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Evaluation of *TRAF3IP2* Gene Expression in Brain Tumor Tissue of Patients with Glioblastoma Multiforme in Comparison to Non-Tumoral Brain Tissue

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Abstract

Background: Glioblastoma, not otherwise specified (NOS), is the most common primary malignant brain tumor. The *TRAF3IP2* gene is an upstream regulator responsible for activating multiple proinflammatory pathways that could influence tumor size, angiogenesis, aggressiveness, and metastasis. In the present study, we aimed to investigate and assess the *TRAF3IP2* gene expression in brain tumor tissue of patients with glioblastoma, NOS and compare it with non-neoplastic brain tissue.

Method: In this case-control study, biopsies were obtained from 15 surgically glioblastoma, NOS removed block samples and 15 non-neoplastic brain tissue samples containing normal white and gray matter as controls. Ribonucleic acid (RNA) was isolated and reverse-transcribed to complementary DNA (cDNA). Quantitative polymerase chain reaction (qPCR) was then carried out to measure *TRAF3IP2* gene expression.

Results: We evaluated data from 30 cases, divided into two groups: case (N = 15) and control (N = 15). Based on our data, the expression of the *TRAF3IP2* gene was 6.95 ± 0.65 times higher in glioblastoma multiforme tissue compared with controls ($P < 0.05$). We also found no significant difference in *TRAF3IP2* gene expression between genders ($P = 0.452$), and there was no significant correlation between *TRAF3IP2* gene expression and age ($P = 0.745$).

Conclusion: The expression of the *TRAF3IP2* gene was almost seven times higher in glioblastoma, NOS brain tissue compared with normal brain samples. This finding could have significant clinical and therapeutic implications.

Keywords: Glioblastoma multiforme, Gene expression, Case-control study

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Introduction

Glioblastoma, not otherwise specified (NOS), is one of the most invasive astrocytic tumors.

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Glioblastoma is the most common primary malignant tumor of the central nervous system (CNS) that occurs in the spinal cord or brain.[1, 2] The overall prevalence of this cancer is 2 to 3 per 100,000 people.[3, 4] The most common site of glioblastoma tumors is the supratentorial region. Glioblastoma, NOS accounts for 20% of all intracranial tumors and 60% of astrocytic tumors, and is more common in men over 60 years of age.[5, 6]

Symptoms of the tumor depend on its location and include headache, nausea, seizures, cranial nerve disorders, blurred vision, irritability, increased intracranial pressure, neutrophilic leukocytosis, decreased level of consciousness, and more. Complications of glioblastoma, NOS tumors depend on the site of the tumor growth.[3, 7]

The primary treatment strategy for glioblastoma, NOS is surgery; however, the prognosis of the tumor is poor, even when the most invasive treatment is used, which includes radiation therapy, chemotherapy, and surgery.[8] Standard treatment for glioblastoma, NOS includes maximal surgical resection of the tumor followed by radiotherapy between 2 and 4 weeks after surgery to remove tumor debris.[9, 10]

So far, the only known risk factors are genetic syndromes and radiation.[11] In addition to malignant cells, glioblastoma lesions include non-malignant cells, including inflammatory cells, endothelial cells, neural cells, and glial cells. Malignant and non-malignant cells secrete pro-inflammatory mediators that cause tumor growth, metastasis, and invasion.[12] Many of these mediators are secreted in response to genes such as NF-κB. As a result, NF-κB activity causes further tumor growth and a poor prognosis.[13]

TRAF3IP2 is the gene responsible for an upstream regulator for NF-κB activity, and as a result, its expression activates multiple pro-inflammatory pathways.[14, 15] NF-κB is a protein complex that controls DNA transcription, cytokine production, and cell survival. NF-κB is crucial in regulating the immune response to infection.[15] Some studies have also targeted the expression of pro-angiogenic mediators, including VEGF, by targeting *TRAF3IP2*. By silencing *TRAF3IP2* expression, NF-κB activity can be inhibited, thus reducing tumor growth, metastasis, and angiogenesis.[16] These studies highlight the possible therapeutic roles of *TRAF3IP2* gene suppression in tumors. Previous studies have indicated the potential of the *TRAF3IP2* gene in glioblastoma, NOS treatments, but there is still

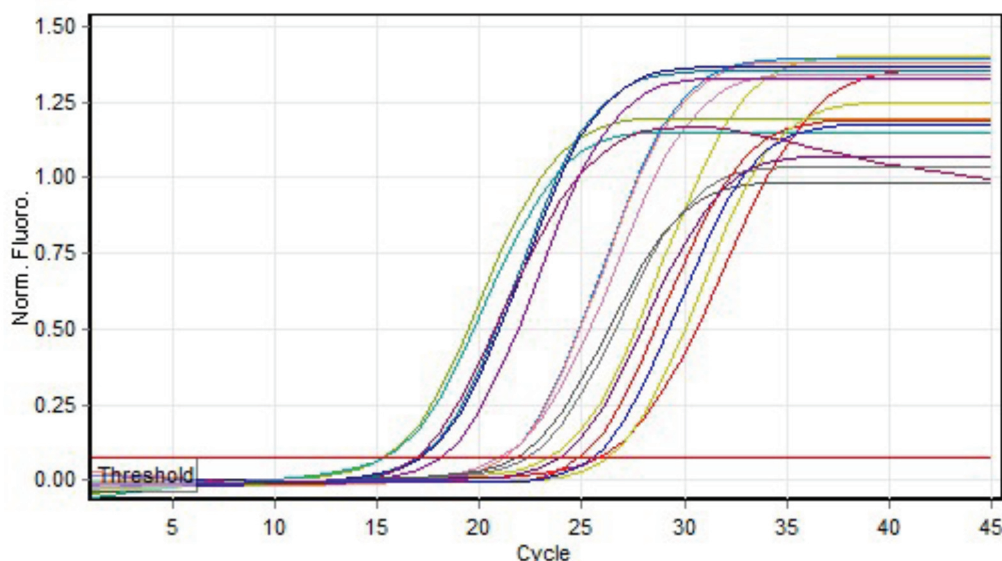

Figure 1. This figure displays the amplification graph of real-time PCR for *TRAF3IP2*. The x-axis represents the cycle number, the y-axis shows the change in fluorescent intensity, and the red horizontal line denotes the threshold.
Norm.Fluoro: Normal Fluorosecence; PCR: Polymerase chain reaction

much to discover in this regard, including the amount of gene expression in glioblastoma, NOS tissue.[17]

In this study, we aim to investigate and assess the *TRAF3IP2* gene expression in brain tumor tissue of patients with glioblastoma, NOS, considering the limited studies on this issue and the importance of glioblastoma, NOS and the potential properties of *TRAF3IP2* expression in glioblastoma, NOS tissue.

Materials and Methods

Ethics statement

The study protocol was approved by the Research Committee of Isfahan University of Medical Sciences and confirmed by the affiliated Ethics Committee (ethics code: IR.MUI.MED.REC.1398.481). Tumor specimens were obtained from the pathology banks of patients diagnosed with glioblastoma, NOS at Al-Zahra University Hospital in Isfahan. All data related to human material used in this case-control study were managed using anonymous numerical codes.

Clinical samples and histology

The inclusion criteria for the study were accessibility of the pathology samples, availability of samples in the pathology unit of Al-Zahra hospital, and a definitive diagnosis of glioblastoma, NOS. The exclusion criterion was damaged samples. The samples were selected from the patient lists in the Treasury. Based on these criteria, 15 cases of glioblastoma, NOS were selected for gene expression analysis. All specimens were primary glioblastoma, NOS, and the patients had not undergone neoadjuvant therapy prior to surgery. Expert pathologists made the diagnosis of glioblastoma, NOS, according to the 2021 WHO criteria.[18] In addition to the glioblastoma, NOS samples, 15 non-neoplastic brain biopsy samples containing normal white and gray matter tissues were obtained from the pathology bank. These control brain specimens were collected during the biopsy of patients with hemorrhagic brain injuries, brain arteriovenous malformations (AVMs), or colloid cysts in the brain. During the biopsy, we evaluated the normal brain tissues. The samples included 21 males and 9 females with a mean age of 49.26 ± 13.91 years.

All biopsy samples were placed into a 10% neutral buffered formalin solution, fixed at room temperature, and then processed routinely into a paraffin-embedded tissue block (FFPE).

Preparation of FFPE tissue sections and RNA extraction

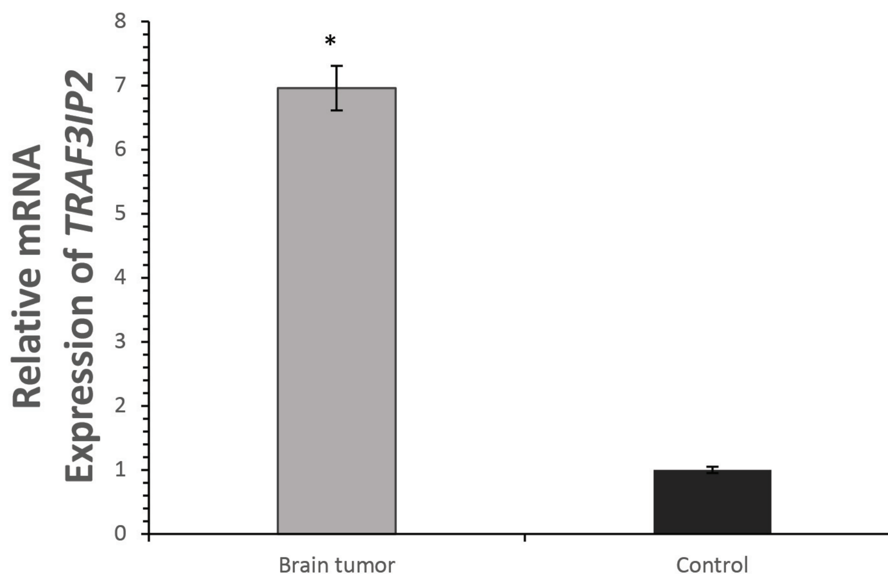

Figure 2. This figure illustrates the relative comparison of *TRAF3IP2* gene expression among samples (*$P < 0.05$). The relative expression of *TRAF3IP2* was almost seven times higher in brain tumors than in normal tissues.

To extract RNA more efficiently, xylene was used to remove the paraffin cuts before the extraction process, followed by ethanol-based rehydration. The manually dissected 50 mg samples were placed into 1.5 mL RNase-free microtubes, and 1 mL xylene was added to each sample, which was then homogenized using vortexing. Subsequently, the microtubes were centrifuged for 5 minutes at 1400 rpm in the Beckman Coulter Microfuge 22r, the xylene was discarded, and the pellet button was rinsed twice with absolute ethanol (Merk KGaA, CAS-NO: 64-17-5).

After preparing the samples, RNA was extracted from selected blocks by manual TRIzol™ method (Yekta Tajhiz Co., Iran, cat. No.: YT9064), according to the protocol reported by Jordon-Thaden and colleagues in 2015.[19] The tissue was digested by incubating the samples in 180 µL TE buffer (1x TE buffer, Sinacolon, Cat. Na EP5071) and 20 mg/mL proteinase K (Adbio, Ref. 91321). First, the sample was incubated at 56°C for two hours, and then, proteinase K was inactivated by raising the temperature to 90°C for one hour. Finally, samples were subjected to an RNA extraction process according to the Trizol method previously described by Jordon-Thaden and colleagues in 2015.[19] All RNA samples were stored frozen at -80°C until used.

Quantitative real-time polymerase chain reaction (qPCR)

The reverse transcription (RT) reaction was carried out using reverse transcriptase enzyme and random hexamer primers, according to the manufacturer's instructions (Addbio kits, Korea, Ct. No.: 22701).

Real-time qPCR was set up according to an Opticon Instrument (Bio-Rad Laboratories, Hercules, CA) using SYBR Green reagent for the detection of PCR products. PCR reactions were performed using 2 µL cDNA with 10 µL of a SYBR Green master mix (GeNet Bio-Korea, Ct. No.: 70201) containing forward and reverse primers, MgCl2, and SYBR Green. Primers for the *TRAF3IP2* gene were designed using Oligo 7 software. The *TRAF3IP2* primers were as follows: forward, 5'-GCTTTATTCAGACTTA-CACCGAT and reverse, 5'-AGTCTAATAC TTTGATTGTAGCCA. The specificity of the primers was checked in the nucleotide database (NCBI, nucleotide BLAST). Glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*) served as a housekeeping gene, and the expression level of target genes was normalized to *GAPDH*.

Table 1. *TRAF3IP2* gene expression, gender, and age

		TRAF3IP2 gene expression	
		Case	**Control**
Sex	Male	6.98 ± 0.62	1 ± 0
	Female	6.56 ± 1.28	1 ± 0
	P value1	0.452	-
Age	Pearson correlation	0.1	-
	P value 2	0.745	-

Statistical analysis

The obtained data were entered into the Statistical Package for Social Sciences (SPSS) version 24. Quantitative data were reported as mean ± standard deviation, and qualitative data were reported as frequency distribution (percentage). Independent t-test and chi-square were used to analyze the data. Relative quantification of gene expression was calculated based on the log $2^{-\Delta\Delta Ct}$ formula.[19, 20] A *P*-value < 0.05 was considered the significance threshold.

Results

In the present study, data from 30 cases were evaluated and divided into two groups: case (N = 15) and control (N = 15). The study population consisted of 21 males (70%) and 9 females (30%) with a mean age of 49.26 ± 13.91. There were no significant differences between the two groups regarding gender ($P = 0.378$) and age ($P = 0.70$). From the amplification curve, it can be seen that the quality of the real-time qPCR is fine (Figure 1).

Based on our data, the expression of the *TRAF3IP2* gene was relatively 6.95 ± 0.65 times higher compared with controls ($P < 0.05$) (Figure 2). These data suggest significantly higher *TRAF3IP2* gene expression in glioblastoma, NOS samples compared with normal brain tissue, which could, in turn, be used in pathological practice.

Further analysis found no significant difference regarding *TRAF3IP2* gene expression between genders ($P = 0.452$), and there was no significant

correlation between *TRAF3IP2* gene expression and age (*P* = 0.745) (Table 1).

Discussion

We evaluated the expression of the *TRAF3IP2* gene in glioblastoma, NOS brain samples and found that its expression was almost seven times higher compared with that of normal brain tissue. This finding highlights the importance of the *TRAF3IP2* gene in the pathogenesis of glioblastoma, NOS. Additionally, our study revealed no significant differences in *TRAF3IP2* gene expression based on age or gender.

Previous studies have also evaluated *TRAF3IP2* gene expression in glioblastoma, NOS. In 2018, Alt et al. assessed *TRAF3IP2* as a therapeutic target in glioblastoma, NOS. They demonstrated that the expression of *TRAF3IP2* was six times higher in glioblastoma, NOS tissue in both animal and human models. They investigated the therapeutic options using this gene and reported that silencing *TRAF3IP2* significantly inhibited the sphere-forming potential of malignant glioblastoma cells. They found that this silencing also suppressed activation of NF-κB and induction of proinflammatory mediators. Another important finding was that targeting *TRAF3IP2* suppressed the expression of various pro-angiogenic mediators.[17] The results of our study were consistent with these findings. However, we only evaluated the expression of the *TRAF3IP2* gene and did not assess possible therapeutic options.

In 2015, Silver et al. reported that gliomas and other primary brain tumors contain a subpopulation of cells that express stem cell-like properties (cancer stem cells or CSCs) and contribute to tumor growth and drug resistance, and possibly tumor recurrence. They suggested that the diagnosis of these genes could result in significant therapeutic progress.[21]

Several other studies have also assessed the expression of the *TRAF3IP2* gene in glioblastoma, NOS. However, the number of such studies is limited. Zan et al. conducted a bioinformatic study in 2019 in China. This study assessed an online microarray dataset, including 26 glioblastoma, NOS samples and six samples from normal brain tissue. The study showed that EPB41L4A-AS1, ZRANB2-AS2, XIST, HOTAIR, *TRAF3IP2*, TPT1-AS1, PVT1, and DLG1-AS1 genes play pivotal roles in the pathogenesis of glioblastoma, NOS. Based on this study, the expression of *TRAF3IP2* was significantly higher in glioblastoma, NOS samples.[22]

Shao et al. also showed the higher expression of *TRAF3IP2* in glioblastoma, NOS in a bioinformatics study conducted in 2018. This study also highlighted the possibility of lncRNAs being utilized in glioblastoma, NOS.[23] Our survey findings were consistent with these studies showing a higher expression of the *TRAF3IP2* gene in glioblastoma, NOS.

The *TRAF3IP2* gene expression has been evaluated in breast cancer, and in 2020, Alt and colleagues investigated the roles of Rab27a, a player in exosome release, and *TRAF3IP2*, an inflammatory mediator, in the development and metastasis of breast cancer. This study also demonstrated that *TRAF3IP2* has higher expression in metastatic breast cancer and showed that silencing this gene blocked the interaction between tumor cells and mesenchymal stem cells injected into the contralateral gland. As a result, *TRAF3IP2* gene suppression could play an essential role in breast cancer.[24] These data suggest that *TRAF3IP2* could be a novel therapeutic option for cancer prevention and treatment.

The importance of the *TRAF3IP2* gene has been mentioned in different previous studies, and some have suggested using this gene in cancer treatment. Based on a report by Alt and colleagues in 2018, the *TRAF3IP2* gene could be a novel therapeutic target in glioblastoma, NOS growth, and dissemination. This study highlighted the roles of *TRAF3IP2* gene suppression in reducing pro-inflammatory/pro-tumorigenic/pro-angiogenic mediators and kinesins.[17] In addition, increased expression of *TRAF3IP2* was established in glioblastoma, NOS brain xenograft models. This study also revealed that targeting *TRAF3IP2* suppresses angiogenesis by decreasing the secretion of several pro-angiogenic mediators, including VEGF, resulting in decreased angiogenesis.[25] In this study, we showed

significantly higher expression of the *TRAF3IP2* gene in glioblastoma, NOS tissue, which was similar to their findings. We believe effective therapeutic strategies could be developed by targeting the *TRAF3IP2* gene.

Furthermore, some studies have also evaluated *TRAF3IP2* gene expression in other tumors and ischemic conditions. In recent research by Alt et al. in 2020, they described that the *TRAF3IP2* gene has significant roles in breast cancer growth and metastasis and contributes to inflammatory situations. A crucial finding of their study was that by targeting and suppressing the expression of the *TRAF3IP2* gene, it suppresses tumor growth as well as macro- and micro-metastasis by reducing LTα (Lymphotoxin Alpha) and PDGFA (Platelet Derived Growth Factor Subunit A) expression in MDA-MB231 cells.[24] Another study by Erikson and colleagues explained that the *TRAF3IP2* gene plays a causal role in myocardial ischemia/reperfusion injury, dysfunction, and adverse remodeling. In this regard, suppressing this gene significantly inhibited myocardial injury and adverse remodeling.[26] These data support the potential of *TRAF3IP2* gene suppression in different conditions.

To the best of our knowledge, all the studies conducted in the common field with the present study were based on bioinformatics and in vitro studies using glioblastoma cell lines and animal models. Despite these valuable studies, there is a lack of investigation of *TRAF3IP2* expression levels in human tumor samples. Notably, this study showed that the expression levels of *TRAF3IP2* in human samples are even higher than those obtained in previous studies. According to our results and these previous reports, *TRAF3IP2* gene targeting could be a novel therapeutic strategy in glioblastoma, NOS, and other conditions, primarily due to its higher expression rates in glioblastoma, NOS tissue.

The limitations of our study included restrictions in the study samples due to the challenging sampling process and the evaluation of only the expression of the *TRAF3IP2* gene. We recommend that further studies concentrate on the effects of suppression and silencing of this gene in cancer therapy based on its potential as a therapeutic target.

Conclusion

The expression of the *TRAF3IP2* gene was almost seven times higher in brain tissue from glioblastoma, NOS, compared with normal brain samples. This finding could have high clinical and therapeutic importance, and we believe that further studies should be conducted in this regard.

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Conflict of Interest

None declared.

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