Cell. Mol. Biol. (ISSN: 1165-158X)

Journal Homepage: www.cellmolbiol.org

Cellular and Molecular Biology

Original Article

Effects of NEAT1 levels on cardiovascular events and prognosis in diabetic nephropathy patients undergoing peritoneal dialysis

Mengjiang Liu[1], Zhaodan Yan[1], Yi Zhang[1], Shengli Zhang[2,*]

[1] Department of Endocrinology, Hubei NO.3 People's Hospital of Jianghan University, Wuhan, China
[2] Department of Cardiology, Hubei NO.3 People's Hospital of Jianghan University, Wuhan, China

Article Info

Article history:

Received: January 11, 2024
Accepted: April 08, 2024
Published: May 31, 2024

Use your device to scan and read the article online

Abstract

The purpose of this study was to provide observational indicators for clinically predicting cardiovascular events in patients with diabetic nephropathy (DN) undergoing peritoneal dialysis by determining the effects of nuclear enriched abundant transcript 1 (NEAT1) levels on the cardiovascular events and prognosis in DN patients receiving continuous ambulatory peritoneal dialysis (CAPD). A retrospective analysis was conducted on the data of 80 DN patients undergoing CAPD. Patients were assigned to NEAT1 high expression group and NEAT1 low expression group. NEAT1 had a substantially increased expression in the serum of DN patients, and it could serve as a potential biomarker for predicting the development of DN. Patients with highly expressed NEAT1 had an higher level of high-sensitivity C-reactive protein (hs-CRP), larger cardiac structural parameters left ventricular end-diastolic diameter (LVED), left ventricular end-systolic diameter (LVESD), interventricular septal diameter (IVSD) and left ventricular posterior wall diameter (LVPWD), but a notably lower cardiac function evaluation indicator left ventricular ejection fraction (LVEF) than those with lowly expressed NEAT1. The coefficient (*r*) of correlation between NEAT1 and hs-CRP level was 0.3585 (*P*=0.0011). The incidence rates of acute myocardial infarction, congestive heart failure and angina in NEAT1 high expression group were higher than those in NEAT1 low expression group. Patients with NEAT1 high expression exhibited a higher mortality rate than NEAT1 low expression group. With the increase in NEAT1 levels, the level of hs-CRP rose in DN patients undergoing CAPD. A higher expression level of NEAT1 indicates poorer cardiac function, higher incidence rates of cardiovascular adverse events and a poorer prognosis in diabetics undergoing CAPD.

Keywords: Diabetic nephropathy, Peritoneal dialysis, Cardiovascular events, NEAT1

1. Introduction

Diabetic nephropathy (DN), a leading microvascular complication of diabetes mellitus (DM), affects nearly 10-30% of diabetics [1]. It also has become a primary cause of end-stage renal disease (ESRD) in most countries [2]. Atherosclerosis (AS) is a main macrovascular complication of DM, and it causes cardiovascular events, thereby resulting in the death of 70% of type 2 DM (T2DM) patients [3]. According to a study, DN patients exhibit a higher incidence rate of AS than those with other renal diseases, since DN is an independent risk factor of AS [4]. Unfortunately, most patients have not been diagnosed until the aggravation of symptoms or occurrence of cardiovascular events, as the onset of AS is insidious in DN patients and there is a lack of sensitive detection methods clinically. Therefore, it is important to find such markers that can effectively evaluate the progression of AS and predict future cardiovascular events for early diagnosis, timely treatment, prognosis improvement and increase in survival rate.

Continuous ambulatory peritoneal dialysis (CAPD) is extraordinarily important in treating patients with uremia. Many studies in China and beyond have demonstrated that CAPD can efficaciously control the symptoms of uremia, relieve anemia and control blood pressure [5]. Currently, it is the most commonly used peritoneal dialysis method worldwide, during which glucose-containing dialysate is taken as the peritoneal dialysis solution, so ESRD patients undergoing CAPD experience more obvious glucose metabolism disorder [6]. Glucose metabolism disorder is not only a factor for the onset and aggravation of cardiovascular diseases but also the leading cause of death in end-stage DN patients [7, 8]. Hence, it can be held that diabetics with ESRD undergoing CAPD are at an extremely high risk of cardiovascular diseases.

Nuclear enriched abundant transcript 1 (NEAT1) is a long non-coding RNA (lncRNA) with a length of about 3.2 kb, and its gene is located on human chromosome 11q13.1 [9]. A study found that NEAT1 regulates cellular immune responses and gene expression by "recruiting" nuclear proteins and RNAs [10]. It can also play a role in the occurrence and progression of many tumors through

* Corresponding author.
E-mail address: 13971408346@163.com (S. Zhang).
Doi: http://dx.doi.org/10.14715/cmb/2024.70.5.25

affecting numerous signaling pathways [11, 12]. Another research suggested that NEAT1 plays a pivotal role in DN-induced fibrosis [13]. However, there have not yet been studies on the effects of NEAT1 levels on end-stage DN patients receiving CAPD currently. The present study, therefore, explored the effects of NEAT1 levels on the cardiac function and incidence rate of cardiovascular events in end-stage DN patients undergoing CAPD, so as to provide observational indicators for clinical control of disease in such patients.

2. Materials and methods

2.1. Research subjects

The data of 80 DN patients undergoing CAPD in Hubei NO.3 People's Hospital of Jianghan University were retrospectively analyzed. All enrollees were administered PD-4 peritoneal dialysate (2,000 mL ×4) daily using a double-chamber double-bag CAPD system (Deerfield, IL, USA).

Inclusion criteria: (1) 18-80-year-old patients clinically diagnosed with T2DM, (2) those in whom the disease progressed into ESRD and who had indications of renal replacement therapy, started undergoing peritoneal dialysis in our hospital and were able to visit the Department of Nephrology of our hospital for re-diagnosis regularly, (3) DN patients with a more than 3-year history of CAPD (the shortest duration was 3 months, and the longest duration was 60 months, and (4) patients who received insulin therapy and were further diagnosed in the hospital for adjusting hypoglycemic and dialytic regimens every 3 months.

Exclusion criteria: (1) patients with a history of malignant tumors, severe infection, malnutrition, cachexia, severe cerebrovascular sequelae or other diseases evidently affecting the quality of life, (2) those who received renal transplantation, had trauma or undergo major surgery, (3) those who had a history of mental disorder, could not cooperate or refused to participate, or (4) those with end-stage renal failure caused by DM rather than DN.

Follow-up endpoints included various complication-induced death, renal transplantation and loss to follow-up (no follow-up was completed in the center for more than 6 months), conversion to hemodialysis and ending of research.

2.2. Collection of information on enrollees

The basic information of enrollees, including age, sex, and duration of DM were collected, and whether patients experienced new malignant tumors or not were identified. The patients with new malignant tumors needed to be excluded. The data collection needed to be terminated when patients had acute severe infections, acute peritonitis, acute myocardial infarction, and acute cerebrovascular disease, and the relevant data were re-collected after the patients experienced stable diseases for at least 3 months.

2.3. Detection of patients' cardiac function indicators using M-mode ultrasonic instrument

All the patients enrolled received cardiac examinations using an M-mode ultrasonic instrument. The subjects were placed in the left side-lying position and rested for several minutes. Upon acquiring a parasternal long axis section of left ventricle, the following cardiac structural parameters were measured by a professional staff member using the M-mode ultrasonic instrument and the M-mode two-dimensional color Doppler flow imaging technique strictly according to the American Society of Echocardiography's Guidelines: left ventricular end-diastolic diameter (LVED), left ventricular end-systolic diameter (LVESD), interventricular septal diameter (IVSD), left ventricular posterior wall diameter (LVPWD) and left ventricular ejection fraction (LVEF). Each parameter was obtained in the same cardiac cycle, and the results for 3 cardiac cycles were averaged. The parameters of the ultrasonic instrument were the same for the measurement of every subject. All the measurements were completed by senior sonographers. The color Doppler echocardiography indicators were collected once per year and then averaged.

2.4. Collection and pre-treatment of samples

A total of 4 mL of fasting venous blood was collected from all patients in the morning, placed in a sterile heparin-anticoagulated tube and divided into two portions. Then one portion was transferred to a 5 mL EP tube and centrifuged at 2,500 g/min for 12 min. Subsequently, the plasma was harvested, aliquoted and reserved in a refrigerator at -80°C.

2.5. Determination of lncRNA NEAT1 expression level in the plasma using quantitative reverse transcription-polymerase chain reaction (qRT-PCR)

Total RNAs were first isolated from PBMCs using TRIzol reagent. After determining the purity and concentration, RNAs with an equal mass were reversely transcribed into complementary deoxyribonucleic acids (cDNAs). The cDNAs were then amplified through qPCR with the SsoFast EvaGreen Supermix PCR kit (Bio-Rad) on the Applied Biosystems ABI7500 PCR system. The relative expression levels of lncRNAs and messenger RNAs (mRNAs) were normalized to glyceraldehyde-3-phosphate dehydrogenase and calculated by the $2^{-\Delta\Delta Ct}$ method. The following primer sequences were used: LncRNA NEAT1 F: 5'-TGGCTAGCTCAGGGCTTCAG-3', R: 5'-TCTCCTTGCCAAGCTTCCTTC-3', GAPDH F: 5'-TGAACGGGAAGCTCACTGG-3', R: 5'-TCCACCACCCTGTTGCTGTA-3'.

2.6. Statistical methods

SPSS20.0 software was employed to detect whether measurement data were normally distributed. Measurement data were displayed as mean ± standard deviation and compared between groups using *t*-test. Enumeration data were analyzed using chi-square test. Spearman correlation analysis was performed, and univariate survival analysis was conducted by the Kaplan-Meier method. *p*-value was examined using the log-rank test, and $P<0.05$ was considered to be statistically significant ($^{*}P<0.05$).

3. Results

3.1. Correlations of NEAT1 with relevant clinical indicators

Among 80 patients eligible for enrollment, 26 were male, 54 were female and their age was 23-80 years old, with a mean of (58.66±8.33) years old. The level of NEAT1 in the serum of all the subjects was determined using qRT-PCR. All the subjects were assigned into two groups: NEAT1 high expression group (n=33) and NEAT1 low expression group (n=47). The statistical analysis results showed that the differences in the duration of dia-

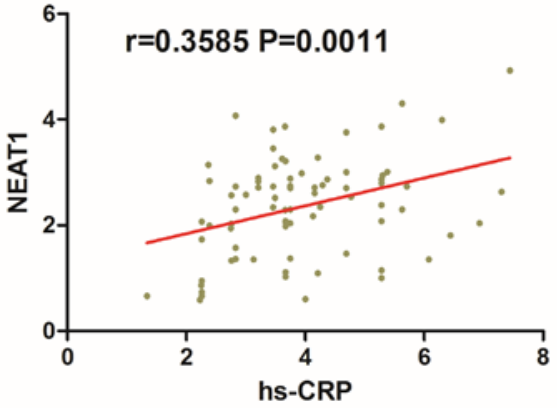

Fig. 1. Correlation between NEAT1 and hs-CRP. As presented in Spearman correlation analysis, the coefficient (*r*) of the correlation between NEAT1 and hs-CRP was 0.3585 (*P*=0.0011).

betes, age, sex, smoking, drinking, BMI, TC, TG, HDL-C, LDL-C, FPG, PTH and Cr were not statistically significant between the two groups of patients ($P>0.05$). NEAT1 high expression group had a dramatically higher level of high sensitivity C-reactive protein (hs-CRP) than NEAT1 low expression group, with a statistically significant difference ($P<0.05$) (Table 1). Spearman correlation analysis was performed to further delve into the correlation between NEAT1 and hs-CRP, and it was found that the correlation coefficient (*r*) was 0.3585 ($P=0.0011$) (Figure 1). The above results imply that NEAT1 is positively correlated with hs-CRP.

3.2. Effects of NEAT1 levels on cardiac function in DN patients undergoing CAPD

In order to further verify whether NEAT1 affects the cardiac function of patients, cardiac ultrasonography was conducted. According to the results, NEAT1 high expression group had larger LVED, LVESD, IVSD and LVPWD and lower LVEF than NEAT1 low expression group ($P<0.05$) (Table 2), indicating that NEAT1 impairs the cardiac function of patients.

3.3. Influences of NEAT1 levels on the incidence rate of cardiovascular events in DN patients undergoing CAPD

The prognosis of patients was followed up to further elucidate the effects of NEAT1 expression levels on the incidence rate of cardiovascular events in patients. It was discovered that highly expressed NEAT1 raised the incidence rates of acute myocardial infarction, congestive heart failure and angina in patients, and the difference between the two groups was statistically significant ($P<0.05$) (Table 3). This finding implies that high expression of NEAT1 can promote the occurrence of cardiovascular events in patients.

Table 1. Comparisons of general data between the two groups of patients.

Variable	Low level (n=47)	High level (n=33)	t/χ^2	*P*
sex (male/female)	16/31	10/23	0.124	0.811
age (years old)	59.3±8.4	58.2±8.1	0.585	0.560
course of disease (years)	5.9±2.2	5.6±2.0	0.623	0.535
Smoking (No/Yes)	10/37	5/28	0.477	0.570
Drinking	8/39	4/29	0.365	0.725
BMI (Kg/m^2)	25.33±4.12	24.4±3.01	1.105	0.272
TC (mmol/L)	4.37±1.33	4.15±1.27	0.742	0.460
TG (mmol/L)	2.23±0.71	2.36±0.94	-0.705	0.483
HDL-C (mmol/L)	1.24±0.34	1.31±0.46	-0.783	0.436
LDL-C (mmol/L)	2.13±1.12	2.02±0.99	0.453	0.652
FPG (mmol/L)	9.66±2.81	9.38±2.37	0.467	0.642
PTH (pmol/ml)	33.93±11.17	35.64±12.04	-0.653	0.516
hs-CRP (mg/L)	3.76±0.82	6.82±2.42	-8.053	<0.001
Cr (μmol/L)	763±53.87	783±63.22	-1.521	0.132

Note: BMI: Body mass index; TC: Total Cholesterol; TG: Triglycerides; HDL-C: High-Density Lipoprotein Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; FPG: Fasting blood glucose; PTH: Parathyroid hormone; hs-CRP: Hypersensitive c-reactive protein; Cr: Creatinine.

Table 2. Comparisons of two groups of ultrasonic test values.

Variable	Low level (n=47)	High level (n=33)	t/χ^2	*P*
LVED(mm)	48.43±4.32	52.88±4.71	-4.370	<0.001
LVESD(mm)	30.24±2.93	32.73±3.01	-3.700	<0.001
IVSD(mm)	10.73±1.65	12.76±2.36	-4.632	<0.001
LVPWD(mm)	10.33±1.22	11.86±1.47	-5.072	<0.001
LVEF(%)	55.97±5.37	46.92±7.24	6.421	<0.001

Note: LVED: Left ventricular end-diastolic diameter; LVESD: Left ventricular end-systolic diameter; IVSD: Interventricular septum thickness; LVPWD: Left ventricular posterior wall thickness at the end of diastole; LVEF: Left Ventricular Ejection Fraction.

Table 3. Correlation between NEAT1 expression and the incidence of cardiovascular events.

Variable	n	Low level (n=47)	High level (n=33)	$\chi 2$	*P*
Acute myocardial infarction					
Yes	10	2	8	7.081	0.013
No	70	45	25		
Congestive heart failure					
Yes	7	1	6	6.258	0.018
No	74	46	27		
Angina attack					
Yes	9	2	7	5.583	0.029
No	71	45	26		

3.4. Effects of NEAT1 levels on the survival prognosis of DN patients undergoing CAPD in the presence of cardiovascular events

After 5 years of follow-up, the correlation between NEAT1 levels and the survival rate of DN patients undergoing CAPD who experienced cardiovascular events (sudden cardiac death, malignant arrhythmia, death after myocardial infarction and death after heart failure) was analyzed. The results manifested that the level of NEAT1 after peritoneal dialysis was correlated with the survival of DN patients undergoing CAPD, with a statistically significant difference ($P<0.05$). The higher the level of NEAT1 was, the worse the survival prognosis of patients with cardiovascular events would be [hazard ratio (HR) =7.995, $P=0.0047$] (Figure 2), suggesting that highly expressed NEAT1 worsens the prognosis of patients suffering from cardiovascular events.

4. Discussion

As the incidence rate of DM is rising rapidly worldwide and the survival time of DM patients is prolonged, there is a growing proportion of DN cases in ESRD patients each year. According to the related epidemiological statistical research, the number of DM patients will exceed 366 million and that of DN patients will reach 100 million by 2030 [19]. DN remains one of the common chronic microvascular complications of DM. Renal involvement will occur in 15-20% of patients with T1DM and 30-40% of patients with T2DM. DN is the leading cause of ESRD and renal replacement therapy in Western countries. With the rapid increase in the global incidence rate of DM, the proportion of DN cases in ESRD patients is also increasing year by year, but the options of dialysis modalities for such patients are still greatly controversial. Weinhandl *et al* [20] held that peritoneal dialysis is better on the whole, while Chang *et al* [21] argued that hemodialysis is more suitable. This study mainly examined the effects of NEAT1 levels in patients with end-stage DN undergoing CAPD on their cardiac function, incidence of cardiovascular events and prognosis.

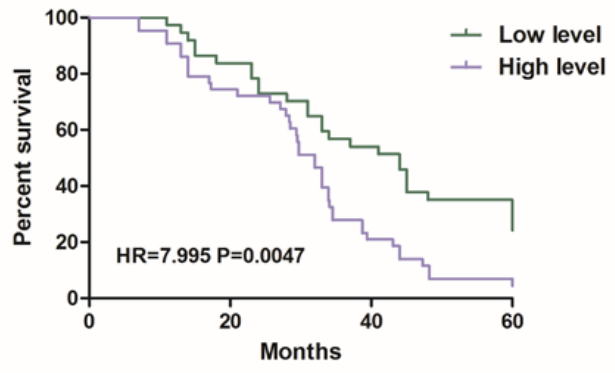

Fig. 2. Effects of NEAT1 levels on the survival prognosis of DN patients undergoing CAPD in the presence of cardiovascular events. After peritoneal dialysis, the survival prognosis of DN patients experiencing cardiovascular events in NEAT1 high-expression group was worse than that in NEAT1 low-expression group (HR =7.995, $P=0.0047$).

LncRNAs are non-coding RNAs with more than 200 nucleotides [14]. They play a vital role in genetic regulation and can modulate all aspects of cellular homeostasis [15]. Besides, mounting lncRNAs can take part in the pathogenesis of DN. For example, lncRNA CYP4B1-PS1-001 is able to regulate the proliferation and fibrosis in the progression of DN, whereas lncRNA ENSMUST00000147869 can save glomerular mesangial cells from DN-induced proliferation and fibrosis [16, 17]. Moreover, lncRNA NR_033515 is capable of promoting proliferation, fibrogenesis and epithelial-mesenchymal transition by sponging miR-743b-5p in DN [18]. LncRNA NEAT1, an important regulator of speckle formation, is associated with several physiological and pathophysiological processes in cardiovascular and cerebrovascular diseases [19-21]. According to a study [22], lncRNA NEAT1 is a crucial regulatory factor of phenotypes of vascular smooth muscle cells, and it is implicated in epidermal growth and development. Additionally, a clinical trial suggested that [23] lncRNA NEAT1 is raised in patients with acute ischemic stroke compared with that in healthy controls, and it is well predictive of heightened disease risk in the case of a larger AUC. Similar to the above results, the findings of the present study showed that patients with highly expressed NEAT1 had increased cardiac indicators LVED, LVESD, IVSD and LVPWD, but decreased LVEF. Moreover, the incidence rates of acute myocardial infarction, congestive heart failure and angina in NEAT1 high expression group were higher than those in NEAT1 low expression group, and the higher the level of NEAT1 was, the worse the survival prognosis of patients suffering from cardiovascular events would be. These results imply that NEAT1 weakens cardiac function, promotes the occurrence of cardiovascular events in end-stage DN patients with undergoing peritoneal dialysis and harms the prognosis of patients.

As a typical inflammatory factor, CRP is acute-phase

protein and has a notably elevated expression level when tissue trauma and acute inflammation occur in organisms, so it serves as a sensitive marker for clinical detection and corroboration of inflammatory responses [24]. Hs-CRP, a trace CRP in the body, can be clinically detected using sensitive testing techniques, and it is more accurate and sensitive in the clinical detection of a low level of related chronic inflammatory responses [25]. Relevant studies have demonstrated that hs-CRP plays an important role in the development and progression of DM, and the increase in its expression level is closely associated with the occurrence of macrovascular and microvascular complications in DM patients. Hence, hs-CRP can act as a pivotal indicator for clinically judging DN [26, 27]. A related study revealed that hs-CRP can be modulated by lncRNAs to take part in the occurrence and development of diseases [28]. In this study, it was found through Spearman correlation analysis that NEAT1 was positively correlated with hs-CRP, suggesting that NEAT1 can positively modulate hs-CRP to affect the cardiac function, incidence rate of cardiovascular events and prognosis in end-stage DN patients undergoing CAPD.

In conclusion, the present study preliminarily analyzed and explored the effects of NEAT1 on the biochemical indicators, cardiac indicators, incidence rate of cardiovascular events and survival outcomes in end-stage DN patients undergoing CAPD. The results of this study lay a foundation for the later study of DN patients undergoing CAPD and the further research into the mechanism of correlation between NEAT1 and the occurrence and prognosis of cardiovascular adverse events in these patients, so as to provide better clinical treatment options and observational indicators for clinically predicting the incidence of cardiovascular events in end-stage DN patients undergoing CAPD.

5. Conclusion

With the rise in NEAT1 levels, hs-CRP is also raised in DN patients undergoing CAPD. Besides, patients with higher NEAT1 levels exhibit worse cardiac function and higher incidence rates of cardiovascular adverse events, as well as worse survival prognosis in the presence of cardiovascular events.

Conflict of Interests

The author has no conflicts with any step of the article preparation.

Consent for publications

The author read and approved the final manuscript for publication.

Ethics approval and consent to participate

This study was approved by the ethics committee of Hubei NO.3 People's Hospital of Jianghan University.

Informed Consent

Signed written informed consent was obtained from the patients and/or guardians.

Availability of data and material

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

Authors' contributions

ML and ZY designed the study and performed the experiments, ZY collected the data, YZ analyzed the data, ML and ZY prepared the manuscript. All authors read and approved the final manuscript.

Funding

None.

References

1. Thomas MC, Cooper ME, Zimmet P (2016) Changing epidemiology of type 2 diabetes mellitus and associated chronic kidney disease. Nat Rev Nephrol 12:73-81. doi: 10.1038/nrneph.2015.173
2. Molitch ME, Adler AI, Flyvbjerg A, Nelson RG, So WY, Wanner C et al (2015) Diabetic kidney disease: a clinical update from Kidney Disease: Improving Global Outcomes. Kidney Int 87:20-30. doi: 10.1038/ki.2014.128
3. Bhupathiraju SN, Hu FB (2016) Epidemiology of Obesity and Diabetes and Their Cardiovascular Complications. Circ Res 118:1723-1735. doi: 10.1161/CIRCRESAHA.115.306825
4. Barrios C, Pascual J, Otero S, Soler MJ, Rodriguez E, Collado S et al (2015) Diabetic nephropathy is an independent factor associated to severe subclinical atheromatous disease. Atherosclerosis 242:37-44. doi: 10.1016/j.atherosclerosis.2015.06.048
5. Popovich RP, Moncrief JW, Nolph KD, Ghods AJ, Twardowski ZJ, Pyle WK (1978) Continuous ambulatory peritoneal dialysis. Ann Intern Med 88:449-456. doi: 10.7326/0003-4819-88-4-449
6. Ohashi H, Oda H, Ohno M, Sakata S (1999) Predictors of survival in continuous ambulatory peritoneal dialysis patients: the importance of left ventricular hypertrophy and diabetic nephropathy. Adv Perit Dial 15:87-90.
7. Tahara A, Takasu T (2018) Prevention of progression of diabetic nephropathy by the SGLT2 inhibitor ipragliflozin in uninephrectomized type 2 diabetic mice. Eur J Pharmacol 830:68-75. doi: 10.1016/j.ejphar.2018.04.024
8. Xue R, Gui D, Zheng L, Zhai R, Wang F, Wang N (2017) Mechanistic Insight and Management of Diabetic Nephropathy: Recent Progress and Future Perspective. J Diabetes Res 2017:1839809. doi: 10.1155/2017/1839809
9. Chen LL, Carmichael GG (2009) Altered nuclear retention of mRNAs containing inverted repeats in human embryonic stem cells: functional role of a nuclear noncoding RNA. Mol Cell 35:467-478. doi: 10.1016/j.molcel.2009.06.027
10. Bond CS, Fox AH (2009) Paraspeckles: nuclear bodies built on long noncoding RNA. J Cell Biol 186:637-644. doi: 10.1083/jcb.200906113
11. Xiong W, Huang C, Deng H, Jian C, Zen C, Ye K et al (2018) Oncogenic non-coding RNA NEAT1 promotes the prostate cancer cell growth through the SRC3/IGF1R/AKT pathway. Int J Biochem Cell B 94:125-132. doi: 10.1016/j.biocel.2017.12.005
12. Cheng N, Guo Y (2017) Long noncoding RNA NEAT1 promotes nasopharyngeal carcinoma progression through regulation of miR-124/NF-kappaB pathway. Oncotargets Ther 10:5843-5853. doi: 10.2147/OTT.S151800
13. Wang X, Xu Y, Zhu YC, Wang YK, Li J, Li XY et al (2019) LncRNA NEAT1 promotes extracellular matrix accumulation and epithelial-to-mesenchymal transition by targeting miR-27b-3p and ZEB1 in diabetic nephropathy. J Cell Physiol 234:12926-12933. doi: 10.1002/jcp.27959
14. Kazemzadeh M, Safaralizadeh R, Orang AV (2015) LncRNAs: emerging players in gene regulation and disease pathogenesis. J Genet 94:771-784. doi: 10.1007/s12041-015-0561-6
15. Grammatikakis I, Panda AC, Abdelmohsen K, Gorospe M

(2014) Long noncoding RNAs(lncRNAs) and the molecular hallmarks of aging. Aging (Albany Ny) 6:992-1009. doi: 10.18632/aging.100710

16. Wang M, Wang S, Yao D, Yan Q, Lu W (2016) A novel long noncoding RNA CYP4B1-PS1-001 regulates proliferation and fibrosis in diabetic nephropathy. Mol Cell Endocrinol 426:136-145. doi: 10.1016/j.mce.2016.02.020
17. Wang M, Yao D, Wang S, Yan Q, Lu W (2016) Long non-coding RNA ENSMUST00000147869 protects mesangial cells from proliferation and fibrosis induced by diabetic nephropathy. Endocrine 54:81-92. doi: 10.1007/s12020-016-0950-5
18. Gao J, Wang W, Wang F, Guo C (2018) LncRNA-NR_033515 promotes proliferation, fibrogenesis and epithelial-to-mesenchymal transition by targeting miR-743b-5p in diabetic nephropathy. Biomed Pharmacother 106:543-552. doi: 10.1016/j.biopha.2018.06.104
19. Clemson CM, Hutchinson JN, Sara SA, Ensminger AW, Fox AH, Chess A et al (2009) An architectural role for a nuclear noncoding RNA: NEAT1 RNA is essential for the structure of paraspeckles. Mol Cell 33:717-726. doi: 10.1016/j.molcel.2009.01.026
20. Li P, Duan S, Fu A (2020) Long noncoding RNA NEAT1 correlates with higher disease risk, worse disease condition, decreased miR-124 and miR-125a and predicts poor recurrence-free survival of acute ischemic stroke. J Clin Lab Anal 34:e23056. doi: 10.1002/jcla.23056
21. Gast M, Rauch BH, Haghikia A, Nakagawa S, Haas J, Stroux A et al (2019) Long noncoding RNA NEAT1 modulates immune cell functions and is suppressed in early onset myocardial infarction patients. Cardiovasc Res 115:1886-1906. doi: 10.1093/cvr/cvz085
22. Wu HJ, Tang GM, Shao PY, Zou HX, Shen WF, Huang MD et al (2019) Long non-coding RNA NEAT1 modulates hypoxia/reoxygenation-induced cardiomyocyte injury via targeting microRNA-520a. Exp Ther Med 18:2199-2206. doi: 10.3892/etm.2019.7788
23. Ahmed A, Dong K, Liu J, Wen T, Yu L, Xu F et al (2018) Long noncoding RNA NEAT1 (nuclear paraspeckle assembly transcript 1) is critical for phenotypic switching of vascular smooth muscle cells. P Natl Acad Sci Usa 115:E8660-E8667. doi: 10.1073/pnas.1803725115
24. Liu TJ, Chang CC, Chen LC, Chu HY, Hsu CS, Chang ST (2018) Relationship of HS CRP and Sacroiliac Joint Inflammation in Undifferentiated Spondyloarthritis. Open Med-Warsaw 13:113-118. doi: 10.1515/med-2018-0018
25. Li Y, Zhong X, Cheng G, Zhao C, Zhang L, Hong Y et al (2017) Hs-CRP and all-cause, cardiovascular, and cancer mortality risk: A meta-analysis. Atherosclerosis 259:75-82. doi: 10.1016/j.atherosclerosis.2017.02.003
26. Elizondo-Montemayor L, Gonzalez-Gil AM, Tamez-Rivera O, Toledo-Salinas C, Peschard-Franco M, Rodriguez-Gutierrez NA et al (2019) Association between Irisin, hs-CRP, and Metabolic Status in Children and Adolescents with Type 2 Diabetes Mellitus. Mediat Inflamm 2019:6737318. doi: 10.1155/2019/6737318
27. Sinha SK, Nicholas SB, Sung JH, Correa A, Rajavashisth TB, Norris KC et al (2019) hs-CRP Is Associated With Incident Diabetic Nephropathy: Findings From the Jackson Heart Study. Diabetes Care 42:2083-2089. doi: 10.2337/dc18-2563
28. Zhang K, Qi M, Yang Y, Xu P, Zhua Y, Zhang J (2019) Circulating lncRNA ANRIL in the Serum of Patients with Ischemic Stroke. Clin Lab 65: doi: 10.7754/Clin.Lab.2019.190143