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RESEARCH

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Evaluation of the expression of the long non-coding RNAs, *LOWEG* and *MINCR*, and their clinical significance in human gastric cancer

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Abstract

Background Gastric cancer (GC) is currently the fifth most common malignancy. Accumulating evidence has recently revealed that maladjustments of diverse long non-coding RNAs may play key roles in multiple genetic and epigenetic phenomena in GC. Long non-coding RNAs (lncRNAs), which are transcriptional products with more than 200 nucleotides, are a subset of non-coding RNAs. LncRNA *LOWEG* and lncRNA *MINCR,* as novel lncRNAs, may have roles in GC progression.

Objective This study aimed to examine the clinical and diagnostic significance of lncRNA *LOWEG* and lncRNA *MINCR* in GC.

Methods The qRT-PCR technique measured lncRNA LOWEG and lncRNA MINCR expression in GC tissues and matched adjacent marginal tissues. The association between clinicopathological parameters and the expression level of lncRNAs was evaluated. Furthermore, The ROC curve was plotted to assess the diagnostic power of lncRNA *LOWEG* and lncRNA *MINCR* as candidate biomarkers in gastric cancer patients.

Results We found that lncRNA *LOWEG* expression was downregulated in cancerous tissues compared to the adjacent marginal tissues (*P*-value < 0.0001). LncRNA *MINCR* expression was upregulated in cancerous tissues compared to adjacent marginal tissues (*P*-value < 0.0001). Downregulation of lncRNA *LOWER* and upregulation of lncRNA *MINCR* did not significantly correlate with clinicopathological parameters. ROC curve analysis showed that lncRNA *LOWEG* and lncRNA *MINCR* could be proposed as reliable diagnostic biomarkers in GC.

Conclusion The expression of the lncRNA *LOWEG* was reduced in tumoral tissues compared to the adjacent marginal tissues, and the expression of lncRNA *MINCR* increased in tumoral tissues. So, as a result, lncRNAs *LOWEG* and *MINCR* could be considered diagnostic biomarkers for GC.

Keywords Gastric cancer, Long non-coding RNA, *LOWEG*, *MINCR*, Clinicopathological parameters, Gene expression, qRT-PCR, Biomarker

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Introduction

Gastric cancer is the fifth most common cancer in the world and the third leading cause of cancer death [1]. This type of cancer is the most common gastrointestinal malignancy in parts of Asia, Central America, and South and Eastern Europe [2]. Out of 10,891,033 cases of gastric cancer in 2020 worldwide, 768,793 deaths due to this disease have been reported. The incidence of gastric cancer shows little difference from the resulting mortality rate, which is more due to the late diagnosis of gastric cancer in the advanced stages of the disease [3]. Gastric cancer is often discovered and diagnosed in advanced stages, and as a result, conventional therapies do not have a significant effect on increasing the life expectancy of patients. Recent advances in diagnosing and treating the disease have increased the long-term survival of patients with early-stage GC [4]. Identifying molecular, genetic, and epigenetic markers and new pharmacogenetic properties will improve diagnosis and treatment.

Non-coding RNAs are classified into short and long non-coding RNAs based on length. The cluster of short non-coding RNAs includes miRNAs, piRNAs, snoRNAs, and siRNAs. LncRNAs are a heterogeneous class of non-coding RNAs [5, 6]. LncRNA sequences are distributed across all chromosomes, covering about 90% of the human genome [7]. LncRNAs are approximately 200–100 kbps in length and, like mRNAs, are often produced by RNA polymerase II in combination with capping, splicing, and polyadenylation processes [8, 9]. Their genes also have regions for transcription factors (such as NF-KB) to bind to their promoter regions [10]. LncRNAs modulate gene expression by altering transcription levels, post-transcriptional modifications, and chromatin remodeling [11]. LncRNAs can also act as scaffolds for the assembly of two or more gene regulatory proteins and regulation of gene expression through miRNA uptake [12, 13]. LncRNAs are more abundant in the nucleus compared to mRNAs. They are cell-specific and are expressed in low levels. They also have fewer exons and shorter sequences than mRNAs [14, 15]. Studies show that lncRNAs have oncogenic or tumor-suppressive properties in developing cancers, including gastric cancer. Their improper expression can also lead to cellular changes and tumorigenesis in gastric cancer [16]. LncRNAs can be classified into the following subgroups based on the position of their genes on the genome: Intergenic, Intronic, Sense, Antisense, and Bidirectional [17, 18]. The lncRNA *LOWEG*, or *CTD-2108O9.1* or *EGFLAM-AS1*, is 331 bp long and on human chromosome 5 (5p13.1). It was first identified in gastric cancer [19]. LncRNA *LOWEG* acts as a tumor suppressor gene that inhibits the invasion of tumor cells by regulating the expression of LIFR (leukemia inhibitory factor receptor) at the translational level in gastric cancer [19]. LncRNA *MINCR* (MYC-induced long non-coding RNA), also known as *TCONS_00015189* or *Long intergenic non-protein-coding RNA 1604*, is an intergenic LncRNA located between two coding genes, *GLI4* and *ZNF696*, on chromosome 8q24.3. It is also positively affecting the expression of *MYC* in MYC lymphomas [20]. MYC-induced lncRNA (*MINCR*) also can modulate the MYC (*c-Myc*) transcription network in Burkitt lymphoma cells. It can play an oncogenic role in cancers such as gallbladder cancer and liver cancer [21]. In this study, the expression level of lncRNA *LOWEG* and lncRNA *MINCR* was examined in GC tissues relative to the adjacent marginal tissues. The association between clinicopathological parameters and lncRNA LOWEG and MINCR expression levels was also addressed. The obtained information may shed more light on using lncRNA *LOWEG* and lncRNA *MINCR* as biomarkers in GC.

Materials and methods

Patient specimens

This study includes 100 gastric cancer patients referred to Valiasr Hospital in Tabriz, Iran, for surgery. Before performing the study, written consent was obtained from all patients. The Research Ethics Committee of the University of Tabriz confirmed the study. This investigation excluded GC cases undergoing radiotherapy, immunotherapy, or chemotherapy. The tissue samples were placed in liquid nitrogen (− 196 °C) until RNA extraction. The patient's clinicopathological data are presented in Table 1.

RNA isolation and real-time reverse transcription PCR

Total RNA was extracted from tissues using TRIzol reagent (RiboEx, GeneAll Biotech, Seoul, Korea, Cat. No. 301-001) according to the manufacturer's instructions. After RNA extraction, its quantity and quality were evaluated by a NanoDrop device. RNA concentration was measured on NanoDrop (Thermo Fisher Scientific, USA), and the adsorption ratio was measured at 260–280 nm, followed by agarose gel electrophoresis.

Table 1 Sequences of primers

Gene	Primer type	Sequences of primers
lncRNA LOWEG	Forward	5′–CCTGAGTCTGGCCGAAATGT–3′
lncRNA LOWEG	Reverse	5′–TTGGACTGGCACACATGGAG–3′
lncRNA MINCR	Forward	5′–CAGAAGAGCTTCATCGGCCC–3′
lncRNA MINCR	Reverse	5′–TCACAGACGCACTCTTCCCA–3′
β-actin	Forward	5′–AGAGCTACGAGCTGCCTGAC–3′
β-actin	Reverse	5′–AGCACTGTGTTGGCGTACAG–3′

Table 2 LncRNA LOWEG expression and clinicopathological parameters of GC patients

Clinical parameters	N	Expression mean lncRNA LOWEG tumoral (± SD)	Expression mean lncRNA LOWEG marginal (± SD)	lncRNA LOWEG P-value
Age				0.313
≤ 50	43	0.052 (0.069)	0.255 (0.363)	
> 50	57	0.048 (0.079)	0.201 (0.292)	
Gender				0.333
Male	57	0.056 (0.074)	0.250 (0.362)	
Female	43	0.041 (0.075)	0.189 (0.266)	
Different tumor sizes				0.425
≤ 5 cm	30	0.055 (0.071)	0.209 (0.252)	
> 5 cm	70	0.047 (0.076)	0.231 (0.352)	
Lymph involvement				0.895
Negative	27	0.044 (0.056)	0.226 (0.262)	
Positive	73	0.052 (0.081)	0.223 (0.346)	
TNM (Tumor stage)				0.477
Stage I and II	67	0.048 (0.071)	0.192 (0.307)	
Stage III and IV	33	0.054 (0.082)	0.289 (0.352)	
Helicobacter pylori infection				0.623
Positive	67	0.050 (0.069)	0.213 (0.322)	
Negative	33	0.050 (0.086)	0.248 (0.332)	
Lauren type				0.942
Intestinal	76	0.055 (0.083)	0.239 (0.344)	
Diffuse	24	0.055 (0.038)	0.178 (0.253)	

Table 3 LncRNA MINCR expression and clinicopathological parameters of GC patients

Clinical parameters	N	Expression mean lncRNA MINCR tumoral (± SD)	Expression mean lncRNA MINCR marginal (± SD)	lncRNA MINCR *P*-value
Age				0.113
≤ 50	43	0.161 (0.207)	0.049 (0.058)	
> 50	57	0.198 (0.210)	0.032 (0.047)	
Gender				0.298
Male	57	0.155 (0.186)	0.036 (0.051)	
Female	43	0.218 (0.231)	0.043 (0.054)	
Different tumor sizes				0.907
≤ 5 cm	30	0.190 (0.244)	0.032 (0.041)	
> 5 cm	70	0.179 (0.193)	0.042 (0.056)	
Lymph involvement				0.172
Negative	27	0.174 (0.259)	0.032 (0.044)	
Positive	73	0.185 (0.188)	0.042 (0.055)	
TNM (Tumor stage)				0.846
Stage I and II	67	0.177 (0.202)	0.037 (0.051)	
Stage III and IV	33	0.192 (0.223)	0.043 (0.055)	
Helicobacter pylori infection				0.435
Positive	67	0.180 (0.228)	0.037 (0.052)	
Negative	33	0.186 (0.164)	0.043 (0.054)	
Lauren type				0.465
Intestinal	76	0.287 (0.218)	0.038 (0.053)	
Diffuse	24	0.186 (0.179)	0.042 (0.051)	

Reverse transcription reactions were performed using reverse transcripts of Rumi's mouse leukemia virus. RB cDNA synthesis Kit (RNA Biotechnology Company, Isfahan, Iran) was used to synthesize the first strand of cDNA from the extracted total RNA. cDNA was amplified using RealQ Plus 2×Master Mix Green High ROX™ (Ampliqon, Denmark, Cat. No. A325402) in a qRT-PCR reaction. The sequence of primers is presented in Table 1. *β-actin* was used as the internal control to normalize the information of qRT-PCR. Each test was repeated two times, and the comparative expression of lncRNA *LOWEG* and lncRNA *MINCR* was figured out using method 2−ΔCT (Tables 2 and 3).

Statistical analysis

Nonparametric tests were used to analyze the data. To statistically analyze the expression of lncRNA *LOWEG* and lncRNA *MINCR* genes in tumor tissue samples and tumor margins of gastric cancer after performing real-time PCR reactions, SPSS 26 software was used. Mann–Whitney test was used to analyze the differences between the data of the two groups. *P*-value < 0.05 was considered statistically significant. ROC curve analysis was performed using GraphPad Prism 9 software. This software was also used to evaluate a gene's potential to be considered a biomarker for the diagnosis or prognosis.

Results

The present study's first aim was to evaluate the expression of lncRNA *LOWEG* and lncRNA *MINCR* genes in GC tissues compared to non-cancerous control tissues. qRT-PCR was used to quantify the expression levels of lncRNA *LOWEG* and lncRNA *MINCR* in 100 pairs of GC cancer tissues and adjacent marginal tissues. Statistical analysis of the data showed that the expression of the lncRNA *LOWEG* gene in tumor tissues decreased compared to the tumor margin samples (CI = 95% and *P*-value < 0.0001, Fig. 1). Statistical analysis of the data also showed that the expression of the lncRNA *MINCR* gene in tumor tissues increased compared to the tumor margin samples (CI = 95% and *P*-value < 0.0001, Fig. 2).

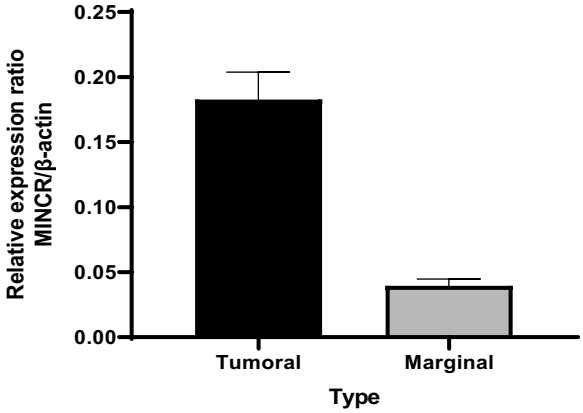

Fig. 2 LncRNA MINCR expression in GC tissues as compared with marginal tissues (*P*-value < 0.0001)

Examination of the ROC curves for both genes (lncRNA *LOWEG* and lncRNA *MINCR*) showed they could be introduced as reliable diagnostic biomarkers for gastric cancer (Figs. 3 and 4).

The second aim was to determine the association between decreased lncRNA *LOWEG* expression. It increased lncRNA *MINCR* expression with clinical parameters such as age, gender, different tumor sizes, lymph node involvement, tumor stage, Helicobacter pylori infection, and Lauren type. The results showed no significant relationship between lncRNA *LOWEG* and lncRNA *MINCR* expression with clinical parameters.

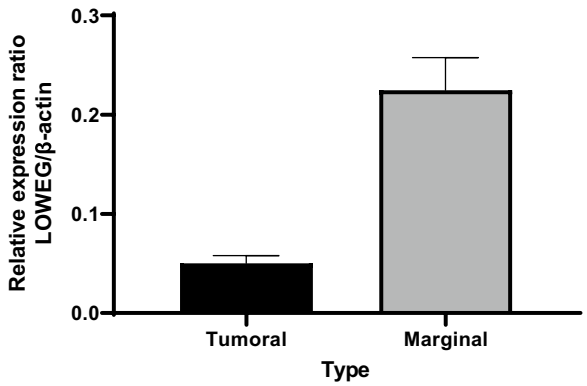

Fig. 1 LncRNA LOWEG expression in GC tissues as compared with marginal tissues (*P*-value < 0.0001)

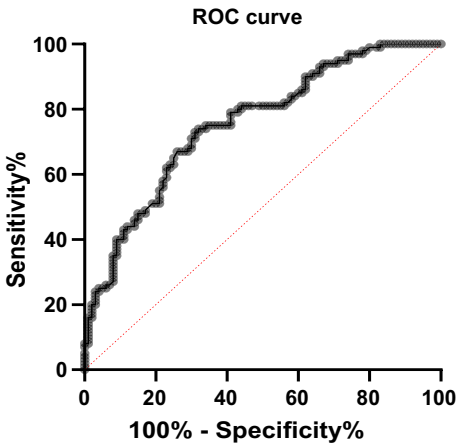

Fig. 3 LncRNA LOWEG gene function as a diagnostic biomarker (area under the ROC curve = 0.75)

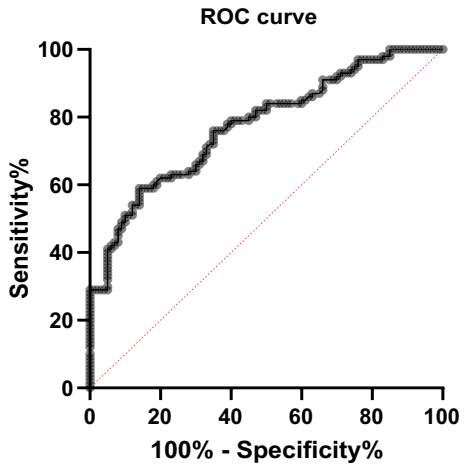

Fig. 4 LncRNA MINCR gene function as a diagnostic biomarker (area under the ROC curve = 0.77)

Discussion

Gastric cancer is the third leading cause of cancer deaths in the world [22]. Gastric cancer is a heterogeneous disease, and different genes can play roles in its mechanism of development and progression [23].

In addition to protein-coding genes, it is approved that non-coding genes are also present in the human genome [24]. LncRNAs are a class of transcribed molecules that make up about 80% of non-coding RNAs. They are involved in several biological processes that can extend their regulatory activities in a trans or cis manner [25]. Improper expression of lncRNAs plays a vital role in tumorigenesis and metastasis of gastric cancer [26, 27]. LncRNAs can be used as diagnostic and prognostic biomarkers in gastric cancer [28]. For example, *H19* is considered the most critical diagnostic solid biomarker for detecting early stages of gastric cancer. This molecule plays a vital role in tumor cell proliferation, metastasis, and invasion through various mechanisms such as *mir-675* processing. [29]. Plasma overexpression of *LINC00152* has been evaluated in gastric cancer patients, with a more excellent diagnostic value than *CA1* and *CEA*. As a result, *LINC00152* can be introduced as a robust diagnostic blood biomarker in gastric cancer [30].

The expression of lncRNA *FENDRR* is reduced in gastric cancer tissues. This molecule suppresses migration and invasion by inhibiting *Fibronectin 1* and *MMP2* / *MMP9* [31]. Upregulation of lncRNA *XIST* through modulation of the *miR-497/MACC1* axis promotes cell invasion and proliferation in GC [32]. LncRNA *PVT1* inhibits the expression of tumor suppressor genes *p15* and *p16* and thus leads to cell cycle progression and cell proliferation [33]. High expression of lncRNA *CCAT2* increases the MYC gene's expression, leading to increased expression of *miR17HG* and *miR20a*. These two molecules are essential in developing metastatic phenotype [34]. C-Myc can bind to the E-Box part of lncRNA *CCAT1* in the promoter region, which leads to the upregulation of its expression in GC and its promotion to metastasis [35]. Several lncRNAs, such as *HOTTIP*, *TUG1*, and *CCAT2*, act as oncogenes, while some lncRNAs, such as *ANRIL*, *MEG3*, and *GAS5*, act as tumor suppressors [36]. *MEG3* increases *p53* expression by inhibiting *p53*-degrading MDM2 [37]. There is a new and extensive interactive system involving ceRNAs in which lncRNAs can act as miRNA sponges by separating miRNAs from their target mRNAs [38, 39]. LncRNA *GAPCINC* modulates CD44 by sponging *miR-211-3p* and increases metastasis [40]. *LoxL1-AS1* modulates upstream stimulus factor 1 (USF1) to perform its oncogenic action in GC by sponging *miR-708-5p* [41].

The gene encoding lncRNA *LOWEG* is located in region 1 of the short arm of human chromosome number 5. LncRNA *LOWEG* prevents the invasion of tumor cells in gastric cancer by regulating *LIFR* expression at the translational level. LIFR can act as a metastasis suppressor by modulating the Hippo-YAP and the PTEN pathways [26–42]—the results of research by Zhao et al. In 2016, it was shown that lncRNA *LOWEG* increases *LIFR* expression, thereby preventing the invasion of gastric cancer cells by acting as a tumor suppressor [19] by Liao et al. In 2017, the expression pattern of lncRNA *LOWEG* in bladder cancer showed that the expression of lncRNA *LOWEG* in bladder cancer tissues is reduced compared to the healthy tumor peripheral tissues. Overexpression of lncRNA *LOWEG* also suppresses bladder tumors by inhibiting cell migration [37]. This study's results were consistent with our study's results on reducing lncRNA *LOWEG* expression in cancer cells compared to healthy tumor margins.

The gene encoding lncRNA *MINCR* is located in region 2 of the long arm of human chromosome 8 and between the genes encoding *GLI4* and *ZNF696*. *MINCR* lncRNA can modulate the MYC transcription network in Burkitt lymphoma cells and inhibit apoptosis in cancer cells [20]—the research results by Chen et al. In 2019, lncRNA MINCR's expression increased in lung cancer tissues and cell lines, in which lncRNA *MINCR* had an oncogenic role [43]. Yang et al. showed that lincRNA *MINCR* activates the Wnt/β-catenin pathway by targeting the *miR-708-5p*/*CTNNB1* axis and exacerbates colon cancer. They also showed that inhibition of lncRNA *MINCR* inhibited colon cancer cell proliferation, migration, and invasion [44]. The results of this study in connection with the increase of lncRNA *MINCR* expression in cancer cells compared to healthy cells peripheral to gastric cancer tumors confirmed the above results.

The fundamental molecular mechanisms of lncRNA *LOWEG* and *MINCR* are not yet recognized. Therefore, more studies are needed to discover their exact molecular mechanism.

Conclusions

The expression of the lncRNA *LOWEG* was reduced in tumoral tissues compared to the adjacent marginal tissues, and the expression of lncRNA *MINCR* increased in tumoral tissues. So, as a result, lncRNAs *LOWEG* and *MINCR* could be considered diagnostic biomarkers for GC.

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Author contributions
We declare that we contributed significantly toward the research study; MAH, AR, and RS designed the study and experiments. TG, EMA, PN, SA, and STG performed the experiments. TG and AR wrote the manuscript, and ST and RS revised the manuscript. AR and TG carried out the data analysis. All authors reviewed, considered, and approved the manuscript.

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Availability of data and materials
Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Ethics approval and consent to participate
All patients signed written informed consent forms to allow their tissue specimens to be used in this project. This project was ethically authorized by the ethical committee of University of Tabriz, Tabriz, Iran (Approval Number: IR.TABRIZU.REC.1399.006).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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