Trends Journal of Sciences Research, 2019, Volume 4, Issue 3, 121-126
http://www.tjsr.org/journal/index.php/tjsr
DOI: 10.31586/Cancer.0403.05

Role of CTSC in Glioblastoma Based on Oncomine and TCGA Database

Xinjie Ning, Juncheng Luo, Gengqiang Ling, Xiaochun Zhong, Shoulian Zheng, Jian Guo, Qingchang Liu, Binchu Xu*

Department of Neurosurgery, The Seventh Affiliated Hospital, Sun Yat-Sen University, Shenzhen, China
*Corresponding author: Binchu Xu (ningxj3@mail.sysu.edu.cn)

Research Article

Open Access

How to cite this article: Nin, X., Luo, J., Ling, G., Zhong, X., Zheng, S., Guo, J., Liu, Q., & Xu, B. (2019). Role of CTSC in Glioblastoma Based on Oncomine and TCGA Database. *Trends Journal of Sciences Research, 4*(3), 121-126.

Received: July 19, 2019

Accepted: August 23, 2019

Published: August 24, 2019

Abstract **Background and objective:** Glioblastoma (GBM) is one of the malignant tumors causing death worldwide. Most patients were found in the middle and late stages and had poor prognosis. The purpose of this study was to investigate the expression and significance of CTSC in GBM. **Methods:** The information about CTSC in Oncomine database was collected and analyzed twice. The role of CTSC in GBM was meta-analyzed. The expression of CTSC in glioma cell lines was retrieved by CCLE database, and the survival of patients was analyzed by TCGA database. **Results:** A total of 1,459 different types of CTSC were collected in Oncomine database, 134 of which had statistical differences in CTSC expression, 89 of which had increased CTSC expression and 45 of which had decreased CTSC expression. A total of 50 studies involving the expression of CTSC in GBM cancer and normal tissues included 1,189 samples. Compared with the control group, CTSC was highly expressed in GBM ($P < 0.05$). Moreover, CTSC was highly expressed in glioma cell lines. There was a correlation between the expression of CTSC and the overall survival rate of GBM. The overall survival rate of patients with high expression of CTSC was worse, while the prognosis of patients with low expression of CTSC was better ($P < 0.05$). **Conclusion:** Through the in-depth mining of oncomine gene chip database, we propose that CTSC is highly expressed in GBM tissues and is related to the prognosis of GBM, which may provide an important theoretical basis for the treatment of glioma..

Keywords: *CTSC, Glioblastoma, Oncomine, TCGA*

1. Introduction

Glioblastoma (GBM) is a serious threat to human health and one of the most lethal malignant tumors, which has caused tremendous economic burden to society[1]. Although many new therapies have been found in recent years, most of them are in the middle and late stages, and the prognosis has not been significantly improved. Studying the mechanism of the occurrence and development of CTSC at the molecular level is conducive to discovering new molecular targets and developing new therapeutic methods. It is very important to reduce patients' pain and prolong patients' survival time.

Oncomine database is the largest oncogene chip database and integrated data mining platform in the world, aiming at mining cancer gene information[2]. So far, 715 gene expression datasets and 86,733 samples of cancer and normal tissues have been collected in this database. Using Oncomine database, we can compare common cancer types and their normal tissues for differentially expressed sorting. We can also explore various cancer subtypes and analyze them based on clinical and pathological data. We can do differentially expressed sorting and co-expression analysis, find differentially expressed genes in a certain cancer, determine the target genes, and then determine the research direction. It can not only save the cost of scientific research, but also save the cost of scientific research. And its information is more comprehensive.

Cathepsin is a kind of proteolytic enzyme widely existing in many kinds of tissue and cell lysozymes, which plays an important role in various physiological activities of the body[3]. There are many kinds of cathepsin with tissue specificity. Different cells, even the same cell, express different proteases in different physiological environments. Cathepsin can be divided into three categories according to the different catalytic centers: serine cathepsin (cathepsin A and G), cysteine cathepsin (cathepsin B, C, L, H, S), and aspartate cathepsin (cathepsin D and E). So far, more than 10 kinds of cathepsin have been found, but the understanding of their physiological functions is far from enough. Cathepsin C, also known as dipeptidyl peptidase I (DPPI), was discovered in the 1940s and is a lysosomal cysteine protease[4]. Previous studies have shown that it is highly expressed in inflammatory cells and may be related to the activation of granulase. In addition, although the enzyme was widely expressed in many tissues, its expression and function were not clear, and there was little systematic study in glioblastoma tissue.

In this study, Oncomine database and TCGA database were used to analyze the expression and prognosis of CTSC in GBM, and the possible relationship between CTSC and GBM was meta-analyzed by secondary analysis, which provided clues and basis for further study of the mechanism of CTSC in the occurrence and development of GBM.

2. Material and Methods

2.1. Plant Material and Experimental Design

Oncomine database extracts data Oncomine database is a gene chip-based database and integrated data mining platform, in which data can be screened and mined according to their own needs. In this study, we set the screening conditions as follows: (1) Cancer Type: Brain and CNS Cancer; (2) Gene: CTSC; (3) Data Type: RNA and DNA copy number; (4) Analysis Type: Cancer vs Normal Analysis; (5) Critical value setting conditions (P < 1E-4, fold change > 2, gene rank = top 10%). Select the bar chart to show the results.

The expression of CTSC in glioma cell lines was retrieved from CCLE database and analyzed by CCLE website (https://portals.broadinstitute.org/ccle) [5].

TCGA database was used for patient survival analysis. The GBM dataset of TCGA database was analyzed online by proggene V2 website (http://watson.compbio.iupui.edu/chirayu/proggene/database/?Url=proggene)[6]. The screening conditions are as follows: (1) Cancer: Brain Cancer; (2) Gene: CTSC; (3) Survival: OS.

Statistical methods :The difference of CTSC expression between normal tissues and GBM patients was analyzed by t-test. The relationship between CTSC expression and GBM prognosis was analyzed by Kaplan-Meier model. All the data were analyzed by SPSS 20.0, and the difference was statistically significant with bilateral $P < 0.05$.

3. Results

The results of CTSC expression in common tumors Oncomine database collected 1459 different types of research results (Figure 1). 134 of them showed significant difference in CTSC expression, and CTSC expression was detected in Oncomine database.There were 89 increased studies and 45 decreased expression studies.

The results of CTSC expression in GBM were found in Oncomine database. Since 2003, there have been seven studies involving the expression of CTSC in GBM and normal tissues (Figure 2), with a total of 1,795 samples. The articles were published in Cancer Cell, 2006, J Clin Oncol, 2008, TCGA Brain 2, No Associated Paper, 2013, etc. A meta-analysis of 7 studies in Oncomine database showed that the median value of CTSC gene ranked 611, P=5.03E-5 among all differentially expressed genes, suggesting that CTSC was highly expressed in GBM.

The expression of CTSC in different cancer cell lines is shown in Figure 3. The expression of CTSC in different cancer cell lines is shown in CCLE database. CTSC is highly expressed in GBM cell lines.

The relationship between CTSC and prognosis of GBM patients Kaplan-Meier Plotter data showed that CTSC expression level had a significant impact on the overall survival time of GBM patients. Compared with the low expression group, the total survival time of GBM patients in CTSC high expression group was significantly reduced. (Figure 4).

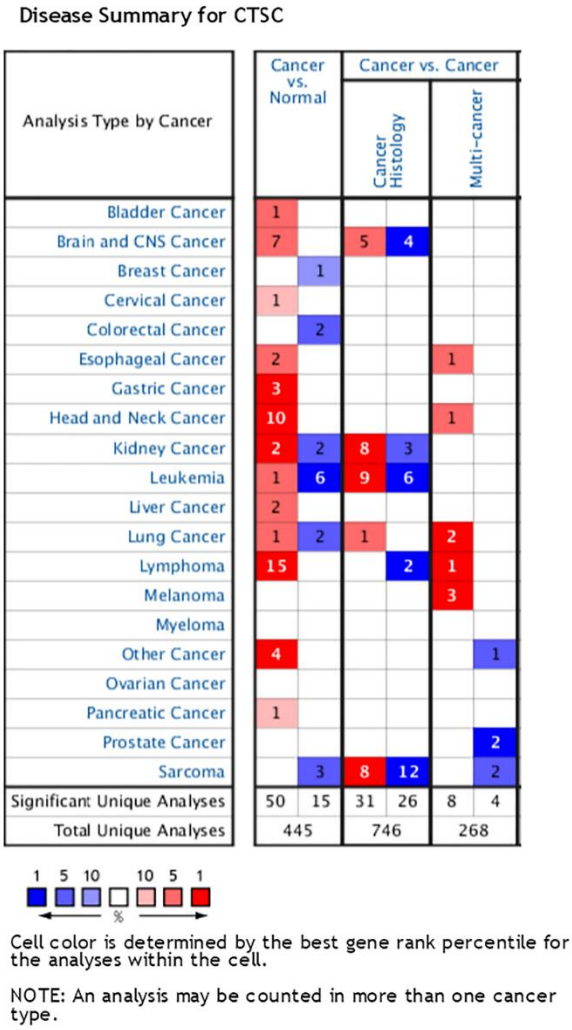

Figure 1. Expression data for CTSC in a variey of normal and cancerous human tissues in database Oncomine

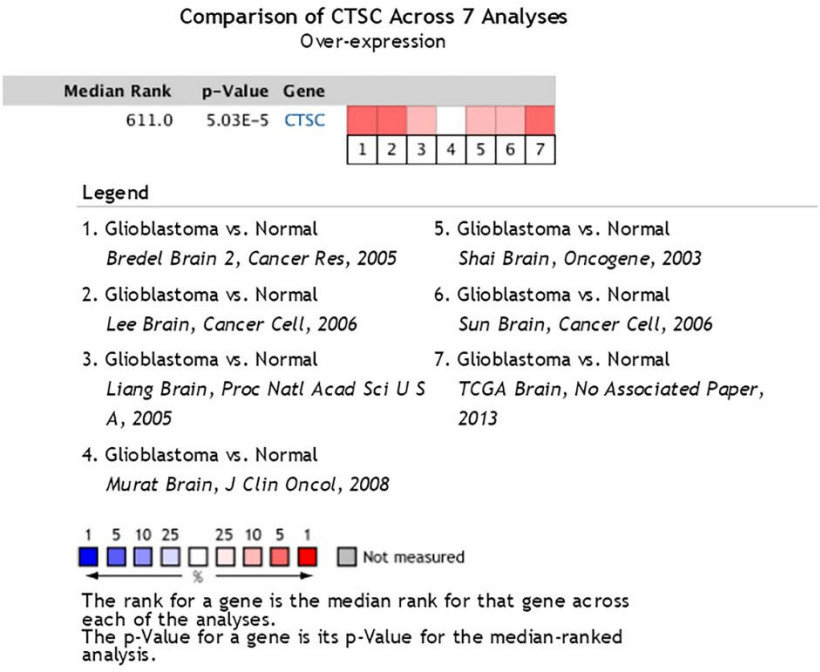

Figure 2. Expression of CTSC in GBM in the studies identified in the Oncomine database. 1-7 represent the 7 studies on the expressions of CTSC in GBM. Darker red indicates higher GBM expression in the chips

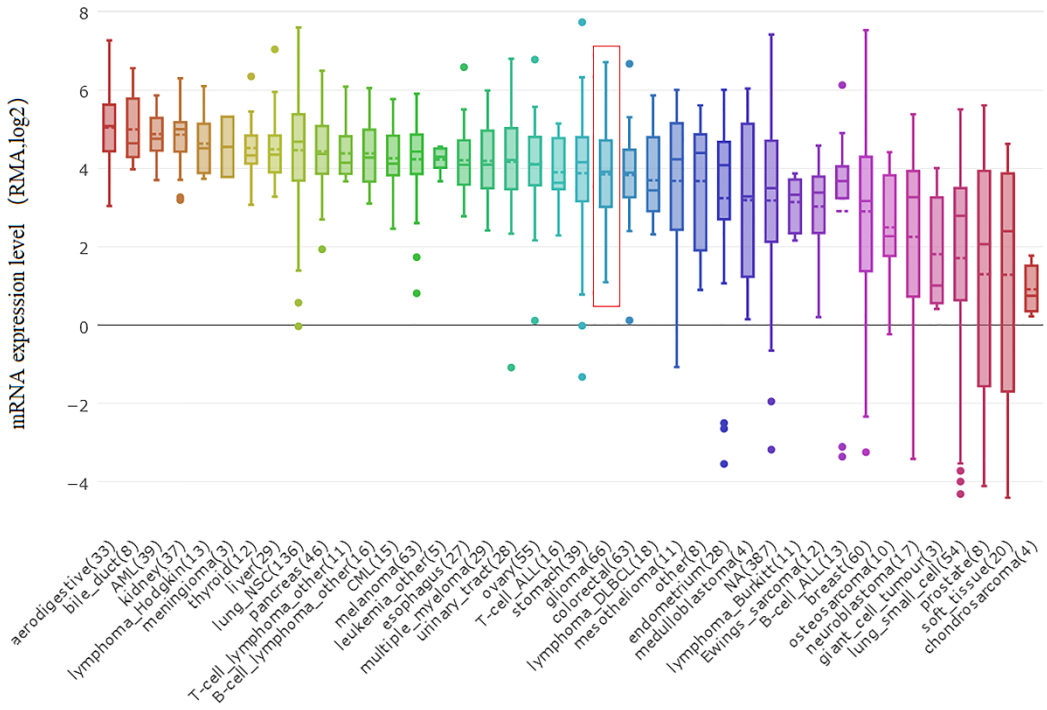

Figure 3. The expression of CTSC in multiple cancer cell lines

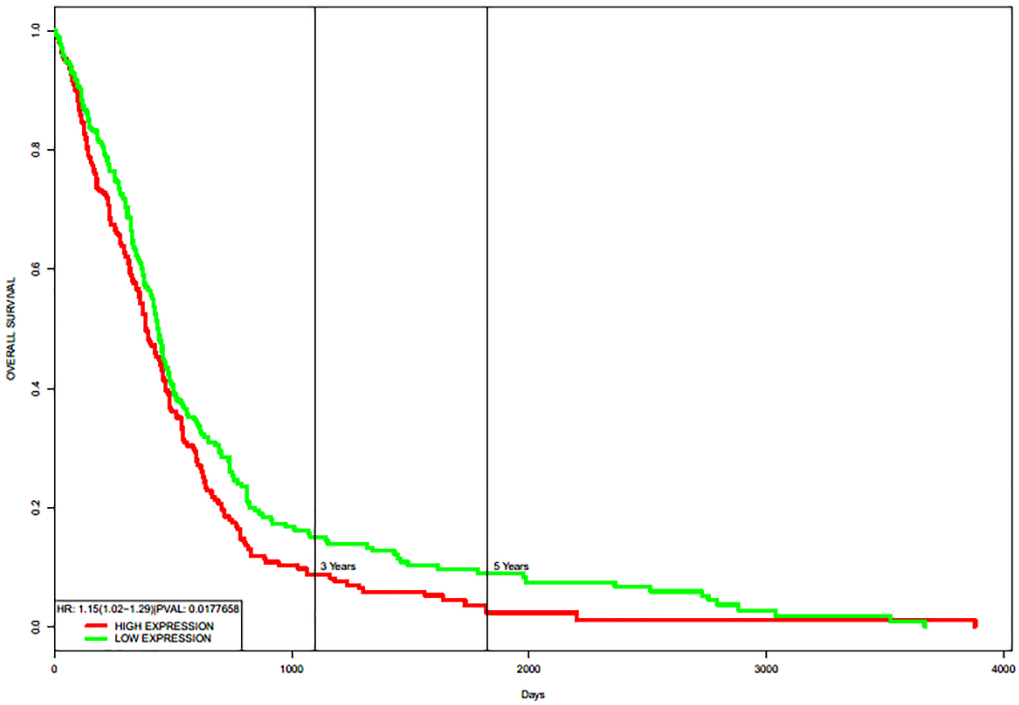

Figure 4. Relationship between the expression of CTSC and the prognosis of GBM

4. Discussion

Glioblastoma is one of the most lethal malignant tumors in the world. Epidemiological statistics show that the incidence of glioblastoma in gliomas is increasing. For a long time, the prognosis of GBM has been poor. With the development of molecular biology technology, a number of glioma-related genes such as PTEN, PDCD4, TP53 have been found one after another, and some targeted therapeutic drugs have been developed, which greatly improve the prognosis of glioma patients[7]. However, mutations of these genes only exist in some glioma patients. Therefore, searching for key molecules

or targets for the occurrence and development of glioblastoma has important theoretical and clinical significance for the development of new targeted drugs for the treatment of GBM, and has always been a research hotspot at home and abroad. Cathepsin C is an important member of the cysteine protease family. The mature human cathepsin C gene (CTSC) has a molecular weight of 200 kDa, and each molecule consists of 206 amino acid residues; four tetramers consisting of four identical subunits, each consisting of three different peptide chains: a light chain, a heavy chain and an exclusion domain; four catalytic active sites grooves on the protein surface block the extension of the groove. The endonuclease activity was removed by stretching. The expression of cathepsin is tissue-specific. Cathepsin is expressed differently in different physiological environments in different cells and even in the same cell. The expression of cathepsin is closely regulated by cells in order to cope with the changes of different physiological environments. Cathepsin C mediates target cell death by treating granulase A and B[8]. Cell death is an important process for the survival of multicellular organisms, in which the lysis of killer cells to target cells is an important way of cell death, such as cytotoxic T lymphocytes (CTLs) and natural killer cells (NK), which are also part of the cellular immune barrier to viruses and cancer cells.

Natural Killer cells lyse cells in two ways: through FAS ligands and receptors, and through membrane penetrating proteins and granzymes[9]. The latter can only be accomplished with the help of cathepsin C. CTLs first form synapses with target cells. Cathepsin C, granzyme A and B, and transmembrane proteins are all encapsulated in synapses. Cathepsin C hydrolyzes the dipeptides at the N-terminal of granzyme and makes it in a fully functional activation state. Then, the transmembrane proteins form a maximum 16-nm transmembrane channel through the calcium ion binding to the phospholipid head of the cell membrane. By endocytosis, the membrane cleft was repaired, and the activated granzymes A and B successfully entered the target cells. These activated granzymes which reached the cytoplasm of the target cells activated downstream apoptotic pathways and eventually led to the death of the target cells.

Pham observed cathepsin C gene knockout (CTSC-/-) mice and wild type mice. It was found that there was no difference in the number of granulase A and B in CTLs cells between the two mice[10]. However, granulase in CTSC-/-mice CTLs cells had no function and could not cause cell death after entering the target cells. It was speculated that cathepsin C could be involved in CTLs-mediated cell death through granulase. Important role. In 1986 and 1987, Doughty MJ and others found that cathepsin C had some relationship with cell growth[11]. They cultured fibroblasts from adult male patients with Duchenne muscular dystrophy and normal males, and measured the activity of cathepsin C in both cells at week 10. It was found that the activity of cathepsin C in skin fibroblasts derived from pseudohypertrophic muscular dystrophy was significantly lower than that in normal skin fibroblasts[12]. This study confirmed that Duchenne-derived cells contained low levels of enzyme activity, which was not due to the redistribution of enzyme in cells. Glycine-phenylalanine had a lower activity in Duchenne-derived cells. After measuring the activity of cathepsin C at different time points and evaluating the growth time and state of corresponding cells, it was found that the activity level of cathepsin C could reflect the growth state of cells. It has also been reported that the activity of cathepsin C changes with the aging of culture medium in vitro, and in tissue, the activity of cathepsin C changes with the growth of cells.

Although most studies have found that CTSC is highly expressed in many tumors[13], including GBM, there is a lack of high reliability due to the small sample size in independent studies, which easily leads to sampling errors. Oncomine database is the largest gene chip database and integrated data mining platform in the world. First, we used Oncomine database to mine GBM gene expression information in colorectal cancer, breast cancer, gastric cancer and other common tumors. The results showed that 89 of 134 studies with statistical differences showed that CTSC was highly expressed in common tumors. The results of GBM chip detection were analyzed by Oncomine database. It was also proved that CTSC was highly expressed in GBM tissues in more than 1,000 samples. At the same time, we used CCLE cell database to confirm the high expression of CTSC in glioma cell lines. The PROGgene database (http://www.compbio.iupui.edu/proggene) is a web application that can be used for studying prognostic implications of mRNA biomarkers in a variety of cancers. We have compiled data from public repositories such as GEO, EBI Array Express and The Cancer Genome Atlas for creating this tool. With 64 patient series from 18 Canc Genome Atlas In our database, this tool provides the most comprehensive resources available for survival analysis to date. In this paper, the prognostic value of CTSC in GBM is first found through PROGgene database. The results showed that the expression of CTSC was clearly correlated with the overall survival rate of GBM, and the overall survival time of patients with high expression of CTSC was significantly reduced. The high expression of CTSC may affect the occurrence of tumors. Perhaps the abnormal expression of CTSC gene will directly

affect the process of cell death and eventually cause tumorigenesis. All our data are from gene chips, and the research methods are consistent, and include the largest sample size so far, eliminating errors caused by sample size problems, and increasing the credibility of the conclusions.

5. Conclusion

We propose that CTSC is highly expressed in GBM tissues and is related to the prognosis of GBM through in-depth mining of CTSC-related information in GBM tissues. Using the database for large sample analysis can avoid the error caused by the small sample size of a single study and provide an important theoretical basis for clinical treatment. The specific mechanism of CTSC in the development of GBM disease needs further experiments to prove in the future.

Acknowledge

No potential conflict of interest was reported by the authors.

References

[1] Kirkpatrick JP, Laack NN, Shih HA, Gondi V. Management of GBM: a problem of local recurrence. J Neurooncol 2017;134:487-93.

[2] Jayaraman A, Jamil K, Khan HA. Identifying new targets in leukemogenesis using computational approaches. Saudi J Biol Sci 2015;22:610-22.

[3] Hou W, Sun H, Ma Y, Liu C, Zhang Z. Identification and Optimization of Novel Cathepsin C Inhibitors Derived from EGFR Inhibitors. J Med Chem 2019.

[4] Fan W, Zhang W, Alshehri S, Neeley TR, Garrison JC. Enhanced tumor retention of NTSR1-targeted agents by employing a hydrophilic cysteine cathepsin inhibitor. Eur J Med Chem 2019;177:386-400.

[5] Shoaib M, Ansari AA, Haq F, Ahn SM. IPCT: Integrated Pharmacogenomic Platform of Human Cancer Cell Lines and Tissues. Genes (Basel) 2019;10.

[6] Goswami CP, Nakshatri H. PROGgeneV2: enhancements on the existing database. BMC Cancer 2014;14:970.

[7] Tang Y, He W, Wei Y, Qu Z, Zeng J, Qin C. Screening key genes and pathways in glioma based on gene set enrichment analysis and meta-analysis. J Mol Neurosci 2013;50:324-32.

[8] Zuo X, Hou Q, Jin J, et al. Inhibition of Cathepsins B Induces Neuroprotection Against Secondary Degeneration in Ipsilateral Substantia Nigra After Focal Cortical Infarction in Adult Male Rats. Front Aging Neurosci 2018;10:125.

[9] Lupo KB, Matosevic S. Natural Killer Cells as Allogeneic Effectors in Adoptive Cancer Immunotherapy. Cancers (Basel) 2019;11.

[10] Yan H, Zhou HF, Akk A, et al. Neutrophil Proteases Promote Experimental Abdominal Aortic Aneurysm via Extracellular Trap Release and Plasmacytoid Dendritic Cell Activation. Arterioscler Thromb Vasc Biol 2016;36:1660-9.

[11] Doughty MJ, Gruenstein EI. Cell growth and substrate effects on characteristics of a lysosomal enzyme (cathepsin C) in Duchenne muscular dystrophy fibroblasts. Biochem Cell Biol 1987;65:617-25.

[12] Gelman BB, Papa L, Davis MH, Gruenstein E. Decreased lysosomal dipeptidyl aminopeptidase I activity in cultured human skin fibroblasts in Duchenne's muscular dystrophy. J Clin Invest 1980;65:1398-406.

[13] Ruffell B, Affara NI, Cottone L, et al. Cathepsin C is a tissue-specific regulator of squamous carcinogenesis. Genes Dev 2013;27:2086-98.