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Original Paper

Expression Changes of Long Noncoding RNA in the Process of Endothelial Cell Activation

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Key Words
Endothelial cell • Activation • lncRNA • Expression changes

Abstract
Background: Endothelial cells have been shown to be in response to a variety of local and systemic stimuli, and are able to transition between quiescent and activated states. Endothelial cell activation is critical for the pathogenesis of various cardiovascular diseases. However, the expression changes of long non-coding RNAs (lncRNAs) are still unknown in the process of endothelial cell activation. Thus, this study was aimed to investigate expression changes of lncRNA before and after endothelial cell activation. ***Materials and Methods:*** In an experimental model of peripheral venous congestion, endothelial cells were activated and analyzed with Affymetrix HG-U133 plus2.0 microarray. We analyzed these microarray data and reannotated the microarray probes for lncRNA. ***Results:*** According to the definition of absolute fold change>2 and p value <0.05, 27 differentially expressed lncRNAs were identified and only 1 lncRNA transcript, ENST00000509256 was down-regualted. Co-expression network of lncRNA and mRNA were constructed to predict function of the dysregulated lncRNA. Gene set enrichment analyses suggested that these ENST00000509256 was associated with many important functions, such as cell-cell signaling and regulation of cell differentiation. ***Conclusion:*** Many lncRNAs are dysregulated upon endothelial cell activation and further experiments are needed to identify the potential biological functions of these lncRNAs.

Introduction

Vascular endothelial cells locate between the blood and tissues and endothelium is the largest endocrine organ of the body. Vascular endothelial cells lie in the innermost of blood

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vessels and are vulnerable to stimulus [1, 2]. *In vitro* evidence indicates that the endothelium may become activated and turn into a primary source of pro-inflammatory, vasoconstrictive, and pro-thrombotic mediators in response to biomechanical stress [1-3]. Endothelial cell activation is involved in various pathogenesis of various diseases, such as heart failure and renal failure [4-6].

Inflammation, hemostasis, and other biological and pathological processes are all modulated by the endothelium through transitions between quiescent and activated states that occur in response to environmental stressors [2, 7-9]. Thus, discover the underlying molecular mechanism of endothelial cell activation is of critical importance to develop therapies for heart failure and renal failure.

Long non-coding RNAs (lncRNAs) are RNA transcripts that are larger than 200nt, without protein-coding capacity [10, 11]. Researchers have focused on protein-coding genes, while lncRNA has been considered as transcription noise and junk RNA. However, recent evidence shows that lncRNAs play important roles in almost every aspect of physiological processes, such as differentiation, proliferation, apoptosis, and inflammation [12-17]. However, the expression profile and function of lncRNA are still unknown in the process of endothelial cell activation.

Colombo PC developed an experimental model of acute, peripheral venous congestion in healthy human subjects and found endothelial cells were activated [3]. With microarray technology, they investigated gene expression of endothelial cells before and after venous congestion. Here, we re-annotated the microarray probe sets and profiled lncRNA expression changes after endothelial cell activation.

Materials and Methods

Peripheral venous congestion model

The detailed methods were described by Colombo PC [9]. Briefly, 24 healthy subjects were enrolled. Blood and endothelial cells were sampled from the antecubital or basilic vein of the non-dominant arm (control arm) at baseline and of the dominant arm (test arm) after 75 min of local venous congestion using angiocatheters and endovascular wires. Peripheral venous pressure was increased 30 mmHg above baseline levels by inflating a tourniquet cuff around the test arm, proximally, just below the shoulder. Blood was also obtained at 75 min from the control arm which was not exposed to venous congestion, thus serving as a control [3]. Magnetic beads coated with EC-specific antibodies were used to separate endothelial cells.

Microarray data processing

The raw microarray data was downloaded from the gene expression omnibus (GEO) database and this dataset could be accessed by the accession number GSE38783. In accordance with Colombo PC [9], the raw files of first normalized using the log scale robust multi-array analysis with default settings [18]. And differentially expressed lncRNAs between after vs. before experiments were calculated using paired *t*-test. Heatmap of differentially expressed lncRNAs was generated by Cluster (V3.0) software.

LncRNA annotation pipeline

The Affymetrix human genome U133 Plus2.0 microarray was used in this study. Annotation of the HGU133 Plus 2.0 was downloaded from the BioMart database. Only probes that were annotated as lncRNA were selected and transcript ID, chromosome location, strand, biologic types, and other annotation information were also downloaded.

LncRNA-mRNA co-expression network

We built lncRNA-mRNA-network to identify the interactions between mRNA and lncRNA [19]. LncRNA-mRNA network was built according to the normalized signal intensity of specific expression of mRNA and lncRNA. For each pair of mRNA-lncRNA, mRNA-mRNA or lncRNA-lncRNA, we calculated the Pearson correlation and choose the significant correlation pairs (P<0.05) with which to construct the network [20].

Gene set enrichment analysis (GSEA)

GSEA is a computational method that determines whether a priori defined set of genes shows statistically significant concordant differences between two biological states [21, 22]. GSEA is a powerful analytical method for interpreting gene expression data and GSEA focuses on genes that share common biological function, chromosomal location, or regulation. Samples were categorized as high expression and low expression according to ENST00000509256 expression and GSEA was performed by the GSEA desktop application with default parameters.

Results

Raw data of 24 samples (12 controls and 12 venous congestion samples) were downloaded from the GEO database. Primary quality of the 24 microarrays was assessed by normalized unscaled standard error (NUSE) algorithm and we found that boxplots of NUSE values were centered around 1, indicating the microarray data were of high quality(Fig. 1A).

Then differentially expressed probes were calculated and 3437 probes were identified with the threshold $P<0.05$, which was consistent with Colombo's report. Then we annotated these probes for lncRNAs using the annotation file we built. With the $P<0.05$ and absolute fold change (FC)>1.5, 227 differentially expressed lncRNAs were identified (Fig. 1B). List of 227 differentially expressed lncRNAs are shown in supplementary file, see www.karger.com/doi/10.1159/000455980). Among the 227 lncRNAs, there are 27 lncRNAs with absolute FC>

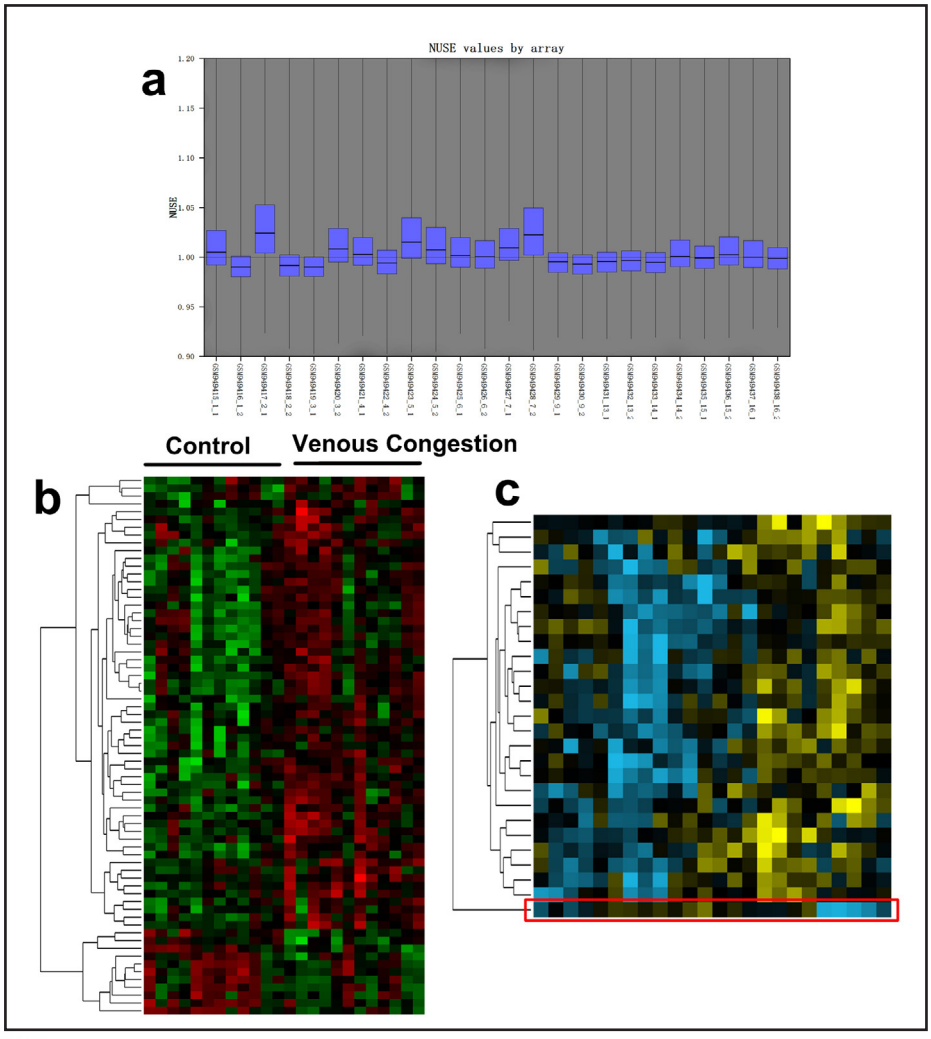

Fig. 1. Quality check of the microarrays analyzed (a) the NUSE values of microarrays were around 1, showing the microarrays were of high quality; heatmap of 227 differentially expressed lncRNAs, red: up-regulation, green: down-regulation (b); heatmap of 27 differentially expressed lncRNAs, yellow: up-regulation, blue: down-regulation (c).

Table 1. 27 differentially expressed lncRNAs with absolute fold change 2. FC: fold change

Ensembl Transcript ID	FC	Chromosome Name	Strand	Transcript Start	Transcript End
ENST00000562811	2.56	1	-1	119597702	119599271
ENST00000482945	2.28	15	-1	58597165	58621504
ENST00000497699	2.10	10	1	28677510	28682677
ENST00000603679	2.36	1	1	100735175	100739039
ENST00000473385	2.02	1	1	211368929	211374785
ENST00000464213	2.05	7	1	80665914	80679277
ENST00000296031	2.57	4	-1	74097676	74099195
ENST00000464961	2.10	3	-1	33496245	33505451
ENST00000497089	2.25	7	-1	27162600	27169444
ENST00000535593	2.22	12	1	21501781	21516231
ENST00000633364	2.45	2	-1	110465051	110472816
ENST00000465128	2.40	X	-1	134771897	134789104
ENST00000479608	2.05	12	1	45836761	45908040
ENST00000556027	2.07	14	-1	53046027	53093664
ENST00000521168	2.42	8	1	67157627	67195518
ENST00000462273	2.13	14	1	104049418	104052665
ENST00000602461	2.17	X	-1	45745211	45770274
ENST00000561973	2.06	X	-1	68013470	68014901
ENST00000509256	-2.00	5	1	32052494	32057949
ENST00000484083	2.16	10	-1	68341130	68376946
ENST00000523031	2.03	8	-1	143280161	143280849
ENST00000565283	2.22	2	-1	36354749	36355114
ENST00000490320	2.06	3	1	160225797	160228054
ENST00000605506	2.32	1	-1	84076331	84077931
ENST00000488625	2.14	10	1	31318495	31529202
ENST00000606008	2.24	3	1	44667412	44669364
ENST00000601365	2.26	19	-1	20004420	20008188

2 (Table 1). Heatmap of the 27 lncRNAs were shown in Figure 1C. Intriguingly, among the 27 lncRNAs with absolute FC> 2, only 1 lncRNA (ENST00000509256) was down-regulated.

Among the 227 differentially expressed lncRNAs, the 4 most common types were processed transcript, retained intron, large introgenic RNA, and antisense RNA. It has been proposed that genes with the same function or in the same pathway would be co-expressed. And co-expressed network has been used to predict potential function of lncRNAs based on this hypothesis. For example, the function of a novel lncRNA in hepatocellular cell carcinoma was predicted by lncRNA-mRNA co-expression network [23]. Thus, we constructed lncRNA-mRNA co-expression network for the differentially expressed lncRNAs (Fig. 2B). Many genes with important regulatory functions were co-expressed with lncRNA, such as WDR20, DCAF8, PDSS2, SMEK2, EIF3A, HNRNPH2, SPRY2, STAU2, LHX2, RIF1 and CDK13, indicating these lncRNAs may also have critical regulatory potency. As shown, lncRNA ENST00000482945 was co-expressed with most mRNAs.

As mentioned, only ENST00000509256 was down-regulated among the 27 lncRNAs. Then we tried to predict its biological functional with further bioinformatics methods. GSEA is a useful method for predicting functions of unknown genes has been widely used by many studies. The most positively correlated gene ontology (GO) items and KEGG pathways were

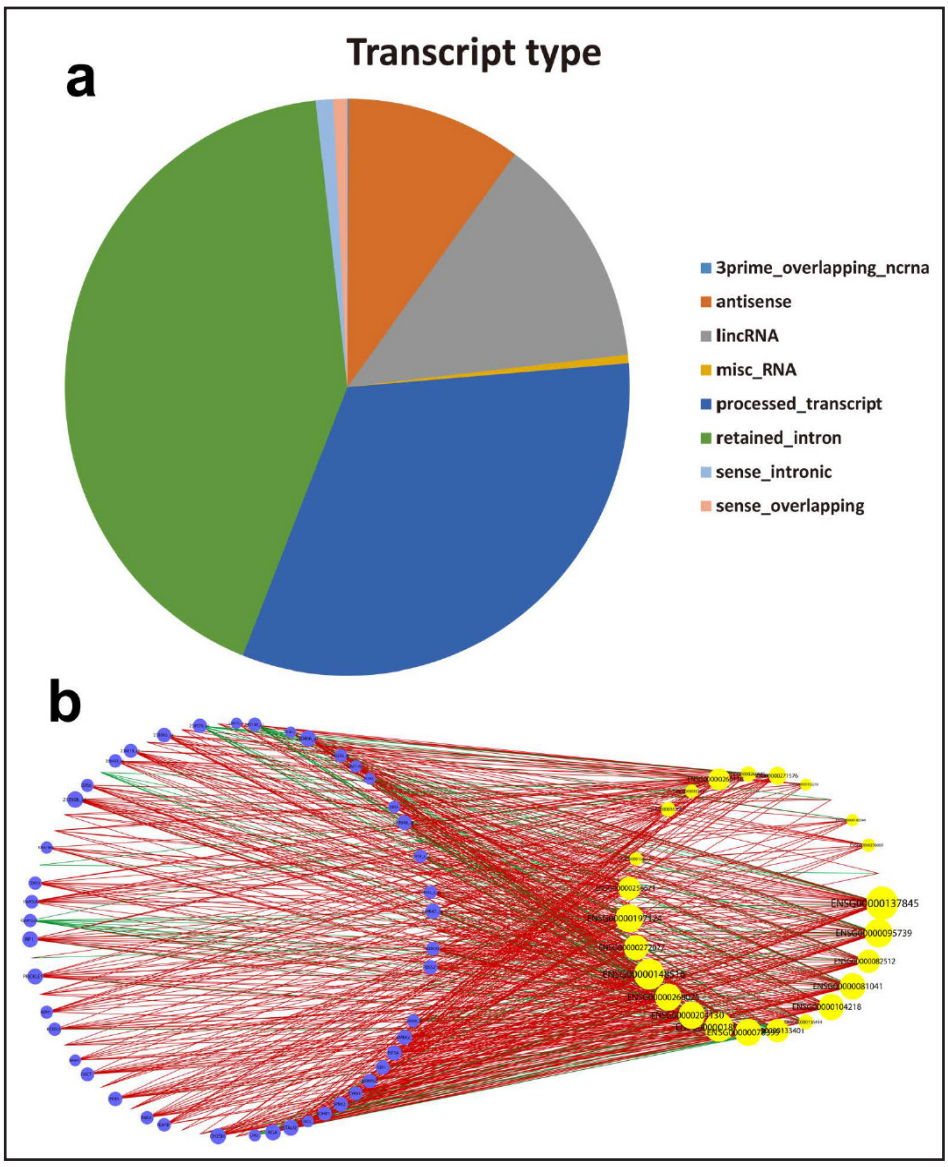

Fig. 2. Biological types of 227 differentially expressed lncRNAs (a); co-expression network between lncRNA and mRNA (b), yellow: lncRNA; blue: mRNA; red line: positive correlation; green line: negative correlation.

shown in Figure 3. According to GSEA results, the most correlated GO item was cell-cell signaling and the most positively correlated KEGG pathway was intracellular transport. The GO items and KEGG pathways that were most negatively correlated with ENST00000509256 were shown in Figure 4. As shown the most correlated GO item was neuroactive ligand receptor interaction and the most negatively correlated KEGG pathway was oxidative phosphorylation.

Discussion

Endothelial cells have been shown to be phenotypically dynamic and, in response to a variety of local and systemic stimuli, are able to transition between quiescent and activated states [1, 2]. In recent years, emerging research has demonstrated that endothelial dysfunction is a major contributor to cardiovascular disease, including hypertension, atherosclerosis, and more recently, congestive heart failure [7, 8]. Activation of endothelial cells causes endothelial cells to undergo a phenotypic switch to a pro-oxidant, pro-inflammatory, vasoconstricted state [13, 14]. By the experimental model, Colombo PC has proved that venous congestion led to endothelial cell activation and releases of inflammatory mediators

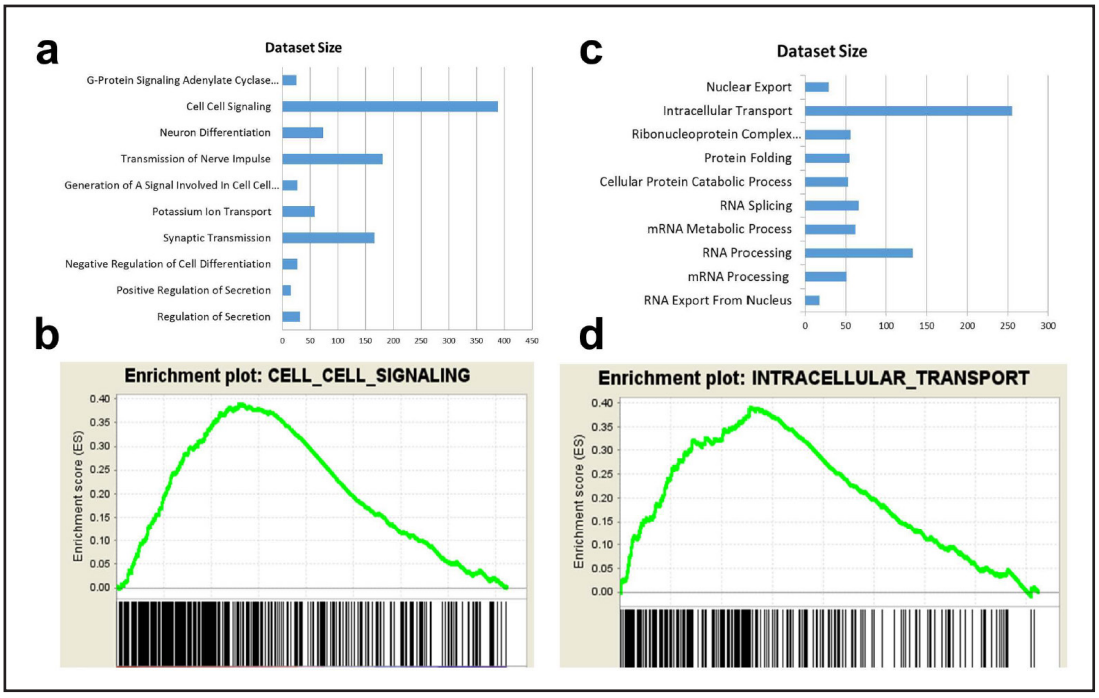

Fig. 3. Positively enriched GO (a, b) and KEGG (c, d) items by ENST00000509256 (a,c: enriched datasets; b, d: enrichment plot).

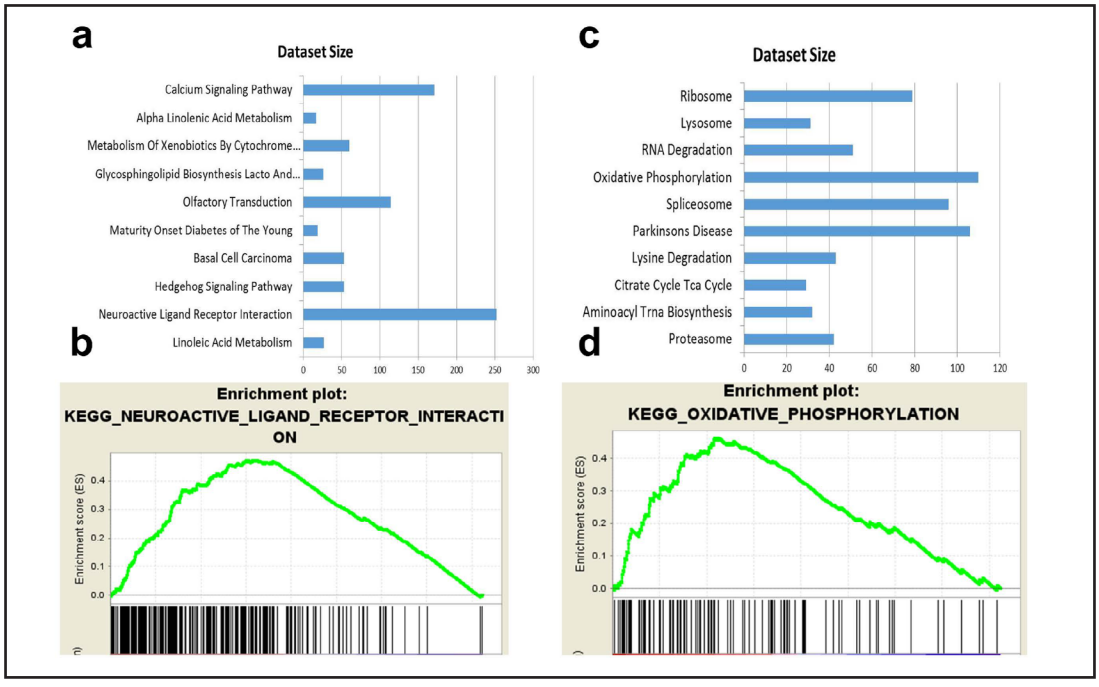

Fig. 4. Negatively enriched GO (a, b) and KEGG (c, d) items by ENST00000509256 (a,c: enriched datasets; b, d: enrichment plot).

and neurohormones [1, 2]. However, the expression changes of lncRNA are still unknown.

It has been proved that noncoding RNAs are involved in many human diseases by altering gene expression at different levels [11, 24-26]. MicroRNAs and lncRNAs are the 2 types of most investigated noncoding RNAs in cardiovascular diseases [27-30]. The functional regulatory roles of microRNAs have been extensively investigated in cardiovascular diseases,

particular in atherosclerosis [27-29, 31, 32]. Mounting evidence has proved that microRNAs control the senescence and dysfunction of endothelial cells, proliferation and migration of vascular smooth muscle cells, and macrophage-drive cytokine production [33]. Among these endothelial microRNAs, the functional roles of miR-126 and miR-143/145 have been well documented [27]. Endothelial cells injury and repair are the fundamental elements in the pathophysiology of atherogenesis. Several miRs have been implicated in modification of vessel restenosis after interventional endothelial injury. Knockout of miR-21 can attenuate neointimal formation post-stenting in a mouse vascular stent model [34] and *in vivo* administration of antagomiRs and miR mimetics also shows beneficial effects on cardiac remodeling [35, 36]. In addition to microRNAs, lncRNAs are also involved in restenosis and vascular remodeling [37, 38].

LncRNAs are emerging as regulators of vascular function in health and disease[37]. Functions of currently known lncRNAs can be classified as followings: 1) scaffold or guide for epigenetic and transcription factors; 2) imprinting; 3) enhancer activation; 4) molecular sponges [24, 39]. For cardiovascular diseases, several lncRNAs have been reported. For example, it has been reported that lncRNA H19 and ANRIL play important roles in atherosclerosis development [40, 41]. Since lncRNAs are complex in both their sheer numbers and mechanisms of action, identifying their contribution to vascular disease is challenging and investigation of lncRNAs in endothelial cells is rare.

In the current study, we systematically investigated lncRNA expression changes in endothelial cells upon venous congestion by analyzing microarray data. The experimental models successfully activated endothelial cells since the levels pro-inflammatory cytokines increased in the congested arm and the mRNA expressions of ET-1, VCAM-1 and CXCL2 also increased [3]. Therefore, the differentially expressed lncRNAs we identified could represent changes of lncRNA expression upon endothelial cell activation. By calculation, we identified 227 differentially expressed lncRNAs. The most 2 common transcript types were processed transcripts and retained intron in our results, which was different from reports from other diseases [42]. The reason may be the annotation files were based on different databases. Then we found there were 27 lncRNAs with absolute fold change>2. Co-expression network were constructed for the 27 lncRNAs and we found many important mRNAs were co-expressed with lncRNAs, suggesting these lncRNAs might have vital biological functions. Notably, there is only 1 down-regualted lncRNA, ENST00000509256 among the 27 lncRNAs and GSEA methods were utilized to predict its potential biological function. GSEA results showed that ENST00000509256 was associated with biological functions, like cell-cell signaling and neuroactive ligand receptor interaction. These items are related with inflammation and it is possible that ENST00000509256 is involved the inflammatory processes upon endothelial activation.

Re-annotation and data mining of published dataset is a feasible and cost-effective method to analyze lncRNA expression profile and identify functional lncRNAs. However, findings of our study should be further validated by cellular experiments. Additionally, the microarray we analyzed was not specially designed to detect lncRNA expression. Thus only small parts of lncRNA were analyzed in this work and further comprehensive studies are warranted.

To summary, we systematically analyzed lncRNA expression changes of endothelial activation in the venous congestion experimental model, and further experiments are needed to identify the potential biological functions of these lncRNAs.

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Disclosure Statement

The authors have declared no conflict of interest.

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