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Expression of lncRNA TUG1 in hypertensive patients and its relationship with change state of an illness

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Abstract. – OBJECTIVE: To investigate the expression of LncRNA TUG1 in hypertensive patients and its relationship with the change state of an illness.

PATIENTS AND METHODS: A prospective analysis was carried out. Eighty-two patients with hypertension admitted to our hospital from March 2016 to February 2019 were regarded as a research group, and 79 healthy people admitted to our hospital during the same [illegible] were regarded as a control group. The [illegible] LncRNA TUG1, platelet activating factor [illegible]F), endothelin-1 (ET-1), serum tumor necrosis [illegible]-tor-α (TNF-α), high sensitive C-reactive pr[illegible] (hsCRP), and the relationship between the [illegible] pression of LncRNA TUG1 and [illegible] clinicopathological characteristics of pa[illegible]h hypertension in the two groups w[illegible]dete[illegible] and finally, the risk factors of h[illegible]tensio[illegible]ere analyzed.

RESULTS: The expres[illegible]ve[illegible] TUG1, PAF, ET-1, TNF[illegible]and [illegible]n the serum of patients in rese[illegible] group w[illegible]nificantly higher than thos[illegible]ontrol group[illegible]05). LncRNA TUG1 ha[illegible]ive correlatio[illegible]with the severity of a[illegible]nes[illegible]ypertensive patients (r=0.881, p<0.0[illegible]1), and [illegible]as a positive correlation w[illegible]the expressio[illegible]ls of PAF, ET-1, TNF-[illegible]d hsCRP (r=0.735, [illegible]0.001; r=0.756, p<0.0[illegible]=0.712[illegible]<0.05; r=0.723, p<0.05). The exp[illegible]on of l[illegible]NA TUG1 in the serum of patie[illegible]h h[illegible]tensio[illegible]as related to hypertensio[illegible] severi[illegible]f disease, hyperlipidemia, an[illegible]ity ([illegible]05). Obesity (OR: 3.469, [illegible]: 2.1[illegible]drinking (OR: 3.677, 95% CI: [illegible]5-4.892), [illegible]erlipidemia (OR: 3.374, 95% CI: [illegible]9-6.988), and the high expression of TU[illegible]; 95% CI: 1.679-7.472) are independent [illegible]ctors for the attack of hypertension.

CONCLUSIONS: LncRNA TUG1 is highly expressed in the serum of hypertensive patients and is closely related to the progression of hypertension. Also, it [illegible]e one of the independent [illegible]factors for hy[illegible]sion and a new molecular target for hyperte[illegible]on treatment.

Key Words:
LncRNA TUG1, [illegible]ertension, Expression, Change of an illness.

Introduction

Hypertension is a common chronic disease with arterial blood pressure rise as its main clinical feature. It has a high morbidity. Its pathogenesis is complex and is caused by a variety of factors. Hypertension is also one of the main risk factors for cardiovascular and cerebrovascular diseases[1,2]. With the increasing morbidity of hypertension in recent years, some researches show that this among adults in the world is as high as 31%[3]. Hypertension, as one of the major risk factors for cardiovascular and cerebrovascular diseases, can promote the occurrence of atherosclerosis by promoting the injury of vascular endothelial cells[4]. At present, the treatment of hypertension is mainly based on long-term medication, and there is no effective treatment method in other aspects[5].

However, in recent years, with the development of molecularly targeted technology and the gradual deepening of hypertension research, the application of molecularly targeted therapy in hypertension has also been given increasing attention. Long non-coding RNA (lncRNA) is a non-coding RNA with a length of more than 200 nt lacking coding ability. LncRNA plays an important role in many biological processes such as immune response or gene imprinting[6]. LncRNA

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TUG1 (taurine up-regulated 1) is a kind of LNC RNA that has regulatory effect on the biological function of tumor cells and is considered as a potential tumor therapeutic target[7]. However, Gao et al[8] have found abnormal expression in vascular endothelial cells, which suggests that TUG1 may play a regulatory role in the physiological process of vascular endothelial cells, but it has not been thoroughly discussed. Moreover, vascular endothelial cells can regulate the tension of blood vessels by secreting vasodilators and vasoconstrictors[9]. Therefore, we speculate whether LncRNA TUG1 is related to the development of hypertension, but there has been no report on the relationship between TUG1 and hypertension.

We have discussed the expression of TUG1 in hypertension and the relationship between TuG1 expression and change state of an illness of patients, in order to provide a new molecular target direction for the treatment of hypertension.

Patients and Methods

General Data

A prospective analysis was carried out [illegible] two patients with hypertension admitted [illegible] hospital from March 2016 to February 2019 [illegible] regarded as research group, including 43 [illegible] patients and 39 female patients, with an average age of (45.36±3.72) years. A [illegible] healthy people who came to our [illegible] physical examination during the same period [illegible] selected as control group, including 41 [illegible] and 38 female patients, with an average age of (45.97±3.66) years. Inclusion criteria were as follows: patients diagnosed with hypertension. Exclusion criteria were as follows: patients with secondary hypertension; patients with serious cardiovascular diseases; patients with other malignant tumor diseases; patients with severe immune system diseases; patients with severe liver and kidney dysfunction. All patients and their families agreed to participate in this study that was approved by the hospital Ethics Committee.

Index Detection

LncRNA TUG1 Expression Detected by qRT-PCR

Altogether 5 ml venous blood from all subjects was drawn on an empty stomach. Then, it was centrifuged at 3000 rpm for [illegible] and the supernatant was detected. TRIzol (Life Biosystems; Invitrogen, Carlsbad, CA, USA) was added into serum to extract total RNA, and the purity, concentration and integrity of total RNA were detected by ultraviolet spectrophotometer and agarose gel electrophoresis. cDNA reverse transcription was performed according to the instructions (TransGen Biotech, Beijing, China), and TUG1 detection was performed according to kit instructions. TUG1 amplification system was as follows: cDNA 1 μL, upstream and downstream primers 0.4 μL respectively, 2×SYBR Green mixture 10 μL, ROX Passive Reference Dye (50X) 0.4 μL, and finally ddH$_2$O added to 20 μL. Amplification conditions were as follows: PCR reaction conditions: pre-denaturation for 2 min, 95°C denaturation for 5 s, 60°C annealing extension for 15 s, a total of 40 cycles. β-actin was used as internal reference, primer sequences were shown in Table I, and the experiment was repeated 3 times.

Detection of Other Relevant Indexes

We have detected hypertension-related vascular endothelial function-related factors and related inflammatory factors in serum of patients in research group, including platelet activating factor (PAF), endothelin-1 (ET-1), serum tumor necrosis factor-α (TNF-α), and high sensitivity C-reactive protein (hsCRP). PAF, ET-1, and TNF-α (Shanghai Enzyme-linked Biotechnology Co., Ltd., ml001091, ml001311, and ml001543) were detected by enzyme-linked immunosorbent assay (ELISA). The operation was strictly in accordance with the kit instructions. The expression of hsCRP was detected by immunofluorescence quantitative method (Boditiech Med Inc., 4555-2014).

Table I. [illegible] sequences.

Factor	Upstream primer	Downstream primer
[illegible]	5'-TAGCAGTTCCCCAATCCTTG-3'	5'-CACAATTCCCATCATTCCC-3'
β-actin	5'-GGGAAATCGTGCGTGACATTAAGG-3'	5'-CAGGAAGGAAGGCTGGAAGAGTG-3'

Statistical Analysis

SPSS 19.0 software package (IBM, Armonk, NY, USA) was used to carry out statistical analysis on the collected data, GraphPad 6 software package was used to draw the required pictures, inter-group comparison was conducted by independent-samples *t*-test, correlation analysis was used by Pearson, and the risk factors of hypertension was analyzed by Logistic regression model. A *p*-value lower than 0.05 was considered to be statistically different.

Results

General Data

There were no significant differences in gender, age, BMI, and other aspects of subjects between the two groups ($p>0.05$), but there were differences in numbers of obesity, drinking, and hyperlipidemia between both groups ($p<0.05$), as shown in Table II.

Comparison of Serum LncRNA TUG1 Expression of Subjects Between the Two Groups

TUG1 expression of patients in research group was (1.87±0.27), significantly higher than that of subjects in control group (1.02±0.10), and differences were statistically significant ($p<0.05$).

We analyzed TUG1 expression in patients with different severity of an illness in research group, and the results showed that the serum TUG1 expression of hypertensive patients with grade 1 (1.53±0.10) was significantly higher than those with level 2 (1.72±0.09) and grade 3 (1.91±0.08), and the serum TUG1 expression of patients with level 2 was significantly higher than those with level 3, and differences were statistically significant ($p<0.05$, Figure 1).

Expression Levels of PAF, ET-1, TNF-α, and hsCRP in Serum of Subjects in the Two Groups

The expression levels of PAF (149.78±22.16) ng/ml, ET-1 (141.[illegible]19) ng/L, TNF-α (65.[illegible]49) pg/ml, and hsCRP (8.52±1.29) ng/ml in research group were significantly higher than those in control group [PAF (119.19±9.16) ng/ml, Et-1 (82.06±15.46) ng/L, TNF-α (31.26±2[illegible] pg/ml, hsCRP (4.16±0.84) ng/ml] with statistically significant differences ($p<0.05$), as shown in Figure 2.

Correlation Analysis Between LncRNA TUG1 and Hypertension

LncRNA TUG1 has a positive correlation with the severity of an illness of hypertensive patients (r=0.881, $p<0.001$), and also has a

Table II. General data.

Factor	Research group n = 79	Control group n = 79	χ^2	*p*-value
Gender			0.005	0.945
Male	43 (54.43)	41 (51.90)		
Female	39 (47.57)	38 (48.10)		
Age (years)			0.000	0.987
≥ 45	52 (63.41)	50 (63.29)		
< 45	27 (36.59)	29 (36.71)		
BMI			0.034	0.854
≥ 22	48 (58.54)	47 (59.49)		
< 22	34 (41.46)	32 (40.51)		
Severity of an illness			–	–
I	26 (31.71)	–		
Level II	33 (40.24)	–		
Level III	23 (28.05)	–		
Drinking history			22.03	< 0.001
Yes	52 (63.41)	21 (26.58)		
No	30 (36.59)	58 (73.42)		
Obesity			14.43	< 0.001
Yes	46 (56.10)	21 (27.85)		
No	36 (43.90)	58 (73.42)		
Hyperlipidemia			9.861	0.002
Yes	45 (54.88)	24 (30.38)		
No	37 (45.12)	55 (69.62)		

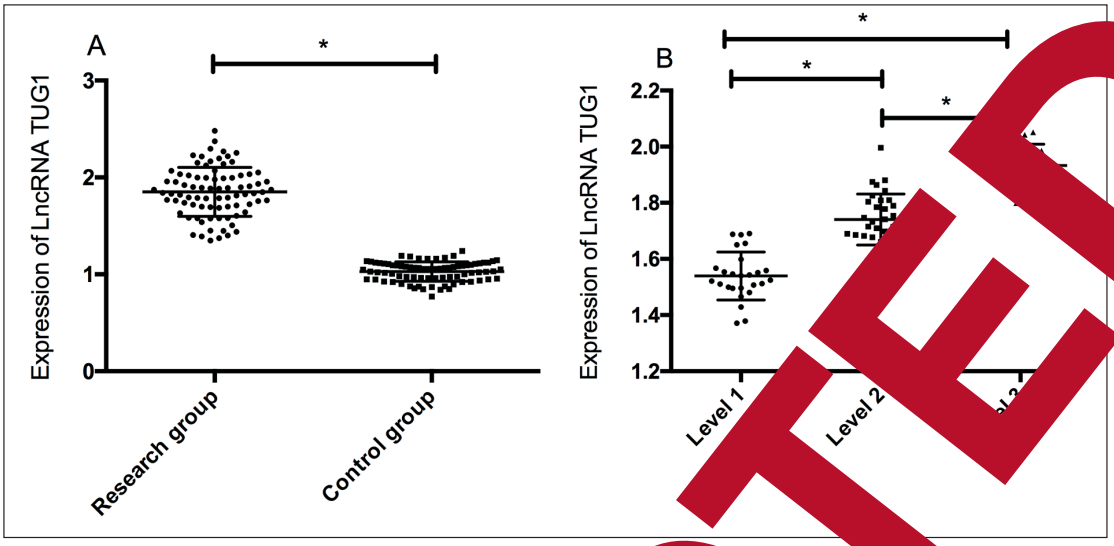

Figure 1. Comparison of serum LncRNA TUG1 expression of su[illegible]ween the two grou[illegible] **A**, TUG1 expression of patients in research group is significantly higher than those in c[illegible] group. **B**, Serum TUG1 expression in hypertensive patients with grade 1 is significantly lower than those with grad[illegible]nd grade 3, and [illegible]um TUG1 expression in those with grade 2 is significantly lower than those with grade 3. *Indicates [illegible]05.

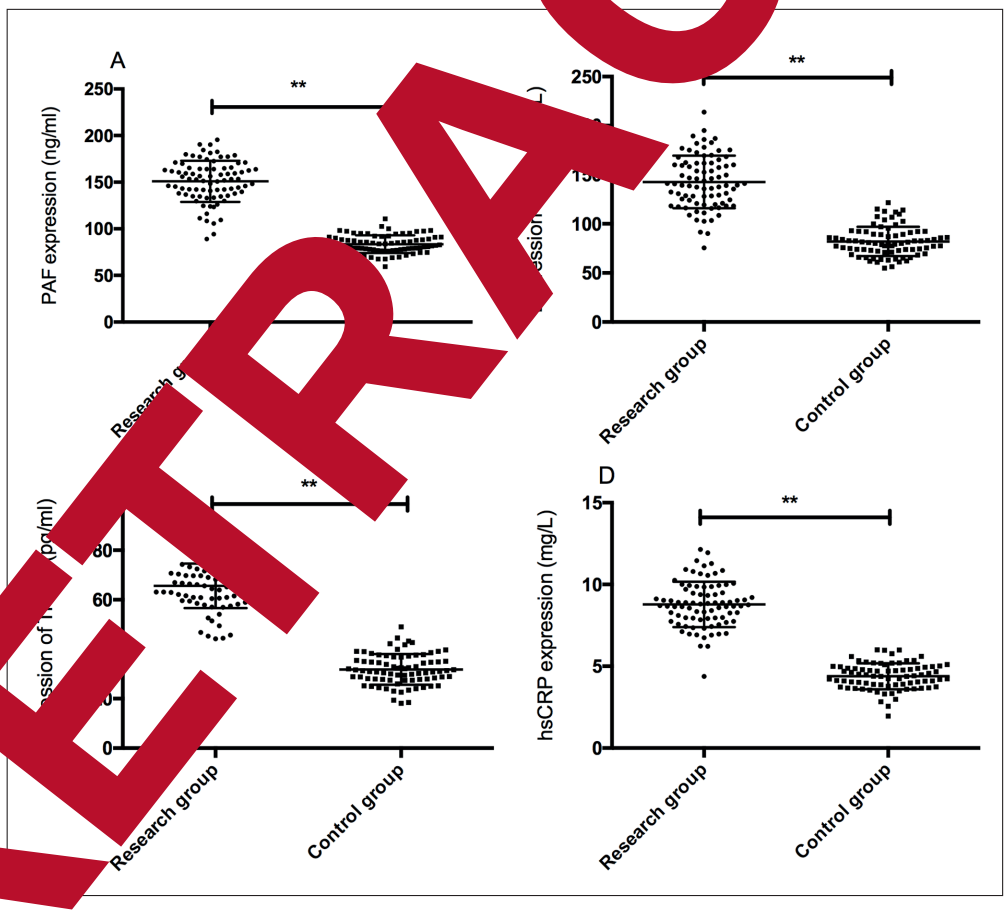

Figure 2. Expression levels of PAF, ET-1, TNF-α, and hsCRP in serum of subjects in the two groups. **A**, Expression of PAF [illegible]arch group is significantly higher than that in control group. **B**, ET-1 expression in research group is significantly higher th[illegible]n control group. **C**, TNF-α expression in research group is significantly higher than that in control group. **D**, hsCRP expre[illegible]n in research group is significantly higher than that in control group. **Indicates $p<0.001$.

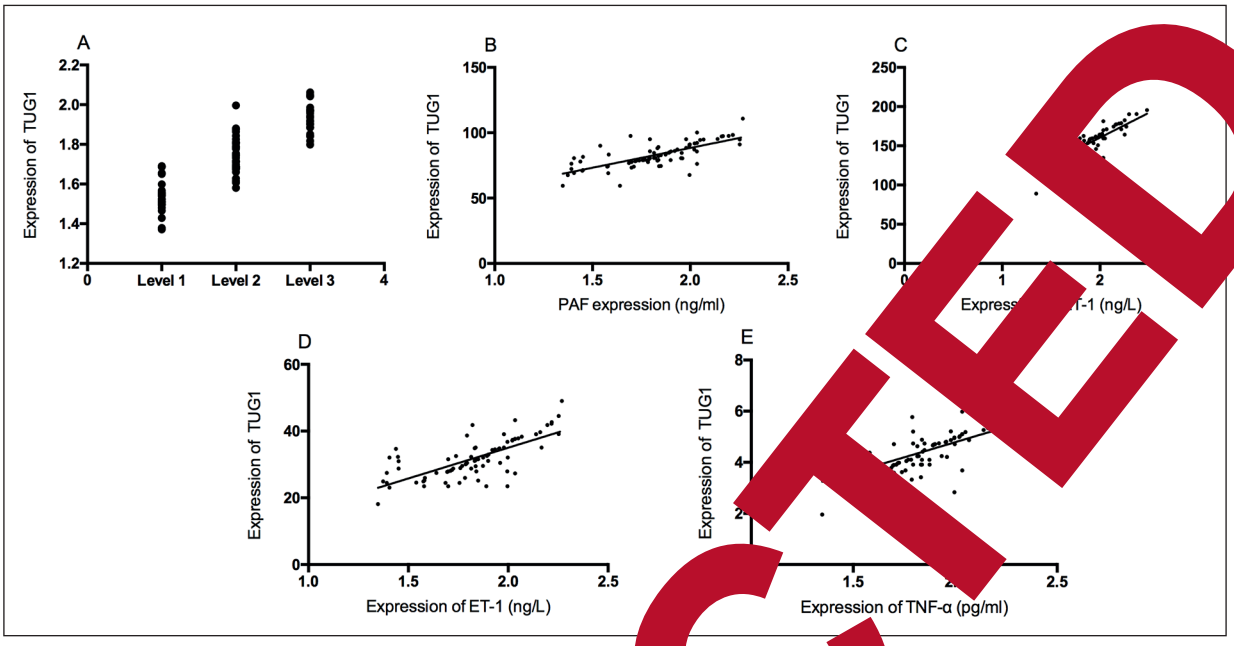

Figure 3. Correlation analysis between LncRNA TUG1 and hyp sion. **A**, LncRN UG1 has a positive correlation with the severity of an illness of hypertensive patients (r=0.881, p<0. **B**, Expression ls of LncRNA TUG1 and PAF are positively correlated (r=0.735, p<0.001). **C**, There is a positive cor between expression levels of LncRNA TUG1 and ET-1 (r=0.756, p<0.001). **D**, There is a positive correlation betwe levels of LncRNA TUG1 and TNF-α (r=0.712, p<0.05). **E**, Expression levels of LncRNA UG1 and hsCRP are p y correlated (r=0.723, p<0.05).

positive correlation with the expression l nde nd age of patients with hypertension of PAF, ET-1, TNF-α, and hsCRP (r=0.7 (p >0.05), and had something to do with the p<0.001; r=0.756, p<0.001; r=0.712, p<0.0 hypertension mode, severity of disease, hyper- r=0.723, p<0.05). It was f the ex- lipidemia, and obesity (p <0.05). More details pression of TUG1 had not to ith the were shown in Figure 3 and Table III.

Table III. Relationship b n L G1 and the clinicopathological characteristics of patients with hypertension.

Factor		TUG1 expression	*t/F* value	*p*-value
Gender			0.722	0.473
	Male (n = 43)	1.76 ± 0.13		
	male (n = 39)	1.78 ± 0.12		
Age			0.639	0.525
	years old (n = 52)	1.77 ± 0.14		
	≥ 45 years old (n = 30)	1.79 ± 0.13		
Hy nsion m			12.27	< 0.001
	Dipper (n = 47)	1.64 ± 0.11		
	Non-dipper (n = 35)	1.93 ± 0.10		
High blo ure le			109.9	< 0.001
	Level 1 (n = 26)	1.53 ± 0.10		
	Level 2 (n = 33)	1.72 ± 0.09		
	Level 3 (n = 24)	1.91 ± 0.08		
H			8.239	< 0.001
	Yes (n = 45)	1.89 ± 0.11		
	No (n = 37)	1.69 ± 0.10		
esity			8.931	< 0.001
	Yes (n = 46)	1.90 ± 0.12		
	No (n = 36)	1.67 ± 0.11		

Table IV. Assignment.

Factor	Assignment
Obesity	Yes = 1; No = 2
Drinking	Yes = 1; No = 2
Hyperlipidemia	Yes = 1; No = 2
TUG1	The data belong to continuous variables and are ana[illegible]zed with[illegible] data

Analysis on Risk Factors of the Attack of Hypertension

We found that the expression levels of obesity, drinking, hyperlipidemia, and TUG1 were different between hypertensive patients and normal subjects through baseline data table and subsequent results ($p<0.05$). We set the expression levels of obesity, drinking, hyperlipidemia, and TUG1 as independent variables and carried out valuation (Table IV). We used Logistic regression analysis as dependent variables to carry out multivariate analysis, and the results showed that obesity (OR: 3.469, 95% CI: 2.175-4.095), drinking (OR: 3.677, 95% CI: 1.695-4.892), hyperlipidemia (OR: 3.374, 95% CI: 1.759-6.988), and the high expression of TUG1 (OR: 2.693, 95% CI: 1.679-7.472) are independent risk factors[illegible] attack of hypertension (Table V).

Discussion

Hypertension is a disease[illegible]sed t[illegible]e interaction of many complex[illegible]ors. Th[illegible]otential molecular markers for its[illegible]osis [illegible] have always been one[illegible]f th[illegible]hotspots[illegible]. LncRNA, as a hot [illegible]tion in[illegible]y in recent years, has also be[illegible]und to play [illegible]important part in the [illegible]n of hyperte[illegible]n[11]. It is well known t[illegible]ncR[illegible] the main component of gene tra[illegible]cription. Fo[illegible]ple, Lanz et al[12] verified t[illegible]LncRNA GAS[illegible]d affect blood pressu[illegible]y regulating the activity of nuclear recep[illegible]. Leun[illegible]al[13] found that LncRNA 362 co[illegible]duce[illegible]hyperp[illegible]liferation of angiotensin II[illegible]found i[illegible]ood vessels of hypertensive patients, thus[illegible]ducing[illegible]tective effects on blood vessels.[illegible]cR[illegible]TUG1[illegible]olved in our research[illegible]s fi[illegible]d in ta[illegible]e-treated mouse reti[illegible]cells, w[illegible]ver[illegible]cated at 22q12.2[14] of[illegible]mosomes. Si[illegible]increasing studies[15,16][illegible]nd that the h[illegible]h expression of TUG[illegible]close[illegible]ted to the prognosis and metastasis of many [illegible]ant tumors. However, its [illegible]hypertension[illegible]ther cardiovascular di[illegible]es is still unclear.

[illegible]n our study, w[illegible]found for the first time that [illegible]expression [illegible]ncRNA TUG1 in serum of [illegible]rtensive pat[illegible]s increased, which suggested th[illegible]UG1 mi[illegible]lso play an important role in the [illegible]of hypertension. Stary et al[17] have found that TUG1 is highly expressed in [illegible]scular endothelial cells, which suggests that [illegible]y be closely related to vascular endo[illegible]elial[illegible]nction, but no further research has been carried out in the future. To further discuss the relationship between LncRNA TUG1 and hypertension, we have detected vascular endothelial injury-related factors and related inflammatory factors in the blood serum of hypertensive patients. The results show that the expression levels of PAF, ET-1, TNF-α, and hsCRP in the blood serum of hypertensive patients are significantly higher than those of normal people. Furthermore, after correlation analysis, we found that LncRNA TUG1 had a positive correlation with the severity of an illness of hypertensive patients, and the expression levels of PAF, ET-1, TNF-α, and hsCRP. Then, we analyzed the expression of LncRNA TUG1 and the clinicopathological characteristics of hypertension patients, and the results showed that the expression of LncRNA

Tab[illegible] Multiva[illegible]alysis.

	β	S.E	Wald	OR	95% CI	*p*-value
[illegible]esity	3.112	0.469	0.013	3.469	2.175-4.095	< 0.05
[illegible]inking	1.305	0.392	0.671	3.677	1.695-4.892	< 0.05
[illegible]lipidemia	1.622	0.218	2.173	3.374	1.759-6.988	< 0.05
[illegible]	5.731	1.138	4.211	2.693	1.679-7.472	< 0.05

TUG1 in the serum was related to hypertension mode, severity of disease, hyperlipidemia, and obesity. It suggested that the expression of LncRNA TUG1 could reflect the state of an illness of hypertensive patients, and TUG1 might play a role in the occurrence and development of hypertension by regulating endothelial cell injury-related factors and inflammatory factors. Zhang et al[18] have found that TUG1 can affect the expression of inflammatory factors by regulating miR-133a when investigating TUG1 in coronary atherosclerosis, which reveals that TUG1 can affect the expression of inflammatory factors. However, it is still unclear how TUG1 acts on the expression of inflammatory factors in hypertension, and further research is needed. Previous studies[19,20] on LncRNA in hypertension believe that the mechanism of LncRNA in hypertension may be through the regulation of protein complexes, cell signaling pathways, and other mechanisms to play its role. There is also research on the mechanism of other LncRNA in hypertension. It is found that Lnc MALAT1[21] can induce the expression of inflammatory factor TNF-α by activating the regulation of glucose by serum amyloid a[n] A3. Shi et al[22] have observed that LncRN[A] can promote the proliferation and migra[tion] of vascular smooth muscle cells (VSMCs) by [activ]vating Wnt/β-catenin pathway in hypertens[ion]. The dysfunction of VSMCs is an i[mpo]rtant bas[is] for vascular remodeling, the [pa]thological feature of hypertension, whi[ch] may b[e] one of the mechanisms of LncRNA [TU]G1 in hy[per]tension. However, how LncRNA [TU]G1 affec[ts] tory factors has not be[en] dis[cov]ered. This leads us to guess whether [Lnc]RNA TUG1 also affects the occurrence an[d] development o[f hy]pertension by regulating c[ell]ular pathways or genes in hypertensive [pa]tients.

Then, we also analyz[ed] the risk factors of hyperten[sion]. The results s[how]ed that obesity, drinki[ng], hyperlipidemia, and the high expression [of] TUG1 were independent risk factors of hy[per]tension. Li et al[23] have shown that the fat conte[nt] in body is positively correlated with blood pr[essure] and [in] obesity is suitable, the circulat[ing] volume and vascular resistance of the bo[dy] will increase, thus increasing cardiac output and eventually causing an increase in [BP]. Therefore, it also suggests that controlling obesity is conducive to the prevention and treatment of hypertension. Hyperlipidemia is usually caused by unreasonable diet structure, and Chen et al[24] have indicated that hyperlipidemia will cause damage to vascular endothelium and hemodynamic disorders, and [cause] hypertension. There are many risk factors that cause hypertension. Drinking is also one of them. Controlling the risk factors of hypertension is an important means to prevent and treat hypertension. However, as an independent risk factor for hypertension, LncRNA TUG1 has [not] been reported in other literatures so far, and there are relatively few related literatures describing its mechanism of action [in] hypertension, and further confirmation is needed in future.

Conclusions

To sum up, LncRNA TUG1 is highly expressed in serum of hypertensive patients, and may be one of the independent risk factors for hypertension and a new molecular target for hypertension treatment. However, there are still some deficiencies in this study. For example, we still haven't clearly explained the mechanism of LncRNA TUG1 in hypertension. Secondly, the sample size we included is not large, which may lead to some deviation in the results. In future experiments, we will further increase the sample size to confirm the conclusion, and will further perform basic experiments to explore the mechanism of LncRNA TUG1 in hypertension.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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