Research Article

# The effect of resistance training on the expression relationship between IL-6 from skeletal muscle with Cathepsin B and FNDC5 from the hippocampus in rats with glioblastoma multiforme

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## Abstract

Glioblastoma multiforme (GBM) is a highly aggressive malignant brain tumor with limited treatment options and a poor prognosis. In this study, we aimed to explore the potential effects of resistance training (RT) on the expression relationship between interleukin-6 (IL-6) from skeletal muscle and its interaction with Cathepsin B and Fibronectin type III domain-containing protein 5 (FNDC5) in the hippocampus of rats with GBM. To investigate the role of RT in GBM, we conducted a study using a rat model. By conducting a 4-week RT intervention (three days/week, 30 to 100% of body weight, 3 sets with 4 repetitions/session) and analyzing the expression levels of gastrocnemius muscle IL-6, hippocampal Cathepsin B, and FNDC5, we aimed to shed light on the potential impact of this RT modality on GBM progression. The results showed that GBM induced a significant decrease in gastrocnemius muscle IL-6, hippocampal FNDC5, and Cathepsin B gene expressions that were adjusted by RT. It means that there are significant increases in the GBM+RT group when compared to GBM. There were significant and positive correlations between variables (gastrocnemius muscle IL-6, hippocampal FNDC5, and hippocampal Cathepsin B gene expressions) which led to tissue crosstalk. In conclusion, this study contributes to our understanding of the molecular mechanisms associated with GBM, revealing potential avenues for future therapeutic interventions. RT may serve as a promising approach to modulate the expression relationship between IL-6, Cathepsin B, and FNDC5, offering a potential strategy for improving outcomes in GBM.

***Key Words:*** **Brain tumor, Cathepsin B, FNDC5, Glioblastoma multiforme, Resistance training, Tissue crosstalk**

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## Introduction

Glioblastoma multiforme (GBM) is the most aggressive form of malignant brain tumor, posing a significant challenge in terms of treatment and prognosis (Wu et al., 2021). The exact cause of GBM is not well understood, although certain risk factors have been identified (Hanif, Muzaffar, Perveen, Malhi, & Simjee Sh, 2017). These include exposure to ionizing radiation, certain genetic syndromes, and a family history of gliomas. However, the majority of GBM cases occur sporadically without any known risk factors (Hanif et al., 2017; Ostrom et al., 2019). The tumor cells infiltrate deeply into surrounding brain tissues, making complete surgical resection extremely challenging (Seker-Polat, Pinarbasi Degirmenci, Solaroglu, & Bagci-Onder, 2022). Additionally, GBM was characterized by a high degree of heterogeneity at the molecular level, leading to its resistance to conventional therapies, including chemotherapy and radiation. As a result of its aggressive growth and invasiveness, GBM has a dismal prognosis (Hanif et al., 2017). Despite advancements in medical technologies and treatment strategies, the prognosis for GBM patients remains poor (Foo et al., 2022). Diagnosis of GBM typically involves neuroimaging techniques such as magnetic resonance imaging (MRI) and biopsy to confirm the presence of malignant glioma cells (Ruiz-López et al., 2021). The current standard treatment approach for GBM involves multimodal therapy, which includes surgical resection, radiation therapy, and chemotherapy (Davis, 2016). However, due to the infiltrative nature of GBM, complete tumor removal is often not feasible, resulting in tumor recurrence. Furthermore, chemotherapy has limited efficacy in GBM due to the presence of the blood-brain barrier, which hampers drug delivery to the tumor site (Wu et al., 2021). In recent years, there has been growing interest in developing targeted therapies and immunotherapies to improve the treatment outcomes for GBM patients (Angom, Nakka, & Bhattacharya, 2023). These approaches aim to exploit specific genetic alterations and immune system responses within the tumor microenvironment to selectively kill tumor cells. However, further research and clinical trials are ongoing to determine the effectiveness and safety of these novel treatment strategies.

Resistance training (RT) has been shown to have beneficial effects on various aspects of health and disease, including cancer (Abou Sawan, Nunes, Lim, McKendry, & Phillips, 2023). Interleukin-6 (IL-6), Cathepsin B, and Fibronectin type III domain-containing protein 5 (FNDC5) are emerging as important molecular factors involved in muscle-brain crosstalk (Zhao, 2022) and may play a role in the pathogenesis and progression of GBM (S. Liu et al., 2022; West et al., 2018).

IL-6 is a pro-inflammatory cytokine that is produced by various tissues, including skeletal muscle. It has been implicated in tumor growth, angiogenesis, and metastasis in various cancers. In addition to its systemic effects, IL-6 has also been shown to have local effects on skeletal muscle, affecting muscle protein synthesis, metabolism, and overall skeletal muscle health (Rašková et al., 2022). Aberrant expression of IL-6 in skeletal muscle has been observed in several cancer types and is associated with muscle wasting and weakness, which can significantly impact the quality of life and survival of cancer patients (Carson & Baltgalvis, 2010). Cathepsin B is a lysosomal protease involved in various physiological and pathological processes, including protein degradation, tissue remodeling, and cancer progression (Yadati, Houben, Bitorina, & Shiri-Sverdlov, 2020). Previous research has shown that Cathepsin B expression is increased in glioma cells and is associated with increased invasion and metastasis (Gondi & Rao, 2013). The potential relationship between IL-6 and Cathepsin B in GBM remains largely unexplored and warrants further investigation. Fibronectin type III domain-containing protein 5 (FNDC5) is a gene that derives irisin- a myokine produced and secreted by skeletal muscle in response to exercise (Azimi Dokht, Gharakhanlou, Naghdi, Khodadadi, & Zare Zade Mehrizi, 2019). It has gained considerable attention due to its potential neuroprotective effects, including promoting neurogenesis and enhancing cognitive function (Jin et al., 2018). Studies have shown that FNDC5 expression was reduced in neurodegenerative diseases, such as Alzheimer's disease, raising the hypothesis that it may play a role in brain health and plasticity (Pignataro et al., 2021). However, the expression and interplay between IL-6, Cathepsin B, and FNDC5 in the context of GBM and the possible impact of RT remain poorly understood.

Given the detrimental effects of IL-6 dysregulation in skeletal muscle and the potential neuroprotective properties of FNDC5 and Cathepsin B, it is worth investigating if RT can modulate the expression relationship between IL-6, Cathepsin B, and FNDC5 in the context of GBM. We are seeking to investigate the effect of RT on the tissue crosstalk (gastrocnemius muscle IL-6, and hippocampal Cathepsin B and FNDC5) in GBM condition. This knowledge could provide insights into exercise-based interventions and potential therapeutic targets that may improve the quality of life and treatment outcomes for patients with GBM.

## Materials and Methods

### Animals

Forty 8-week-old Wistar rats (223 ± 16.99 grams) were purchased from Pasteur Institute, Tehran, Iran. The rats were placed individually in transparent polycarbonate cages (all 5 rats in one cage) under laboratory conditions of 22±2 degrees Celsius relative humidity of 55% and a 12-hour light-dark cycle. Standard pellet food and water were freely available to the rats. After one week of familiarization with the laboratory environment and training on the treadmill, the rats were divided into 3 groups (n=8 in each group), healthy control, brain tumor (GBM), and GBM + resistance training (RT). The study was approved by the Ethics Committee of the Islamic Azad University, Tehran, Iran.

### Culture of glioma cells

The C6 glioma cells of the Wistar rats (National Center for Genetic Resources) were prepared in a flask in RPMI medium (Roswell Park Memorial Institute), 300 mg/ml penicillin, 720 mg/ml streptomycin (Jabarban Hayan Pharmaceuticals) and were cultivated 2 g/liter sodium bicarbonate 10%. The final volume of the cell culture medium was 1000 ml; its pH was adjusted to 1.7. After washing, the supernatant was neutralized with PBS (buffered saline Pho) and 0.025% trypsin-EDTA solution and with 10% FBS medium. Then the solution was centrifuged at 1200 rpm for 5 minutes and the cells were separated. The initial density for cell culture was considered to be 100,000 cells/cm2. Finally, 10 microliters of trypan blue dye (0.4% weight-volume) and 90 microliters of cell suspension and neobar slide were used for cell counting and survival. The percentage of stained cells (blue) was determined as the percentage of dead cells.

### Injection of glioma cells

To inject cancer cells, animals were first anesthetized using ketamine (80 mg/kg) and xylazine (10 mg/kg). Cultured C6 glioma blastoma cells were injected with a concentration of 5*105 cells/30 µL by making a skin incision in the back of the skull and removing the periosteum according to Swanson's instructions using an infusion pump and a stereotaxic device in the right frontal cortex area with a depth of 2.5 mm in rats to a volume of 10 microliters. The tumor size was measured by a digital caliper after sacrificing the animals. Tumor grading was graded from 1 to 4. Grade 4 is the highest degree of damage and grade 1 is the lowest amount of tissue damage (Swanson, 2018).

### RT program

After the induction of cancer cells in the animals and a period of one-week familiarization training (rehabilitation), the animals enter the main training body. The main combined training program was designed for 4 weeks, 3 days a week by modifying

the previous programs and the initial pilot on rats; in this way, RT in the range of 30 to 100% of body weight was performed by tying weights to the tails of rats in 3 sets with 4 repetitions in the form of climbing a ladder (Molanouri Shamsi, Mahdavi, Quinn, Gharakhanlou, & Isanegad, 2016).

### Tissue collection

48 hours after the last training session, rats were sacrificed after being anesthetized with xylazine and ketamine solution. The tumor of the brain was removed and fixed in 4% buffered formalin. Formalin-fixed brains were embedded in paraffin, sectioned at 5-µm thickness, and stained with hematoxylin and eosin. Histological analysis was evaluated based on the scoring criteria (Haemotoxylin and Eosin-H&E method). The gastrocnemius muscle and hippocampus tissues were immediately frozen in liquid nitrogen and kept at frizzer at -70 C degree (Zarezadehmehrizi, Rajabi, Gharakhanlou, Naghdi, & Azimidokht, 2019).

### RNA extraction and cDNA production

To extract total RNA, it was homogenized at a ratio of 1 to 10 in Isol RNA-reagent Lysis according to the instructions of the kit (Qiagen, Germany). To remove the protein components, the resulting product was centrifuged at 4C for 10 minutes at 12000 rpm. The supernatant was removed and mixed with chloroform with primary Isol at a ratio of 0.5 to 1. The product was centrifuged at 4C for 15 minutes at 12000 rpm. The mineral and aqueous parts were separated, and the RNA-containing part was removed, and mixed with isopropanol at a ratio of 0.5 to 1. Afterwards, it was left for 10 minutes at room temperature, followed by keeping at 4 °C for 10 minutes. Then it was centrifuged at 12000 rpm. The plate containing RNA was dissolved in 20 µL of Free-RNAs water. The concentration of RNA was measured using a nono drop device and the ratio of 260 to 280 between 1.8 and 2 was defined as optimal purity. After extracting RNA with high purity and concentration from all the studied samples, the stages of cDNA synthesis were performed according to the manufacturer's protocol (Fermentas, USA). Then, the synthesized cDNA was used to perform the reverse transcription reaction.

### Real-time PCR

Distilled water containing 10 microliters of lyophilized primer, 0.5 microliters of forward primer and reverse primer (Primer Reverse), 1 microliter of cDNA, and 8 microliters of DEPC water were used to prepare the primers. For Biagen, the total RNA of the cells was extracted according to the Cinagen protocol using q RT-PCR method using Kiazol solution (Cinagene, Tehran, Iran). The quality of extracted RNAs was evaluated by spectrophotometry. To prepare single-stranded cDNA, Oligo dt primer and reverse transcription enzyme were performed according to the relevant protocol. Each PCR reaction was performed in an ABI Step One machine according to the manufacturer's protocol. Real-time PCR reaction cycles for IL-6, Cathepsin B, and FNDC5 genes were performed at three temperatures of 94, 60, and 72 degrees Celsius. A melting chart was performed to check the accuracy of PCR reactions. GAPDH (Glyceraldehyde-3-phosphate dehydrogenase) was used as IL-6, Cathepsin B, and FNDC5 genes reference genes. The expression levels of control and experimental genes were measured together. The fold change for each gene was determined by the Pfaffl formula (Shirvani, Rahmati-Ahmadabad, Broom, & Mirnejad, 2019). Primer sequences used are shown in Table 1.

**Table 1.** Primer sequences.

| Genes name | Primer sequences |
|---|---|
| IL-6 | Forward: 5´- AGACTTCACAGAGGATACCACCCAC - 3´ |
| | Reverse: 5´- CAATCAGAATTGCCATTGCACAA - 3´ |
| Cathepsin B | Forward: 5´- GCTTCGATGCACGGGAACAATG - 3´ |
| | Reverse: 5´- CATTGGTGTGGATGCAGATCCG - 3´ |
| FNDC5 | Forward: 5´- CAGCTAGCCACAGGTTCTCC - 3´ |
| | Reverse: 5´- CTCTCTCCCAGGGCTTTGTG - 3´ |
| GAPDH | Forward: 5´- CAAGTTCAACGGCACAGTCA - 3´ |
| | Reverse: 5´- CCCCATTTGATGTTAGCGGG - 3´ |

### Statistical analysis

All data are described as mean ± standard deviation. To determine the normality of the data, we use the Shapiro-Wilk test. Also, the homogeneity of variances was measured by Levene's test. To determine the significance of the difference between the variables in the groups, One-way ANOVA and Tukey's post hoc test were used. Data analysis was done using SPSS version 26 at a significance level of $P \leq 0.05$ and Graph pad Prism software was used to draw graphs.

## Results

The histological changes in the tumor of the brain are shown in Figure 1. As can be seen, the GBM group shows high cell proliferation and destruction compared to the control group. In the GBM+RT group, although tissue penetration is observed, there is still tissue swelling and inflammation.

The results showed that GBM induced a significant decrease in IL-6, FNDC5, and Cathepsin B gene expressions that were adjusted by RT (Figure 1 a, b, and c). It means that there are significant increases in GBM+RT when compared to GBM.

The relationships between variables are in Table 2. There were significant and positive correlations between variables (gastrocnemius muscle IL-6, hippocampal FNDC5, and hippocampal Cathepsin B gene expressions).

## Discussion

The results of this study provide valuable insights into the molec-

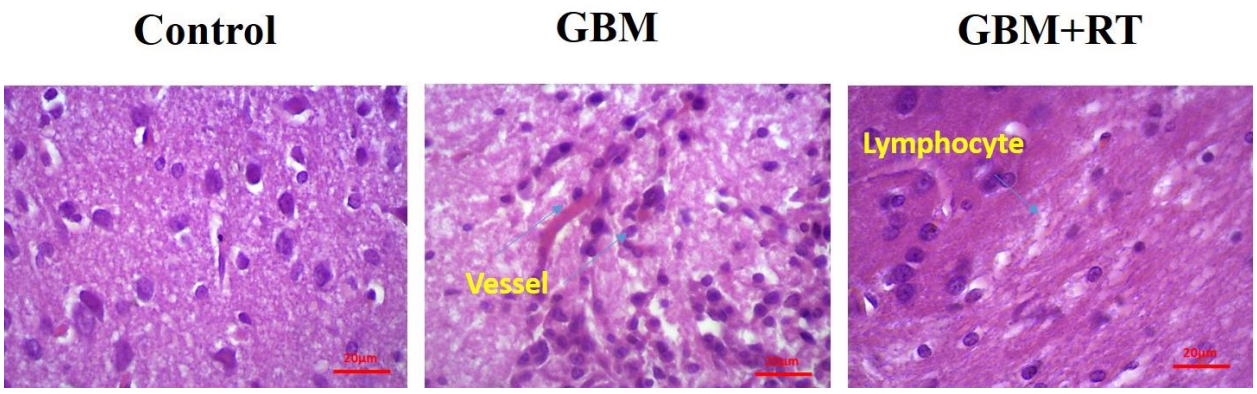


**Figure 1.** Induction of tumor in the brain of rat in different groups. Representative images of hematoxylin and eosin (H&E, magnification 20 um). GBM: Glioblastoma Multiform, RT: Resistance Training.

-lar alterations associated with GBM and the potential benefits of RT in ameliorating these alterations. The significant decrease in gastrocnemius muscle IL-6 and hippocampus FNDC5 and Cathepsin B gene expressions observed in the GBM group is consistent with previous studies highlighting the role of inflammation and proteolysis in GBM progression. The positive and significant correlation between variables shows that during RT, the skeletal muscle communicates with the brain through the mentioned variables. Our findings showed skeletal muscle-brain crosstalk in the context of GBM and contributed to the development of exercise-based interventions to improve patient outcomes.

The reversal of GBM-induced changes in gene expressions by RT is encouraging and indicative of the anti-inflammatory effects of exercise. IL-6 has been widely implicated in tumor progression, and its suppression by RT suggests a potential mechanism by which exercise may attenuate tumor growth (Gustafson et al., 2021). FNDC5, as a myokine with anti-inflammatory properties, may contribute to the beneficial effects of RT in GBM patients (Young, Valaris, & Wrann, 2019). The significant positive correla-

-tions between IL-6, FNDC5, and Cathepsin B gene expressions further support the interconnectedness of these molecules in GBM.

The precise mechanisms through which RT increases the expressions of FNDC5, IL-6, and Cathepsin B in cancer conditions are not yet fully understood. However, multiple hypotheses have been proposed based on available evidence. FNDC5 is a precursor protein that is cleaved and secreted as a myokine called irisin (Rabiee et al., 2020). RT has been shown to increase irisin expression and secretion. One proposed mechanism is that RT induces skeletal muscle contractions, leading to an increase in peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α) expression (Lira, Benton, Yan, & Bonen, 2010). PGC-1α, a transcriptional coactivator, has been shown to upregulate the expression of FNDC5. Consequently, elevated FNDC5 levels result in increased irisin secretion, which may exert anti-inflammatory effects and promote metabolic health (Wrann et al., 2013). The relationship between RT and IL-6 is complex. IL-6 is a pleiotropic cytokine that can have both pro- and anti-inflammatory effects de-

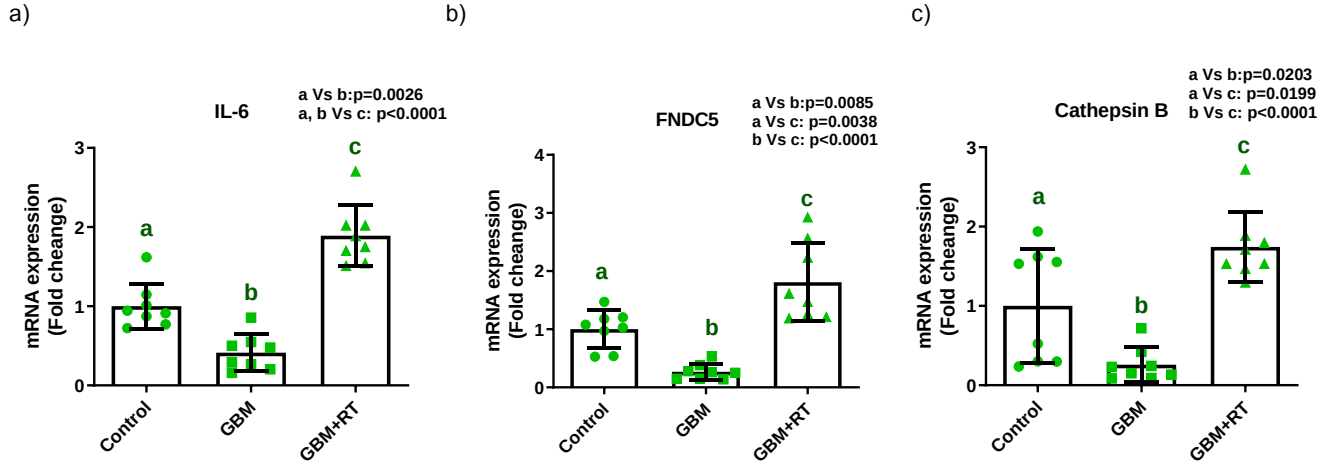


**Figure 2.** Gastrocnemius muscle IL-6 (a), hippocampal FNDC5 (b), and hippocampal Cathepsin B (c) genes expression in different group's i.e. healthy control, cancer (GBM), and GBM + resistance training (RT).

**Table 2.** The relationship between variables.

| Variables | | Hippocampal FNDC5 | Gastrocnemius muscle IL-6 | Hippocampal Cathepsin B |
|---|---|---|---|---|
| Hippocampal FNDC5 | Pearson Correlation | 1 | .873** | .552** |
| | Sig. (2-tailed) | | .000 | .005 |
| | N | 24 | 24 | 24 |
| Gastrocnemius muscle IL-6 | Pearson Correlation | .873** | 1 | .696** |
| | Sig. (2-tailed) | .000 | | .000 |
| | N | 24 | 24 | 24 |
| Hippocampal Cathepsin B | Pearson Correlation | .552** | .696** | 1 |
| | Sig. (2-tailed) | .005 | .000 | |
| | N | 24 | 24 | 24 |

**. Correlation is significant at the 0.01 level (2-tailed).

-pending on the context. During exercise, including RT, IL-6 is produced and released from skeletal muscle. One proposed mechanism suggests that IL-6 serves as an autocrine signaling molecule, stimulating muscle tissue to adapt and improve its metabolic and functional capacity (Nash et al., 2023). Additionally, IL-6 has been shown to induce acute immune responses and promote muscle protein synthesis. The release of IL-6 during RT may be an adaptive response to the increased demand on muscle tissue. However, the specific mechanisms by which RT affects IL-6 expression, and its subsequent impact on cancer conditions, require further investigation (Nash et al., 2023). Cathepsin B is a lysosomal cysteine protease involved in protein degradation. RT has been associated with increased Cathepsin B expression, particularly in skeletal muscle (Ni, Lan, Xu, Nakanishi, & Li, 2022). The upregulation of Cathepsin B during RT may be related to increased protein turnover and the remodeling of muscle tissue (Wang, Zheng, Yang, Zhou, & Zhang, 2023). It is thought that RT-induced mechanical stress and muscle damage trigger cellular responses, including the upregulation of Cathepsin B, to facilitate tissue repair and remodeling. However, the specific mechanisms linking RT and Cathepsin B expression in cancer conditions remain to be elucidated (C. Liu et al., 2023). It is important to note that the relationship between RT and the expressions of FNDC5, IL-6, and Cathepsin B in cancer conditions may be influenced by various factors, including the type and intensity of the training protocol, individual differences in response, and the tumor microenvironment. Further research is needed to fully understand the cellular and molecular mechanisms underlying these relationships and their impact on cancer progression and treatment outcomes.

Although our findings are promising, it is an experimental study. Future studies with randomized controlled trials are warranted to confirm our results and establish a causal relationship between RT and molecular alterations in GBM.

## Conclusion

In conclusion, our study demonstrates that RT can significantly reverse the GBM-induced decrease in the gene expressions of gastrocnemius muscle IL-6, and hippocampus FNDC5 and Cathepsin B. The positive correlations observed among these genes suggest potential molecular interplay (tissue crosstalk) in GBM conditions. These findings highlight the potential of RT as a therapeutic intervention to modulate the molecular alterations associated with GBM and improve outcomes. Further research is required to explore the underlying mechanisms and to optimize RT protocols for GBM.

## What is already known on this subject?

Glioblastoma multiforme (GBM) is a highly aggressive malignant brain tumor with limited treatment options and a poor prognosis.

## What this study adds?

RT can reverse the GBM-induced decrease in the gene expressions of gastrocnemius muscle IL-6, and hippocampus FNDC5 and Cathepsin B.

**Organ Cross-Talk Tips:**

- Resistance exercise training can increase crosstalk between muscle and tumor in brain.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** The study was approved by the Ethics Committee of the Islamic Azad University, Tehran, Iran (IR.IAU.SRB.REC.1401.029).

**Informed consent** Animal study.

## Author contributions

Conceptualization: S.R.; Methodology: S.R.; Software: S.R.; Validation: S.R.; Formal analysis: S.R.; Investigation: S.R.; Resources: S.R.; Data curation: S.R.; Writing - original draft: S.R.; Writing - review & editing: S.R.; Visualization: S.R.; Supervision: S.R.; Project administration: S.R.; Funding acquisition: S.R.

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