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RESEARCH ARTICLE

Gene expressions of TRP channels in glioblastoma multiforme and relation with survival

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Abstract Glioblastoma multiforme (GBM) is one of the most lethal forms of cancer in humans, with a median survival of 10 to 12 months. Glioblastoma is highly malignant since the cells are supported by a great number of blood vessels. Although new treatments have been developed by increasing knowledge of molecular nature of the disease, surgical operation remains the standard of care. The TRP (transient receptor potential) superfamily consists of cation-selective channels that have roles in sensory physiology such as thermo- and osmosensation and in several complex diseases such as cancer, cardiovascular, and neuronal diseases. The aim of this study was to investigate the expression levels of TRP channel genes in patients with glioblastoma multiforme and to evaluate the relationship between TRP gene expressions and survival of the patients. Thirty-three patients diagnosed with glioblastoma were enrolled to the study. The expression levels of 21 TRP genes were quantified by using qRT-PCR with dynamic array 48×48 chip (BioMark HD System, Fluidigm, South San Francisco, CA, USA). TRPC1, TRPC6, TRPM2, TRPM3, TRPM7, TRPM8, TRPV1, and TRPV2 were found significantly higher in glioblastoma patients. Moreover, there was a significant relationship between the overexpression of TRP genes and the survival of the patients. These results demonstrate for the first time that TRP channels contribute to the progression and survival of the glioblastoma patients.

Keywords Glioblastoma multiforme · TRP channels · Survival

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Introduction

Glioblastoma multiforme (GBM), also known as grade IV astrocytoma, is the most aggressive cancer in humans [1]. It arises from astrocytes and accounts for 50–60 % of astrocytic tumors, 12–15 % of all intracranial neoplasms [2–4], and is seen in approximately four to five people per 100,000 [5]. These tumors are highly malignant because they are surrounded by a great number of blood vessels which enables the cells to reproduce quickly. Two types of GBM have been described: primary and secondary [6]. Primary glioblastoma has no history of preexisting low-grade tumor. Mean age of patients with primary GBM is 62, and they have usually short clinical history [7]. Secondary GBM develops from preexisting low-grade glioma [5]. Patients with secondary GBM tend to be younger (mean age 45 years) and usually have longer clinical course [8]. The median survival of glioblastoma patients is 10–12 months [9].

Many factors have been identified that influence the process of tumorigenesis, proliferation, and invasion. TRP (transient receptor potential) channels are a group of cation-selective channels that have roles in different physiological processes like thermosensation, bone remodeling, and vascular tone regulation [10]. TRP channels are cation channels which are important for cellular calcium homeostasis and Ca^{2+} signaling. TRP channels change the cytosolic Ca^{2+}

concentration and also form intracellular pathways for calcium release from many organelles [11]. Calcium has key roles in several cellular processes including muscle contraction, transmitter release [12], cell proliferation [13], gene transcription [14], and apoptosis [11, 15].

Recent studies have clarified that TRP channels are related with cancer progression, and several works have shown that changes in the expression of TRP channels contribute to malignancy. Impairment in the function of calcium channels is involved in tumor development. Because high expression of plasma membrane Ca^{2+} channels increases Ca^{2+} influx and promotes Ca^{2+}-dependent proliferative pathways [16, 17]. High Ca^{2+} can increase proliferation, aberrant differentiation, and apoptosis, which leads to the uncontrolled proliferation and invasive trait of cancer.

Recent findings suggest that TRP channels affect calcium-dependent mechanisms not only in cancer but also in stroma cell migration. TRP channels influence cancer and stroma cell migration via affecting growth factor and cytokine signaling, cytoskeletal remodeling, and adaptation to tumor microenvironment where oxidative stress and hypoxia occur [18].

TRP channels response to hypoxia-related stimuli by increasing their expression or activity [19]. This response often involves increased migration and production of cytokines [20–23]. It was shown that expression of TRPC6 channels in glioblastoma is higher than in normal brain tissue, and thereby, it was found that suppression of TRPC6 greatly inhibited invasion and cell migration in glioblastoma in response to hypoxia, probably by inhibiting interactions between actin and myosin [20].

Several studies revealed that different TRP channels exhibit their effect on stromal cell migration via PI3K activation which is linked to reorganization of cytoskeleton and ERK signaling which regulates the actomyosin network [18]. Examples include TRPV2-dependent migration of macrophages [24], chemotaxis of monocytes relying on TRPC3 channels [25], TRPM7-dependent polarization and fibroblast migration [26], and TRPC6-dependent chemotaxis of neutrophils [27, 28].

About 30 TRPs have been identified, and they are classified into six different families: TRPA (ankyrin transmembrane protein), TRPV (vanilloid), TRPC (canonical), TRPM (melastatin), TRPP (polycystin), and TRPML (mucolipin) [29]. Gene expression levels of TRP channels may be associated with the pathogenesis and progression of glioblastoma multiforme. Therefore, we aimed to examine expression levels of TRP channels in GBM patients and to establish whether these expression levels are correlated with survival of the patients.

Materials and methods

A total of 33 patients who were diagnosed with glioblastoma multiforme and operated between 2001 and 2010 in Gaziantep University, Medical Faculty, Department of Neurosurgery were enrolled to the study. The patients were evaluated according to an established standard protocol. Local ethics committee approvals were obtained (Gaziantep University Ethics Committee date: 24.05.2010 and no. 15) before the enrolment of any patients in the study, which was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. Written informed consent was obtained from all patients before study entry. Files of all patients who were selected for evaluation were obtained from the registries of the Gaziantep University and reviewed. They were confirmed based on the reports issued by the Department of Pathology and the registries of the Division of Medical Oncology. Age, gender, date of operation, postoperative therapies, and date of death were recorded. All patients received radiotherapy with temozalamid oral therapy and adjuvant temozalamid chemotherapy.

Using the tissue samples reported with the diagnosis of glioblastoma multiforme, the expressions of TRP genes at the level of mRNA were evaluated via real-time PCR. Total RNA was isolated by using commercially available kits (QIAcube, Qiagen, Germany). The obtained RNA was prepared for the study by being measured with UV spectrophotometry. cDNA was obtained through the use of the reverse transcription assay kit (Precision Reverse Transcription Kit, Qiagen, Germany). Gene expression levels of TRPC1, TRPC3, TRPC4, TRPC5, TRPC6, TRPC7, TRPM1, TRPM2, TRPM3, TRPM4, TRPM5, TRPM6, TRPM7, TRPM8, TRPV1, TRPV2, TRPV3, TRPV4, TRPV5, TRPV7, TRPA1, and the housekeeping gene glyceraldehyde-3-phosphate dehydrogenase (GAPDH) were quantified by using qRT-PCR with dynamic array 48×48 chip (BioMark HD System, Fluidigm, South San Francisco, CA, USA).

Data analysis

Data was analyzed by using BioMark digital array software. Relative gene expressions were determined by using the $2^{-\Delta\Delta Ct}$ method. For normalization of the expressions, GAPDH was used as housekeeping gene. Fold-change values between 0.1 and 0.5 were considered as significant downregulation, and >2.0 was considered significant upregulation. All results were given as fold changes and relative gene expressions.

Results

A total of 33 patients diagnosed with glioblastoma multiforme were enrolled to the study. Since normal brain tissue sampling during surgery is not ethic, gene expression levels were compared with a normal brain tissue belonging to a man who died in a traffic accident. The patients were also evaluated after being intergrouped.

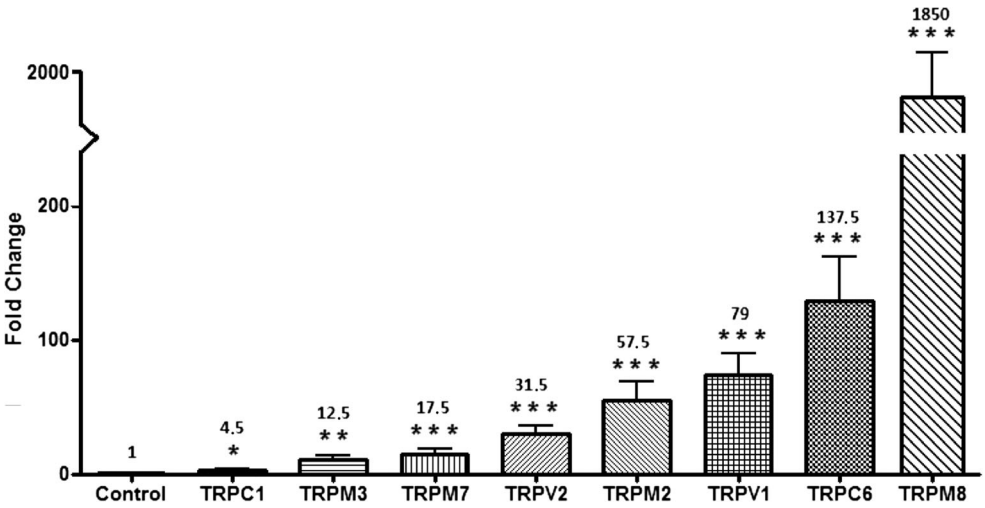

Fig. 1 TRP gene expression levels in glioblastoma patients (the results were presented as fold-change). Housekeeping gene glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used for normalization. Quantification was performed by using qRT-PCR with dynamic array 48×48 chip (BioMark HD System, Fluidigm, South San Francisco, CA, USA). (*$p<0.05$; **$p<0.01$; ***$p<0.001$)

Gene expression levels of TRPA, TRPC, TRPM, and TRPV channels were quantified by using qRT-PCR in patients with glioblastoma multiforme. Accordingly, TRPC1, TRPC6, TRPM2, TRPM3, TRPM7, TRPM8, TRPV1, and TRPV2 were found significantly higher compared to the control (Fig. 1).

Mean survival time of the patients enrolled to the study was calculated as 11 months, similar to the median survival time reported in the literature [9]. To clarify if there is any correlation between survival time and TRP gene expressions, we classified the study group into two subgroups by their survival time. Group 1 includes the patients who survived for less than 12 months; group 2 includes the patients who survived for more than 12 months.

The mean survival time was determined to be 4 months for the group who survived for less than 12 months ($n=18$) and 17 months ($n=15$) for the group who survived for more than 12 months. It was found that age, which is among the important prognostic factors, was negatively correlated with survival time in our patients.

Interestingly, we found a correlation between survival time and the gene expression of TRPC1, TRPC6, TRPM2, TRPM3, TRPM7, TRPM8, TRPV1, and TRPV2 channels. Gene expression levels of patients who survived more than 12 months were significantly higher compared to the patients who survived less than 12 months (Fig. 2).

Of the patients enrolled to our study, 21 (64 %) were males and 12 (36 %) were females. At the time of diagnosis, mean age of male patients was 62 years and the mean age of female patients was found to be 63.5 years. The mean age of all patients was 63 years. To understand if there is any age-related difference in TRP gene expressions, we classified the patients into two groups in terms of their ages. First group includes patients younger than 50-years-old ($n=12$), whereas the other group includes patients older than 50-years-old ($n=21$). We compared the gene expression levels of patients younger and older than 50-years-old, and no significant alteration detected. Also, there is no statistical difference found between gender and the gene expressions of TRP channels.

Discussion

It has been shown that TRP channels play an active role in carcinoma, but there are a few studies that investigate gene expressions of TRP channels in GBM, whereas no study was performed to correlate gene expression data with survival of the patients. This is the first study that discussed this issue.

Despite comprehensive research, there is no effective treatment for glioblastoma, so the clinical challenge remains. Glioblastoma multiforme, the most malignant subtype, proliferates

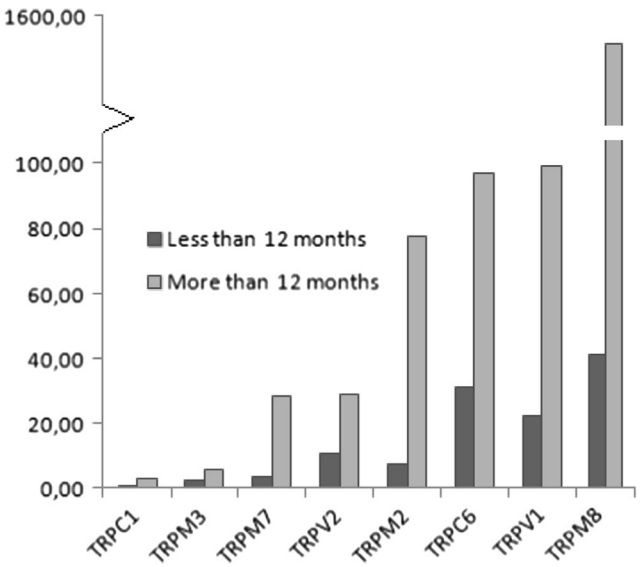

Fig. 2 Comparison of TRP gene expression levels in glioblastoma patients with different survival times (less than 12 months and more than 12 months). Quantification was performed by using qRT-PCR with dynamic array 48×48 chip (BioMark HD System, Fluidigm, South San Francisco, CA, USA)

extensively, and its progression is a complex process only partly understood. TRP channel family affects a variety of pathological and physiological processes [30, 31]. These cation channels regulate cellular calcium homeostasis, cell proliferation, differentiation, and apoptosis. TRP ion channel family has recently shown to have roles in malignant cancer growth and progression [32–35].

We have found TRPC1, TRPC6, TRPM2, TRPM3, TRPM7, TRPM8, TRPV1, and TRPV2 significantly higher compared to the control. Although the expression levels or activity of TRPC, TRPM, and TRPV family members have been associated with malignant growth and progression [36, 37], some of them (TRPM2, TRPV1, TRPV2) have role in apoptosis and suppression of glioblastoma cell growth [38–40]. To understand the role of high expression levels of TRP channels on contribution to tumor progression and survival of the patients, we will discuss each TRP channel separately.

The TRPC1 protein is widely expressed throughout the mammalian brain and is thought to control Ca^{2+} entry in response to depletion of endoplasmic Ca^{2+} stores. Bomben's study group revealed that suppression of TRPC1 by shRNA or pharmacological inhibition of its activity causes incomplete cytokinesis and decelerates the growth of human glioma cells [41]. It is seen that TRPC1 channels have an important role during cytokinesis of glioma cells most likely via regulating their calcium signaling.

TRPC6 is a receptor-activated calcium channel. Dysfunctions of this channel have been associated with a wide range of diseases including glioblastomas. We found TRPC6 overexpressed in glioblastoma patients. Ding X et al. showed that TRPC6 channels were essential for the development of glioma. Inhibition of TRPC6 activity or expression induced cell cycle arrest at the G2/M phase and suppressed cell growth [42]. Another study showed that knockdown of TRPC6 expression inhibits glioma growth, invasion, and angiogenesis [20]. Both studies revealed that TRPC6 is a key mediator of glioblastoma cell growth. Therefore, TRPC6 might be a therapeutic target in the treatment of glioblastomas.

Another gene we have found upregulated in glioblastoma patients was TRPM2. The protein encoded by this gene is a calcium permeable cation channel and is activated by oxidative stress. TRPM2 makes the cells susceptible to cell death by induction of necrotic cell death [38].

TRPM3, most recently described melastatin subfamily member, is a cation permeable TRP channel. It has begun to be elucidated in recent years. The roles of TRPM3 in brain physiology are still not clear [43]. There was also no gene expression data published in glioblastoma patients. We showed for the first time that TRPM3 is upregulated in our study group compared to the control. Further studies are needed to reveal its role in glioblastoma.

Transient receptor potential cation channel TRPM7 is a ubiquitous, Ca^{2+} and Mg^{2+} permeable ion channels that are special in being both a serine/threonine kinase and an ion channel. In studies of glioma cells silenced for TRPM7, it was demonstrated that Notch and STAT3 pathways are downregulated in glioma cells grown in monolayer [44]. TRPM7 promotes proliferation, invasion, and migration of glioma cells by activating JAK2/STAT3 and/or Notch signaling pathways.

TRPM8, transient receptor potential melastatin 8 ion channel, has a role in increasing intracellular Ca^{2+} concentration. TRPM8 involvement in glioma cell migration has also been reported [45].

TRPV1 is a vanilloid receptor, also sometimes referred as capsaicin receptor since it is sensitive to capsaicin, an ingredient in hot chili peppers [46]. TRPV1 stimulation promotes tumor cell death via endoplasmic reticulum stress pathway [40]. TRPV1 expression is downregulated in the majority of grade IV GBM. Gene and protein expressions of TRPV1 are inversely correlated with GBM grading [36].

In gliomas, recent evidence indicates that TRPV2, transient receptor potential vanilloid type 2, negatively regulates proliferation and survival of glioma cells. Activation of the TRPV2 has been found to inhibit proliferation of human glioblastoma cells [47]. Moreover, TRPV2 overexpression was found to inhibit glioblastoma stem-like cell (GSC) proliferation in a xenograft mouse model and promotes the differentiation of GSCs toward a more mature glial phenotype. It is seen that TRPV2 promotes glioma cell differentiation and inhibits their proliferation [39].

Despite revealing the genetic pathways of gliomagenesis and the role of their alterations, there are still significant gaps in the progress and deep understanding of the role of TRP ion channels in glioma. Further studies are required to better understand their contribution on malignant transformation and tumorigenesis as well as triggering apoptosis and prolonging survival time of GBM patients. Despite the existence of tumorigenic potential, antitumorigenic activities of TRP channels give us a clue that they might contribute to prolong survival time of GBM patients. Better integration of knowledge will enable us to understand GBM, prognosis, and to delivery a specific target therapies in this devastating disease.

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