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Original Paper

Identification of Prognostic Value of Rs3735590 Polymorphism in 3′-Untranslated Region (3′-UTR) of Paraoxonase 1 (PON-1) in Chronic Obstructive Pulmonary Disease Patients who Received Coronary Artery Bypass Grafting (CABG)

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Key Words
Prognosis • Rs3735590 • 3′-UTR • *PON1* • COPD • CABG

Abstract
Background/Aims: In the treatment of serious and symptomatic coronary heart disease (CHD), coronary artery bypass grafting (CABG) is a frequently utilized intervention. In addition, the risk of CHD is strongly associated with the low activity of paraoxonase-1 (*PON1*), whose 3′-UTR harbors an rs3735590 polymorphism. The aim of this study was to investigate whether the rs3735590 polymorphism could be used as a prognosis marker in chronic obstructive pulmonary disease (COPD) patients undergoing CABG. In addition, the hypothesis, i.e., the rs3735590 polymorphism may be involved in the regulation of *PON1* gene expression via modulating its interaction with miRNAs, was tested in this study. ***Methods:*** 292 patients diagnosed with COPD and treated with CABG were recruited for this study. Genomic DNA was extracted from clinical samples, and real-time quantitative PCR and Western-blot were used to measure the expression of miR-616 and *PON1* in liver cells of different genotypes. ***Results:*** 292 COPD patients were divided into three groups according to their genotypes, i.e., rs3735590: CC (212), TC (75), and TT (5), respectively (TC and TT were merged in one group of T carriers for statistical analyses). Patients with the CC genotype were associated with a shorter event-free survival time as compared to patients with the T genotypes. In addition, *PON1* was confirmed as a direct target gene of miR-616, while experiments with primary cells of different genotypes showed that miR-616 inhibited the expression of *PON1* in CC cells. On the contrary, rs3735590 impaired such inhibitory effect of miR-616 in TT cells. ***Conclusion:*** The rs3735590 polymorphism of *PON1* acts as a prognostic biomarker in COPD patients treated by CABG.

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Introduction

In the treatment of serious and symptomatic coronary heart disease (CHD), coronary artery bypass grafting (CABG) is a frequently utilized intervention. However, stenosis occurs in up to 30% of vein grafts within the 1st year following CABG procedure and in about 50% of vein grafts during the next ten years. The primary reason leading to graft occlusion is the development of thrombosis in the early period following surgery, and subsequent intimal hyperplasia that results in graft failure in the first year following implantation. In addition, stenosis generally occurs in grafts during the development of atherosclerosis more than 1 year after the surgery [1].

The correlation between the diagnosis of chronic obstructive pulmonary disease (COPD) or a decreased forced expiratory volume (FEV1) and post-CABG mortality and morbidity have suggested that COPD is a risk factor of postoperative morbidity and mortality following CABG [2, 3]. Nevertheless, improvements have been made in surgical techniques in the past decades, thus resulting in a decreased rate of postoperative complications. In addition, the discovery of new biomarkers to link CABG with COPD and to predict the prognosis of CABG will be of great clinical significance [4, 5].

The risk of CHD is closely associated with the low activity of paraoxonase-1 (*PON1*) [6]. Moreover, it has been shown that a correlation is present between a natural anti-atherosclerotic agent, PON1, and the prognosis of CHD patients following CABG [7]. Meanwhile, *PON1* is an enzyme involved in the lipid metabolism, while a low level of PON1 activity is associated with a decreased concentration of high-density lipoproteins (HDL) that suggests a greater risk of CHD and a poor prognosis in patients receiving surgical interventions [7]. Consistent with such results, the variants located in *PON1* gene have been found to be associated with the risk of COPD [8].

MicroRNAs (miRNAs), a class of single-stranded and conserved non-coding RNAs, can modulate a diverse set of biological processes including cellular development, differentiation and proliferation [9]. The biological functions of miRNAs have not been fully clarified, although it is suggested that some miRNAs are present only in a certain type of cells or tissues [10]. Recently, miRNAs have also been discovered in a number of different body fluids, such as serum and plasma, while the levels of circulating miRNAs have been identified as new biomarkers associated with numerous disorders [10]. A recent study has also demonstrated an elevated level of circulating miRNA in patients suffering from acute myocardial infarctions [11].

PON1 is related to the prognosis in patient undergoing CABG, whereas a polymorphism (rs3735590) has been located in the miR-616 binding site within the 3'UTR of PON1 [7, 12]. The aim of this study was to investigate whether rs3735590 polymorphism could be used as a prognosis marker in COPD patients undergoing CABG. In this study, we tried to validate that *PON1* acts as a target gene of miR-616 in the CC genotype, and the rs3735590 polymorphism could point to poor prognosis in COPD patients undergoing CABG.

Materials and Methods

Subjects

292 COPD patients undergoing CABG treatment were enrolled into this research. Coronary angiogram was used to confirm the occurrence of CHD, and Event-free survival was recorded and evaluated in the statistical analysis. Peripheral blood samples were collected from the 292 patients using a Lymphocyte Separation Medium (Human) (Applygen Technologies Inc. Beijing, China) in accordance with the manufacturer's guideline. The research was carried out according to the latest version of the Declaration of Helsinki. The participants all signed the form of informed consent for participation in the study after the potential risks have been explained to them. The institutional Ethics and Research Committees at China-Japan Union Hospital of Jilin University has approved this study.

Genotyping

Following the isolation of DNA from the leucocytes in the blood samples, PCR was used to amplify the fragment containing the rs3735590 polymorphism. The PCR product was purified for direct sequencing on an ABI 3730xl sequencer (Applied Biosystems, Foster City, CA). Each test was repeated three times.

Luciferase assay

PCR was used to amplify the 3'UTR of PON1 that harbors the binding site of miR-616. The PCR products were subsequently inserted into multiple sites of a pMIR-REPORT expression reporter vector (Ambion, Naugatuck, CT) in accordance with the manufacturer's instruction. An Easy Mutagenesis System kit (TransGen Biotech, Beijing, China) was used to mutate the 3'UTR of human PON1. In order to carry out the luciferase reporter assay, primary cells (CC genotype) were seeded into 48-well plates and co-transfected with 20 ng of pRL-TK and 400 ng of luciferase reporter vector using Lipofectamine 2000 (Invitrogen, Carlsbad, CA). A Dual-Luciferase Reporter Assay System (Promega, Madison, WI) was used to detect the luciferase activity. Three independent experiments were carried out.

Isolation and culture of primary liver cells

Liver tissues of different genotypes were collected from the patients and digested in 0.30% trypsin (Sigma, St. Louis, MO) for 30 min at 37°C, followed by incubation in 0.2% collagenase (Gibco/Invitrogen, Carlsbad, CA) at 37°C for 5 additional hours. A 40-μm cell strainer (BD Falcon, Bedford, MA) was used to prepare a single-cell suspension, which was then centrifuged for 12 min at 1,000 rpm to obtain a cell pellet. The cells were then cultured at 37°C and 5% CO_2 in an RPMI 1640 medium (Gibco/Invitrogen, c) contained 10% fetal bovine serum (FBS) (Gibco/Invitrogen, Carlsbad, CA) and 1% PS (100 μg/mL streptomycin and 100 U/mL penicillin). After 12 hours of incubation, the medium was replaced to remove non-adherent cells.

RNA isolation and real-time quantitative PCR

An RNeasy Mini Kit (Qiagen, Hilden, Germany) was used to isolate total RNA from tissue samples and primary cells. A UV absorbance spectrophotometer (Nanodrop; Thermo Scientific, Wilmington, DE) was used with 1.5% (m/v) agarose gel electrophoresis to determine the quality and quantity of isolated RNA. Moloney Murine Leukemia Virus Reverse Transcriptase (Applied Biosystems, Foster City, CA) was used to reversely transcribe the RNA into cDNA. Real-time PCR was performed on an ABI 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA) using SYBR-Green I (Qiagen, Hilden, Germany). The cycle threshold (Ct) values were calculated using the SDS software (Applied Biosystems, Foster City, CA), and the values of $2^{-\Delta\Delta Ct}$ were used to determine the relative gene expression of PON1 mRNA and miR-616.

Cell culture and transfection

Cells were cultured to 80% confluency and were co-transfected with miR-616 mimics and inhibitors using Lipofectamine™ 2000 (Invitrogen, Carlsbad, CA). Each transfection was performed in triplicate.

Paraoxonase activity

A 50-mM NaOH/glycine buffer (pH 10.5) containing 1.0 mM $CaCl_2$ and 1.0 mM paraoxon was used to assay the paraoxonase activity, which was calculated by measuring the absorbance of the samples at 412 nm on a spectrophotometer (DU 640; Beckman, San Jose, CA).

Western blot analysis

A Hanks's balanced salt solution (pH 8.0, Beyotime, Beijing, China) was used to wash the cells, which were subsequently lysed in a lysis buffer containing 2 mg/mL pepstatin, 2 mg/mL aprotinin, 5 mg/mL leupeptin, 1 mM phenyl methyl sulfonyl fluoride, 1 mM DTT, 2 mM EDTA, 10 mM NaCl, 0.1% SDS, 1% NP-40 and 50 mM Tris–HCl. A Bradford protein assay kit (Bio-Rad, Hercules, CA) was used to measure the protein concentration of lysates.

10% SDS PAGE was used to separate the proteins, which were then transferred onto a nitrocellulose membrane (Whatman, Maidstone, UK). TBST (0.05% Tween 20, 150 mM NaCl and 10 mM Tris–HCl, pH 8.0) supplemented with 5% BSA was used to block the membrane for 60 min. The primary anti-PON1 antibody (1:3000, Cell Signaling Technology, Boston, USA) was used to blot the membrane at 4°C for 12 hours or at 25°C for 1 hour, followed by incubating the membrane for another 1 hour at 37°C with appropriate secondary antibodies conjugated to horseradish peroxidase (HRP) (1:10000, Cell Signaling Technology, Boston, MA). An enhanced chemiluminescence-detection system (Bio-rad, Hercules, CA) was used to visualize the protein bands.

Statistical analysis

SPSS for Windows rel. 14 (SPSS Inc. IBM, Chicago, IL) was used to statistically analyze the data. Nonparametric Mann-Whitney test was used to compare continuous variables, whereas Fisher exact test was used to analyze discontinuous variables. Spearman test was used to calculate the correlations, while the event-free survival between the two groups of patients was compared using a log-rank test and the Kaplan-Meier method. The multivariate HR (hazard ratio) was assessed using competing risk models. Since the number of patient samples harboring the TT genotype was low, TC and TT samples were combined into one group (i.e., group of T genotypes) in the analysis. All results were shown as mean ± standard deviation (SD). A P value of < 0.05 was considered statistically significant.

Results

Demographic and clinicopathological features of the participants recruited in the study

292 participants were diagnosed with COPD and underwent CABG treatments. These patients were divided into three groups according to their genotypes, PON1: CC: 212, TC: 75 and TT: 5, respectively, and then the patients in the TC and TT groups were merged in one group of T carriers for statistical analyses. The demographic and clinicopathological features of the subjects, such as age, gender, and the levels of total cholesterol, LDL, HDL, and triglyceride, were summarized in Table 1. The demographic and clinicopathological features in different groups were compared using the student t-test, and no significant difference was observed, except that the level of HDL cholesterol in the CC group was much lower than that in the T group.

Table 1. Demographic and clinical characteristics of the study groups

Characteristic	CC (n=212)	TC/TT (n=75+5)	*p*-Value
Men (%)	150 (70.75)	58 (72.50)	0.821
Age (years ± SD)	60.22 ± 8.24	61.32 ± 9.21	0.451
Level of total cholesterol (mmol/l ± SD)	5.21 ± 0.92	5.12 ± 1.21	0.512
Level of LDL cholesterol (mmol/l ± SD)	3.32 ± 0.52	3.12 ± 0.71	0.564
Level of HDL cholesterol (mmol/l ± SD)	1.32 ± 0.24	2.25 ± 0.52	＜0.001
Triacylogliceroles (mmol/l ± SD)	1.78 ± 0.35	1.52 ± 0.41	0.251
Body mass index (kg/m2 ± SD）	25.14 ± 4.51	26.12 ± 4.14	0.345
Smokers (%)	60 (28.30)	22 (27.50)	0.185
Hypertensives (%)	128 (60.38)	49 (61.25)	0.212
Family history of CAD (%)	26 (12.26)	10 (12.50)	0.621
Diabetes (%)	32 (15.09)	13 (16.25)	0.145
Severity of coronary artery disease			
Patients with 1-vessel disease (%)	17 (8.02)	6 (7.50)	
Patients with 2-vessel disease (%)	54 (25.47)	18 (22.50)	
Patients with 3-vessel disease (%)	141 (66.51)	56 (70.00)	0.847
Vessels involvement			
Patients with left main stenosis (%)	15 (7.08)	5 (6.25)	
Patients with RCA main stenosis (%)	130 (61.32)	51 (63.75)	
Patients with LAD main stenosis (%)	35 (16.51)	11 (13.75)	
Patients with Cx main stenosis (%)	32 (15.09)	13 (16.25)	0.931
Patients with implanted			
1 graft (%)	15 (7.07)	4 (5.00)	
2 grafts (%)	84 (39.63)	29 (36.25)	
3 grafts (%)	92 (43.39)	37 (46.25)	
4 grafts or more(%)	21 (9.91)	10 (12.50)	0.793
Surgical time (min)	214.51 ± 56.14	220.15 ± 72.14	0.582

PON1 rs3735590 polymorphism acted as a prognosis marker in CHD patients undergoing cardiac surgery

Complete risk models were utilized to determine whether the rs3735590

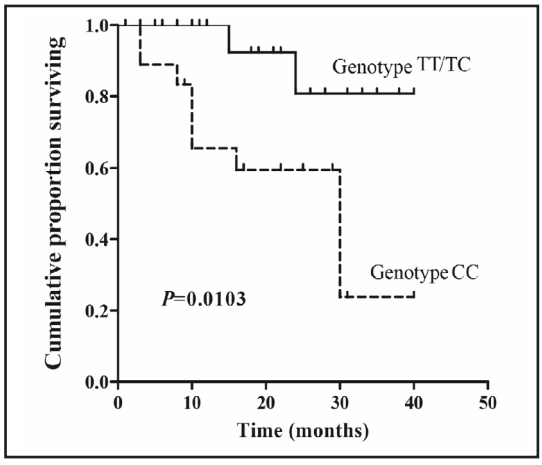

Fig. 1. PON1 rs3735590 is a prognosis marker for CHD patients. Kaplan-Meier curves of CHD patients with post-CABG event-free survival based on PON1 rs3735590.

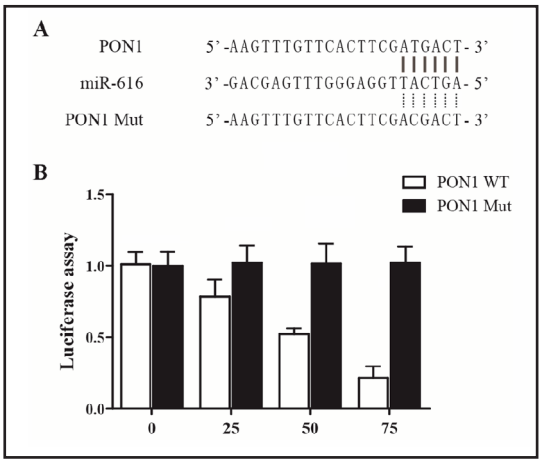

Fig. 2. PON1 containing mutant 3'UTR lost miR-616 induced inhibition. A: Schematic presentation of miR-616 and wild-type/mutant 3'-UTR of PON1. B: Luciferase activity following the transfection of primary hepatocytes (genotyped as CC) with the miR-616 mimics and the plasmids carrying the wild-type or mutant 3'UTR of PON1.

polymorphism played a crucial role in the event-free survival of CHD patients post CABG. As shown in Fig. 1, the CC genotype was apparently associated with a reduced event-free survival time as compared to T genotypes, indicating that PON1 rs3735590 was involved in the survival of post-CABG CHD patients. In addition, the PON1 T allele evidently increased the survival rate of post-CABG CHD patients.

PON1 was a target gene of miR-616

According to the results of our computational analysis performed using an online target predicting tool (www.targetscan.org), *PON1* was identified as a potential target gene of miR-616 (Fig. 2A). To investigate whether miR-616 was involved in the regulation of PON1 expression, a DNA fragment for the 3'UTR of *PON1* was constructed to contain the predicted binding site for miR-616. In addition, the DNA fragment containing a mutated *PON1* 3'UTR, which lacked the binding site for miR-616, was also constructed for comparison. Subsequently, primary hepatocytes genotyped as CC were co-transfected with PON1-WT (wild type)-3'UTR or PON1-MT (mutant)-3'UTR constructs in conjunction with different concentrations of miR-616 (25 nM, 50 nM, and 75 nM). The luciferase activity in transfected cells was detected at 48 hour after the transfection. As shown in Fig. 2B, miR-616 mimics suppressed the luciferase activity in cells transfected with wild-type PON1 3'UTR constructs. On the contrary, miR-616 mimics did not affect the luciferase activity in cells transfected with the mutant PON1 3'UTR construct, indicating that *PON1* was a direct target of miR-616.

Rs3735590 impaired the inhibitory effect of miR-616 on PON1 expression

To investigate whether miR-616 interacts with *PON1* rs3735590, the expression of miR-616 and PON1 was further measured in CC hepatocytes using qPCR and Western blotting. In addition, the paraoxonase activity in primary hepatocytes genotyped as CC was also measured. The results showed that miR-616 mimics down-regulated the expression of PON1 and inhibited the paraoxonase activity in primary hepatocytes (Fig. 3). On the contrary, miR-616 inhibitors up-regulated the expression of PON1 and increased the paraoxonase activity (Fig.4). Therefore, it can be confirmed that miR-616 regulates the PON1 expression in primary hepatocytes genotyped as CC.

Since the hepatocytes genotyped as TT lost miR-616 mediated reduction in luciferase activity, we also tested whether rs3735590 impaired the inhibitory effect of miR-616 on

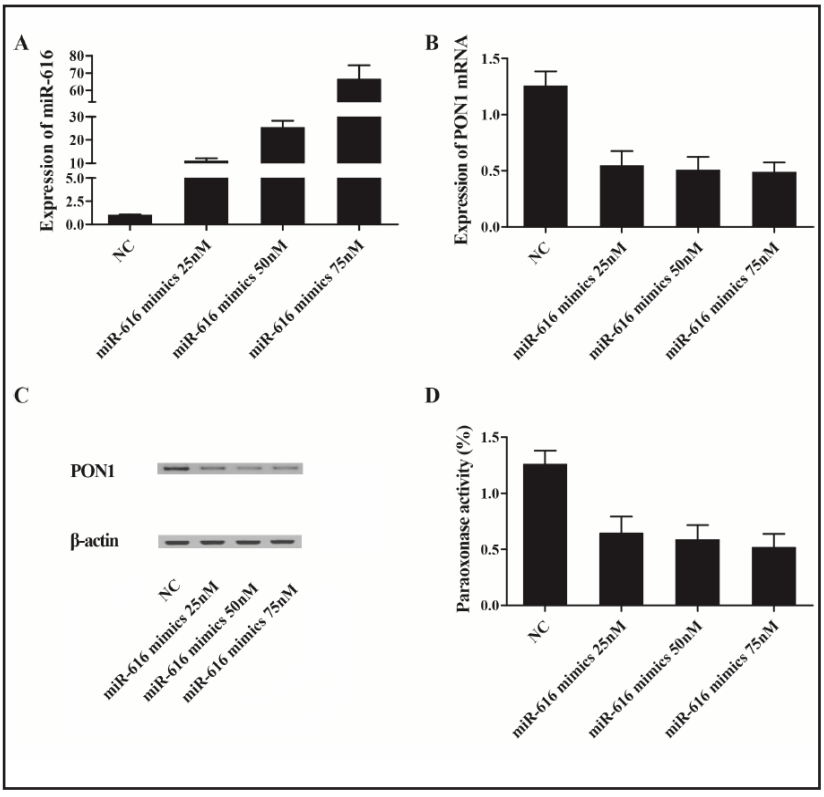

Fig. 3. Expression of PON1 (containing WT 3'UTR) was inhibited by miR616 mimics. We evaluated the mechanism by which miR-616 interacted with PON1 rs3735590. The primary hepatocytes (genotyped as CC) were transfected with different concentrations of miR-616 mimics. A. The mRNA expression level of PON1 in cells transfected by different concentrations of miR-616 mimics. B. The protein expression level of PON1 in cells transfected by different concentrations of miR-616 mimics. C. Paraoxonase activity in cells transfected by different concentrations of miR-616 mimics.

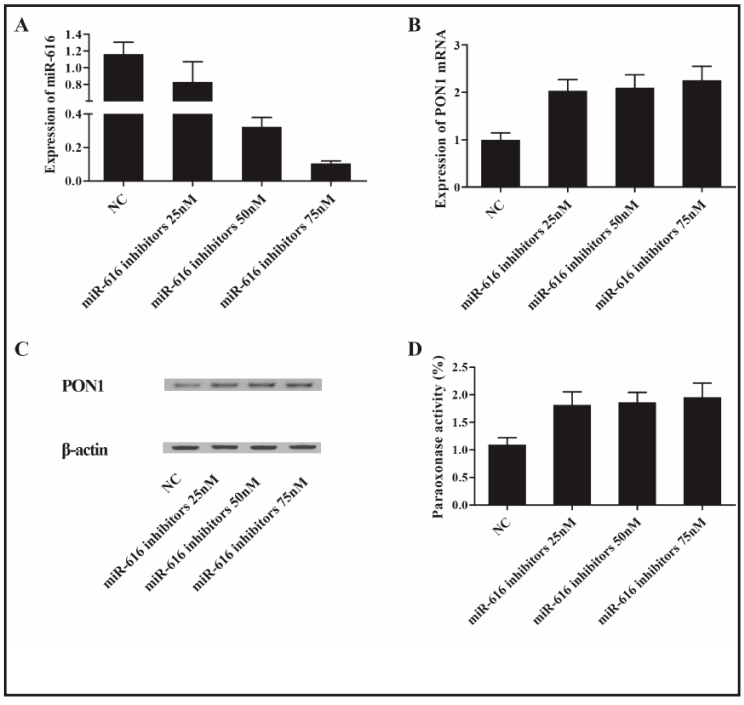

Fig. 4. Expression of PON1 (containing WT 3'UTR) was upregulated by miR-616 inhibitors. We evaluated the mechanism by which miR-616 interacted with PON1 rs3735590. The primary hepatocytes genotyped (genotyped as CC) were transfected with different concentrations of miR-616 inhibitors. A. The expression level of miR-616 in cells transfected by different concentrations of miR-616 inhibitors. B. The mRNA expression of PON1 in cells transfected by different concentrations of miR-616 inhibitors. C. The protein expression of PON1 in cells transfected by different concentrations of miR-616 inhibitors. D. Paraoxonase activity in cells transfected by different concentrations of miR-616 inhibitors.

the expression of PON1 in TT hepatocytes. Although miR-616 mimics were successfully transfected into TT hepatocytes (Fig. 5A), the expression of PON1 was not affected (Fig. 5B &C). Meanwhile, the paraoxonase activity was also not affected by the presence of miR-616 mimics (Fig. 5D). Similarly, miR-616 inhibitors did not increase the expression of *PON1* or paraoxonase activity in primary hepatocytes genotyped as TT (Fig. 6).

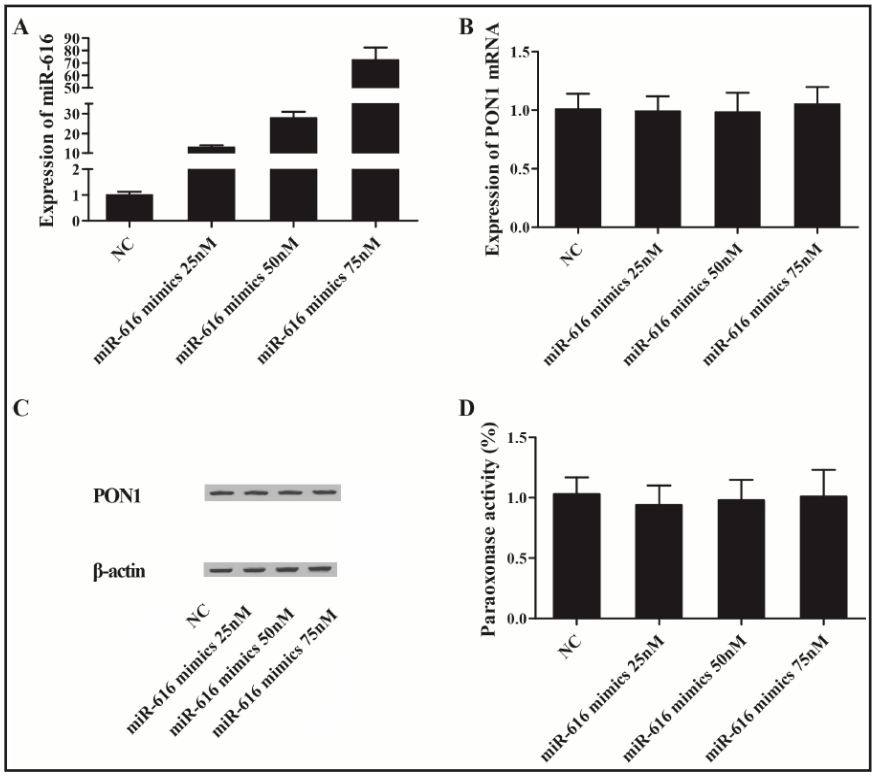

Fig. 5. MiR616 mimics did not affect the expression of PON1 harboring the mut 3'UTR. We evaluated the mechanism by which miR-616 interacted with PON1 rs3735590. The primary hepatocytes (genotyped as TT) were transfected with different concentrations of miR-616 mimics. A. The expression of miR-616 in cells transfected by different concentrations of miR-616 mimics. B. The mRNA expression of PON1 in cells transfected by different concentrations of miR-616 mimics. C. The protein expression of PON1 in cells transfected by different concentrations of miR-616 mimics. D. Paraoxonase activity in cells transfected by different concentrations of miR-616 mimics.

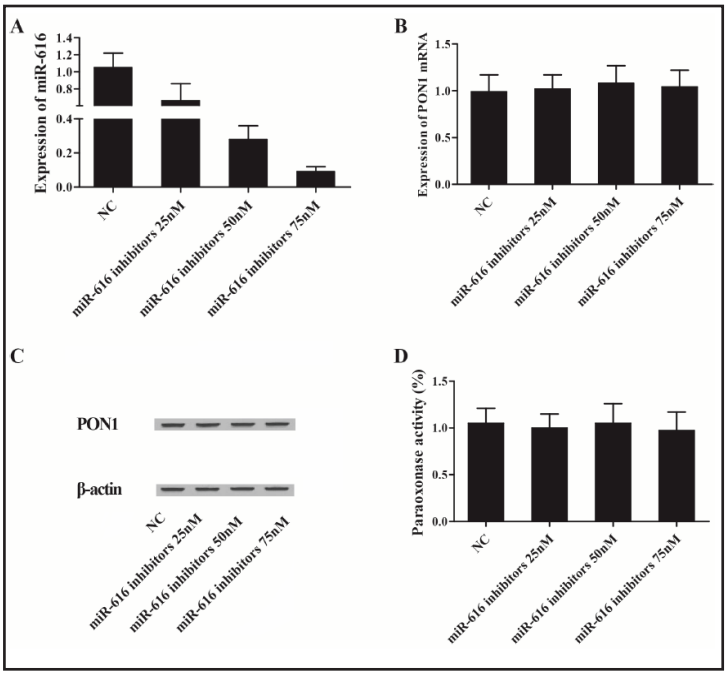

Fig. 6. MiR616 inhibitors did not affect the expression of PON1 harboring the mut 3'UTR. We evaluated the mechanism by which miR-616 interacted with PON1 rs3735590. The primary hepatocytes (genotyped as TT) were transfected with different concentrations of miR-616 inhibitors A. The expression of miR-616 in cells transfected by different concentrations of miR-616 inhibitors. B. The mRNA expression of PON1 in cells transfected by different concentrations of miR-616 inhibitors. C. The protein expression of PON1 in cells transfected by different concentrations of miR-616 inhibitors. D. Paraoxonase activity in cells transfected by different concentrations of miR-616 inhibitors.

Discussion

PON1 is an enzyme synthesized in the liver and released in the blood stream, and is primarily correlated with the level of HDL [13]. As an antioxidant, PON1 can hydrolyze lipid

peroxides, which in turn catalyze the breakdown of oxidized phospholipids originated from low-density lipoproteins (LDL) [14]. Hence, PON1 plays a critical role in lipid metabolism and protects the body against the development of atherosclerotic plaques [15]. In addition, it has been shown that patients suffering from cardiovascular disorders have lower serum PON1 activity [16]. Among different risk factors, a correlation exists between polycystic ovarian syndrome and the elevated incidence of cardiovascular diseases as well as reduced serum PON1 activity [17]. Furthermore, it has been shown that in different disorders induced by oxidative stress, the activity of PON1 was decreased to trigger an imbalance between antioxidants and oxidants [18]. Since a reduced level of PON1 arylesterase and decreased paraoxonase activity were observed in COPD patients [19], some studies have suggested that the PON1-192R genotype is more prone to CHD, and hence the PON1-192 polymorphism might act as a biomarker for atherosclerosis [20]. The acquired factors rather than genetic factors may account for the reduced level of PON1 in CHD [21], which seems to be relevant in CHD patients, where the level of lipid peroxides is increased [22]. Recent data have also suggested that the polymorphisms in the promoter region of PON1 gene could significantly affect the expression of PON1, and there is a correlation between the low expression of PON1 and an elevated incidence of CHD in diabetic patients [23, 24].

MiRNAs play an inhibitory role in gene expression via binding to the 3′UTR of their target mRNAs. The amount of circulating miRNAs in humans can be accurately measured, and those patients suffering from acute myocardial infarction exhibited different levels of plasma miRNAs [25, 26]. MiRNAs, such as miR-133a, miR-133b and miR-499, were more quickly released and detected in the blood during the early myocardial injury post CABG. For example, in 30% of the patients undergoing CABG, the peak of plasma miR-499 occurred at 1 h following reperfusion [27]. Similarly, the expression of miR-616 in malignant prostate tissues was higher than that in benign prostate specimens. In addition, stable over-expression of miR-616 in LNCaP cells promoted castration resistance and the proliferation of prostate cancer cells [28].

The binding affinity of miRNAs can be changed by modifying the sequence of their 3′UTRs [29-31], suggesting that the expression of a particular gene may be impacted by the single-nucleotide polymorphisms (SNPs) located in its miRNA binding sites, thus affecting the pathogenesis and progression of individual disorders. If the binding of a miRNA to its target gene can be impacted by an SNP, such SNP is known as a miR-SNP [32]. In a study of Liu et al, the expression of PON1 was elevated and the binding ability of miR-616 to the 3'-UTR of PON1 was reduced when the cells were transfected with a plasmid construct carrying the T allele in the SNP known as rs3735590. In addition, the TT genotype at rs3735590 reduced miR-616 binding affinity, thus leading to the overexpression of PON1. PON1 was identified as a target gene of miR-616, and a correlation between the TC genotype and a markedly reduced risk of both thinner intima media thickness (IMT) and ischemic stroke was found in the Han Chinese population [12]. Liu et al. also suggested that the SNP rs3735590 (C>T) in human could affect the binding of miR-616 to PON1, thus leading to a higher risk of carotid atherosclerosis and ischemic stroke [12]. In our study, miR-616 inhibited PON1 in primary hepatocytes genotyped as CC. On the contrary, rs3735590 impaired the inhibitory effect of miR-616 on the expression of PON1 in primary hepatocytes genotyped as TT. The paraoxonase activity also showed a similar trend. In addition, 292 COPD patients undergoing CABG were enrolled in this study and were divided into three groups based on their PON1 genotype (CC: 212, TC: 75 and TT: 5, respectively, and the TC and TT groups were merged in one group of T carriers for statistical analyses). It was found that the level of HDL cholesterol in subjects carrying the CC genotype was significantly lower than that in subjects carrying T genotypes. In addition, the PON1 rs3735590 polymorphism (CC) was associated with a shorter time of event-free survival.

Conclusion

The presence of the minor allele of rs3735590 interfered with the binding of miR-616 to the 3' TUR of PON1, and the rs3735590 polymorphism could function as a prognostic biomarker in COPD patients undergoing CABG.

Abbreviations

CABG (coronary artery bypass grafting); CHD (coronary heart disease); COPD (chronic obstructive pulmonary disease); FEV_1 (Forced Expiratory Volume in the first second); HDL (High-density lipoprotein); IMT (intima media thickness); LDL (Low-density lipoprotein); NC (Negative control); PON1 (Paraoxonase 1); SNP (single-nucleotide polymorphism); UTR (untranslated region).

Disclosure Statement

None.

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