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Modulative effects of lncRNA TCONS_00202959 on autonomic neural function and myocardial functions in atrial fibrillation rat model

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Abstract. – OBJECTIVE: Atrial fibrillation (AF) is a typical cardiac arrhythmia. The autonomic nervous system can modulate the myocardial system with complicated mechanisms. Long non-coding RNA (lncRNA) is involved in myocardial diseases, and lncRNA TCONS_00202959 is down-regulated in AF. However, the detailed effects of AF on automatic functions or cardiomyocytes are not well known yet.

MATERIALS AND METHODS: Sprague-Dawley (SD) rats were randomly divided into control group, AF group (which was prepared by injecting the acetylcholine-CaCl2 solution) and treatment group (receiving lentiviral transfection of lncRNA TCONS_00202959 on AF rats). Real Time-quantitative PCR (RT-PCR) was used to measure the expression of lncRNA TCONS_00202959. Atrial effective refractory period (AERP) and AF induction rate were measured, along with heart rate variability (HRV) analysis to reveal autonomic nervous function. The expression of tyrosine hydroxylase (TH) and choline acetyltransferase (CHAT) was analyzed in atrial tissues.

RESULTS: The expression of lncRNA TCONS_00202959 was decreased in the AF group compared to the control group ($p < 0.05$), which also had shortened AERP and elevated AF induction rate. The analysis of the autonomic nervous function revealed lower standard deviation of NN intervals (SDNN), SDNN of atrial (SDANN), root mean square of successive differences (RMSSD) and SDNN intervals in all 5-min segments (SDNNindx), plus elevated power ratio of low frequency (LF)/high frequency (HF). TH expression was increased whilst CHAT expression was decreased ($p < 0.05$). The treatment group showed enhanced expression of lncRNA TCONS_00202959, elongated AERP plus decreased AF induction rate. The treatment rats also had higher SDNN, SDANN, RMSSD and SDNNindx, lower LF/HF ratio, decreased TH expression and increased CHAT expression ($p < 0.05$ compared to the AF group).

CONCLUSIONS: AF rats had decreased expression of lncRNA TCONS_00202959, which can help to prevent AF pathogenesis by suppressing cardiac autonomic nervous function.

Key Words:
LncRNA TCONS_00202959, Atrial fibrillation, Autonomic nervous, TH, CHAT.

Introduction

Atrial fibrillation (AF) is a typical cardiac arrhythmia in clinical practice of cardiology, and has a high incidence with persistence and popularity[1]. The incidence of AF rapidly increases with age. Therefore, worldwide prevalence of AF is sharply elevated as the transition of world population toward aging[2,3]. AF can cause or aggravate heart failure, and is an important factor of stroke[4]. Multiple factors can induce AF, including intracardiac reasons such as hypertension, cardiac failure, congenital disease or coronary heart disease, and extracardiac factors such as pulmonary artery embolism, hyperthyroidism, severe infection or mental/environmental stress[5]. AF frequently causes dysfunction of atrial constriction, lower cardiac output, and aggravates myocardial ischemia, leading to left atrial embolism and heart failure[6]. The embolism caused by AF can be detached to induce cerebral or pulmonary embolism, making it a severe cardiovascular disease threatening health worldwide[7,8]. The autonomic nervous system consists of the sympathetic nerve and vagal nerve, both of which are important for the cardiovascular system with complicated mechanisms[9]. Previous studies reported that the activation of the sympathetic nerve is correlated with heart arrhythmia, and the parasympathetic

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nerve is related with prevention of cardiac arrhythmia[10,11]. Therefore, dysregulation of the autonomic nervous system is closely related to the occurrence of heart arrhythmia[12]. Researchers[13] showed the presence of large amounts of non-coding RNA transcripts in eukaryotes occupied a major portion of human genome. Based on their length, non-coding RNA can be divided into long noncoding RNA (lncRNA) and small interference RNA (siRNA or miRNA). Those transcripts more than 200 nt length belong to lncRNA and do not participate in protein coding. Initially, lncRNA was founded as the "noise" of transcription. But with deeper research, we have established its involvement in regulating epigenetic control, transcriptional regulation and post-transcriptional regulation, all of which contribute to the gene expression regulation[14]. Although not participating in protein coding, lncRNA can mediate cardiovascular disease *via* epigenetic or transcriptional modulation[15]. Previous knowledge showed the down-regulation of lncRNA TCONS_00202959 in AF[16]. However, its detailed effects on autonomic nervous function and myocardial tissues have not been reported yet. Therefore, this work established a rat AF model in which the effect of lncRNA TCONS_00202959 on AF autonomic function and cardiomyocytes was analyzed.

Materials and Methods

Experimental Animals

A total of 45 healthy Sprague-Dawley (SD) rats (males and females, 2 months old, specific pathogen free (SPF) grade, body weight 250 ± 20 g) were purchased from the Laboratory Animal Center of Shaanxi University of Traditional Chinese Medicine, and were kept in a SPF grade animal facility with temperature (21 ± 1°C) and relative humidity (50%-70%) controlled. A 12 h light/dark cycle was adopted daily. The design of experimental protocol minimized the animal pain and was carried out by an experienced person. Rats were used for all experiments, and all procedures were approved by the Animal Ethics Committee of the Central Hospital of Enshi Autonomous Prefecture, Enshi, Hubei, China.

Major Equipment and Reagent

Acetylcholine was purchased from Sigma-Aldrich (St. Louis, MO, USA). Chemical reagents for Western blot were purchased from Beyotime (Shanghai, China). Enhanced chemiluminescence (ECL) reagent was purchased from Amersham Biosciences (Piscataway, NJ, USA). Rabbit anti-mouse tyrosine hydroxylase (TH), rabbit anti-mouse choline acetyltransferase (CHAT) monoclonal antibody and goat anti-rabbit horseradish peroxidase (HRP) labeled IgG secondary antibody were purchased from Cell Signaling Technology (Danvers, MA, USA). Lentivirus plasmid was constructed by Jikai Gene (Shanghai, China). The RNA extraction kit and reverse transcription kit were purchased from Axygen (Tewksbury, MA, USA). Other commonly used reagents were purchased from Sangon Biotech Co. Ltd. (Shanghai, China). Model 7700 fast fluorescent quantitative PCR cycler was purchased from Applied Biosystems (Foster City, CA, USA). Model V6004 animal ECG monitor was purchased from SurgiVet (Pensacola, FL, US). Four-electrode cannula was purchased from Metronic (Shah Alam, Selangor, Malaysia). Model LEAD7000 multi-electrode physiological controller was purchased from Jinjiang Bio (Beijing, China).

Animal Model Preparation and Grouping

A total of 45 healthy SD rats were fed under normal conditions for 2 weeks and were randomly assigned into 3 groups. The AF model was prepared by tail vein injection of the acetylcholine-$CaCl_2$ mixture. The treatment group received lentivirus-mediated transfection of lncRNA TCONS_00202959 after preparing the AF model.

Preparation of Rat AF Model and Treatment

Based on previous reports[17], AF rats received tail vein injection of 10 mg/ml $CaCl_2$ plus 60 μg/ml acetylcholine mixture for 1 week. After surgery, 24 ml/kg saline was used for peritoneal injection as liquid replenishment. The normal group received an equal volume of Phosphate-Buffered Saline (PBS) with similar steps as those in the model group. For treatment, lentivirus vector and lncRNA TCONS_00202959 were co-transfected into 293T cell line, which was kept in-house. Viral particles were harvested and condensed. In the meantime, 4×10^7 lentiviral particles containing miR-151 plasmid were injected along with model preparation.

Analysis of Electrophysiological Indexes and Autonomic Nervous Functions

10 days after transfection, rats were anesthetized by 1% sodium pentobarbital and were fixed on the plane. After opening the chest cavity, atrial

effective refractory period (AERP) and AF induction rate were measured. Rat trachea received intubation, and right atrium was exposed for programmed electro stimuli using a 4-electrode cannula. The AF induction rate was measured by S1-S2 programmed stimuli, whose endpoint was reached when S1-S2 duration was gradually decreased to 5 ms from 30 ms longer than refractory period. Electrophysiological indexes were further measured using S1-S1 programmed stimuli, with 300 ms length and 3 ms interval. AERP was measured until no AF occurred. Heart rate variability (HRV) analysis software and dynamic electrocardiogram (ECG) were used to analyze the autonomic nervous function, in which standard deviation of NN intervals of atrial (SDANN) was defined as the standard deviation of time elapsing between two QRS complexes (R-R interval) average and standard deviation of NN intervals (SDNN) equals to the standard deviation of R-R interval average at every 5 min among 24 h duration. Root mean square of successive differences (RMSSD) was calculated as the averaged square of deviation of R-R interval difference between adjacent period and SDNN intervals in all 5-min segments (SDNNindx) interval was based on the averaged standard deviation of R-R interval at every 5 min among 24 h duration. Low frequency (LF)/high frequency (HF) ratio was calculated based on the spectral measurement of HRV.

Real Time-PCR for LncRNA TCONS_00202959 Expression in Rat Myocardial Tissues

Under sterile conditions, TRIzol reagent was used to extract mRNA from myocardial tissues. Complementary DNA (cDNA) was further synthesized based on relevant primers (Table I). Real Time-PCR (RT-PCR) was used to detect target gene expression under the following conditions: 52°C for 1 min, followed by 90°C 30 s, 58°C 50 s and 72°C 35 s for 35 cycles. For receptor for advanced glycation end products (RAGE) and NF-κB, parameters were: 55°C for 1 min, followed by 35 cycles each containing 90°C 30 s, 62°C 50 s and 72°C 35 s. Data were collected by an ABI 7700 Fast fluorescent quantitative PCR cycler, and cycle threshold (CT) values for standard samples were calculated based on internal reference gene glyceraldehyde-3-phosphate dehydrogenase (GAPDH) to plot the standard curve. Quantitative analysis was then performed using the $2^{-\Delta Ct}$ method.

Western Blotting for Measuring Myocardial Expression of TH and CHAT

The expression of tyrosine hydroxylase (TH) and choline acetyltransferase (CHAT) in myocardial tissues was measured by Western blotting. In brief, cardiomyocytes were extracted for adding the lysis buffer, which was used to lyse tissues for 15-30 min. Tissues were homogenized by ultrasound for 5 s at 4 times, and were centrifuged at 10000×g for 15 min. The supernatant was saved and quantified for protein concentration for storage at -20°C in further assays. In Western blotting, proteins were separated by 10% sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) and were transferred to polyvinylidene difluoride (PVDF) membrane by a semi-dry approach with 100 mA for 1.5 h. Non-specific binding was removed by 5% defatted milk powder under room temperature for 2 h. Primary antibody (1:500 diluted TH and 1:2000 diluted CHAT monoclonal antibody) was added for 4°C overnight incubation. On the next day, the membrane was rinsed by Phosphate-buffered saline and Tween-20 (PBST), and 1: 2000 diluted goat anti-rabbit secondary was added for 30 min dark incubation at room temperature. The membrane was illuminated using development substrate for 1 min, followed by X-ray exposure. Protein imaging system and Quantity One software (Bio-Rad, Hercules, CA, USA) were used to scan X-ray film for measuring band density. All experiments were repeated four times (n=4) for statistical analysis.

Statistical Analysis

SPSS 16.0 software package (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. Enumeration data were presented as percentage and were compared by chi-square test. Measure-

Table I. Primer synthesis sequence.

Gene	Forward primer 5′-3′	Reverse primer 5′-3′
GADPH	AGTGCCAGCCTCGTCTCATAG	CGTTGAACTTGCCGTGGGTAG
Lnc RNA TCONS_00202959	GATATCCAGGGAGTTTGGGA	ATGTCCAGGGTTCATTGGTCTGT

ment data were shown as mean ± standard deviation (SD). Tukey's post-hoc test was used to validate the ANOVA for comparing measurement data among groups. A statistical significance was defined when $p < 0.05$.

Results

Expressional Change of LncRNA TCONS_00202959 in Rat Cardiac Tissues

Real Time-PCR was used to analyze the expressional change of lncRNA TCONS_00202959 in rat cardiac tissues. The results showed a significantly decreased expression of lncRNA TCONS_00202959 in AF rat myocardial tissues ($p < 0.05$ compared to the control group). Lentivirus induced transfection of lncRNA TCONS_00202959 into atrial tissues can facilitate its expression ($p < 0.05$ compared to AF group, Figure 1).

AERP Analysis of All Groups of Rats

Electrophysiological indexes were measured to test AERP change. Results showed significantly shortened AERP of rat atrial tissues in AF group ($p < 0.05$ compared to the control group). After up-regulating the expression of lncRNA TCONS_00202959 in atrial tissues, AERP was remarkably up-regulated ($p < 0.05$ compared to AF group, Figure 2).

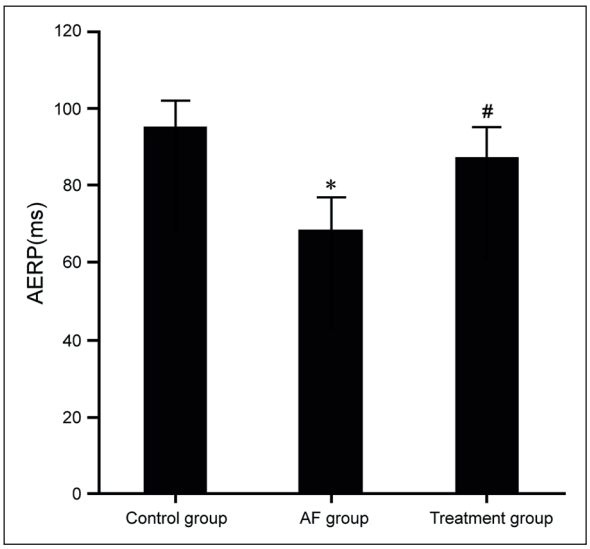

Figure 2. AERP analysis of all groups of rats. $^{*}p < 0.05$ compared to the control group, $^{\#}p < 0.05$ compared to the AF group.

AF Induction Rate Analysis Among All Groups

We further analyzed the incidence of AF across all groups, and found remarkably increased AF induction rate in AF group (9/15, or 60%), which was significantly higher than control group (1/15, 6.7%, $p < 0.05$). After up-regulating lncRNA TCONS_00202959 expression in atrial tissues, AF induction rate was significantly decreased (4/15, or 26.7%, $p < 0.05$ comparing to AF group, Figure 3).

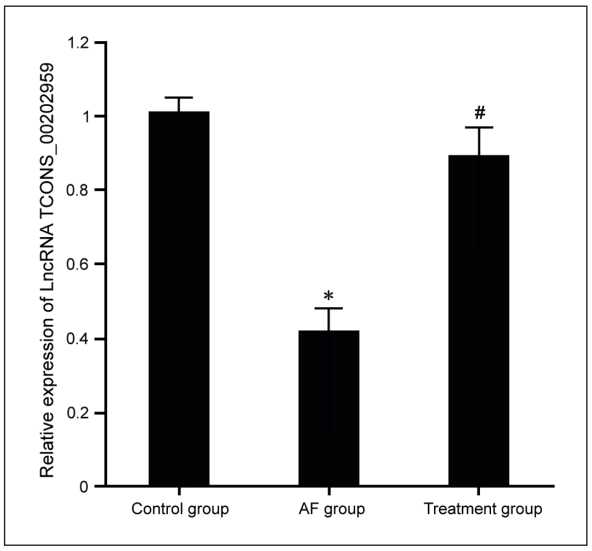

Figure 1. Expression change of lncRNA TCONS_00202959 in rat cardiac tissues. $^{*}p < 0.05$ compared to the control group, $^{\#}p < 0.05$ compared to the AF group.

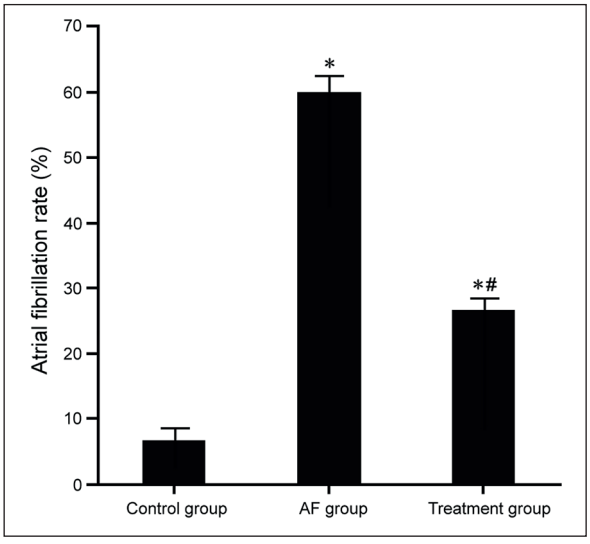

Figure 3. Analysis of AF induction rates among all groups. $^{*}p < 0.05$ compared to the control group, $^{\#}p < 0.05$ compared to the AF group.

Table II. Analysis of autonomic nervous functions among all groups.

Group	SDNN (ms)	SDANN (ms)	RMSSD (ms)	SDNNindx (ms)	LF/HF
Control	128 ± 17.2	121.3 ± 12.4	31.2 ± 9.1	49.1 ± 4.2	5.7 ± 0.7
AF	85.1 ± 1 1.7*	81.2 ± 12.3*	17.8 ± 7.2*	31.1 ± 5.3*	3.5 ± 0.9*
Treatment	106.6 ± 15.2*#	115.9 ± 10.6#	28.1 ± 6.5#	40.9 ± 5.7*#	4.8 ± 0.6*#

*$p < 0.05$ compared to the control group, #$p < 0.05$ compared to the AF group.

Analysis of Autonomic Nervous Functions Among All Groups

We further analyzed the parameters for AF rat autonomic nervous function including SDNN, SDANN, RMSSD, SDNNindx and LF/HF ratio. The results showed that AF rats had decreased autonomic nervous function indexes SDNN, SDANN, RMSS and SDNNindx, whilst the LF/HF ratio was increased ($p < 0.05$ compared to the control group). After up-regulating lncRNA TCONS_00202959 expression in atrial tissues, the parameters for autonomic nervous functions including SDNN, SDANN, RMSSD and SDNNindx were increased with lower LF/HF ratio ($p < 0.05$ compared to AF group, Table II).

Analysis of TH and CHAT Expression in Rat Heart Tissues

Western blot was employed for revealing the expressional change of TH and CHAT in rat heart tissues among all groups. The results found enhanced TH expression plus decreased CHAT expression in AF rat heart tissues ($p < 0.05$ compared to the control group). The treatment group had elevated expression of lncRNA TCONS_00202959, plus lower TH and higher CHAT expression ($p < 0.05$ compared to AF group, Figure 4).

Discussion

Most of the newly discovered loci related with cardiovascular diseases locate in the non-coding region of genes, thus affecting the expression and function of lncRNAs. Moreover, single gene polymorphism analysis showed that most of the cardiovascular disease-related candidates are within lncRNA[18]. Therefore, lncRNAs may participate in the onset and progression of cardiovascular diseases. LncRNA Carl can inhibit mitochondrial fission by modulating prohibitin 2 (PHB2), providing novel targets for treating cardiac ischemia. Besides, circulated lncRNAs have been found to be associated with ST-segment elevated myocardial infarction or heart failure[19,20]. Studies have found abnormal expression of lncRNA TCONS_00202959 in AF patients, but they lacked a full explanation for mechanisms. This work generated a rat AF model to confirm decreased expression of lncRNA TCONS_00202959, and further analyzed the effect of lncRNA TCONS_00202959 on rat AF pathogenesis. The results confirmed the decreased lncRNA TCONS_00202959 expression in AF group, which also had shortened AERP and elevated AF induction rate. The treatment group received transfection of lncRNA

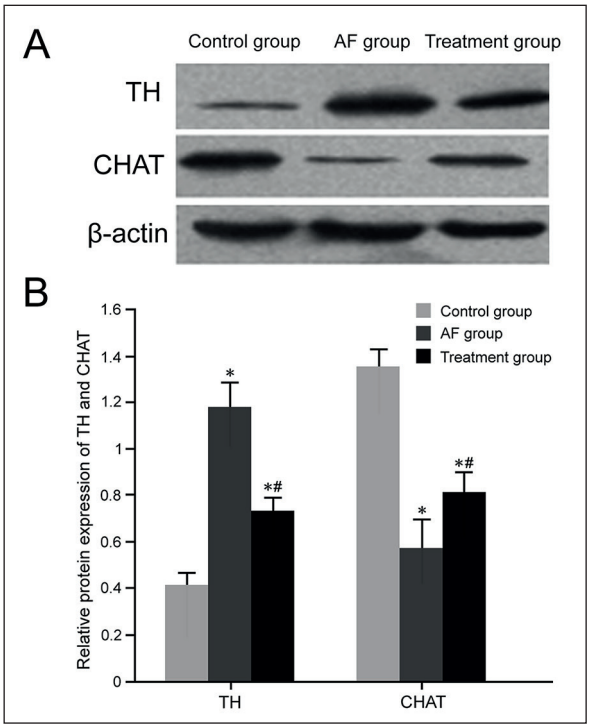

Figure 4. TH and CHAT expression in rat heart tissues. ***A,*** Western blot for TH and CHAT expression in cardiac tissues among all groups of rats. ***B,*** Expressional analysis of TH and CHAT in rat heart tissues. *$p < 0.05$ compared to the control group, #$p < 0.05$ compared to the AF group.

TCONS_00202959 to facilitate its up-regulation, leading to elongated AERP and decreased AF induction rate. These findings showed that lncRNA TCONS_00202959 had effects on myocardial tissues, and the regulation of lncRNA TCONS_00202959 can decrease AF incidence. Autonomic nervous can modulate cardiac function, and central parasympathetic/sympathetic nerves plus peripheral parasympathetic/sympathetic nerves can exert wide and complicated roles in atrial muscles. The establishment of the neural regulatory network can be attributed to the autonomic nervous system, which can modulate electrophysiological properties at multiple layers, as it can enhance the stimuli of atrial muscular transduction, the formation of reentrant and shortened AERP[21]. The sympathetic nerve can enhance the stimuli of neural plexus, shorten AERP and increased AF sensitive window, further contributing to AF pathogenesis[22]. Therefore, the balance between the sympathetic and parasympathetic nerves can help to stabilize myocardial function and to prevent AF occurrence. This work demonstrated that AF group showed decreased autonomic nervous system function indexes SDNN, SDANN, RMSSD and SDNNindx and increased LF/HF ratio, whilst sympathetic nerve indicator TH showed up-regulation plus decreased expression of parasympathetic nerve protein CHAT. The treatment group had elevated expression of lncRNA TCONS_00202959, increased autonomic nervous function indexes SDNN, SDANN, RMSSD and SDNNindx, decreased LF/HF ratio plus lower TH expression and higher CHAT expression. These results suggest that lncRNA TCONS_00202959 during the AF process can modulate expression and function of cardiac autonomic nervous function, and compromise myocardial function. Therefore, lncRNA TCONS_00201959 can work as a potentially novel target for preventing AF. In the next step, we aimed to further investigate the related mechanism of lncRNA TCONS_00202959 in AF and substantiate them in clinical trials.

Conclusions

We observed that rat AF model had decreased expression of lncRNA TCONS_00202959. The regulation of lncRNA TCONS_00202959 can inhibit the expression or function of rat cardiac autonomic nervous, thus preventing AF pathogenesis.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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