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LINC01366 and LINC01433 in Glioblastoma Multiforme: A Potential Role at the Intersection of Inflammation and Angiogenesis

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ABSTRACT

Glioblastoma multiforme (GBM) is an aggressive cancer with a poor prognosis. Inflammation and angiogenesis are important processes in GBM that are interrelated. In this study, bioinformatic investigations were performed to detect common and key genes in the inflammatory and angiogenesis pathways of GBM. Additionally, relevant long non-coding RNAs (lncRNAs) were recognized as important gene regulators. Consequently, real-time PCR and correlation analyses were used to investigate changes in gene and lncRNA expression levels and explain their relationship. RELA emerged as a common key gene in these biological processes. LINC01366 and LINC01433 were identified as putative RELA regulators in different metabolic pathways using computational assays. According to our findings, the expression levels of RELA, LINC01366 and LINC01433 were found to be significantly upregulated in GBM samples. Correlational studies revealed a significant positive relationship of gene expressions between LINC01366 and LINC01433, indicating that they may have a coordinated effect on GBM biology. Nevertheless, there was no significant correlation between these lncRNAs and RELA. The current study highlights the high expression of LINC01366 and LINC01433 in GBM and emphasizes the importance of studying lncRNAs as putative regulators in the pathophysiology of GBM. Further research is needed to clarify their specific functions, in particular the associated inflammatory and angiogenesis pathways.

Keywords: LINC01366, LINC01433, RELA, Glioblastoma multiforme, inflammation, angiogenesis

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Introduction

Glioblastoma multiforme (GBM), a deadly brain tumor with high vascularization, rapid progression, and infiltrative growth, has a survival rate at the poorest level. GBM is the most common malignant tumor that affects the central nervous system (1, 2). The characteristics of GBM include high vascularization, aggressive and rapid clinical progression, and an infiltrative growth pattern (3). Inflammation increases the risk of cancer progression at the onset and in the early and late stages of GBM (4).

The nuclear factor kappa B (NF-κB) pathway, the key player in inflammatory mediators, causes the release of cytokines that promote the survival, invasion, and angiogenesis of GBM cells through direct and indirect pathways (5). P50/RelA is one of the most studied NF-kB dimers. This family of transcription factors regulates the expression of genes involved in immune regulation, survival, apoptosis, and angiogenesis (6, 7). As a result, NF-κB transcription factor family can be a key mediator in the matchmaking of inflammation and angiogenesis in cancer. A study on colorectal carcinoma indicated a significant correlation between the gene expression of RELA and VEGF. Consequently, a significant association between the microvessel density and the expression of RELA was observed in colorectal carcinoma cases (8). Bevacizumab (an anti-VEGF inhibitor), Sunitinib, and Imatinib (Tyrosine kinase inhibitors) are some potent agents in anti-angiogenic strategies in the treatment of different malignancies (9).

Aberrant expression levels of long non-coding RNAs (lncRNAs) play crucial and controversial roles in immune regulation, angiogenesis, stemness, and metastasis of cancer (10, 11). Increasingly, the functions and effects of changes in the expression level of lncRNAs in GBM are being studied. For example, H19 and CCAT1 are overexpressed lncRNAs in GBM, involved in invasion, migration, and survival. Also, these mentioned lncRNAs are being studied for their key effects on the metastasis of cancer (12).

Protein-coding and non-coding RNAs can communicate by competing for binding to shared miRNAs (13). MiRNAs, a group of non-coding RNAs, play key roles in the regulation of translation at different levels (14). At the post-transcriptional level, lncRNAs can function as competing endogenous RNAs (ceRNAs) and have a co-regulating relationship with protein-coding RNAs. RNA editing, binding affinity of miRNAs to their sponges, RNA secondary structures, abundance of components, and RNA-binding proteins are several factors that may influence the ceRNA activity (15). It has been indicated that the disturbance in the balance of ceRNA network components or other factors can cause various malignancies such as head and neck squamous cell carcinoma (HNSCC), pancreatic cancer, colorectal cancer (CRC), and GBM (16-19).

LINC01366 and LINC01433 have been found to be appropriate candidates in various studies of cancer cells and tissues. The overexpression of LINC01433 is observed in non-small cell lung cancer (20), breast cancer (21), and gastric cancer (22).

In our bioinformatic section, we emphasized the need to detect the involved and novel choices in inflammation- and angiogenesis-related lncRNAs of GBM. In the experimental section, we focused on the changes in the expression levels of the selected target gene (RELA), its predicted related lncRNAs (LINC01366 and LINC01433), and their correlation with gene expression in GBM. This study was done due to the emerging roles of the lncRNAs in possible GBM progression, diagnosis, and treatment strategies in the future.

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Materials and methods

Bioinformatic studies

The upregulated GBM genes were extracted from The Cancer Genome Atlas (TCGA) using TCGAbiolinks R package. The primary list included 1327 lncRNAs. The extracted genes were imported into ToppGene (http://toppgene.cchmc.org). From the biological processes section of the ToppGene database, genes involved in both inflammation- and angiogenesis-related processes were identified. Subsequently, the separated genes were analyzed in the TRRUST database (http://www.grnpedia.org/trrust/) to identify the transcription factors in the list. The next step was to investigate the functions, interactions and previous studies on the identified genes. After the final selection from the considered list, the interacting miRNAs were extracted. The predicted lncRNAs that may interact with the identified miRNAs were obtained from the RNAInter database (23). Finally, the selected lncRNAs were checked for their existence in the first list extracted with the TCGAbiolinks R package, which contained 1327 lncRNAs.

Patients and sample collection

The code of ethics for the present study was obtained from the Ethics Committee of Shahrekord University of Medical Sciences (IR.SKUMS.REC.1401.198). After obtaining informed consent form, a total of 25 GBM tissue samples were collected from the patients' routine therapeutic surgery. GBM tissues were diagnosed according to WHO standards. Additionally, 10 non-tumor brain tissues were collected from Iran National Tumor Bank (Iran University of Medical Sciences, Iran) as a control group (24, 25). All samples were rapidly transported on ice and stored at -70 ºC in the laboratory.

RNA extraction, cDNA synthesis, and qPCR

Total RNA of tumoral and normal brain tissues was extracted using the YTzol kit (Yekta Tajhiz Azma, Iran) according to the manufacturer's instructions. The concentrations of extracted total RNAs from each sample were measured using the Thermo Scientific™ NanoDrop 2000. Then, the cDNA of each sample was synthesized from total RNA (2 µg) using the cDNA synthesis kit (Ana Cell Tec, Iran).

The primers for RELA, LINC01366, LINC01433, and GAPDH (housekeeping gene) were designed using AlleleID 7 software and Integrated DNA Technologies (IDT) (Coralville, IA, USA). The annealing temperature of the primers was set at 60ºC. The qPCR analyses were performed using the ExcelTaq™ 2X Q-PCR Master Mix (SMOBIO) in duplicate on a Rotor-Gene Q MDx (Qiagen). The Pfaffl method was used to analyze the data on changes in gene expression. Using the LinRegPCR 2017.1 software, primer efficiencies were calculated from the raw Cq data (26-29). The Pfaffl formula was used to calculate the relative RNA expression of RELA, LINC01366 and LINC01433.

RELA forward primer: 5´-CTATGTGGAGATCATTGAGCAG- 3´
RELA reverse primer: 5´ -GGTGGGTCTTGGTGGTAT- 3´
LINC01366 forward primer: 5´ -CGGACATTAGGCAGACAC- 3´
LINC01366 reverse primer: 5´ -CCAGGGACCAGGACTATG- 3´
LINC01433 forward primer: 5´ -TCTGGAAGCAAGGACAAC- 3´
LINC01433 reverse primer: 5´ -AGGACACACATTTTCTCGG- 3´
GAPDH forward primer: 5´ -CTCTCTGCTCCTCCTGTTCG- 3´
GAPDH reverse primer: 5´ -ACGACCAAATCCGTTGACTC- 3´

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Statistical analysis

All data were expressed as mean ± SD. Relative gene expressions in tumor and normal groups were analyzed using the Pfaffl formula. Statistical analyses of the data, including correlation of gene expressions between RELA, LINC01366 and LINC01433, and drawing of the figures and graphs were done using the GraphPad Prism 8 (GraphPad Software Inc.). The intergroup data were compared using the Student's t-test. Pearson's method was used to calculate the correlations between the expression of RELA, LINC01366 and LINC01433 genes. A value of $P<0.05$ was considered significant. The tests were performed in triplicate.

Results

Bioinformatics and computational studies

In the first phase, 5791 upregulated genes in GBM were extracted using the TCGAbiolinks R package, containing 1327 lncRNAs. After importing the extracted genes into ToppGene (http://toppgene.cchmc.org), 4464 genes were identified as the protein coding members of the list. A list of 344 genes involved in both inflammation- and angiogenesis-related biological processes were obtained. From the extracted list, 38 genes were identified as the upregulated transcription factors in GBM. After an overall screening of 38 transcription factors, RELA was selected as a critical candidate for investigation. By using RNAInter, LINC01366 and LINC01433 were discovered as potential competitors of RELA at the post-transcriptional level.

By using the RNAInter database, LINC01366 was predicted to affect RELA mRNA expression through

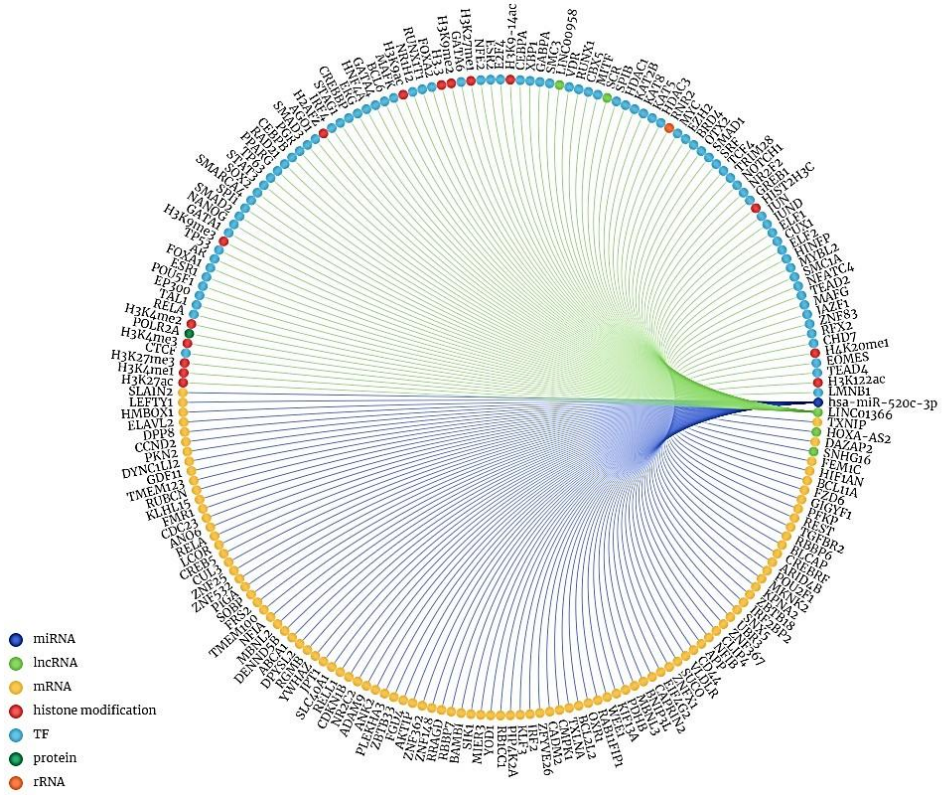

Fig. 1. LINC01366 can affect RELA mRNA expression via the ceRNA network RELA/miR-520c-3p/LINC01366. In addition to this ceRNA network, LINC01366 can also interact directly with the RELA transcription factor (http://www.rnainter.org).

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the ceRNA network RELA/miR-520c-3p/LINC01366. Interestingly, in addition to this ceRNA network, LINC01366 was also observed to interact directly with the RELA transcription factor (Figure 1).

After analyzing the RELA interactors, it was predicted that LINC01433 can also influence the mRNA expression of RELA via the ceRNA network RELA/miR-124-3p/LINC01433. In addition, it has been observed that the RELA transcription factor may interact with LINC01433 (Figure 2).

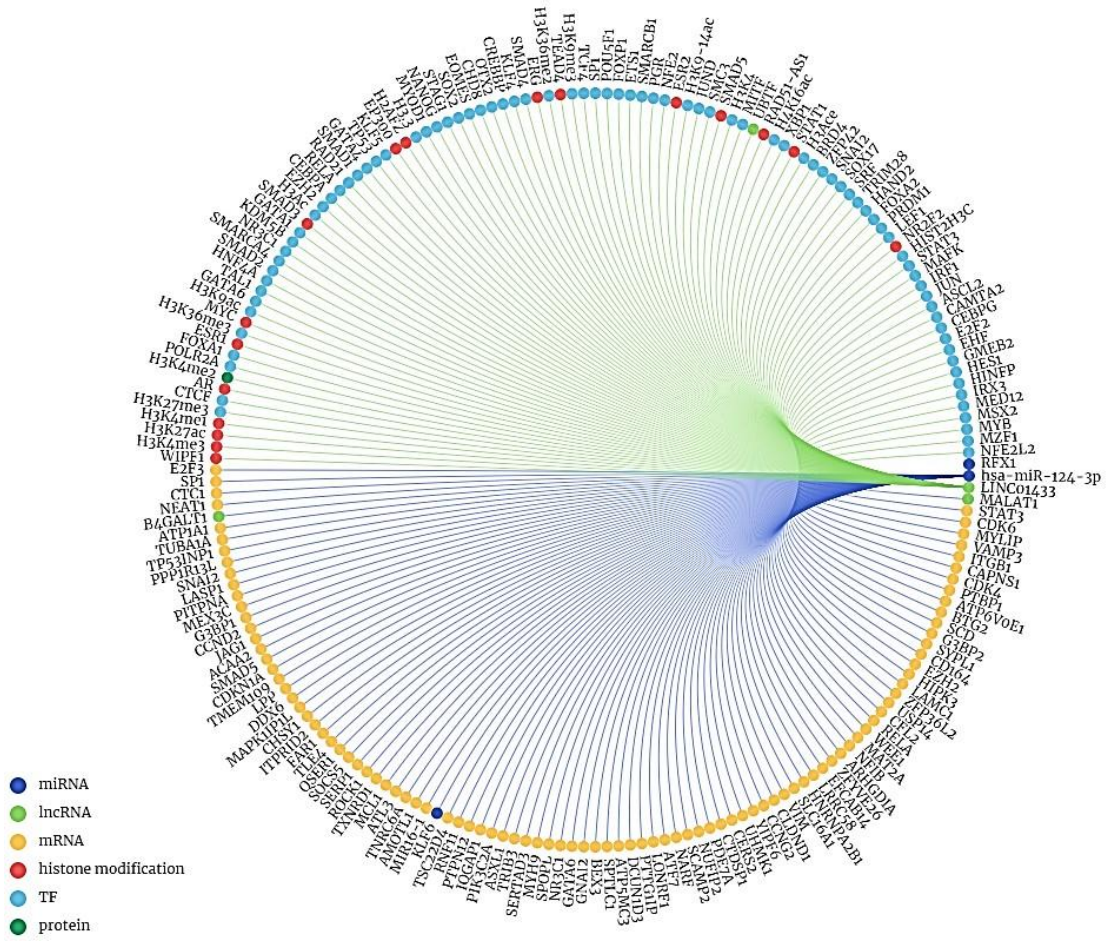

Fig. 2. LINC01433 can affect the mRNA expression of RELA through ceRNA network RELA/miR-124-3p/LINC01433. In addition, the RELA transcription factor may interact with LINC01433 (http://www.rnainter.org).

Statistical data of patients

After receiving the patient data, it was found that among the 25 samples, 17 samples were male and 8 samples were female. These data indicate a higher incidence of GBM in men. In addition, 15 patients were older than 55 years, while 10 patients were younger than 55 years.

Expression of RELA

After extraction of total RNA and cDNA synthesis, the relative expression levels and changes in expression of the RELA, LINC01366 and LINC01433 genes were analyzed by qPCR assay. The qPCR assay analysis revealed that RELA was upregulated in GBM ($^{*}P < 0.05$, fold change = 1.65) (Figure 3).

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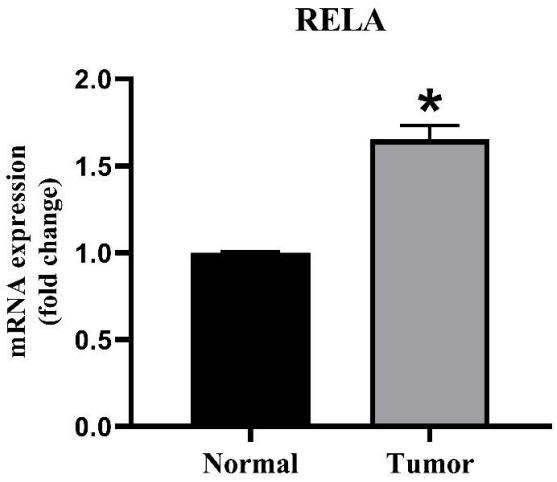

Fig. 3. Relative expression analysis of RELA by qPCR assay. The expression of RELA is increased in tumor tissue of GBM patients compared to normal brain tissue (*P < 0.05, fold change = 1.65).

Expression of LINC01366 and LINC01433

Moreover, the present study evaluated the relative expression levels of LINC01366 and LINC01433 in both normal and tumor tissues to account for the changes in expression levels in GBM patients. LINC01366 was significantly upregulated in tumor tissue of GBM patients ($^{***}P < 0.001$, fold change = 4.93). Similarly, the expression of LINC01433 was remarkably increased in GBM tissue compared to normal brain tissue ($^{**}P < 0.01$, fold change = 7.97) (Figure 4).

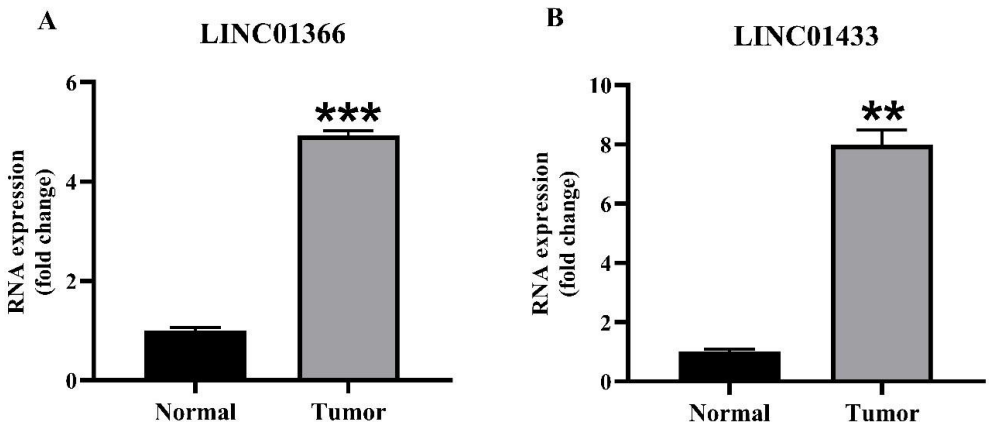

Fig. 4. Relative expression of LINC01366 and LINC01433 by qPCR assay. A. Expression analysis of LINC01366 shows significant upregulation in GBM tissues (***P < 0.001, fold change = 4.93). B. The expression of LINC01433 is significantly increased in tumor tissue of GBM patients compared to normal brain tissue (**P < 0.01, fold change = 7.97).

Correlation analysis between the expressions of RELA, LINC01366, and LINC01433 genes

After analyzing the relative expression levels of RELA, LINC01366, and LINC01433, the correlation between the expression of these three genes was investigated. The data were analyzed after calculating the relative expression of each gene for each sample. The correlation between the expression of RELA and

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LINC01366 was not significant (r = 0.125, $P > 0.05$). Likewise, the expression levels of RELA and LINC01433 were not found to correlate (r = -0.01856, $P > 0.05$). In contrast to the above correlation results, the expression of LINC01366 and LINC01433 showed a remarkable positive correlation (r = 0.8055, $^{****}P < 0.0001$). The results are shown in Figure 5.

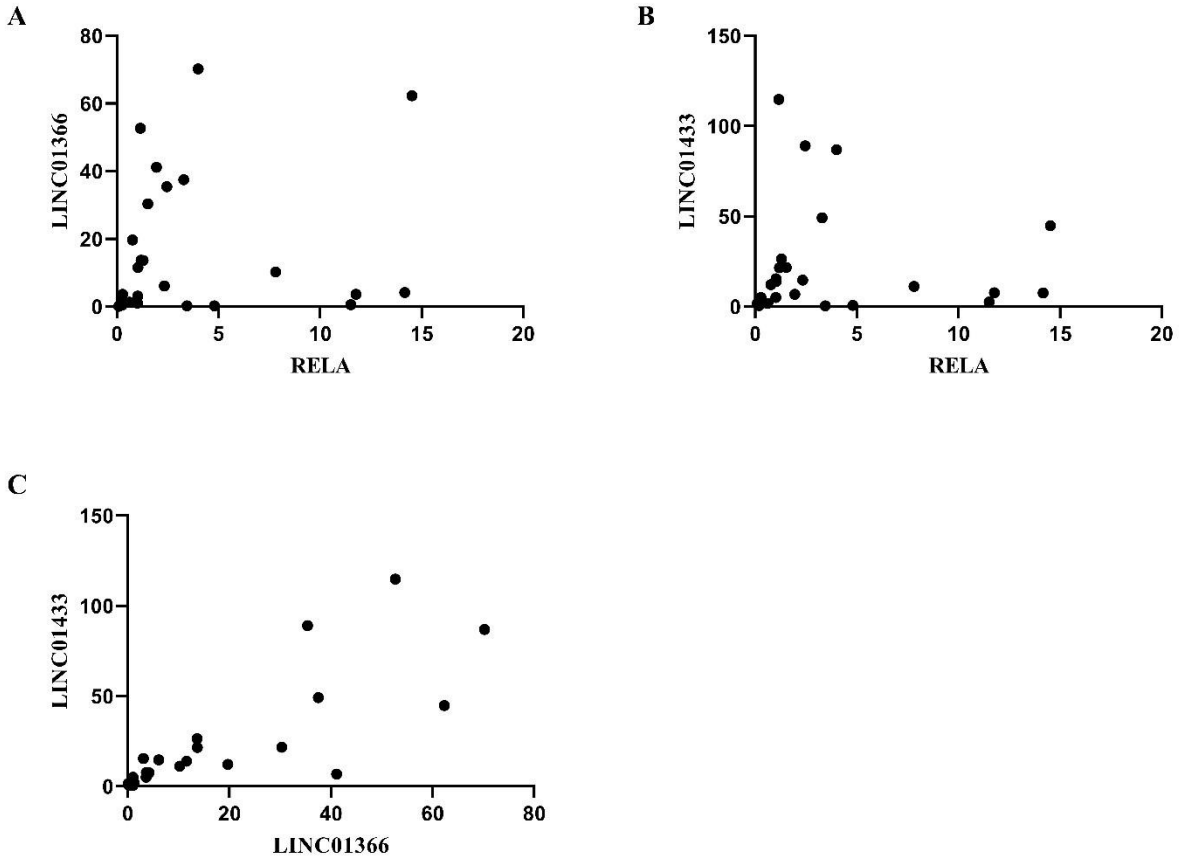

Fig. 5. Correlation between the expression of RELA-LINC01366, RELA-LINC01433 and LINC01366-LINC01433 genes; A. The relative expression levels of RELA and LINC01366 show no significant correlation in GBM tissues (r = 0.125, P > 0.05). B. The correlation of relative expression levels between RELA and LINC01433 is non-significant (r = -0.01856, P > 0.05). C. The relative expression levels of LINC01366 and LINC01433 are significantly correlated in GBM tissues (r = 0.8055, ****P < 0.0001).

Discussion

In recent years, lncRNAs have been shown to represent an important layer of gene regulators in different diseases. This group of non-coding RNAs can influence cell proliferation, survival, invasion, apoptosis, etc. through interacting with specific proteins, RNAs and chromatin. LncRNAs have indicated potential properties for diagnostic and therapeutic approaches in cancer (30). Despite the aforementioned roles, some lncRNAs may act as tumor suppressor elements (31). Therefore, up- or down-regulation of a lncRNA does not prove its progressive or preventive role in biological processes of cancer. There are some preclinical studies and clinical trials that include lncRNAs as an important part of their investigation. For example, PCA3 is a validated lncRNA for clinical application in the diagnosis of prostate cancer (32).

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Furthermore, TargomiRs and MRX34 are examples of noncoding RNA-based agents indicating antitumor activity and acceptable safety in clinical trials (33).

In this study, after the identification of common genes in inflammatory and angiogenic biological processes, a list of transcription factors was generated using the TRRUST database. The overall investigation of the members of the list of transcription factors was done based on their previously studied functions. The genes most associated with inflammatory and angiogenic biological processes based on the present study were RELA, ETS1, SMAD1, SP100, GATA3, HLX, IRF1, SOX11, SOX2, HIF1A, MYB, and MYC. Several factors such as the novelty of the lncRNAs and the associated biological functions of the transcription factor were considered when selecting the appropriate candidate for the ongoing study.

RELA is a double-edged sword in cancer. Its activation can lead to impaired apoptosis. On the other hand, activation of NF-κB is essential for cell apoptosis. In addition, the activation of NF-κB leads to cell proliferation in malignant diseases. It is also involved in angiogenesis through various mechanisms. Despite the mentioned approaches, NF-κB has been defined as a tumor suppressor factor in several cell lines and mouse models (34). As a result, neither the distinct functions of lncRNAs nor the exact functions of RELA in cancer are known. A study on CRC indicated a significantly higher expression of NF-κB compared to normal colon tissue. However, no significant correlation was found between NF-κB expression and tumor location. Interestingly, no significant correlation was also observed between NF-κB expression and stage of CRC (35).

Although no other studies on the expression of LINC01366 by qPCR have been performed to date, our study suggests its overexpression in GBM. LINC01366 was detected as an upregulated lncRNA in thyroid carcinomas (36). In addition, LINC01366 was identified as an upregulated and autophagy-related lncRNA in GBM in a systematic analysis of DNA methylation changes of autophagy-related lncRNAs in GBM (37). Further studies are needed to investigate the expression of LINC01366 in other cancers.

Similar to the current study on LINC01433 in GBM, the expression of this lncRNA is increased in nasopharyngeal carcinoma (NPC). In addition, overexpression of LINC01433 promotes invasion and proliferation of NPC cells (38). In another study, the high expression of LINC01433 in breast cancer was confirmed by qPCR assay. Moreover, LINC01433 has been shown to promote migration, cell proliferation and epithelial to mesenchymal transition in breast cancer cells (21).

In the present study, the analyzed data suggested that the expression of RELA might not be correlated with LINC01366 and LINC01433. However, the correlation of LINC01366 and LINC01433 expression was remarkable. This positive correlation of gene expressions may be due to various reasons. One of the possible reasons could be that they have a common regulator for their expression. Another reason may be their related role in a biological process or their involvement in a common or related approach to cancer.

Different methods are used to investigate the nature and functions of a lncRNA. Expression analysis, loss-of-function and gain-of-function methods, study of interactions, and knockout models are some common methods used to study lncRNAs (31). The current study, despite the existing limitations, investigated the dysregulated expression of LINC01366 and LINC01433 in GBM. Nevertheless, further studies are needed to investigate the interactions and precise functions of LINC01366 and LINC01433 in cancer. In summary, the present computational study identified RELA as a common and important gene for

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inflammation and angiogenesis in the progression of GBM. Through the analysis, we identified LINC01366 and LINC01433 as potential regulators of RELA in addition to its discovery. Strikingly, the findings of the ongoing study revealed significant upregulation of RELA, LINC01366 and LINC01433 in GBM samples, suggesting their potential as therapeutic targets or diagnostic markers. Moreover, the experimental positive correlation between the expression of LINC01366 and LINC01433 genes highlights their coordinated impact on GBM biology, warranting further investigation of their specific functions, particularly in the context of inflammatory and angiogenesis pathways. This study underscores the importance of exploring lncRNAs as potential regulators in GBM pathophysiology, with suggestions for advancing therapeutic interventions and improving patient outcomes.

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