Up-regulated lncRNA-PVT1 expression in peripheral blood mononuclear cells of patients with coronary artery disease is correlated with decreased interleukin-10 production

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Received: 15 June 2021 / Accepted: 20 January 2022 / Published online: 1 February 2022
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Abstract

Objectives Plasmacytoma variant translocation 1 (PVT1) is a newly discovered long non-coding RNA, which has not been previously studied in the inflammatory responses of the peripheral blood mononuclear cells (PBMCs) of patients with coronary artery disease (CAD).

Materials and methods This cross-sectional study was conducted on 15 CAD patients and 15 non-CAD (NCAD) individuals. The PVT1 expression was assessed in the PBMCs of the participants using a real-time polymerase chain reaction. Interleukin (IL)-10, IL-22, and matrix metalloproteinase-9 (MMP-9) were measured in the plasma and supernatant of cultured PBMCs in the presence or absence of lipopolysaccharide (LPS) using flow cytometry and enzyme-linked immunosorbent assay.

Results An increased expression of PVT1 was observed in the untreated PBMCs of CAD patients, compared to the NCAD group. The PVT1 was significantly up-regulated after LPS treatment in the PBMCs of both groups. Plasma MMP-9 levels were found to be higher in CAD patients than in the control individuals. The level of IL-10 and IL-22 production by the non-treated PBMCs of CAD cases was significantly lower than the NCAD group. Overall, in the examined population, PVT1 expression was negatively correlated with IL-10 secretion. Moreover, the results showed a significant negative correlation between PVT1 expression and IL-10 production by untreated cells.

Conclusions The PVT1 expression augmented in the PBMCs of CAD patients, which could be associated with the decreased IL-10 generation by the PBMCs of these patients.

Keywords Coronary artery disease · Interleukin-10 · Long non-coding RNA · PVT1
Introduction

Coronary artery disease (CAD), is the dominant cause of cardiovascular-related deaths [1]. The most common form of CAD is atherosclerosis, which is a chronic inflammatory disease of the arterial walls arising from a maladaptive inflammatory response and an imbalance in lipid metabolism [2]. Numerous converging lines of clinical and experimental evidence show that inflammation plays a pivotal role in all phases of the atherosclerotic process [3]. The role of inflammatory cytokines has been previously evaluated remarkably [4]. It has been shown that pro-inflammatory cytokines, including interleukin (IL)-1β, IL-6, and tumor necrosis factor-alpha (TNF-α) present a pro-atherogenic effects in general [5], while anti-inflammatory cytokines e.g. IL-10, could reduce the risk of atherosclerosis progression and ameliorate the development of atherosclerosis and vascular complications [6]. IL-22, a member of the IL-10-related cytokine superfamily, has a dual nature in inflammation, which might cause a pro-inflammatory or anti-inflammatory impact to modulate the immune responses of the tissue [4]. Overall, it seems that IL-10 and IL-22 have beneficial influences in protecting against metabolic disorders, as well as diminishing chronic inflammation and related complications [7].

Matrix metalloproteinases (MMPs) play a crucial role in extracellular matrix metabolism. The MMPs have demonstrated an important involvement in cardiovascular diseases, namely atherosclerosis, coronary artery disease, and myocardial infarction [8]. The MMP-9 is of importance in the instability of atherosclerotic plaques. In addition, it can be found in plasma due to the proteolytic rupture of the cellular membranes. Therefore, MMP-9 can be evaluated in several clinical situations in which inflammation is an underlying contributor, such as CAD [9]. Long non-coding RNAs (lncRNAs), a new class of non-coding RNAs with a length of > 200 nucleotides, are considered a significant component in the epigenetic regulation of gene expression. Increasing evidence has demonstrated that lncRNAs are involved in the regulation of numerous physiologic and pathologic processes, particularly the regulation of injury, invasion, and inflammatory responses [10].

Plasmacytoma variant translocation 1 (PVT1) is a newly discovered lncRNA and is located at chromosome 8q24, a known cancer-related region. The PVT1 functions as an oncogene and its up-regulation is tightly associated with a series of human cancers [11]. The dysregulation of PVT1 is involved in the etiology of a wide variety of human disorders, such as cardiovascular diseases [12]. During the past few years, PVT1 has received increasing attention due to its contribution to aberrant inflammatory and immune responses in various diseases, including osteoarthritis [13], epilepsy [15], abdominal aortic aneurysm [16], sepsis-induced acute kidney injury [17], and cardiac dysfunction [18].

Previous studies have highlighted the potential of PVT1 as a promising therapeutic target for inflammatory disorders. However, the importance of PVT1 in inflammatory responses in CAD and atherogenesis has not been thoroughly elucidated to date. Therefore, to investigate the possible role of PVT1 in the immune and inflammatory responses in CAD, we established an experimental model of lipopolysaccharide (LPS)-stimulated human peripheral blood mononuclear cells (PBMCs). Using the mentioned model, we detected the expression of PVT1 in PBMCs from patients with CAD under both LPS-stimulated and unstimulated conditions. Furthermore, the correlation of PVT1 expression with the plasma levels and in vitro production of IL-10 superfamily cytokines (IL-10 and IL-22) and MMP-9 by PBMCs was investigated.

Materials and methods

Study design and participants

This study was approved by the Medical Ethics Committee of Fasa University of Medical Sciences and informed written consent was obtained from all participants. Our study was performed following the principles of the Declaration of Helsinki [19]. Thirty peripheral blood samples were collected from male patients who had undergone CT angiography or coronary angiography for suspected coronary artery disease in the Al Zahra Heart Hospital, Shiraz, Iran during October 2018–January 2019. We divided the patients into two groups, including CAD and non-CAD (NCAD), each containing 15 patients. The diagnosis of CAD was made by a cardiologist based on over 50% stenosis in at least one coronary artery proven by angiography. The exclusion criteria were diabetes mellitus, malignancy, infection, blood diseases, chronic renal or liver failure, history of inflammatory diseases, and use of immunosuppressive agents.

Isolation and culture of PBMCs

To prepare the PBMCs, 10 mL peripheral blood samples were collected from participants in sterile tubes containing EDTA. Centrifugation was performed over Ficoll-Hypaque gradients (Lymphodex, InnoTrain, Germany) at 400 g for 20 min at 4 °C. The interface fraction containing PBMCs was carefully collected and washed twice with RPMI 1640 medium. The PBMCs were cultured in the RPMI medium supplemented with 50 U/mL penicillin, 50 µg/mL streptomycin, and 10% fetal bovine serum at 37 °C in a 5% CO₂ incubator. In order to evaluate the PVT1 expression, 2 × 10⁶ PBMCs/well were incubated in the presence or absence of...
100 ng/mL of LPS (Sigma-Aldrich, Germany) for 5 h in 24-well culture plates. Moreover, 10^5 PBMCs/well were cultured and incubated in the presence or absence of 100 ng/mL LPS for 48 h in 96-well culture plates to evaluate the levels of IL-10, IL-22, and MMP-9 in cell culture supernatants.

**RNA isolation and quantitative real-time reverse transcription PCR (qRT-PCR)**

The total RNA from PBMCs cultures was extracted using the One Step-RNA Reagent (Bio Basic, Germany) according to the manufacturer’s protocol. First-strand cDNA was synthesized utilizing the RevertAid First Strand cDNA Synthesis Kit (Thermo Scientific, USA). The qRT-PCR for PVT1 beta-actin as the internal reference gene was carried out using the ABI 7500 Sequence Detection System (Applied Biosystems, USA). The primer sequences for PVT1 were sense 5′-GTC TTG GTG CTC TGT GTT -3′ and anti-sense 5′-CCC GTT ATT CTG TCC TTC TC-3′. In addition, the sense and snit-sense primers for beta-actin were 5′-GCC TTT GCC GAT CCGC-3′ and 5′-GCC GTA GCC GTT GTCG-3′, respectively. The 2^−ΔΔCt method was applied to calculate relative gene expression.

**MMP-9 measurement**

The MMP-9 in plasma and the supernatant of PBMCs culture was detected using an MMP-9 enzyme-linked immunosorbent assay (ELISA) kit from BT LAB (BT LAB, China) according to the manufacturer’s instructions.

**Cytokines assay**

The plasma samples and the supernatant of the cultured PBMCs were used to assess IL-10 and IL-22 levels. Cytokines were measured by LEGENDplex™ Human Th22 Panel (Biolegend, USA) using a flow cytometer (FACS Calibur, BD, USA) according to the manufacturer’s instructions.

**Statistical analysis**

The SPSS software version 22 (IBM Inc., USA) and GraphPad Prism version 8.2 (San Diego, CA, USA) were used to perform statistical analysis. The normality of the continuous variables was evaluated by the Kolmogorov–Smirnov test. Normal variables are presented as mean ± standard deviation (SD) and non-parametric variables are presented as the median and interquartile range (IQR). The study groups were compared using the Student’s t test, Mann–Whitney U test, and one-way analysis of variance (ANOVA). Spearman’s correlation coefficient was applied to determine the relationship of PVT1 expression with other variables. P < 0.05 was regarded statistically significant for all tests.

### Results

**Characteristics of study population**

The demographic and anthropometric characteristics of the study population are presented in Table 1. There were no significant differences in age, waist circumference (WC), hip circumference (HC), body mass index (BMI), and weight to hip ratio (WHR) between the study groups.

### PVT1 expression in PBMCs

The relative expression of PVT1 was first assessed at the basal stage in the PBMCs of NCAD and CAD groups. The relative expression of PVT1 was significantly higher in the CAD patients than in the NCAD group (P = 0.034).
(Fig. 1). In addition, PVT1 expression in the PBMCs of the CAD ($P = 0.001$) and NCAD ($P = 0.002$) subjects increased significantly upon stimulation.

Plasma levels of MMP-9, IL-10, and IL-22

Plasma levels of MMP-9, IL-10, and IL-22 were measured to determine the inflammatory conditions, as well as their correlation with PVT1 expression. As presented in Fig. 2, exclusively MMP-9 was significantly ($P = 0.037$) higher in CAD cases, compared to the control subjects with the levels of cytokines being comparable between the investigated groups.

![Fig. 2](image)

Comparison of MMP-9, IL-10, and IL-22 in the plasma of CAD and NCAD patients. A MMP-9 was significantly higher in the CAD patients; B and C IL-10 and IL-22 were comparable between the CAD and NCAD patients. *P value < 0.05

MMP-9, IL-10, and IL-22 production by PBMCs

In order to assess the effect of LPS and the correlation of PVT1 with MMP-9 and anti-inflammatory cytokines production, we analyzed the supernatant of PBMCs in the absence and presence of LPS after 48 h. The level of IL-10 generation was significantly lower in the non-treated PBMCs of the CAD group ($P = 0.002$) (Fig. 3A) and LPS-induced PBMCs of the NCAD group ($P = 0.048$), compared to the non-treated PBMCs of the NCAD group (Fig. 3B). Moreover, the secretion of IL-22 was significantly lower in the untreated PBMCs of the CAD group than in the NCAD group ($P = 0.044$) (Fig. 3C).

![Fig. 3](image)

Alterations in MMP-9, IL-10, and IL-22 production following the stimulation of the isolated PBMCs with LPS. Isolated PBMCs were cultured in the presence or absence of LPS (100 ng/mL) for 48 h. Afterward, the concentrations of MMP-9, IL-10, and IL-22 were measured in the culture supernatants. *P value < 0.05 and **P value < 0.01; the sign of “+” means the groups stimulated with LPS, the sign of “−” means the group not stimulated with LPS.
Relationship of PVT1 with MMP-9, IL-10, and IL-22

Correlation analyses were performed to assess the relationship of PVT1 expression with MMP-9, IL-10, and IL-22 expression in PBMCs (Table 2). A significant negative correlation was observed between PVT1 expression and supernatant IL-10 in the supernatant of untreated PBMCs ($r = -0.399$, $P = 0.043$).

Discussion

Our data demonstrated that PVT1 was significantly up-regulated in the PBMCs of CAD patients. Up- or down-regulated expression of PVT1 has been reported in diverse pathologic conditions. It has been noted that PVT1-knockdown could ameliorate streptozotocin-induced oxidative stress and elevate insulin secretory capacity in pancreatic β cells in the experimentally induced diabetic rats [20]. In addition, Chang et al. reported that Plasma PVT1 was downregulated in chronic heart failure and further downregulated in chronic heart failure patients complicated with progressive chronic kidney disease. Moreover, after treatment of progressive chronic kidney disease, plasma PVT1 was upregulated [21]. In contrast to these findings, an elevated expression of PVT1 has been previously revealed as the level of PVT1 expression significantly increased in cancers. A meta-analysis on a total of 23 studies reported that high PVT1 expression levels correlated with poor overall survival, larger tumor size, distant metastasis, and some other risk factors in patients with cancer [22]. In addition, it has been found to be up-regulated in atrial muscle tissues from atrial fibrillation patients [23] and the myocardial tissues of sepsis rats [16].

More importantly, a very recent study by Quan et al. indicated similar findings to ours, in which PVT1 was highly expressed in the PBMCs of CAD patients, compared to healthy controls, and was also up-regulated upon LPS-stimulation in both groups.

To study the role of PVT1 in the production of the IL-10 superfamily cytokines and MMP-9, we assessed the generation of IL-10, IL-22, and MMP-9 in both basal and LPS-treated states. LPS was used to maintain cell stimulation in vitro; however, finding results and relationships in two different situations will be more reliable. The IL-10 is a pleiotropic cytokine with immune regulatory properties, which is produced mostly by Tregs and B regulatory cells. This cytokine is believed to have inhibitory effects on plaque development and atherosclerosis progression due to its anti-inflammatory characteristics [25]. In the present study, an inverse correlation between PVT1 expression and IL-10 production from untreated PBMCs of the total population of participants (Table 2). Therefore, PVT1 might be the factor contributing to the secretion of anti-inflammatory cytokine IL-10 by PBMCs.

To the best of our knowledge, this is the first study showing the relationship between PVT1 expression and IL-10 production in NCAD and CAD patients. Zhao et al. reported the high expression of PVT1 in the cartilage of patients with osteoarthritis and IL-1β-stimulated chondrocytes. Moreover, in line with this finding, it has been reported that PVT1 inhibition antagonized the production of inflammatory cytokines upon IL-1β stimulation, including prostaglandin E2, IL-6, IL-8, and TNF-α [13]. However, the precise molecular mechanisms of this correlation are not well understood and different factors might be involved, such as anti-inflammatory microRNAs (e.g., microRNA (miR)-146a).

Liu et al. showed that miR-146a was down-regulated and negatively correlated with the PVT1 level in prostate cancer. In addition, It has been was suggested that PVT1 is a mediator of miR-146a expression by inducing the methylation of CpG islands in its promoter so that the miR-146a overexpression eliminates the effects of PVT1 knockdown on prostate cancer cells. Liu et al. showed that miR-146a was down-regulated and negatively correlated with the PVT1 level in prostate cancer [26].

It should be noted that miR-146a, as a target of PVT1, could be an anti-inflammatory mediator [27], which directly correlates with the production of anti-inflammatory cytokines TGF-β1 and IL-10 [28] Thus, a probably mechanism can be suggested that increasing the expression of PVT1 by reducing the expression of miR-146a reduces the production of IL-10 in the PBMCs of the CAD patients; However, more research is needed in this regard.

In this study, we also found a higher level of MMP-9 in the plasma of CAD patients, in comparison with healthy controls. However, in spite of some other studies in other pathologic conditions, namely aortic aneurysm model [13]
and lung cancer [16], no significant correlation was observed between PVT1 expression and plasma or supernatant levels of MMP-9. Relatively little research has been conducted on the relationship between IL-22 and coronary artery disease. According to the study of Gong et al., the elevated serum IL-22 was associated with the incidence of type 2 diabetes mellitus and CAD. Furthermore, they showed that IL-22 was able to protect the endothelial cells against high lysophosphatidylcholine and glucose-induced injury [29]. Our results demonstrated that serum IL-22 levels augmented in response to LPS-induced inflammation. Therefore, keeping IL-22 levels high through inhibiting inflammation could be suggested as another therapeutic approach for microvascular diseases with chronic low-grade inflammation, such as diabetes and CAD. However, interleukin has been introduced as a double-edged sword [29] and further evaluations are required in this area.

Conclusion

The PVT1 expression increased in the PBMCs of CAD patients, which could be correlated with decreased IL-10 production by the PBMCs of these patients. However, further in vivo and in vitro studies are required to explore the precise molecular mechanism of PVT1 up-regulation and its relationship with inflammatory responses in CAD patients.

Limitation

The small sample size should be acknowledged as a limitation of the present study; in case of more samples taking, better results might be obtained.

Acknowledgements We greatly appreciate all participants in the study. We also thank the assistance provided by the staff of the Al-Zahra Heart Hospital of Shiraz, Iran.

Funding This study was funded by Fasa University of Medical Sciences, Grant No. 97093. Dr. Behnoosh Miladpour is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Data availability All data will available from corresponding author, with reasonable request. A preprint of this study has already been published (https://doi.org/10.21203/rs.3.rs-50028/v2).

Declarations

Conflict of interest No potential conflicts of interest relevant to this article were reported.

Ethical approval This study approved with the ethic code of IR.FUMS.REC.1397.144.

Consent to participate All research procedures were completely explained to the participants and they signed the consent forms.

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