ORIGINAL RESEARCH ORİJİNAL ARAŞTIRMA

DOI: 10.5336/medsci.2024-105015

# Investigation of *RN7SL1* Expression in Human Umbilical Vein Endothelial Cells After Oxidized Low-Density Lipoprotein Stimulation: Experimental Study

## Oksitlenmiş Düşük-Yoğunluklu Lipoprotein Uyarımından Sonra İnsan Göbek Kordonu Damar Endotel Hücrelerinde *RN7SL1* Ekspresyonunun Araştırılması: Deneysel Çalışma

Burcu BAYYURT[a], Serdal ARSLAN[b]

[a]Sivas Cumhuriyet University Faculty of Medicine, Department of Medical Biology, Sivas, Türkiye
[b]Mersin University Faculty of Medicine, Department of Medical Biology, Mersin, Türkiye

**ABSTRACT Objective:** Oxidized low-density lipoprotein (ox-LDL) damages endothelial cells (ECs) and induces pathogenic processes related to atherosclerosis (AS). Long non-coding RNAs (lncRNAs) have been accepted to be transcripts code no proteins and have important roles in gene expression regulation. LncRNAs have been thought important targets in the fight against cardiovascular diseases (CVDs). RNA component of signal recognition particle (SRP) 7SL1 (*RN7SL1*) is a lncRNA. *RN7SL1* was associated with inhibition of cell cycle arrest. Since *RN7SL1* is associated with cell cycle arrest and ox-LDL affects EC cell apoptosis, hypothesis of our study is that ox-LDL may alter the expression of this lncRNA in ECs. There was no study yet on *RN7SL1* and CVDs including AS. We aimed to compare *RN7SL1* gene expression between ECs treated with ox-LDL and normal ECs. **Material and Methods:** We investigated expression level of lncRNA *RN7SL1* in human umbilical vein endothelial cells (HUVECs) induced with ox-LDL in this study. We performed measurement with SYBR green dye using quantitative PCR (real-time PCR, qPCR) method. **Results:** We found that expression of *RN7SL1* was up-regulated 6.06 fold statistic significantly in HUVECs after ox-LDL treatment (P<0.001**). *RN7SL1* up-regulation may modulate EC cycle and apoptosis in AS, since ox-LDL stimulation increased expression of *RN7SL1* gene in HUVECs. **Conclusion:** According to findings of the current study, our interest focused on that *RN7SL1* may associated with vascular damage of the ECs at initation of the AS. Our results further will guide future studies related to the *RN7SL1* and CVDs including AS.

**Keywords:** Gene expression;
human umbilical vein endothelial cell;
oxidized low-density lipoprotein; *RN7SL1*

**ÖZET Amaç:** Oksitlenmiş düşük-yoğunluklu lipoprotein [oxidized low-density lipoprotein (ox-LDL)] endotel hücrelerine [endothelial cells (ECs)] zarar verir ve ateroskleroz (AS) ile ilişkili patojenik süreçleri başlatır. Uzun kodlama yapmayan ribonükleik asitler (lncRNA'lar) protein kodlamayan transkriptler olarak kabul edilir ve gen ifadesinin düzenlenmesinde önemli rolleri vardır. LncRNA'ların kardiyovasküler hastalıklarla [cardiovascular diseases (CVD)] mücadelede önemli hedefler olduğu düşünülmektedir. Sinyal tanıma partikülünün [signal recognition particle (SRP)] RNA bileşeni 7SL1 (*RN7SL1*) bir lncRNA'dır. *RN7SL1*, hücre döngüsü durmasının inhibisyonu ile ilişkilendirilmiştir. *RN7SL1*; hücre döngüsünün durdurulması ile ilişkili olduğundan ve ox-LDL; EC hücresi apoptozunu etkilediğinden, çalışmamızın hipotezi, ox-LDL'nin, bu lncRNA'nın EC'lerdeki ekspresyonunu değiştirebileceği yönündedir. *RN7SL1* ve CVD'ler kapsamındaki AS ile ilişkili henüz bir çalışma yapılmamıştır. Çalışmamızda ox-LDL ile muamele edilen ve normal EC'ler arasında *RN7SL1* gen ekspresyonunu karşılaştırmayı amaçladık. **Gereç ve Yöntemler:** Bu çalışmada ox-LDL ile indüklenen insan göbek kordonu damar endotel hücrelerinde [human umbilical vein endothelial cells (HUVEC'ler)] lncRNA *RN7SL1* ekspresyon düzeyini araştırdık. Kantitatif polimeraz zincir reaksiyonu [polymerase chain reaction (PCR)] (gerçek zamanlı PCR, qPCR) yöntemini kullanarak SYBR green boyası ile ölçüm yaptık. **Bulgular:** Ox-LDL uyarımından sonra HUVEC'lerde *RN7SL1* ekspresyonunun istatistiksel olarak anlamlı şekilde 6,06 kat arttığını bulduk (p<0,001**). Ox-LDL uyarımı HUVEC'lerde *RN7SL1* geninin ekspresyonunu artırdığından, *RN7SL1*'in yukarı regülasyonu AS'de EC döngüsünü ve apoptozu düzenleyebilir. **Sonuç:** Mevcut çalışmanın bulgularına göre, *RN7SL1*'in AS başlangıcında EC'lerin vasküler hasarı ile ilişkili olabileceği düşünülmektedir. Sonuçlarımız ayrıca *RN7SL1* ve AS dâhil CVD'lerle ilgili gelecekteki çalışmalara rehberlik edecektir.

**Anahtar Kelimeler:** Gen ekspresyonu;
insan göbek kordonu damar endotel hücre;
oksitlenmiş düşük-yoğunluklu lipoprotein; *RN7SL1*

**TO CITE THIS ARTICLE:**
Bayyurt B, Arslan S. Investigation of *RN7SL1* expression in human umbilical vein endothelial cells after oxidized low-density lipoprotein stimulation: Experimental study. Turkiye Klinikleri J Med Sci. 2025;45(1):43-8.

**Correspondence:** Burcu BAYYURT
Sivas Cumhuriyet University Faculty of Medicine, Department of Medical Biology, Sivas, Türkiye
**E-mail:** ebayyurt@yahoo.com.tr

Peer review under responsibility of Turkiye Klinikleri Journal of Medical Sciences.

***Received:*** 31 Jul 2024 ***Received in revised form:*** 20 Jan 2025 ***Accepted:*** 04 Feb 2025 ***Available online:*** 25 Feb 2025

Low-density lipoprotein (LDL) is accepted a biomarker for cardiovascular diseases (CVDs) and promotes atherosclerosis (AS).[1] Oxidative stress stimulates activation of vascular smooth cells and macrophages. This increases accumulation of extracellular cholesterol in vessel wall, and transforms macrophages to pro-inflammatory and pro-thrombotic phenotypes resulting in formation of atherosclerotic plaque. The formation of foam cells which is caused by oxidized LDL (ox-LDL) is serious step in build-up of the atherosclerotic plaque.[2] Ox-LDL is originated from circulating LDL.[3] Ox-LDL-stimulated oxidative stress is a main factor of the endothelial cell (EC) damage. Ox-LDL deposited in vascular wall and induces apoptosis of the vascular EC. A lot of studies reported that the vascular EC damage initiates and develops the AS.[4]

Ox-LDL frequently contributes to the CVDs.[5] Therefore, ox-LDL has been an accepted critical target for treatment of the CVDs and noticed as a biomarker for atherosclerotic processes and coronary artery diseases.[6] Thus, inhibition of the ox-LDL-induced EC damage is a possible strategy to prevent or slow AS progression.[3]

Protein coding transcripts form less than 3% of the genome, while non-coding ribonucleic acids (ncRNAs) are transcripts called which have little or no ability to encode protein, represents large part of the genome according to high-throughput genomic platforms.[7] NcRNAs are shown that they are functionally active as RNA molecules as well as one of the major regulatory networks of gene expression at the epigenetic, transcriptional, and post-transcriptional levels.[8] NcRNAs can be classified as small ncRNAs and long non-coding RNAs (lncRNAs). The lncRNAs can regulate gene expression at multiple levels.[9] Recently, lncRNAs have been interesting because of their biomarker and therapeutic potential, but knowledge about them is still limited.[10]

RNA component of signal recognition particle (SRP) 7SL1 (*RN7SL1)* (~300 nt) is a lncRNA which is located chromosome 14 and an essential component of the SRP which targets proteins to membranes of the cell.[11] In addition, the *RN7SL1* has been categorized as RNA polymerase III transcript.[12]

The study hypothesis was focused on determining that ox-LDL alters *RN7SL1* gene expression in human umbilical vein endothelial cells (HUVECs). We aimed to compare expression level of *RN7SL1* gene in HUVECs induced with ox-LDL versus normal HUVECs. Therefore, we targeted to uncover whether ox-LDL induction may effect *RN7SL1* gene expression in pathogenesis of the AS.

## MATERIAL AND METHODS

### CELL LINE

HUVECs were obtained from American Type Culture Collection. HUVECs were cultured with human EC growth medium/Dulbecco's Modified Eagle Medium [CAPRICORN (Capricorn Scientific GmbH, Germany)] supplemented with 10% fetal bovine serum (Capricorn Scientific GmbH, Germany) and 1% penicillin-streptomycin (Capricorn Scientific GmbH, Germany) at 5% $CO_2$ and 37°C under 95% relative humidity. The cells were removed from the culture medium with 0.25% trypsin every 2-3 days and subcultured, and the cells in the logarithmic growth phase were used for experiments.[13] After achieving ~80-90% confluence, HUVECs were classified 2 groups. Former group was control group, in which HUVECs were grown in EC growth medium; and latter group was experiment group in which HUVECs were grown in 40 µg/ml concentration of ox-LDL [Invitrogen LOT2160046, L34357 (ThermoFisher Scientific, USA)] for 24 hour.[14]

### QUANTITATIVE POLYMERASE CHAIN REACTION

Total RNA including lncRNAs was isolated from HUVECs by using RNeasy Mini Kit (Qiagen, Germany) (QIAGEN, catalog no: 74104) and reverse transcription kit (A.B.T.™ with RNase Inh. High Capacity, catalog no: C03-01-20) (Atlas Biyoteknoloji, Ankara) was utilized to synthesize complementary DNA. Quantitative Polymerase Chain Reaction (qPCR) amplification was conducted using SYBR Green (A.B.T.™ 2X qPCR SYBR-Green MasterMix kit, catalog no: Q03-02-01 ve Q03-02-05) (Atlas Biyoteknoloji, Ankara) on qPCR instrument (Rotor-Gene Q, QIAGEN Hilden, Germany). In qPCR, we

provided primers of *RN7SL1* and splicing factor 3 subunit 1 (*SF3A1)* genes as optimized assays. Primer spesific to human *RN7SL1* (QIAGEN, catalog no: LPH21289A-200, 20161110006) was used for qPCR. *SF3A1* (QIAGEN, catalog no: PPH19231A) was internal control (housekeeping) gene used in qPCR.

### ETHICAL CONSIDERATION

Ethics committee approval was not required for this study because of there was no study on animals or humans.

### STATISTIC ANALYSIS

"GeneGlobe Data Analysis Center" (https://geneglobe.qiagen.com/us/analyze QIAGEN, Hilden, Germany) was used to analyze the gene expression data obtained from result of qPCR by uploading to the analysis system. Fold change (FC) calculations (gene expression ratios) were calculated performing method of $2^{-\Delta\Delta CT}$. FC was calculated as the ratio of the relative gene expression between the control group and experiment group. Numbers greater than 1 indicate increased gene expression (up-regulation), numbers between 0 and 1 indicate decreased gene expression (down-regulation), and a FC value of 1 indicates no change. p-value was calculated based on a student's t-test of the replicate $2^{-\Delta\Delta CT}$ values for each gene in each control group and experiment group comparison. p-value results less than 0.05 were accepted significant.[15]

**TABLE 1:** Expression change of *RN7SL* gene in HUVECs after ox-LDL treatment.

| Genes | Control group HUVECs | Experiment group HUVECs+ox-LDL | FC | FR | p value |
|---|---|---|---|---|---|
| *RN7SL* | | | | | |
| Mean of Ct (Cq) | 23.10 | 19.98 | 6.06 | Up-regulation | <0.001** |
| *SF3A1* | | | | | |
| Mean of Ct (Cq) | 27.91 | 27.39 | 1.00 | 1.00 | Nan |

**p value<0.001. HUVECs: Human umbilical vein endothelial cells; ox-LDL: Oxidized low-density lipoprotein; FC: Fold change; FR: Fold regulation; Ct (Cq):Threshold cycle; HUVECs+ox-LDL: HUVECs induced with ox-LDL; *SF3A1* (control gene): Splicing factor 3a subunit 1; *RN7SL:* Ribonucleic acids component of signal recognition particle (SRP) 7SL1.

## RESULTS

We measured expression level of *RN7SL* gene in both experiment and control group. Ct values in 2 groups were used to calculate changes in gene expression. We compared expression level of *RN7SL* gene between HUVEC induced with ox-LDL and HUVEC without ox-LDL. Expression of the *RN7SL* gene was up-regulated statistic significantly (p<0.001**) in HUVECs induced with ox-LDL compared to the HUVEC without ox-LDL (Table 1).

Expression of the *RN7SL* gene increased 6.06 fold in HUVEC induced with ox-LDL when compared to the control group (P<0.001**). Fold change of expression of the *RN7SL* gene between groups was shown in Figure 1.

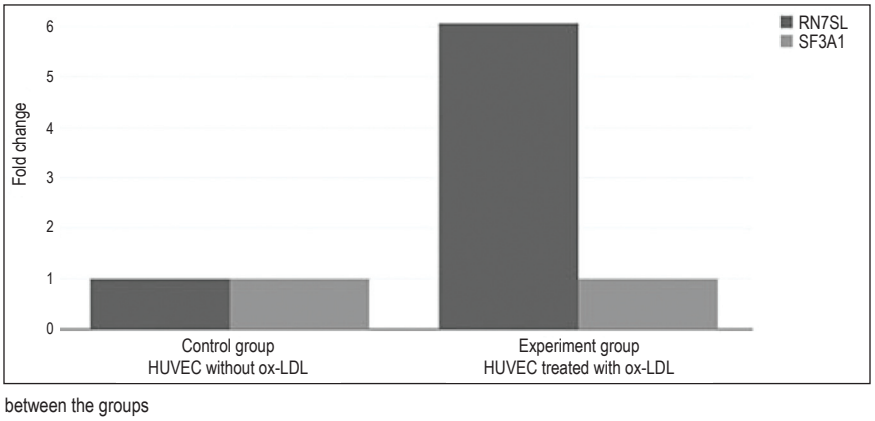


**FIGURE 1:** Fold change between the groups

HUVEC: Human umbilical vein endothelial cells; ox-LDL: Oxidized low-density lipoprotein; *RN7SL1* (gene of interest):RNA component of signal recognition particle (SRP) 7SL1; *SF3A1* (control gene):Splicing Factor 3a Subunit 1.

## DISCUSSION

AS is cause of variety of complex complications and severely threaten health of public. There is not any specific and influential therapeutic strategy for AS.[16] Evidence has shown that ox-LDL can promote the EC damage that contributes to progression of the AS.[17] Prior studies have observed that circulating ox-LDL relates to every phase of the AS, from subclinical AS to prominent CVDs such as hypertension peripheral and coronary artery disease. The ox-LDL has prognostic significance in forecasting risk of the CVD.[5] Numerous molecular mechanisms including ncRNAs can influence gene expression.[18] The lncRNAs have a major role in complex formation of heart and disregulation of them have been related to a lot of CVDs.[19] LncRNA Disease v2.0 database (School of Life Sciences, East China Normal University, China) (www.rnanut.net/lncrnadisease, accessed on September 16, 2021) noticed that there are more than 205.959 interactions between lncRNAs and diseases including the CVDs.[20] Recent studies implicated that some lncRNAs act in controlling the development of atherosclerotic plaques, resulting in AS. HUVECs are typical cells which are utilized to study the AS pathogenesis.[21] Thus, it is important to research potential mechanism of ox-LDL-stimulated HUVECs dysfunction for understanding pathogenesis of the AS. In our current study, we investigated the expression change of the *RN7SL* gene in ox-LDL-stimulated HUVECs.

Findings of a study by Lin et al. demonstrated that increasing level of the ox-LDL concentration (20-200 μg/ml) caused cytotoxic effects, directly up-regulated production of reactive oxygen species in the HUVECs.[3] Thus, the ox-LDL was utilized as a stimulation agent of the endothelial damage of the HUVECs as an *in vitro* model.[3]

Recently, lncRNAs have been identified as additional epigenetic markers that regulate gene expression without changing DNA sequence. They have been shown to play significant regulatory influences in CVDs.[22] RNA-binding proteins and ncRNAs are potential post-transcriptional regulators of the gene expression.[23] LncRNA *RN7SL1*, transcribed by RNA polymerase III, is involved in protein synthesis.[24] *RN7SL1* play a role in determining the site of synthesis of the proteins and their secretion by the cell.[25] Activation of the expression of the *RN7SL1*, which is among necessary RNAs to maintain a high level of protein synthesis, has been found in many types of tumors. Thus, tumor cells are characterized by a high level of the *RN7SL1*. *RN7SL1* is required for cell growth and increased in cancer tissues. The *RN7SL1 was* demonstrated to be mostly up-regulated in varied cancers.[26] Reverse transcription followed by qPCR indicated higher *RN7SL1* levels in lung, liver, stomach, and breast tumors than in normal adjacent tissues.[23] Conveniently these findings, in our study, we found that expression of the *RN7SL1* gene was up-regulated in ox-LDL stimulated HUVECs compared to the normal cells. The *RN7SL1* binds to untranslated region of mRNA which encode *p53* that is transcription factor and tumor suppressor. Thus, the *RN7SL1* prevents HuR to bind *p53* mRNA and represses translation and expression of the *p53*. Down-regulation of *RN7SL1* promoted HuR binding to *p53* mRNA, causing to elevated *p53* translation and therefore trigger cell cycle arrest, autophagy, and senescence.[23] There is a study illustrates a modulatory paradigm whereby lncRNA *RN7SL1* is associated with mRNAs to regulate binding of protein and effect mRNA fate.[27] Reducing the level of the *RN7SL1* leads to suppression of the proliferation of different types of tumor cells. Recently, it has been found that p53 plays regulatory roles in CVDs and may involve in vascular remodeling, AS. p53 may have a divergent role in EC functions. Different effects of p53 were described in cardiovascular physiology.[28] In our study, the expression of the *RN7SL1* in ECs which were stimulated with ox-LDL was significantly increased compared to normal cells. Since *RN7SL1* prevents translation and expression of the p53, it may regulate apoptosis in ECs stimulated with ox-LDL in AS pathogenesis.[23] The *RN7SL1* in the ribonucleoprotein complex acts in regulation of the proteins in the cells and reduction in expression of it leads a malfunction in the antiviral response.[29] Additionally, it was reported that the *RN7SL1* has been demonstrated to perform as a cofactor in the natural antiviral function of cytidine deaminases.[30] Furthermore, expression of the *RN7SL1* was statistic signif-

icantly down-regulated in psoriatic lesion compared to perilesional healthy skin.[31]

Since the *RN7SL1* is a component of the large subunit of the ribosome, it play role in ribosome function. Particularly, the *RN7SL1* is responsible for the SRP required for relating the nascent peptide chain linked to the ribosome with endoplasmic reticulum. Its reduced levels can disrupt translocation of transmembrane or secreted proteins to the endoplasmic reticulum, which is effective in myelin, causing the hypomyelination phenotype.[32] During neural differentiation of mouse embryonic stem cells into neurons and glial cells, the *RN7SL1* expression was shown to be significantly increased. This could suggest that the expression of the *RN7SL1* may have an impact on protein expression and cell differentiation.[33]

Based on this literature, the expression of the *RN7SL1* varied in different diseases compared to healthy controls. In this study, *RN7SL1* was up-regulated in HUVECs treated with ox-LDL. *RN7SL1* may be sensitive to ox-LDL and induced after ox-LDL treatment. Since lncRNA *RN7SL1* is widely involved in cell proliferation, it may decrease apoptotic effect of ox-LDL.[34] Cardiovascular risk factors that increase ox-LDL level trigger of endothelial damage and apoptosis, and further result in endothelial injury and dysfunction. In addition to genes in regulating EC death, ncRNAs also participate in EC apoptosis.[35] *RN7SL1* may change effect of ox-LDL on apoptosis and thus influence apoptosis of EC.

The expression of the *RN7SL1* gene will need to be supported by in vivo studies. Today, our current knowledge of the molecular mechanisms responsible for the development of CVDs is still limited, and new molecular function studies are needed. Researches about epigenetic mechanisms in cardiovascular pathophysiology has implicated to new biomarkers for treatments. Therefore, we think that our study may has important potential to guide in the process where epigenetics has major role in diseases pathogenesis. Further studies on the effects of *RN7SL1* in ECs on atherosclerotic plaque formation are required before the therapeutic potential can be assessed.

## CONCLUSION

Here, we emphasized that the expression of the *RN7SL1*, a lncRNA, up-regulated in ECs with the effect of ox-LDL *in vitro*. In conclusion, we may provide a specific look at the role of epigenetics in the development of CVDs.

### *Source of Finance*

*The remaining materials from projects supported by Sivas Cumhuriyet University Scientific Research Projects Unit (Project no: T-893 and T-683) were used.*

### *Conflict of Interest*

*No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.*

### *Authorship Contributions*

***Idea/Concept:*** *Burcu Bayyurt, Serdal Arslan;* ***Design:*** *Burcu Bayyurt;* ***Control/Supervision:*** *Serdal Arslan;* ***Analysis and/or Interpretation:*** *Burcu Bayyurt;* ***Literature Review:*** *Burcu Bayyurt;* ***Writing the Article:*** *Burcu Bayyurt;* ***Critical Review:*** *Serdal Arslan;* ***References and Fundings:*** *Serdal Arslan;* ***Other:*** *Burcu Bayyurt.*

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