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Original Article

Linc-OIP5 working as a ceRNA of miR-616 promotes PON1 expression in HUEVC cells

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Abstract: Coronary atherosclerosis affects human health all over the world. PON1 was found to be associated with coronary atherosclerosis but the specific mechanism is still unclear. Non-coding RNA plays an important role in many diseases. In recent years, studies have focused on non-coding RNA in coronary atherosclerosis. In this study, we investigated the effect of non-coding RNA Linc-OIP5 on PON1 expression. Results showed that in the serum of patients with coronary atherosclerosis, there was lower PON1 activity and PON1 level, the same trend in Linc-OIP5, and the opposite trend in miR-616 expression. Through further cell experiments, with up-regulation or down-regulation of Linc-OIP5 and miR-616, we found that Linc-OIP5 positively regulated the expression of PON1 gene and its protein level, while miR-616 negatively regulated the expression of PON1 gene and protein. Through further functional experiments, we also found that the levels of superoxide dismutase (SOD) and nitric oxide (NO) related to oxidative stress also had corresponding changes. Further dual luciferase reporter assay demonstrated that Linc-OIP5 regulated PON1 expression as a ceRNA of miR-616. Thus Linc-OIP5 working as a ceRNA of miR-616 apparently promotes PON1 expression in HUEVC cells and Linc-OIP5 and miR-616 may be an ideal target for the treatment of coronary atherosclerosis in the future.

Keywords: Coronary atherosclerosis, PON1, miR-616, Linc-OIP5, superoxide dismutase, nitric oxide

Introduction

Atherosclerotic cardiovascular disease (ASCVD) poses a great threat to public health and is the main cause of death in the world [1]. Although the exact pathogenesis of ASCVD is not clear, it is believed that genetic factors play an important role in its occurrence and development.

MicroRNAs (miRNAs) are about 21 nucleotide RNAs. miRNAs can bind to 30 untranslated regions (UTR) of target mRNA for post-transcriptional regulation. Research shows that miRNAs play an important role in the biological processes of embryo development, cell proliferation and differentiation, cell apoptosis, fat metabolism, and tumorigenesis [2, 3]. Some miRNAs have been found to be involved in atherosclerosis [4, 5].

Evidence shows that LncRNAs are involved in many human pathophysiologic processes including cardiovascular diseases [6, 7]. It has been proven that LincRNA-OIP5 affects atherosclerosis by affecting endothelial cell apoptosis [8]. Here, we demonstrate that LincRNA-OIP5 is lowly expressed in the blood of patients with coronary heart disease, and that LincRNA-OIP5 promotes PON1 expression by acting as a competing endogenous RNA (ceRNA) of miR-616 in HUVEC cells.

Materials and methods

PON1 LACtonase activity

Using dihydrocoumarin (DHC) as a substrate, the activity of PON1 LACase activity was determined according to the modified method described [9]. PON1 LACase activity was measured in a cuvette containing 1 mM DHC, 50 mm Tris HCl buffer (pH 8.0), in a total volume of 1 mL. The reaction was started by adding 2.5 μL serum or cell culture medium, and the absorbance increase at 270 nm was monitored at

25°C for 3 minutes. The molar extinction coefficient was used for calculation.

Western blot analysis

Blood and HUVEC treated with siRNA, mimics or inhibitors were collected and dissolved on ice for 10 minutes in the lysis buffer. BCA protein detection kit was used to determine the protein concentration. The cell extracts were centrifuged at 14000× g and 4 C, and the same amount of protein sample (40 g) was loaded onto 10-12% SDS-PAGE gel. After electrophoresis, the gel was blotted onto the PVDF membrane and blocked with 5% (w/v) non-fat milk for one hour at room temperature. The membrane and rabbit anti-PON1 polyclonal antibody (1:1000) were incubated overnight at 4°C. Then incubation was with the second antibody binding with HRP (1:5000) for one hour. The bands were observed by ECL chemiluminescence.

Quantitative real time polymerase chain reaction (real-time PCR)

The total RNA of blood and cells was extracted by Trizol (Invitrogen, Carlsbad, California, USA) according to the manufacturer's protocol. We reverse transcribed the cDNA using PrimeScript™ RT reagent Kit (Takara, Japan), and then used SYBR Premix EX Taq II Kit (Takara, Japan) to perform qPCR on Stepone Plus real-time PCR machine (Applied Biosystems, USA). U6 and β-actin were used as internal controls. Primers were synthesized by Sangon Biotech (Shanghai, China) and the sequences were as follows: PON1 (Forward Sequence 5' to 3') GGATCCATGGCGAAGCTGATTGCGTCTAC, (Reverse Sequence 5' to 3') GCGGCCGCGAGCTCACAGTAAAGAGCTTTG, LincRNA-OIP5 (Forward Sequence 5' to 3') AGAGAATGGAGAGTGAGGCTACC, (Reverse Sequence 5' to 3') 5'-CCAGGCATGGACAGAGGGAT-3', miR-616 (Forward Sequence 5' to 3') ACACTCCAGCTGGGAGTCATTGGAGGGTTT, (Reverse Sequence 5' to 3') TGGTGTCGTGGAGTCG; All reactions were performed in triplicate. Relative gene expression values were compared using the $2^{-\Delta\Delta Ct}$ method.

Plasmid construction

The Linc-OIP5 fragment containing miR-616 binding site was amplified and cloned into pmirGLO vector (Promega, Madison, Wisconsin, USA). PmirGLO-Linc-OIP5-wild-type (pmirGLO-Linc-OIP5-wt) was obtained. We used QuikChange fixed point mutation Kit (Agilent, Santa Clara, California, USA) to mutate the putative binding site of miR-616 in Linc-OIP5 and synthesize pmirGLO-Linc-OIP5 mutant (pmirGLO-Linc-OIP5-mut). The above plasmids were used for the following luciferase analysis. Similarly, the Linc-OIP5 fragment containing the miR-616 binding site was amplified and cloned into the KpnI and XhoI restriction sites (Promega) of pcDNA3.1 vector to synthesize pcDNA3.1-Linc-OIP5-wild-type (pcDNA3.1-Linc-OIP5-wt); pcDNA3.1-Linc-OIP5-mut was also obtained with the rapid change site mutation Kit (Agilent).

Transfections

The procedure was carried out as previously described [10]. Plasmids, mimics, or inhibitor were transfected into HUVEC cells by using Lipofectamine 2000 (Invitrogen, USA) according to the manufacturer protocol. Linc-OIP5-siRNA, miR-616 mimics and miR-616 inhibitor were purchased from GenePharma (Suzhou, China). The sequence of siRNAs, miR-616 mimics, miR-616 inhibitor and miR-616 mimics control were si-LincRNA-OIP5-1# 5'-GTGACTTAAACAGCTTAAATT-3' si-LincRNA-OIP5-2# 5'-TAAACAGTGACTTTAAATTGT-3' si-LincRNA-OIP5-3# 5'-CATAAATTCTGAAATTAGTT-3'. miR-616 mimics, 5'-AGUCAUUGGAGGGUUUGAGCAG-3'; miR-616 mimics control, 5'-ACUACUGAGUGACAGUAGA-3'; miR-616 inhibitor, 5'-GAGUAUCCCG UUGCCAACGAGA-3'. After transfection, total RNA and proteins from HUVECs cells were isolated at 48 h for real-time PCR and Western blot.

Biochemical assays

HUVECs in logarithmic growth stage was dispersed with trypsin and seeded in 6-well plates at a density of 1×10^5 cells/ml (2 ml/well) overnight. After treatment, the NO content and SOD activity in the supernatant were estimated using commercial kits according to the manufacturer's protocol. HUVECs in a 6-well plate were collected in pre-cooled PBS by cell scraper. The HUVECs were lysed by ultrasound for 5 s. Then, 20 μl cell lysate, 20 μl enzyme working solution, 20 μl enzyme diluent and 200 μl substrate working solution were added into each well of 96-well plate, incubated at 37°, and the activity of SOD was measured. To measure NO content, 20 μl cell lysate, 20 μl enzyme working solution, 20 μl enzyme diluent and 200 μl substrate working solution were added and

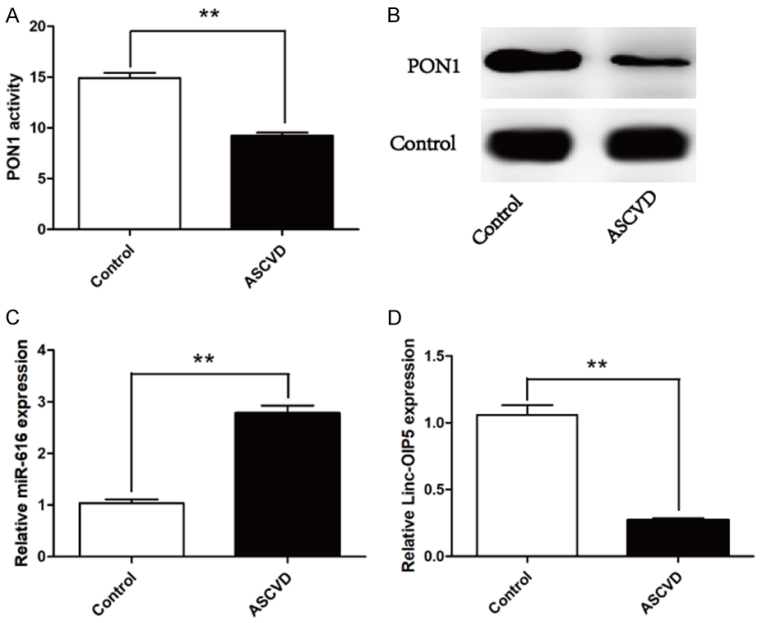

Figure 1. A. PON1 activity is low in patients with atherosclerotic cardiovascular disease. B, D. PON1 protein level and Linc-OIP5 gene expression are low in patients with atherosclerotic cardiovascular disease. C. However, miR-616 gene expression is high in in patients with atherosclerotic cardiovascular disease. **P<0.01.

we added 100 μL of 1× Nitric Oxide Fluorometric Probe to each tested well. We covered the plate wells to protect the reaction from light and incubated at 37°C for 2 hours. We added 100 μL of 1× Cell Lysis Buffer to each tested well, mixed well and incubated for 5 minutes. For measurement: 150 μL of the mixture was transferred to a 96-well plate suitable for fluorescence measurement. Fluorescence was read with a fluorometric plate reader at 480 nm. Values were expressed as the mean ± standard deviation from three independent experiments.

Dual luciferase reporter assay

MiR-616 mimics/mimic control and the constructed reporter plasmids (pmirGLO-Linc-OIP5-wt/pmirGLO-Linc-OIP5-mut) were co-transfected into cultured HUVEC cells with Lipofectamine 2000 (Invitrogen, USA) and incubated for 48 h. Then, the change in fluorescence intensity was evaluated according to the manufacturer's protocol by using the dual luciferase report analysis system (Promega).

Statistical analysis

All data are listed as mean ± standard deviation (SD) from individual experiments. The two groups were compared, and multiple groups were compared using ANOVA. All data presented in this study have been repeated at least three times from three independent runs and are presented as mean ± SD. *p*-values <0.05 were considered significant. Statistical analysis was performed using SPSS19 (IBM, Armonk, New York, USA).

Results

The relationship of PON1, miR-616, and Linc-OIP5 with coronary atherosclerosis

First, we measured the PON1 activity, gene expression and protein expression of PON1 in the blood of patients with coronary atherosclerotic heart disease and normal people. PON1 activity in the blood of patients with coronary atherosclerotic heart disease was significantly lower (**Figure 1A**). In addition, the expression level of PON1 protein in the blood of patients with coronary atherosclerotic heart disease was also relatively low (**Figure 1B**). Second, we measured the level of miR-616 and Linc-OIP5 in the blood of patients with coronary atherosclerotic heart disease and normal people. We found that the level of miR-616 was negatively correlated with PON1 (**Figure 1C**). The level of Linc-OIP5 was positively correlated with the expression level of PON1 (**Figure 1D**).

Downregulation of Linc-OIP5 expression in HUEVCs inhibits PON1 expression

According to the expression of Linc-OIP5 in the blood of patients with atherosclerotic heart disease and normal people, we further verified the effect of Linc-OIP5 on the oxidative stress of HUVECs. Linc-OIP5 siRNA were transfected into HUVEC cells. After 36 hours of transfection, the expression level of Linc-OIP5 was detected again by real-time PCR, and the subsequent SOD activity and NO content were measured. As shown in **Figure 2A**, transfection of Linc-OIP5 siRNA significantly reduced Linc-OIP5 expression, and Linc-OIP5 siRNA2 showed the

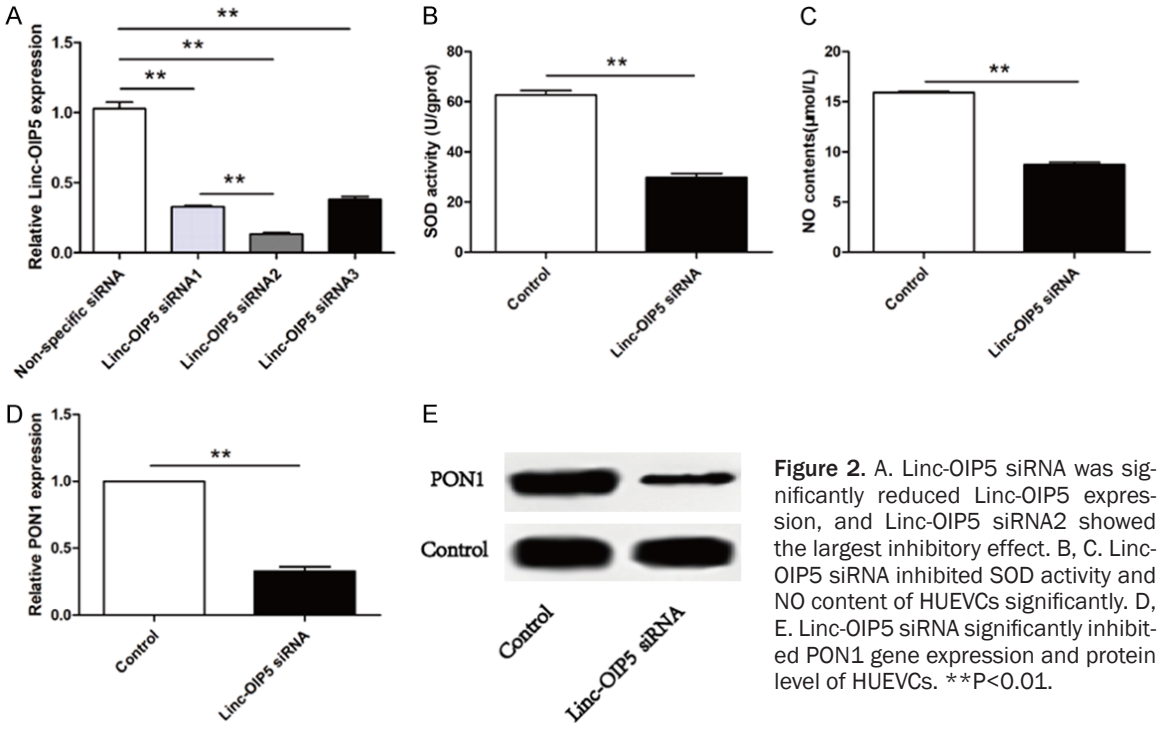

Figure 2. A. Linc-OIP5 siRNA was significantly reduced Linc-OIP5 expression, and Linc-OIP5 siRNA2 showed the largest inhibitory effect. B, C. Linc-OIP5 siRNA inhibited SOD activity and NO content of HUEVCs significantly. D, E. Linc-OIP5 siRNA significantly inhibited PON1 gene expression and protein level of HUEVCs. **P<0.01.

largest inhibitory effect (**P<0.01). Therefore, Linc-OIP5 siRNA2 was selected as the experimental material for RNAi. The results of SOD activity and NO content showed that Linc-OIP5 siRNA inhibits SOD activity and NO content (**Figure 2B**, **2C**). Here, we also examine the impact of Linc-OIP5 on PON1. As shown in **Figure 2D** and **2E**, PON1 protein expression in Linc-OIP5 siRNA group was decreased significantly (**P<0.01).

miR-616 can inhibit PON1 expression of HUEVCs through Linc-OIP5

Accumulated evidence shows that LncRNA can indirectly regulate miRNA through a competitive binding mechanism as competitive endogenous RNA (ceRNA). On the basis of previous studies, we wondered whether Linc-OIP5 can inhibit miR-616 of HUEVCs cells through a similar mechanism.

miR-616 mimics and miR-616 inhibitors were used to observe the changes of SOD, NO, and the expression of the PON1 gene. miR-616 mimics can inhibit SOD activity and NO content (**Figure 3A**, **3B**), while miR-616 inhibitors can promote SOD activity and NO content. miR-616 mimics can inhibit PON1 activity and decrease PON1 gene and protein expression. miR-616 inhibitor has the opposite effect (**Figure 3C-E**).

We studied whether miR-616 could target Linc-OIP5. The results of luciferase assay showed that the co-transfection of pmirGLO-Linc-OIP5-wt and miR-616 mimics significantly reduced the fluorescence compared with the negative control (NC), but when we co-transfected pmirGLO-Linc-OIP5-mut and miR- 616 mimics, this effect disappeared (**Figure 3F**). Finally, the above results provided us with evidence to prove that Linc-OIP5 was a potential target of miR-616.

Linc-OIP5, as a ceRNA of miR-616, affects PON1 expression in HUEVC cells

In the above experiments, we confirmed that Linc-OIP5 and PON1 are both targets of miR-616. Therefore, we studied the relationship between Linc-OIP5 and PON1. First, we confirmed that upregulation of Linc-OIP5 (pcDNA3.1-Linc-OIP5-wt transfection) resulted in an increase in PON1 expression at mRNA and protein levels (**Figure 4A-C**). However, regulation of Linc-OIP5 (pcDNA3.1-Linc-OIP5-wt transfection) inhibited the expression of miR-616 (**Figure 4D**). At the same time, we measured the synergistic effect

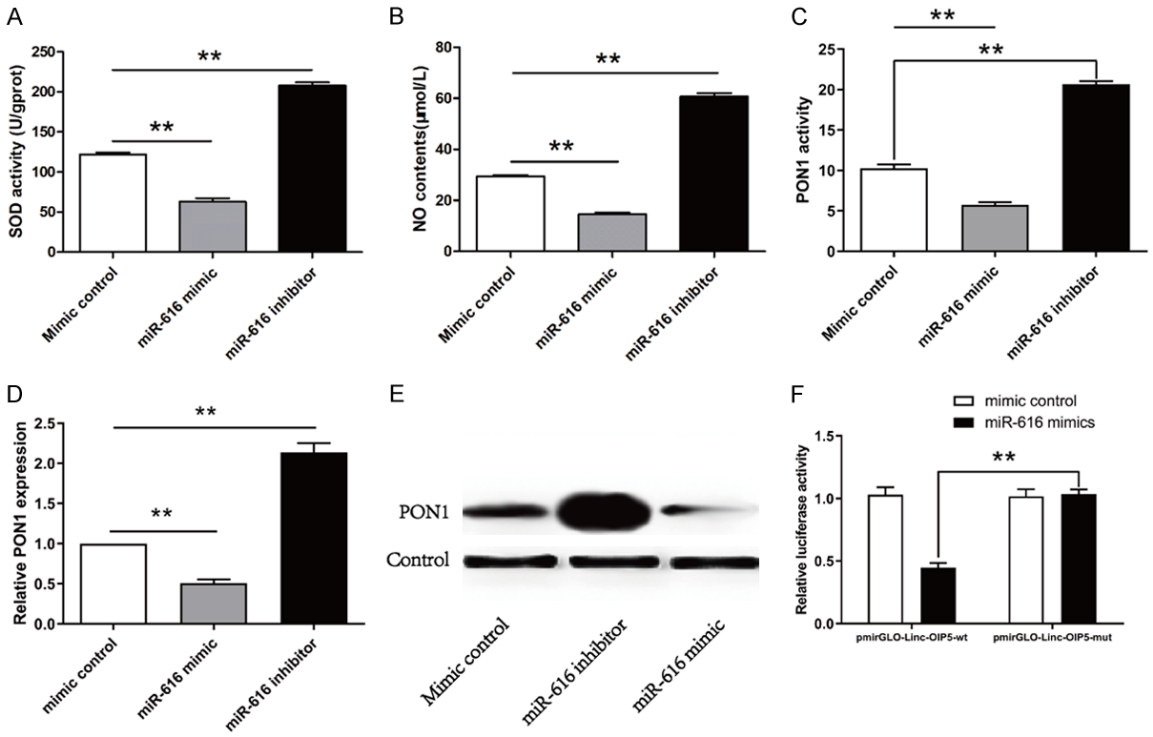

Figure 3. A, B. miR-616 mimic inhibited SOD activity and NO content of HUEVCs significantly. C-E. miR-616 mimic inhibited PON1 activity, PON1 gene expression and PON1 protein level of HUEVCs. F. Weakened fluorescence was present after co-transfection of miR-616 mimics and pmirGLO-Linc-OIP5-wt, which was detected by luciferase assays. **P<0.01.

of miR-616-mimics and Linc-OIP5. As shown in **Figure 4E**, **4F**, compared with pcDNA3.1-Linc-OIP5-mut, pcDNA3.1-Linc-OIP5-wt promoted the expression of PON1 at mRNA and protein levels, and miR-616-mimics (co-transfection of miR-616-mimics and pcDNA3.1-Linc-OIP5-wt) reversed the promotion effect. In addition, the expression of PON1 was more inhibited by co-transfection of miR-616-mimics and pcDNA3.1-Linc-OIP5-mut (due to the inhibitory effect of miR-616 on PON1).

In addition, pcDNA3.1-Linc-OIP5-wt could induce SOD activity and NO content of HUEVCs, but miR-616-mimics (pcDNA3.1-Linc-OIP5-wt and miR-616-mimics co-transfection) could attenuate its promoting effect (**Figure 4G**, **4H**) (P<0.01). In conclusion, the above results support that Linc-OIP5, as the ceRNA of miR-616, increases the expression of PON1 in HUEVC cells and promotes Linc-OIP5 mediated anti-oxidative stress effect.

Discussion

Coronary atherosclerosis is an inflammatory disease of chronic lipoprotein metabolism disorder, which can cause ischemic cardiovascular events [11]. The pathologic process of coronary atherosclerosis includes vascular endothelial cell membrane damage and osmotic ability changes, vascular smooth muscle cell intimal migration and increase, macrophage inflammatory response, and foam cell aggregation [12].

Our study results showed that Linc-OIP5 and PON1 were expressed lower in the coronary atherosclerosis group. However, miR-616 was expressed higher in the coronary atherosclerosis group.

PON1 is a calcium-dependent HDL-related esterase, which has anti-atherosclerosis effects. It can hydrolyze oxidized lipids and oxidize low density lipoprotein, protect HDL and LDL from oxidative modification, and inhibit the formation of giant cell-derived foam cells, and has anti-atherogenic effects [13, 14]. In recent years, many studies have proposed that the serum concentration and activity of PON1 is a better predictor of coronary heart disease, and the decrease of PON1 activity and concentra-

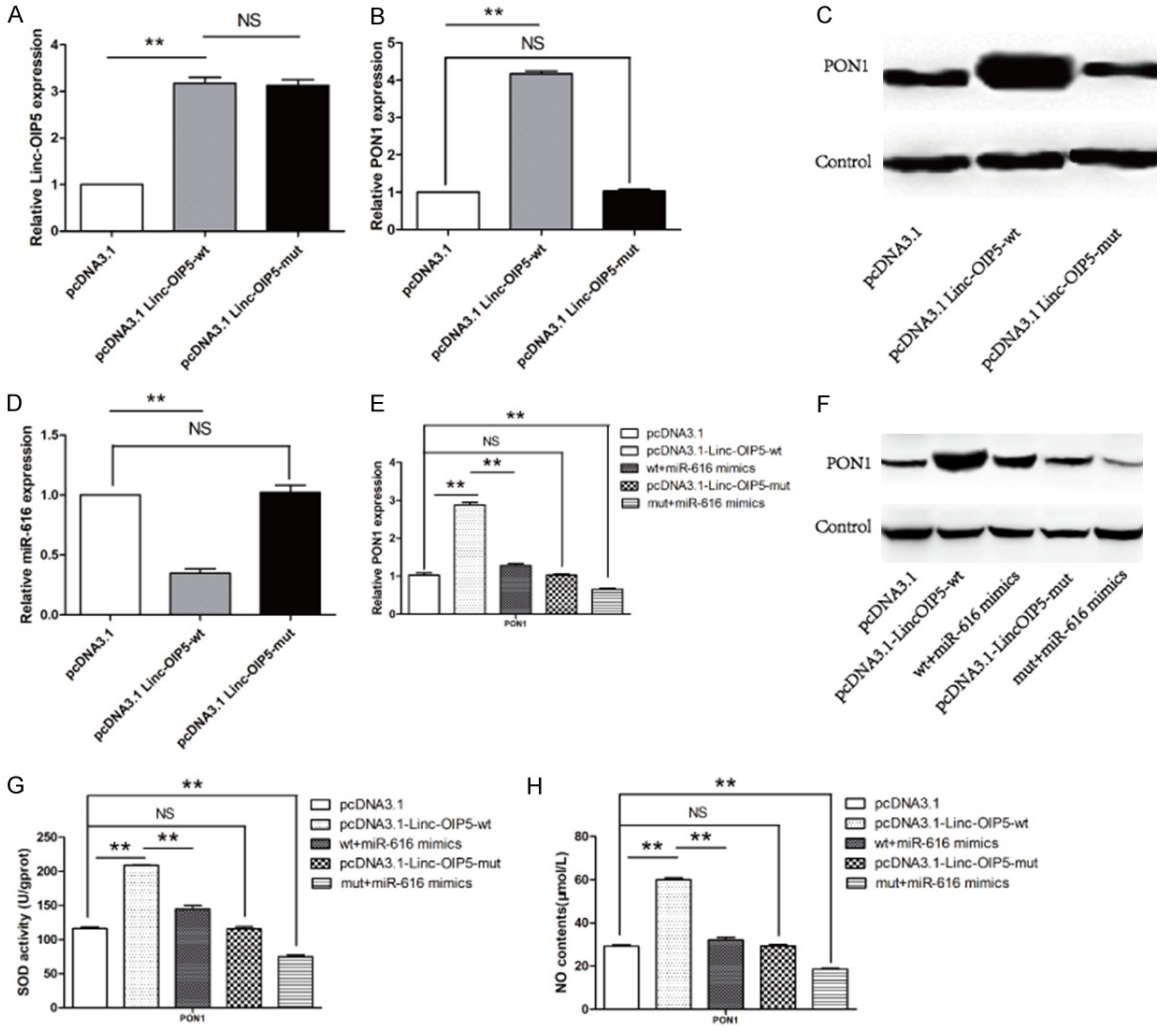

Figure 4. A. pc-DNA3.1 Linc-OIP5-wt and pc-DNA3.1 Linc-OIP5-mut both significantly promote Linc-OIP5 expression. B, C. pc-DNA3.1 Linc-OIP5-wt promotes PON1 gene expression and protein level of HUEVCs significantly; however, pc-DNA3.1 Linc-OIP5-mut did not affect PON1 expression. D. pc-DNA3.1 Linc-OIP5-wt inhibited miR-616 gene expression of HUEVCs significantly; however, pc-DNA3.1 Linc-OIP5-mut did not affect miR-616 expression. E, F. pc-DNA3.1 Linc-OIP5-wt promoted PON1 gene expression and protein level of HUEVCs; however, this effect was counteracted by miR-616 mimics. G, H. pc-DNA3.1 Linc-OIP5-wt promoted SOD activity and NO content of HUEVCs, and this effect could also be counteracted by miR-616 mimics. **P<0.01.

tion can be an independent risk factors for coronary heart disease [13]. Much work has been carried out on the regulation of serum concentration and activity.

Many studies have shown that the decrease in PON1 activity is related to the increase of oxidative stress, inflammation, and atherosclerotic plaque formation, so the risk of cardiovascular disease is increased [15]. Zhu et al. reported that PON1 can affect oxidative stress in the human body, and then affect the occurrence and development of atherosclerosis [16]. Oxidative stress is a pathological reaction that causes certain oxidative damage to the body due to the imbalance between the reactive oxygen species produced in the process of metabolism and the antioxidant system of endogenous scavenging of reactive oxygen species [17]. Under the multiple risk factors for coronary atherosclerosis, oxidative stress can stimulate the production of a large number of ROS through a variety of ways. Through various mechanisms, it can activate the inflammation around the blood vessels, damage the endothelial cells, and cause endothelial dysfunction.

SOD and NO are important indicators of oxidative stress [18].

In this study, we also found that the levels of SOD and NO were positively correlated with the level of PON1. Further cell experiments showed that Linic-OIP5 was associated with PON1 expression. Linic-OIP5 can affect the expression of PON1. To date, how Linc-OIP5 affect PON1 is unknown. It is reported that PON1 is regulated by miR-616. However, whether Linc-OIP5 could affect PON1 through miR-616 remains unclear.

MicroRNA (miRNA) is an endogenous microRNA that widely exists in eukaryotes and regulates gene expression and combines with mRNA [19]. Long noncoding RNA (LncRNA) is 8 more than 200 bp in length and does not participate in coding [20]. The first ceRNA hypothesis was proposed in 2011. It is believed that LncRNA can be used as a competitive endogenous RNA (ceRNA) to bind with miRNA, affect the regulation of miRNA on target mRNA, and then regulate the expression of related target genes [21].

LncRNA, which regulates miRNA as a ceRNA, has been widely reported in many tumor-related diseases [22, 23]. Our luciferase reporter assays showed that Linc-OIP5 was a ceRNA of miR-616 regulation of PON1 expression.

Our further results from functional analyzes indicated that Linc-OIP5 could also work as a ceRNA of miR-616 to affect oxidative stress (NO, SOD) and PON1 expression.

Conclusions

In the serum of patients with coronary atherosclerosis, we found lower PON1 activity and levels, the same trend in Linc-OIP5, and the opposite trend in miR-616 expression. Through further cell experiments, we found Linc-OIP5 regulated PON1 expression as a ceRNA of miR-616. Thus, it is suggested that Linc-OIP5 may be an ideal target for the treatment of coronary atherosclerosis in the future.

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Disclosure of conflict of interest

None.

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