) is implicated in CH. The purpose of this study was to investigate the roles of LINC00174 and miR-150-5p in relation to CH progression.*
Methods: *A mechanical cyclic stretch was applied to create 4 groups of H9 cardiomyocytes: 15 % 7, 15, 24 and 48 hr stretches, as well as unstretched control. Transfection method was used to up-regulate expression levels of LINC00174 and miR-150-5p in H9 cardiomyocytes. RT-qPCR and Western blot were used to determine the effect of LINC00174 on mRNA expression levels of miR-150-5p, proliferation and apoptosis biomarkers. Cell proliferation was determined by CCK-8 assay and the target gene of LINC00174 was detected by luciferase reporter assay.*
Results: Expression level of LINC00174 was high in H9 stretched cardiomyocytes. When overexpressed, it enhanced the mRNA expression of proliferation biomarkers and down-regulated apoptosis biomarkers. More so, miR-150-5p was down-regulated in H9 stretched cardiomyocytes and it was a direct target of LINC00174. Furthermore, miR-1505p restoration reversed the effects of LINC00174 overexpression on proliferation and apoptosis biomarkers.
Conclusion: *LINC00174 and miR-150-5p may be novel biomarkers for early diagnosis of CH.*

Keywords: *Cardiac hypertrophy, protein expression, LINC00174, miR-150-5p, restoration*

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INTRODUCTION

Cardiac hypertrophy (CH) is an independent cause of morbidity and mortality from heart diseases and an adaptive reply to overload (pressure [PO] or volume [VO]) [1, 2]. The disease condition is characterized by the expansion of cardiomyocytes (CMs) and heart mass, which are a central process of hypertrophic cardiomyopathy, myocardial infarction and other cardiovascular diseases [3]. Persistent CH results in heart failure and sudden death [4]. Decreasing cardiac

pressure or volume overload is one of the clinical therapeutics used to manage CH, although these therapeutics are yet to achieve the desired results [3].

Long non-coding RNAs (LncRNAs) is a type of functional RNA molecules with length of more than 200 nucleotides. They were one time considered to be the "noise" of genome transcription due to their shortage in protein-coding procedure [5]. LncRNAs serve to regulate their adjacent or distant target genes by connecting with microRNAs (miRNAs) and contact with proteins [6]. Recent researches confirmed that lncRNAs play important roles in the development of cardiovascular illnesses through moderating cardiac progression, homeostasis and regeneration [7]. Other affiliates of the lncRNA family such as LINC00174 (long intergenic non-protein coding RNA 174) have also been speculated to play important roles in tumor progression and other pathophysiological processes.

Micro RNAs are non-coding single-stranded RNAs made up of 17–25 nucleotides that regulate gene expression by binding to mRNAs at the 3′ untranslated region (UTR), suppressing protein mixture [8] . They are also associated with different gene expressions located in the pathophysiologic cardiac disorder [9]. In previous years, cumulative evidence suggested that important roles are played by miRNAs in cardiovascular illnesses. For instance, miR-124, miR-21 and miR4-97 have been indicated to be crucially associated with myocardial infarction, fibrosis, and CH [10, 11, 12]. However detailed information showing the relationship between miR-150-5p and LINC00174 to CH is still unclear.

This study was aimed at investigating the effect of LINC00174 on progression of cardiac hypertrophy and its association with miR-150-5p.

EXPERIMENTAL

Cell culture

In this study, hESC-CMs (Thermo fisher, UK, Leicestershire) were seeded at 8×10^4 cells/well in 6-well silicone elastomer-bottomed culture plates coated with type I collagen (Thermo fisher, Beijing, China) and grown to 80% confluence in Dulbeco's Modified Eagle Medium/ 10% fetal bovine serum and a 5% CO_2 humidified atmosphere at 37°C. A computer-driven, stretch-inducing device purchased from Strain UnitFX-5000, Flexcell, was used to expose the co-culture cells to nonstop cycles of stretch. The mechanical stretch was conducted with the condition in which each cycle had 5 s of stretch and 5 s of relaxation (0.1 Hz, 5 % versus 15 % elongation, 0.1 Hz) for 7, 24 and 48 hr. The 15% duration (0.1Hz) for 48 hr produced significant results, therefor all subsequent experiments were performed following those conditions [13]. In the experimental set up, mechanical cyclic stretch was applied to H9 cardiomyocytes *in vitro*. Following the mechanical stretch, 4 groups of the H9 cardiomyocytes were produced: the control group, which was not exposed to mechanical stretch; 15 % 7 hr stretch, 15 % 24 hr stretch and 15 % 48 hr stretch.

Cell transfection

Gene-Pharma (Thermo Fisher, UK, Leicestershire) was used to synthesize the miR-150-5p mimic and its negative controls, miR-NC. H9 cardiomyocytes were transfected by Lipofectamine 2000 (Thermo fisher, Beijing, China) with either miRNA mimics or NCs based on the manufacturer's instructions [14].

RT-qPCR

TRIzol (Abcam, UK, Cambridge) was used to separate total RNA from cells. For the generation of cDNA, a Prime Script RT reagent kit (Abcam, UK, Cambridge) was employed. The Prime Script RT reagent kit was used for reverse transcription following the manufacturer's instructions. RT-qPCR was done on a CFX Connect qPCR system kit (Abcam, UK, Cambridge) with a SYBR Premix Ex Taq II kit (Thermo fisher, Beijing, China). Nucleotide sequences of the primers used to measure expression levels are shown in Table 1. The $2^{-\triangle\triangle Cq}$ method was used to assess the mRNA expression levels, while β actin was used as a calibrator. The assays for gene expression were performed at least 3 times [13].

Western blotting

RIPA reagent (Thermo fisher, Beijing, China) was used to extract the total protein of cells, by including protease suppressor, phenylmethy-sulfonyl fluoride and phosphate suppressors, NaF and Na_3VO_4. Protein extraction reagent was used for protein separation (Thermo fisher, Beijing, China). The bicinchonic acid assay (Abcam, UK, Cambridge) was used to examine the protein concentration. Tris buffered saline, Tween blocking solution, with 5% non-fat milk immersed on the membranes for 2 hr and they were put in incubation with primary antidote: Primary antibodies Caspase 3 Mouse Monoclonal 31A1067 WB 1ug/Ml (Thermo fisher, Beijing, China),

Table 1: Primer sequences of target genes

Target	Direction	Nucleotide sequence
Caspase-3	Sense	5'-TGACTGGAAAGCCGAAACTC-3'
	Antisense	5'- AGCCTCCACCGGTATCTTCTV-3'
Caspase-8	Sense	5'- CGGGATCCGCCATGGACTTCAGCAGAAATC-3'
	Antisense	5'- TCCCCCGGGCACCATCAATCAGAAGGG-3'
Ki67	Sense	5'-GAAAGAGTGGCAACCTGCCTTC-3'
	Antisense	5'-GCACCAAGTTTTACTACATCTGCC-3'
PCNA	Sense	5'- GTTACCATAGAGATGAATGAACCAGTTC-3'
	Antisense	5'- CCTTCTTCATCCTCGATCTTGGGA-3'
β actin	Sense	5'- CACCATTGGCAATGAGCGGTTC-3'
	Antisense	5'- AGGTCTTTGCGGATGTCCACGT-3'

Caspase 8 Polyclonial mouse WB cat PA5-95391 100 ug (Thermo fisher, Beijing, China), Ki67 Monoclonial antibody mouse WB cat MA5-14520, 500ul (Thermo fisher, Beijing, China), PCNA Monoclonial human antibody 1:50 WB cat MA5 - 12557 500ul (Thermo Fisher, Beijing, China), GAPDH rabbit polyclonial 1:50000 (Thermo Fisher, Beijing, China). Caspase 3 Rabbit monoclonial 100ug 0.1-0.2ug/mL, Caspase 8 goat Polyclonial 2mg/mL, Ki67 goat polyclonial 2mg/mL (Thermo Fisher, Beijing, China). PNCA goat polyclonial WB 0.1-0.4 ug/mL. All Western blot assays were repeated at least 3 times [13].

CCK-8 assay

After transfection, cells were collected for the preparation of cell suspension after incubated at 37°C for 24 h. Each well of a 96-well plate was inoculated with a total of 100 µL of cell suspension and each group had three replicate wells. After the inoculation, cell proliferation was evaluated at intervals (0, 1, 2, and 3 days). Microplate reader (Abcam, UK, Cambridge) was used to express cell viability, determined at 450 NM and expressed as a percentage. An aliquot of 10 µL of the CCK-8 solution (Abcam, UK, Cambridge) was used to treat cells before they were incubated for 2 h. Lastly, EnSpire™ 2300 Multilabel Reader (Thermo Fisher, Beijing, China) was used to read wavelength of each well at 450 nm [15].

Cell proliferation

CCK-8 assay was used to determine the effects of mechanical stretch on hESC-CMs cell proliferation. Cells were treated with 10 % elongation (0.1 Hz) for 6 hr, 1×10^4 and seeded into 96-well plate; the unstretched cells were treated as controls. The combination treatment was performed using mechanical stretch with hESC-CMs alone, so as to determine the effect of mechanical stretching on hESC-CMs proliferation and contraction ability. An aliquot of 10 µl CCK-8 (5 mg/ml) was added to the wells and incubated at 37°C for 4 hr. A microplate reader (Abcam, UK, Cambridge) was used to record the Absorbance at 565 nm.

Luciferase reporter assay

The wild-type or mutant-type (MT) 3'UTR of miR-150-5p were synthesized by RiboBio (Abcam, UK, Cambridge) and were introduced into the multiple cloning sites of the vectors of luciferase-expressing pMIR-REPORT (Thermo Fisher, Beijing, China) and then transfected into H9 cardiomyctes with Lipofectamine 2000 (Abcam, UK, Cambridge) for 48 hr according to the instructions provided by the manufacturer. Dual Luciferase Reporter Assay System (Abcam, UK, Cambridge) was used to measure luciferase activity on a Luminoskan™ Ascent Microplate Luminometer (Abcam, UK, Cambridge) [16].

Statistical analysis

Statistics were shown in the form of mean ± standard deviation (SD) from at least 3 independent assays *in vitro*. The Student *t* test was used to examine the statistical significance between groups. Data were analysed using one-way analysis of variance (ANOVA). $P < 0.05$ was recognized as statistically significant

RESULTS

LINC00174 was up-regulated in H9 stretched cardiac hypertrophy cells

To elucidate the functions of LINC00174 in CH, RT-qPCR was employed to check the expression level of LINC00174 in H9 stretched cardiomyocytes. The results obtained from the RT-qPCR (Figure 1) revealed that LINC00174 expression was substantially high in H9 stretched cardiomyocytes. The 15 % 48 hr stretch cardiomyocytes had the highest level of gene expression, followed by the 15 % 24 hr stretch, while the least value was recorded for the 15 % 7 hr stretch.

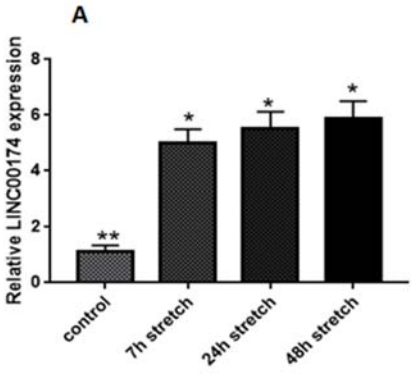

Figure1: Expression of LINC00174 in H9 stretched cardiomyocytes

The effects of different hours of exposure to cyclic mechanical stretch on H9 cardiomyocytes. All the assays were performed three times and the mean values and standard deviation were acquired. ** P<0.05

Overexpression of LINC00174 promoted H9 stretch cardiac hypertrophy cell proliferation

To analyse the part played by LINC00174 in CH, H9 stretched cardiomyocytes were transfected with LINC00174-oe prior to cyclic stretch stimulation. The RT-qPCR results revealed that LINC00174 expression was significantly elevated in H9 stretched cardiomyocytes as shown in Figure 2A. CCK8 assay showed that, 48 hr stretched cardiomyocytes had the highest cell viability, followed by the 24 hr stretched cardiomyocytes, while the 7 hr stretched cardiomyocytes had the least cell viability (Figure 2B). Through RT-qPCR, up-regulation of LINC00174 showed a significant (P<0.05) increase in the proliferation of biomarkers Ki67 and PCNA. Meanwhile, due to LICNC00174 up-regulation, the apoptosis biomarkers Caspase 3 and Caspase 8 were significantly decreased in LINC00174-oe group, compared to the NC group (Figure 2C). To further confirm the effects of LINC00174 up-regulation on H9 stretched cardiomyocytes, Western blot was performed to measure protein levels. The results revealed that the expression of proliferation biomarkers were increased in linc00714-oe group and the expression of apoptosis biomarkers were decreased in LINC00174-oe, compared to the NC group as shown in Figure 2D.

MiR-150-5p was down-regulated in H9 stretched cardiac hypertrophy cells

The expression of miR-150-5p was examined in H9 cyclic mechanical stretched cardiomyocytes. The results obtained indicated that miR-150-5p expression was significantly (P<0.05) down-regulated in H9 stretched cardiomyocytes, while the unstretched control group showed high miR-150-5p gene expression level. In order to elucidate the association between LINC00174 and miR-150-5p, Starbase Prediction software (Sun Yat-sen University China) was employed to examine the binding sites between LINC00174 and miR-150-5p (Fig3B). Consequently, to further confirm the binding of miR-150-5p to LINC00174, the luciferase reporter analysis was performed. The luciferase activity of wild-type miR-150-5p was weakened by the up-regulation of LINC00174, while the miR-150-5p MUT failed to exhibit reduced relative luciferase activity, therefore, establishing the direct binding of linc00612 to miR-150-5p in cardiac hypertrophy (Figure 3C).

Restoration of miR-150-5p affected H9 stretched cardiac hypertrophy cell proliferation and apoptosis

Since the expression of miR-150-5p was low in H9 stretched cardiomyocytes, we therefore performed miR-150-5p restoration through creating miR-150-5p mimics, which were transfected into H9 stretched cardiomyocytes. The results obtained demonstrated that cell proliferation was reversed due to miR-150-5p up-regulation (Figure 4A). Moreover, RT-qPCR was employed to detect effects of miR-150-5p mimics on mRNA expression level of proliferation and apoptosis biomarkers. The results showed that expression of proliferation biomarkers Ki67 and PCNA were decreased, while the apoptosis biomarkers caspase 3 and caspase 8 were increased as a result of miR-150-5p up-regulation (Figure 4B). In addition, Western blot revealed that miR-150-5p up-regulation reversed the increased effects on proliferation and enhanced apoptosis biomarkers (Figure 4C).

DISCUSSION

Cardiac hypertrophy (CH) is connected to several physiological and pathological components. Its development is firmly correspondent with the expression of the embryonic genes [17, 18]. Furthermore, previous studies have stated that miRNAs and lncRNAs are important members of the molecular species for the development of cardiovascular illnesses, including CH [7]. There are several researches indicating the mechanism of lncRNAs in numerous illnesses, including CH, by acting as a competing endogenous RNA (ceRNA). For example, lncRNA HOTAIR could operate as a ceRNA in late phases of gastric cancer [19] and lncRNA H19 acted as a ceRNA in cardiac fibrosis [20].

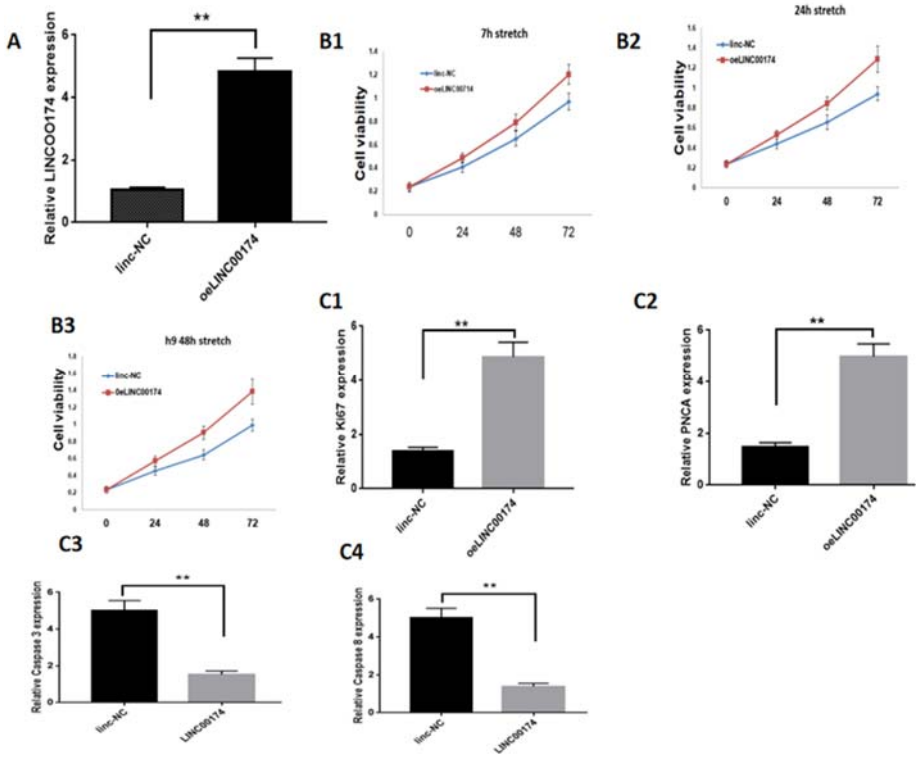

Figure 2: LINC00174 overexpression promoted cell proliferation in cardiac hypertrophy cells. (A) After transfection with LINC00174-oe, RT-qPCR was used to analyse the expression of LINC00174-oe in stretched cardiomyocytes. (B) Cell viability at different hours of stretch was analysed by CCK-8 assay. (C) The expression levels of apoptosis and proliferation biomarkers were examined by RT-qPCR. (D) The protein levels of apoptosis and proliferation biomarkers were examined by Western blot. All the assays were performed three times. ** P<0.05

Figure 3: Expression of miR-150-5p was down-regulated in stretched cardiomyocytes**.** (A) Expressions of miR-150-5p in stretched cardiomyocytes and control group measured by RT-qPCR. (B) Starbase Prediction revealed the binding site for LINC00174 in the 3'-UTR of miR-150-5p. (C) Luciferase reporter assay showed that LINC00174 up-regulation suppressed the luciferase activity of miR-150-5p WT compared to the MUT one. All the assays were performed three times. ** P<0.05

Apart from lncRNAs, comprehensive investigations have been done on miRNAs to deliberate on the nosogenesis of CH as a result of their varied biological purposes. Several miRNAs have been noticed to be dysregulated in CH. Among these different miRNAs, some were up-regulated in CH, for instance miR-208, miR-499 and miR-21, while others such as miR-30 and miR-1 were low in expression levels [21, 22].

In this study, we employed cyclic mechanical stretch which provides groundwork for the progression of pharmacological methods as well as for determining possible circulating biomarkers of cardiac hypertrophy dysfunction. The expression level of LINC00174 in H9 stretched hypertrophic cardiomyocytes was determined by RT-qPCR and results obtained revealed that LINC00174 was up-regulated compared to the unstretched control group. Moreover, in order to investigate the role of LINC00174, we analysed the effect of LINC00174 overexpression in stretched hypertrophic cardiomyocytes cell viability and the results demonstrated that cell viability was highest in cardiomyocytes exposed to 48 hr mechanical stretch.

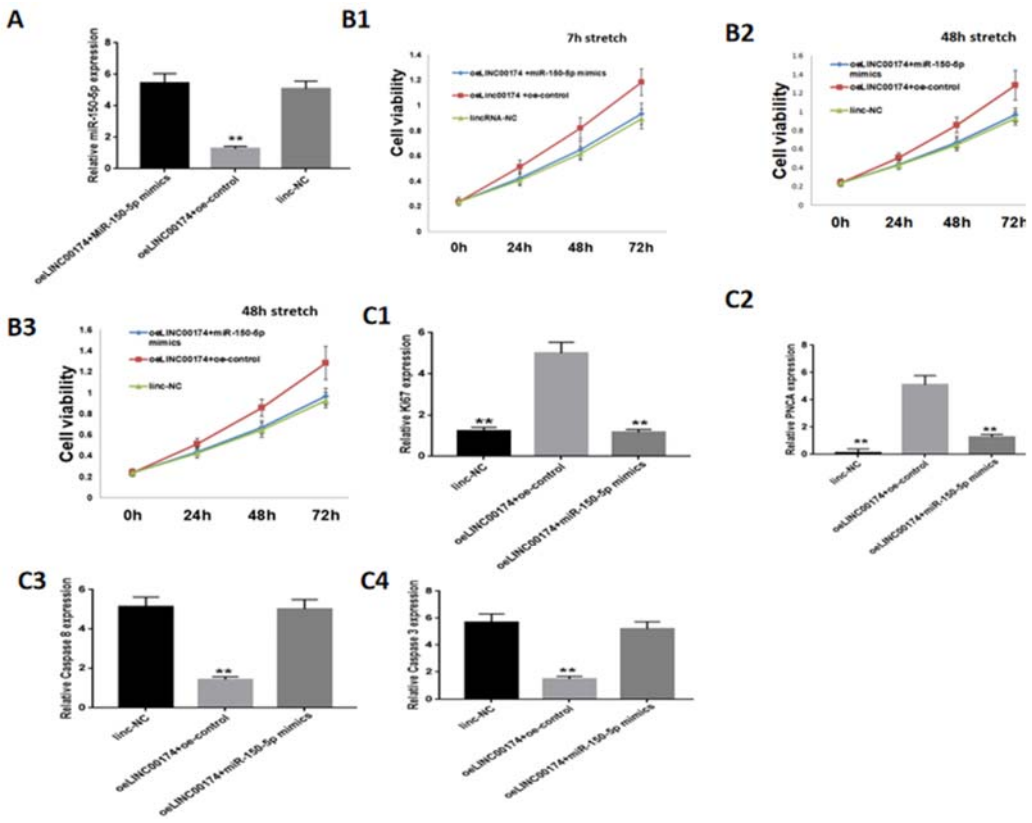

Figure 4: Restoration of miR-150-5p withdraws the effect of LINC00174-oe in stretched cardiomyocytes. (A) The relative miR-150-5p expression level in stretched cardiomyocytes. (B) CCK-8 assay showed that miR-150-5p restoration repressed cell viability in stretched cardiomyocytes. (C) The mRNA expression levels of apoptosis and proliferation biomarkers were examined by RT-qPCR. (D) The protein levels of apoptosis and proliferation biomarkers were examined by Western blot. All the assays were performed three times. ** P<0.05

Furthermore, Western blot and RT-qPCR demonstrated that the up-regulation of LINC00174 repressed the expression of apoptosis biomarkers (caspase 3 and caspase 8), while the proliferation biomarkers (Ki67 and PCNA) were elevated. These results indicated that LINC00174 promoted CH. We used the tool of biostatistics to explore the interaction between miR-150-5p and LINC00174. The results obtained suggested that miR-150-5p might be a direct target of LINC00174. In order to confirm our observation, luciferase reporter assay was performed for further investigation. The results confirmed miR-150-5p to be a direct target of LINC00174. These results suggested that LINC00174 could be an oncogene in cardiac hypertrophy. As a result of this finding, we performed miR-150-5p restoration in order to analyse changes that might be associated with it. The 48 hr stretched cardiomyocytes were transfected with miR-150-5p mimics and RT-qPCR analysis showed that cell proliferation was significantly decreased in H9 stretched cardiomyocytes. Additionally, the up-regulation of miR-150-5p reversed the effects of LINC00174 on apoptosis (caspase 3 and caspase 8) and proliferation (Ki67 and PCNA) biomarkers.

CONCLUSION

In general, our study revealed that LINC00174 was up-regulated in H9 stretched cardiomyocytes and its overexpression promoted cardiac hypertrophy cell proliferation and inhibited apoptosis. However, on the other hand, expression of miR-150-5p was low. In addition, miR-150-5p restoration reversed proliferation and elevated the apoptosis biomarkers. The study also showed that miR-150-5p was a direct target of LINC00174. Our findings suggest that miR-150-5p and LINC00174 could be novel biomarkers for cardiac hypertrophy treatment.

DECLARATIONS

Acknowledgement

None declared

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. All authors read and approved the manuscript for publication.

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