Research Article

Expression Profiles of Long Noncoding RNA and mRNA in Epicardial Adipose Tissue in Patients with Heart Failure

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The expression profile of long noncoding RNA (lncRNA) in human epicardial adipose tissue (EAT) has not been widely studied. In the present study, we performed RNA sequencing to analyze the expression profiles of lncRNA and mRNA in EAT in coronary artery disease (CAD) patients with and without heart failure (HF). Our results showed RNA sequencing disclosed 35673 mRNA and 11087 lncRNA corresponding to 15554 genes in EAT in total, while 30 differentially expressed lncRNAs (17 upregulated and 13 downregulated) and 278 differently expressed mRNAs (129 upregulated and 149 downregulated) were discriminated between CAD patients with and without HF (P<0.05; fold change>2); lncRNA ENST00000610659 drew specific attention for it was the top upregulated lncRNA with highest fold change and corresponded to UNC93B1 gene, which was proved to be related to HF and encoded UNC93B1 protein regulating toll-like receptor signaling, and both of them significantly increased in HF patients in qRT-PCR validation; the top significant upregulated enriched GO terms and KEGG pathway analysis were regulation of lymphocyte activation (GO:0051249) and T cell receptor signaling pathway (hsa04660), respectively. The current findings support the fact that EAT lncRNAs are involved in the inflammatory response leading to the development of HF.

1. Introduction

Recent studies have reported on long noncoding RNA (lncRNA) expression profiling in various human tissues [1]; however, expression profile of lncRNA in human epicardial adipose tissue (EAT) has yet to be described in detail. It is known that a large proportion of the mammalian genome is transcribed as lncRNA, which resides within or between coding genes. In addition, many lncRNAs have been shown to be functional and involved in specific physiological and pathological processes, through transcriptional or posttranscriptional regulatory mechanisms [2, 3]. To date, however, lncRNAs have never been included in analyses of the human EAT transcriptome. EAT is a key cardiometabolic factor, where, by releasing various inflammatory factors [4], EAT can modulate cardiac function and correlate with heart failure (HF) [5, 6], independently of metabolic status or the presence of coronary artery disease (CAD).

In the present study, we sought to supplement EAT lncRNA and mRNA expression profiles to provide a more complete picture of the myocardial transcriptional landscape in heart failure and also provide possible biomarkers for HF.

2. Materials and Methods

2.1. Study Participants. EAT samples were taken from 10 CAD patients who underwent coronary artery bypass graft surgery, in the Department of Heart Center, Beijing Chao-yang Hospital of Capital Medical University. Subjects were divided into two groups: HF group (n=5) and non-HF group (n=5). HF group included patients with Brain Natriuretic Peptide (BNP)>500ng/L and abnormal echocardiography finding (left ventricular end diastolic diameter [LVEDD]>50mm in female and >55mm in male and left ventricular ejection fraction [LVEF]<50%); non-HF group included patients with BNP<100 ng/L and normal views in echocardiography. The protocol was approved by the Ethics Committee of Beijing Chao-yang Hospital affiliated with Capital Medical University and written informed consent was obtained from participants before the study.
2.2. RNA Sequencing Procedure. Total RNA was extracted from the EAT and quantified using a NanoDrop ND-1000 instrument. 1-2μg total RNA was used to prepare the sequencing library in the following steps: (1) Total RNA is enriched by oligo (dT) magnetic beads (rRNA removed). (2) Using KAPA Stranded RNA-Seq Library Prep Kit (Illumina), RNA-seq library preparation incorporates dUTP into the second cDNA strand and makes the RNA-seq library strand-specific. (3) After completing, libraries were qualified with Agilent 2100 Bioanalyzer and quantified by absolute quantification method. (4) Sequence the libraries on the Illumina HiSeq 4000 instrument (we followed the methods of Wang et al. 2019 [7]).

2.3. Quantitative RT-PCR. qRT-PCR was used to measure selected IncRNA ENST00000610659 and UNC93B1 mRNA. Total RNA samples were extracted from the EAT samples using TRIzol (Invitrogen, Carlsbad, CA). The relative expression levels of mRNA and IncRNA were quantified using Viia 7 Real-Time PCR System (Applied Biosystems, Foster City, USA) according to standard methods. IncRNA ENST00000610659: the forward primer was 5’ CCGTCT-CAACAAGACGGTTC 3’, the reverse primer was 5’ AAG- GCTCCACTCCGCACAAA 3’; UNC93B1 mRNA: the forward primer was 5’ GCTCACCTACGGCGTCTACC 3’, the reverse primer was 5’ CGCTAGTGTCGTTCGTGTTGC 3’.

2.4. Statistical Analysis. R package was used to calculate the FPKM value and differential expression for gene and transcript level and perform hierarchical clustering, GO enrichment, pathway analysis, scatter plots, and volcano plots with the differentially expressed genes. Descriptive statistics for each variable were determined. Continuous variables were expressed as the mean ± SD and compared using unpaired Student’s t-test, and categorical variables were expressed as percentages and numbers and were compared using the chi-squared test. Significant GO enrichment and pathways were selected by Fisher’s exact test, and p<0.05.

3. Results

3.1. Characteristics of Participants. The present study comprised 10 CAD patients (5 with HF and 5 without). The main clinical characteristics of the two groups are summarized in Table 1. There were no significant differences in subject characteristics between the two groups; they were well balanced with regard to main clinical and laboratory characteristics. The CAD patients with HF had higher BNP level and LVEDD and lower LVEF.

3.2. RNA Sequencing Data. Using RNA sequencing, we detected 46760 transcripts (including 35673 protein-coding and 11087 non-protein-coding with linear structure and length>200bp) corresponding to 15554 genes in EAT in total. The top 30 highly expressed protein-coding and non-protein-coding transcripts are summarized in Table 2. Scatter plot (Figure 1) was performed to group IncRNA and mRNA and display the levels of IncRNA and mRNA in CAD patients with and without HF according to their expression levels among samples, and the results indicated that the IncRNA and mRNA expression profiles in CAD patients with HF were distinctly different from those in CAD patients without HF. 85 IncRNA and 866 mRNA whose levels changed significantly (p<0.05) were identified, including 45 upregulated and 40 downregulated IncRNA, as well as 404 upregulated and 462 downregulated mRNA.

Using a 2-fold expression difference as a cutoff, a total of 30 differentially expressed IncRNAs (17 upregulated and 13 downregulated) (Figure 2, Table 3) and 278 differentially expressed mRNAs (129 upregulated and 149 downregulated)
Table 2: The 30 highly expressed protein-coding and non-protein-coding transcripts in EAT in CAD patients.

| Track ID       | Gene Name    | Transcript Type         | Length(bp) | Protein |
|----------------|--------------|-------------------------|------------|---------|
| ENST00000165086.8 | NPIPB4       | Processed transcript    | 464        | No      |
| ENST00000173785.4 | KLF6         | Processed transcript    | 925        | No      |
| ENST00000214893.9 | ERMP1        | Processed transcript    | 4974       | No      |
| ENST00000216463.8 | TIMM9        | Processed transcript    | 1075       | No      |
| ENST00000216520.6 | ERH          | Processed transcript    | 668        | No      |
| ENST00000217890.10 | ARSD        | Processed transcript    | 2160       | No      |
| ENST00000230914.4 | MRPS30       | Processed transcript    | 4331       | No      |
| ENST00000233699.8 | POLE4        | Processed transcript    | 602        | No      |
| ENST00000237177.10 | CASP8AP2    | Processed transcript    | 6719       | No      |
| ENST00000244070.7 | PPP4R1L      | Processed transcript    | 1474       | No      |
| ENST00000253320.8 | TXLNGY       | Retained intron         | 7299       | No      |
| ENST00000254409.9 | CLUHP3       | Processed transcript    | 1812       | No      |
| ENST00000254299.8 | GCH1         | Processed transcript    | 2901       | No      |
| ENST00000256692.5 | PLEKHA8P1    | Processed transcript    | 1839       | No      |
| ENST00000263511.8 | CROC5P3      | Processed transcript    | 5368       | No      |
| ENST00000264785.11 | WDR1       | Processed transcript    | 549        | No      |
| ENST00000265450.5 | TSPAN14      | Processed transcript    | 2588       | No      |
| ENST00000265870.7 | SLC25A16     | Processed transcript    | 2295       | No      |
| ENST00000267868.9 | GTF2A2       | Processed transcript    | 518        | No      |
| ENST00000266651.1 | ANP32A       | Processed transcript    | 1084       | No      |
| ENST00000273411.2 | RPL9P5       | Processed transcript    | 449        | No      |
| ENST00000274820.7 | RPL13P5      | Processed transcript    | 349        | No      |
| ENST00000276906.10 | EBP         | Processed transcript    | 904        | No      |
| ENST00000282943.9 | ADGRA3       | Processed transcript    | 3534       | No      |
| ENST00000286777.6 | RWDD2B       | Processed transcript    | 1625       | No      |
| ENST00000294661.8 | C1orf52      | Processed transcript    | 3391       | No      |
| ENST00000295549.8 | LINC01116    | lincRNA                | 1407       | No      |
| ENST00000295748.7 | AZI2         | Processed transcript    | 3127       | No      |
| ENST00000296031.4 | CXCL2        | Processed transcript    | 577        | No      |
| ENST00000296325.9 | LRPA1        | Processed transcript    | 1078       | No      |
| ENST00000361682.4 | MT-CO1       | Protein coding          | 1542       | 513aa   |
| ENST00000362079.2 | MT-CO3       | Protein coding          | 784        | 261aa   |
| ENST00000363139.0 | MT-N1D       | Protein coding          | 956        | 318aa   |
| ENST00000363188.2 | MT-N4D       | Protein coding          | 1378       | 459aa   |
| ENST00000364733.3 | MT-N2D       | Protein coding          | 1042       | 347aa   |
| ENST0000036789.2  | MT-CYB       | Protein coding          | 1141       | 380aa   |
| ENST0000036779.1  | MT-CO2       | Protein coding          | 684        | 227aa   |
| ENST00000368511.1 | MT-ATP8      | Protein coding          | 207        | 68aa    |
| ENST0000033825.11 | FTL          | Protein coding          | 871        | 175aa   |
| ENST0000036335.1  | MT-N4L       | Protein coding          | 297        | 98aa    |
| ENST0000036556.7  | MT-N5        | Protein coding          | 1812       | 603aa   |
| ENST0000036272.7  | MT-N3        | Protein coding          | 346        | 115aa   |
| ENST0000036899.2  | MT-ATP6      | Protein coding          | 681        | 226aa   |
| ENST00000320868.9 | HBA1         | Protein coding          | 577        | 142aa   |
| ENST00000335232.6 | EEF1A1       | Protein coding          | 1923       | 462aa   |
| ENST00000327726.10 | CFD         | Protein coding          | 1201       | 253aa   |
| ENST00000320745.4 | JUNB         | Protein coding          | 1830       | 347aa   |
| ENST00000339384.4 | EGR1         | Protein coding          | 3137       | 543aa   |
| ENST00000356524.9 | SAA1         | Protein coding          | 518        | 122aa   |
| ENST00000633942.1 | PLIN4        | Protein coding          | 6484       | 1372aa  |
| ENST00000367029.5 | G0S2         | Protein coding          | 876        | 103aa   |
Table 2: Continued.

| TrackID | GeneName | TranscriptType | Length(bp) | Protein |
|---------|----------|----------------|------------|---------|
| ENST00000309311.7 | EEF2 | Protein coding | 3158 | 858aa |
| ENST000000251595.11 | HBA2 | Protein coding | 576 | 142aa |
| ENST00000335295.4 | HBB | Protein coding | 628 | 147aa |
| ENST00000256104.4 | FABP4 | Protein coding | 941 | 132aa |
| ENST00000451311.7 | TMSB4X | Protein coding | 622 | 44aa |
| ENST000000233143.6 | TMSB10 | Protein coding | 461 | 44aa |
| ENST000000330871.3 | SOCS3 | Protein coding | 2734 | 225aa |
| ENST00000336615.9 | PNPLA2 | Protein coding | 2416 | 504aa |
| ENST00000300055.10 | PLIN1 | Protein coding | 2916 | 522aa |

Note: EAT, epicardial adipose tissue; CAD, coronary artery disease; Track ID, The transcript name in Ensembl database; Gene Name, The corresponding gene name of transcript; Transcript Type, the biotype of transcript; Protein, the residue number of protein.

Figure 1: The scatter plot of the differential expressed (p<0.05) lncRNA (a) and mRNA (b) in patients with heart failure (HF) and without heart failure (non-HF) (red or green represented upregulated or downregulated genes, respectively); 85 lncRNA and 866 mRNA were identified, including 45 upregulated and 40 downregulated lncRNA, as well as 404 upregulated and 462 downregulated mRNA.

![scatter plot of differential expressed lncRNA and mRNA](image)

3.3. GO and KEGG Pathway Analysis of Differentially Expressed mRNAs. The Gene Ontology (GO) project (Figure 4) provided a controlled vocabulary to describe gene and gene product attributes in any organism. The ontology covered three domains: Biological Process (BP), Cellular Component (CC), and Molecular Function (MF). For upregulated genes, the top enriched GO terms in three domains were regulation of lymphocyte activation (GO:0051249) in BP, T cell receptor complex (GO:0042101) in CC, and phosphotyrosine residue binding (GO:0001784) in MF; for downregulated genes, those were oxidation reduction process (GO:0055114) in BP,
Figure 2: The hierarchical clustering and volcano plot of the substantially differential expressed (P<0.05; fold change>2) lncRNA ((a1) and (a2)) and mRNA ((b1) and (b2)) in patients with and without heart failure (red or green represented upregulated or downregulated genes, respectively); 30 lncRNA and 278 mRNA were identified, including 17 upregulated and 13 downregulated lncRNA, as well as 129 upregulated and 149 downregulated mRNA.
Figure 3: qRT-PCR analysis of expression of lncRNA ENST00000610659 (left) and UNC93B1 mRNA (right) in patients with heart failure (HF) and without heart failure (non-HF) (n=5 in each group), **p<0.05.

Table 3: Differentially expressed lncRNA in EAT in CAD patients with HF compared with CAD patients without HF.

| IncRNA             | Type                  | Regulation | Gene Name | Fold Change | P Value |
|--------------------|-----------------------|------------|-----------|-------------|---------|
| ENST00000610659    | exon sense-overlapping| Up         | UNC93B1   | 4.778       | 0.0118  |
| ENST00000379935    | natural antisense     | Up         | RBL2      | 3.711       | 0.0347  |
| ENST00000603935    | exon sense-overlapping| Up         | ZSWIM8    | 3.329       | 0.0039  |
| ENST00000439904    | exon sense-overlapping| Up         | SLCO2A1   | 2.955       | 0.0179  |
| ENST000006222120   | intergenic            | Up         | LINC00963 | 2.952       | 0.0000  |
| ENST00000514805    | exon sense-overlapping| Up         | TRIM52    | 2.901       | 0.0294  |
| ENST00000492356    | exon sense-overlapping| Up         | RPS2D1    | 2.869       | 0.0461  |
| ENST00000394225    | exon sense-overlapping| Up         | NDUFCL1   | 2.840       | 0.0331  |
| ENST00000548989    | exon sense-overlapping| Up         | CRIP2     | 2.247       | 0.0248  |
| ENST00000465589    | exon sense-overlapping| Up         | OBSL1     | 2.229       | 0.0067  |
| ENST00000398078    | exon sense-overlapping| Up         | PDXK      | 2.111       | 0.0157  |
| ENST00000476113    | exon sense-overlapping| Up         | TCEA2     | 2.111       | 0.0223  |
| ENST00000421064    | natural antisense     | Up         | AP000347.2| 2.099       | 0.0220  |
| ENST00000470322    | exon sense-overlapping| Up         | ACTRIA    | 2.083       | 0.0304  |
| ENST00000587762    | intergenic            | Up         | AC020916.1| 2.054       | 0.0443  |
| ENST00000512955    | exon sense-overlapping| Up         | AMOTL2    | 2.052       | 0.0164  |
| ENST00000508948    | exon sense-overlapping| Up         | ARRDCC3   | 2.012       | 0.0289  |
| ENST00000543826    | exon sense-overlapping| Down       | ADGRD1    | 0.161       | 0.0021  |
| ENST00000467318    | exon sense-overlapping| Down       | DDX56     | 0.243       | 0.0126  |
| ENST00000556961    | exon sense-overlapping| Down       | FBLN5     | 0.251       | 0.0033  |
| ENST00000505923    | exon sense-overlapping| Down       | WDFY3     | 0.283       | 0.0221  |
| ENST00000578571    | exon sense-overlapping| Down       | PTPRM     | 0.305       | 0.0360  |
| ENST00000427261    | intergenic            | Down       | RP11-640M9.2| 0.331     | 0.0051  |
| ENST0000039685     | exon sense-overlapping| Down       | TMTC1     | 0.370       | 0.0256  |
| ENST00000439351    | exon sense-overlapping| Down       | TACC2     | 0.391       | 0.0341  |
| ENST00000480603    | exon sense-overlapping| Down       | PPIA      | 0.414       | 0.0048  |
| ENST00000345896    | exon sense-overlapping| Down       | CERS2     | 0.453       | 0.0391  |
| ENST00000498053    | exon sense-overlapping| Down       | LRRFIP1   | 0.475       | 0.0350  |
| ENST00000467178    | exon sense-overlapping| Down       | CIZ1      | 0.486       | 0.0448  |
| ENST00000468975    | exon sense-overlapping| Down       | ARFGAP1   | 0.495       | 0.0128  |

Note: EAT, epicardial adipose tissue; CAD, coronary artery disease; HF, heart failure; lncRNA, The lncRNA name in Ensembl database; Type, the type of lncRNA; Regulation, the regulation expression of lncRNA; Gene Name, The corresponding gene name of lncRNA.
Figure 4: Enriched GO terms analysis for differentially expressed mRNAs. Top 10 significantly upregulated GO terms—Biological Process (a) and Molecular Function (c); all significantly upregulated GO terms—Cellular Component (b); top 10 significantly downregulated GO terms—Biological Process (d) and Molecular Function (f); all significantly downregulated GO terms—Cellular Component (e).
extracellular space (GO:0005615) in CC, and oxidoreductase activity (GO:0016491) in MF, respectively.

Pathway analysis (Figure 5) showed that, when comparing to controls, 17 pathways were significantly upregulated while 4 pathways were significantly downregulated. The top 3 significantly upregulated pathways were T cell receptor signaling pathway (hsa04660), primary immunodeficiency (hsa05340), and endometrial cancer (hsa05213). Meanwhile, the significantly downregulated pathways were drug metabolism cytochrome P450 (hsa00982), tyrosine metabolism (hsa00350), complement and coagulation cascades (hsa04610), and Jak-STAT signaling pathway (hsa04630).

4. Discussion

In the present study, we assessed the expression profiles of EAT IncRNA and mRNA in CAD patients with and without HF. The results showed a total of 35673 mRNA and 11087 IncRNA corresponding to 15554 genes in EAT were detected, and using a 2-fold expression difference as a cutoff, a total
of 30 differentially expressed lncRNAs (17 upregulated and 13 downregulated) and 278 differentially expressed mRNAs (129 upregulated and 149 downregulated) were discriminated between CAD patients with and without HF.

The differentially expressed lncRNAs corresponded to genes associated with inflammatory response or other factors which are involved in HF. UNC93B1, the top upregulated gene lncRNA corresponded to, encodes UNC93B1 protein that is involved in innate and adaptive immune response by regulating toll-like receptor signaling [8, 9] and is proved to be related to left ventricular diastolic function, heart failure morbidity, and mortality [10]. RBL2 is related to TGF-beta signaling [11]. LINC00963 encodes lncRNA963 playing an important role in chronic renal failure, which is closely associated with chronic diseases such as congestive heart failure [12]. TRIM52 encodes TRIM52 protein that positively regulates the nuclear factor-kappa B signaling pathway [13]. RPS21 (also known as HLDF) encodes HLDF protein that is involved in the mechanisms of blood pressure regulation [14]. AMOTL2 is required for migration and proliferation of endothelial cells during angiogenesis [15]. FBLN5 protein expression significantly decreases in human aneurysmatic aortas and may mediate cell-extracellular matrix interactions and elastic fibre assembly by inflammation [16]. TMTC1 is associated with the risk of incident HF [17]. LRRFIP1 is associated with adiposity and inflammation [18], and LRRFIP1 protein may regulate platelet function [19].

EAT refers to the fat depot that exists on the surface of the myocardium and is contained entirely beneath the pericardium, which generates various inflammatory factors [20, 21]. Factors released from EAT have vasocrine and paracrine effects on the myocardium contributing to modulating properties on cardiac function [4, 22]. As our study showed, lncRNA can also be released from EAT and may be involved in HF; top upregulated lncRNA in HF corresponded to genes associated with inflammatory response and top upregulated enriched GO terms and KEGG pathway of mRNA were also about inflammatory cells activity.

The present study showed the expression profiles of EAT lncRNA and mRNA in CAD patients and also characterized specific EAT lncRNA expression in HF. The EAT lncRNA may be important effector molecules for cardiovascular disease. Through the paracrine and vasocrine transmission, the EAT lncRNA may diffuse across the interstitial fluid or blood into the myocardium to be involved in the development of HF. Our data supplement lncRNA expression profiles in the EAT for lncRNA identifying in heart tissues and also provide possible biomarkers for HF, and further studies are needed to prove it.

**Data Availability**

The data used to support the findings of this study are available from the corresponding author upon request.

**Conflicts of Interest**

The authors declare that they have no conflicts of interest.

**Authors’ Contributions**

Meili Zheng and Lei Zhao analyzed the results and wrote the paper; Xinchun Yang designed the study. Meili Zheng and Lei Zhao contributed equally to this work.

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**References**

[1] M. K. Iyer, Y. S. Niknafs, R. Malik et al., “The landscape of long noncoding RNAs in the human transcriptome,” Nature Genetics, vol. 47, no. 3, pp. 199–208, 2015.

[2] T. Hung, Y. Wang, M. F. Lin et al., “Extensive and coordinated transcription of noncoding RNAs within cell-cycle promoters,” Nature Genetics, vol. 43, no. 7, pp. 621–629, 2011.

[3] K. C. Wang and H. Y. Chang, “Molecular mechanisms of long noncoding RNAs,” Molecular Cell, vol. 43, no. 6, pp. 904–914, 2011.

[4] S. Cherian, G. D. Lopaschuk, and E. Carvalho, “Cellular cross-talk between epicardial adipose tissue and myocardium in relation to the pathogenesis of cardiovascular disease,” American Journal of Physiology-Endocrinology and Metabolism, vol. 303, no. 8, pp. E937–E949, 2012.

[5] R. Fontes-Carvalho, M. Fontes-Oliveira, F. Sampaio et al., “Influence of epicardial and visceral fat on left ventricular diastolic and systolic functions in patients after myocardial infarction,” American Journal of Cardiology, vol. 114, no. 11, pp. 1663–1669, 2014.

[6] T. P. Fitzgibbons and M. P. Czech, “Epicardial and perivascular adipose tissues and their influence on cardiovascular disease: basic mechanisms and clinical associations,” Journal of the American Heart Association, vol. 3, no. 2, Article ID e000582, pp. 1–15, 2014.

[7] Y. Wang, L. Xie, E. Tian et al., “Oncostatin M inhibits differentiation of rat stem Leydig cells in vivo and in vitro,” Journal of Cellular and Molecular Medicine, vol. 23, no. 1, pp. 426–438, 2019.

[8] J. Pohar, N. Pirher, M. Benčina, M. Manček-Keber, and R. Jerala, “The role of UNC93B1 protein in surface localization of TLR3 receptor and in cell priming to nucleic acid agonists,” The Journal of Biological Chemistry, vol. 288, no. 1, pp. 442–454, 2013.

[9] B. L. Lee and G. M. Barton, “Trafficking of endosomal Toll-like receptors,” Trends in Cell Biology, vol. 24, no. 6, pp. 360–369, 2014.

[10] J. Ārnālīv, J. Sundström, L. Lind et al., “hUNC-93B1, a novel gene mainly expressed in the heart, is related to left ventricular diastolic function, heart failure morbidity and mortality in elderly men,” European Journal of Heart Failure, vol. 7, no. 6, pp. 958–965, 2005.

[11] J. Shi, Y. Zhuang, X. K. Liu, Y. X. Zhang, and Y. Zhang, “TGF-beta induced RBL2 expression in renal cancer cells by down-regulating miR-93,” Clinical & Translational Oncology, vol. 16, no. 11, pp. 986–992, 2014.

[12] W. Chen, L. Zhang, Z. Zhou et al., “Effects of long non-coding RNA LINC00963 on renal interstitial fibrosis and oxidative stress of rats with chronic renal failure via the foxo signaling
pathway,” *Cellular Physiology and Biochemistry*, vol. 46, no. 2, pp. 815–828, 2018.

[13] W. Fan, T. Liu, X. Li et al., “TRIM52: A nuclear TRIM protein that positively regulates the nuclear factor-kappa B signaling pathway,” *Molecular Immunology*, vol. 82, pp. 114–122, 2017.

[14] E. I. Elisratova, M. A. Gruden, and V. V. Sherstnev, “Involvement of HLDF protein and Anti-HLDF antibodies in the mechanisms of blood pressure regulation in healthy individuals and patients with stable hypertension and hypertensive crisis,” *Bulletin of Experimental Biology and Medicine*, vol. 153, no. 5, pp. 664–666, 2012.

[15] Y. Wang, Z. Li, P. Xu et al., “Angiomotin-like2 gene (amotl2) is required for migration and proliferation of endothelial cells during angiogenesis,” *The Journal of Biological Chemistry*, vol. 286, no. 47, pp. 41095–41104, 2011.

[16] M. Orriols, S. Varona, I. Martí-Pàmies et al., “Down-regulation of Fibulin-5 is associated with aortic dilation: role of inflammation and epigenetics,” *Cardiovascular Research*, vol. 110, no. 3, pp. 431–442, 2016.

[17] N. L. Smith, J. F. Felix, A. C. Morrison et al., “Association of genome-wide variation with the risk of incident heart failure in adults of European and African ancestry: a prospective meta-analysis from the cohorts for heart and aging research in genomic epidemiology (CHARGE) consortium,” *Circulation: Cardiovascular Genetics*, vol. 3, no. 3, pp. 256–266, 2010.

[18] M. Plourde, M. Vohl, C. Bellis et al., “A variant in the LRRFIP1 gene is associated with adiposity and inflammation,” *Obesity*, vol. 21, no. 1, pp. 185–192, 2013.

[19] A. H. Goodall, P. Burns, I. Salles et al., “Transcription profiling in human platelets reveals LRRFIP1 as a novel protein regulating platelet function,” *Blood*, vol. 116, no. 22, pp. 4646–4656, 2010.

[20] B. Gaborit, C. Sengenes, P. Ancel, A. Jacquier, and A. Dutour, “Role of epicardial adipose tissue in health and disease: a matter of fat?” *Comprehensive Physiology*, vol. 7, no. 3, pp. 1051–1082, 2017.

[21] T. Mazurek, L. Zhang, A. Zalewski et al., “Human epicardial adipose tissue is a source of inflammatory mediators,” *Circulation*, vol. 108, no. 20, pp. 2460–2466, 2003.

[22] V. B. Patel, J. Mori, B. A. McLean et al., “ACE2 deficiency worsens epicardial adipose tissue inflammation and cardiac dysfunction in response to diet-induced obesity,” *Diabetes*, vol. 65, no. 1, pp. 85–95, 2016.