Original paper

Folia Neuropathologica

ADAMTS8 inhibits glioma development *in vitro* and *in vivo*

Baosheng Zhou, Yong Liu, Guangshuo Ma, Xiuyu Wang, Hongwei Lu, Binge Chang, Xuequan Feng

Neurosurgical Department, Tianjin First Central Hospital, Nankai District, Tianjin, China

Folia Neuropathol 2023; 61 (2): 144-152 *DOI: https://doi.org/10.5114/fn.2023.129380*

Abstract

Introduction: *In recent years, novel RNAs have been revealed to be regulators in glioma. ADAMTS8 has been reported to be reduced in brain tumours. In this study, we aimed to explore the role of ADAMTS8 in glioma.*

Material and methods: *Online bioinformatic tools, Gepia and Chinese Glioma Genome Atlas database (CGGA) were used to analyse the differential expression of ADAMTS8, overall survival and disease-free survival rates and the correlations between ADAMTS8 and matrix metallopeptidases (MMP2 and MMP9) in glioma. RT-qPCR and western blot experiments were performed to measure the mRNA and protein expression. ADAMTS8 expression was regulated in cells through transfection. Thereafter, the effect of ADAMTS8 on cells was investigated through the cell viability, apoptosis and transwell experiments. The epithelial-mesenchymal transition (EMT)-related proteins and also MMP2 and MMP9 were examined. The subcutaneous tumour model was established to validate the suppressive role of ADAMTS8 in tumour growth.*

Results: *ADAMTS8 expression was reduced in glioma tissues and cells. Higher expression of ADAMTS8 was correlated with higher survival rates. ADAMTS8 was correlated with MMP2 and MMP9 in glioma tissues. In glioma cells, overexpression of ADAMTS8 could inhibit the viability, invasion, migration and EMT, and MMP2 and MMP9, but promote the apoptosis of cells. The upregulation of ADAMTS8 could inhibit the tumour growth in vivo.*

Conclusions: *ADAMTS8 was inhibited in glioma and the higher expression of ADAMTS8 might be related to better prognosis among glioma patients. Overexpression of ADAMTS8 inhibited the development of glioma in vitro and in vivo.*

Key words: *glioma, brain tumour, ADAMTS8, EMT, survival rate.*

Introduction

Glioma is the most prevalent primary brain tumour in human beings. According to the latest World Health Organization (WHO) CNS5 classification, glioma is divided into 4 families, including the adult diffuse gliomas, paediatric low-grade diffuse gliomas, paediatric high-grade diffuse gliomas and circumscribed astrocytic gliomas. Among these, glioblastoma (GBM), accounting for 57% of all the occurrences of gliomas, is one of the most malignant types that lead to high mortality and recurrence of solid tumour [32]. The low-grade gliomas (LGG) have better prognosis [1]. The survival rate in general for GBM patients is low even after the surgery combined with chemotherapy of radiotherapy [2].

In recent years, novel targets have been discovered in gliomas. CircNEIL3 was revealed to be enriched in glioma tissues and cells and its upregulation could promote the glioma progression and might be a potential therapeutic target [25]. Piwil1 was found upregulated in glioma stem-like cells and knockdown could suppress tumour progression, suggesting that Piwil1 might be a therapeutic target for GBM [15]. Long non-coding RNA (lncRNA) ST7-AS1 expression was found low in glioma tissues and cells and overexpression suppressed the glioma cell growth [30]. Similarly, YAP facilitated the glioma progression, suggesting that YAP might be a therapeutic target [38].

ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) family members were detected to be in human brain tumours [14,17]. ADAMTS1

Communicating author:

Xuequan Feng, Neurosurgical Department, Tianjin First Central Hospital, No. 24 Fukang Road, Nankai District, Tianjin, 300192, China, e-mail: erc12258@126.com

upregulation was discovered to be correlated with the malignant progression in low-grade gliomas [13]. Further research showed that knockout of ADAMTS1 could inhibit the tumour sphere formation and angiogenesis-like features *in vitro* in glioma [29]. ADAMTS5 was upregulated in GBM tissues and cells, and overexpression in GBM cells could promote the cell invasion through degradation of brevican [24]. So far, it has been reported that ADAMTS8 is downregulated in several tumours including colorectal cancer [16], oesophageal squamous cell carcinoma [33], breast cancer [35] and lung cancer [10]. Further studies reported that ADAMTS8 upregulation could inhibit the progression of lung cancer, breast cancer and colorectal cancer *in vitro* and *in vivo* [6,16,35,37]. In addition, ADAMTS8 might act as a prognostic marker for metastasis in breast cancer patients in the lymph node-negative early stage [17]. ADAMTS8 has been reported to be reduced in brain tumours [11]. However, the role of ADAMTS8 in brain tumours is not confirmed yet. Therefore, whether ADAMTS8 could act as a tumour suppressor or not in glioma is what we try to explore in this study.

Material and methods

Ethical statement

This study did not involve any human specimens. The animal experiments were carried out strictly in accordance with the Animal Welfare Act of Tianjin First Central Hospital.

Online database analysis

Gepia online database was used to analyse the mRNA expression level of ADAMTS8 in GBM and LGG. The overall survival and disease-free survival analysis was performed in patients with GBM and LGG with 95% confidence interval. In addition, the Chinese Glioma Genome Atlas database (CGGA, http://www.cgga.org.cn/) was used to perform the overall survival analysis among patients with primary glioma or recurrent glioma. The correlations between ADAMTS8 and MMP2 or MMP9 were analysed.

Cell culture

The glioma cell lines T98G, U251 and U87 were purchased from Procell (Wuhan, China). HEB, the astrocyte cell line of human brain was bought from Mingzhou Bio (Ningbo, China). Cells were cultured in DMEM solution with 10% FBS (Evergreen, Zhejiang, China).

Cell transfection

The short hairpin RNAs (sh-RNA) against ADAMTS8 were synthesized by GenePharma (Suzhou, China) with the non-targeted sequences as the negative control (sh-NC). The overexpressed plasmid pc-ADAMTS8 was constructed based on pc-DNA3.1 plasmid. The glioma cells were transfected with shRNAs and pc-ADAMTS8 using the Lipo6000 Reagent (Beyotime, Shanghai, China). The pc-NC and pc-ADAMTS8 plasmids were stably transfected into the U87 cells and G418 was used to screen the stable transfected cells.

RT-qPCR

The total RNAs were extracted using Beyozol reagent (Beyotime). The ADAMTS8 mRNA expression level was detected using the SYBR PrimeScript RT-PCR Kit on 7500 RT-PCR system (Applied Biosystems, CA, USA), with GAPDH as the internal control. The primer sequences were listed in Table I.

Western blot

Total protein was extracted using RIPA from cells and then the SDS-PAGE method was applied to separate the proteins. The proteins were transferred to PVDF membranes. The primary antibodies against ADAMTS8 (bs-5859R, 1 : 500, Bioss, China), E-cadherin (bs-1016R, 1 : 500, Bioss), Vimentin (bs-8533R, 1 : 500, Bioss), Snail (bs-21598R, 1 : 500, Bioss), MMP2 (ab181286, 1 : 1000, Abcam, USA), MMP9 (ab76003, 1 : 1000, Abcam, USA) and GAPDH (bs-41373R, 1 : 1000, Bioss) were used to incubate the membranes overnight at 4°C. HRP-labelled Goat Anti-Rabbit IgG (H+L) antibody from Beyotime was used as the secondary antibody, which was diluted at 1 : 2000 and used to incubate the membranes for an hour at 37°C. The ECL kit was added on the membranes and the blot bands were then visualized on the western blot imager (Peiqing, Shanghai, China). The relative expression was analysed using Image J (NCBI).

CCK8 analysis

Cells after transfection were selected and 2000 cells/100 µl were seeded onto each well of the 96-well plates for viability test. The CCK8 kit from Beyotime was applied. Then, 10 µl CCK8 solution was added in 3 replicates at 0, 24, 48 and 72 h respectively. After incubation for 1 h, the plates were detected on a microplate reader at 450 nm for OD values.

Table I. Primer sequences

ADAMTS8-F	ACTGTCTCCTGGATGCCC
ADAMTS8-R	AAAGATCTGCCTGCACTGCT
GAPDH-F	ACCACAGTCCATGCCATCAC
GAPDH-R	TCCACCACCCTGTTGCTGTA

Apoptosis assays

Cells after transfection were collected and seeded into 24-well plates and then the apoptosis kit was used as per the manufacturer's instructions (Annexin V/PE, Biolegend Co., Changsha, China). The apoptosis rates in each group were detected on the lab flow cytometer (BD Biosciences, CA, USA).

Transwell experiments

Cells after transfection were selected from each group and then seeded into the serum-free upper chambers of Transwell for further culture. The upper chambers used in invasion assays were pre-coated with Matrigel (BD Biosciences). The lower chambers were filled with 10% fetal bovine serum (FBS). The cells that migrated and invaded were collected and fixed using 1% paraformaldehyde. Thereafter, the haematoxylin was used to stain the fixed cells. Finally, the cell numbers from each group were observed under microscope and cell images were taken from five different fields.

Animal experiments

Six Balb/c nude mice at the aged of 4 weeks old were purchased from Vital River (Beijing, China). The stable transfected U251 cells were injected subcutaneously on the back of the mice. The tumour volumes were estimated on Day 7, 13, 18, 24, 30, 35, 40 and 45. The mice were sacrificed on Day 45 and tumour tissues were separated from the mice. Tumours from each group were weighed. The tumour images were taken on a smart cell phone.

Statistical analysis

GraphPad 8 was used for data analysis and figure generation (Prism, CA, USA). All groups in assays were examined in triplicate. The Kruskal-Wallis test was applied in multiple groups. Unpaired *t* test was used within two groups. Two-Way ANOVA analysis was applied in analysis of cell viability.

Results

ADAMTS8 is associated with higher survival in primary glioma patients

According to the Gepia database, the mRNA expression of ADAMTS8 was suppressed in GBM and LGG tumour tissues (Fig. 1A). The survival analysis on Gepia further showed that the glioma patients with a higher ADAMTS8 expression might be correlated with higher overall survival and higher disease-free survival rates, which suggests that ADAMTS8 might be a prognosis biomarker in glioma (Fig. 1B, C). The survival analysis based on CGGA database further showed that a higher expression of ADAMTS8 was associated with higher overall survival in primary glioma patients (Fig. 1D). However, the correlation between the ADAMTS8 expression and overall survival rate was not significant in recurrent glioma patients (Fig. 1E). *In vitro*, the ADAMTS8 mRNA and protein expression levels were lower in glioma cell lines than the normal HEB cells (Fig. 1F-H).

The upregulation of ADAMTS8 inhibits the viability and promotes the apoptosis of the glioma cells

The U87 and T98G cells were transfected with the shRNAs against ADAMTS8 and the overexpressed plasmids. Then RT-qPCR and western blot assays were used to validate the transfection efficiency. Results showed that ADAMTS8 mRNA and protein levels were enhanced in pc-ADAMTS8 groups in both cell lines (Suppl. Fig. 1A, B, E-G). Similarly, in the sh-ADAMTS8 groups of both cell lines, the mRNA and protein levels of ADAMTS8 were inhibited (Suppl. Fig. 1C, D, H-J). Further, we performed the CCK8 and apoptosis experiments to examine the effect of ADAMTS8 in glioma cell lines. It was validated that ADAMTS8 upregulation could reduce the viability but facilitate the apoptosis of U251 and T98G cells (Fig. 2A, C). On the contrary, the knockdown of ADAMTS8 in U251 and T98G cells could increase the viability and suppress the apoptosis of U251 and T98G cells (Fig. 2B, D).

The upregulation of ADAMTS8 inhibits the mobility and EMT of the glioma cells

The transwell assays were performed to examine the migration and invasion of U251 and T98G after the upregulation or downregulation of ADAMTS8. The findings were that the upregulation of ADAMTS8 could suppress the migration and invasion of cells (Fig. 3A, B, E, F). In contrast, the knockdown of ADAMTS8 was discovered to enhance the cell mobility (Fig. 3C, D, G, H). Furthermore, the EMT biomarkers were detected in each group by western blot. E-cadherin was promoted in both cell lines after the upregulation of ADAMTS8 while the Vimentin and snail were inhibited (Fig. 3I, Suppl. Fig. 2A, C, E, G, I, K). On the other hand, the knockdown of ADAMTS8 in both cell lines were found to inhibit E-cadherin and promote snail and Vimentin (Fig. 3I, Suppl. Fig. 2B, D, F, H, J). In addition, ADAMTS8 was negatively correlated with MMP2 and MMP9 in glioma tissues according to CGGA database (Suppl. Fig. 3). Further, we confirmed in glioma cells that ADAMTS8 upregulation could inhibit the secretion of MMP2

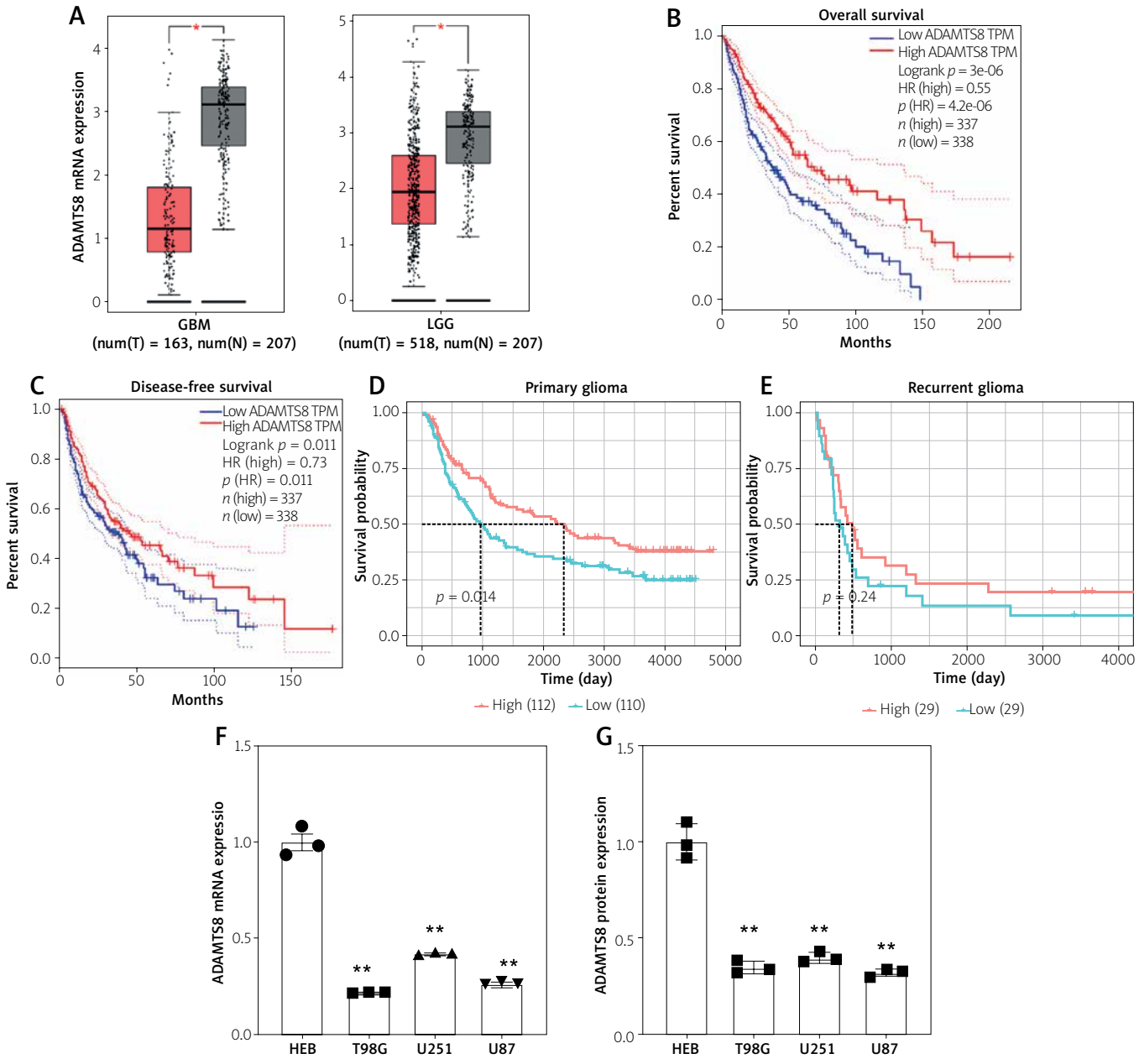
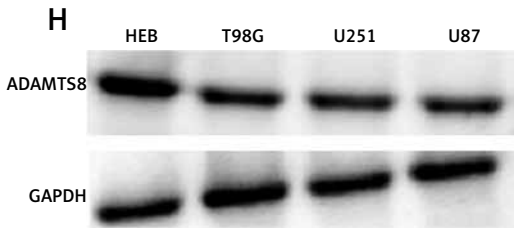


Fig. 1. ADAMTS8 expression is reduced in glioma. **A**) Gepia database was used to analyse the differential expression of ADAMTS8 in glioma tissues and normal ones. **B, C**) The overall survival and disease-free survival rates were assessed on Gepia in glioma patients. **D, E**) CGGA database was used to perform the overall analysis among patients with primary or recurrent glioma. **F-H**) RT-qPCR and western blot experiments were performed to measure the ADAMTS8 mRNA and protein expression in glioma cells and normal HEB cells. $^{**}p < 0.03$.



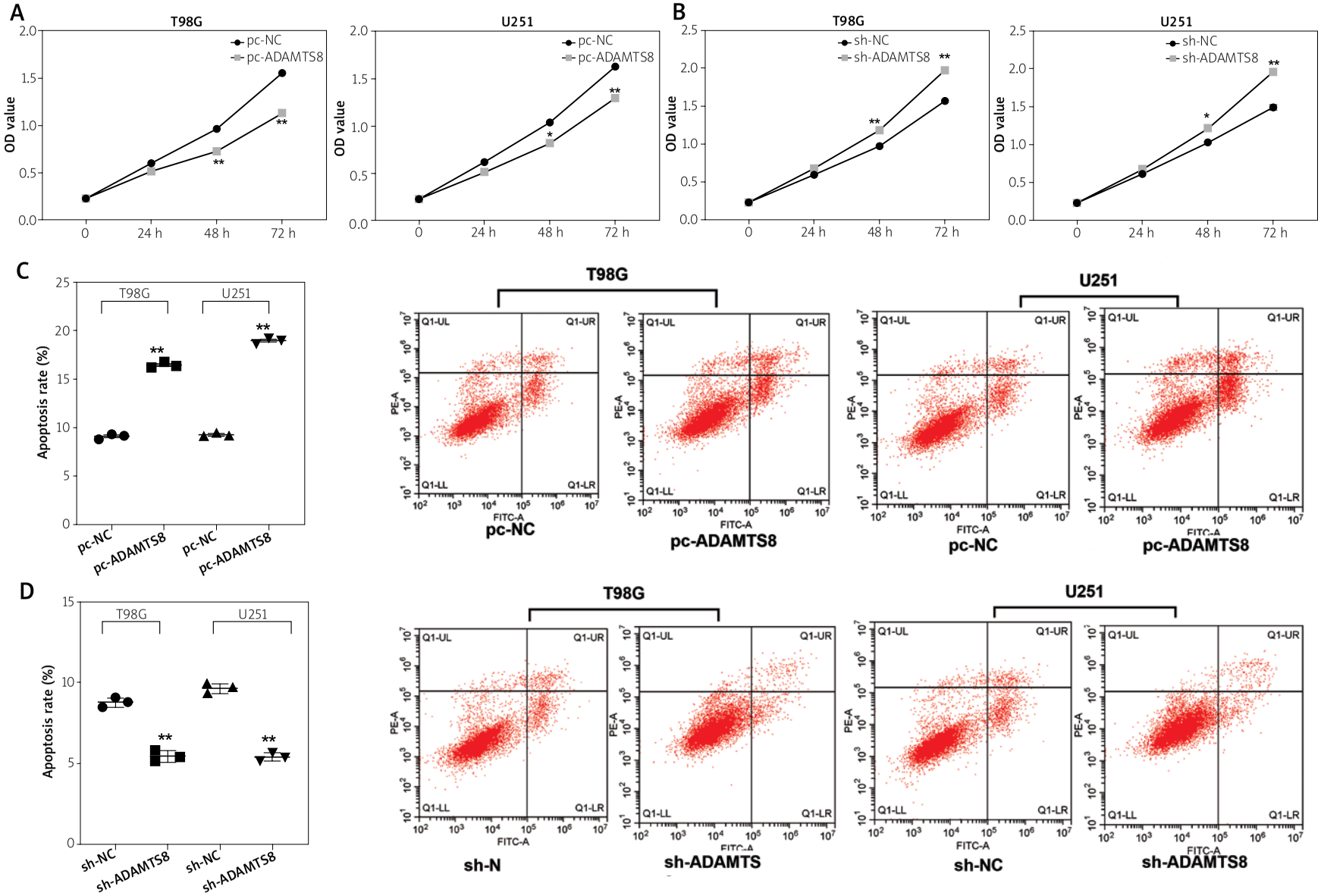


Fig. 2. The upregulation of ADAMTS8 inhibits the viability and promotes the apoptosis of the glioma cells. The glioma cell lines T98G and U251 were selected for further transfection to regulate the ADAMTS8 expression inside. **A, B**) CCK8 assays; **C, D**) Apoptosis assays. $^{**}p < 0.03$.

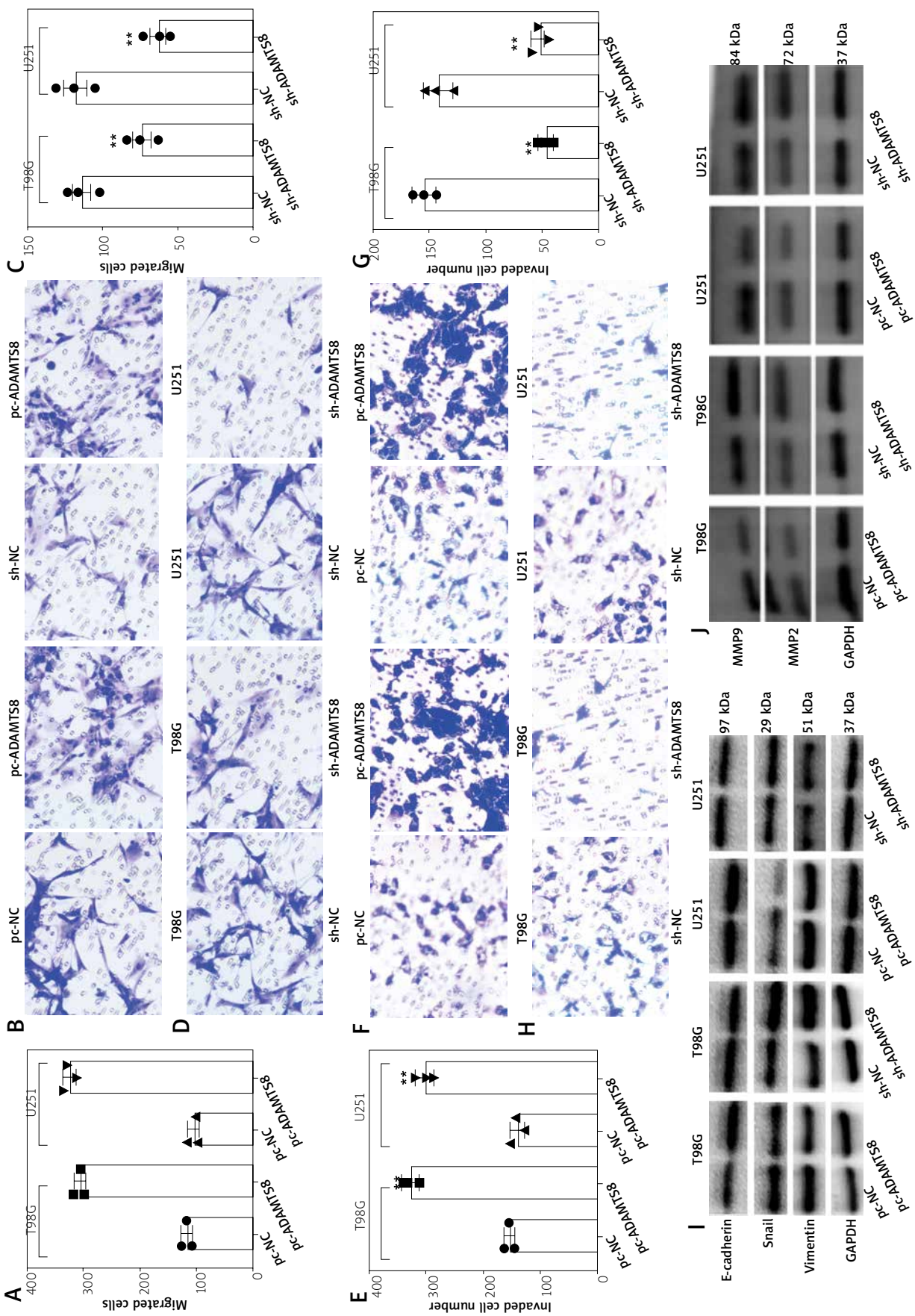


Fig. 3. The upregulation of ADAMTS8 inhibits the mobility and EMT of the glioma cells. The glioma cell lines T98G and U251 were selected for further transfection to regulate the ADAMTS8 expression inside. **A-D**) Migration assays. **E-G**) Invasion assays. **I**) Western blot assays for EMT-related proteins. **J**) Western blot for MMP2 and MMP9 examination. $^{**}p < 0.03$.

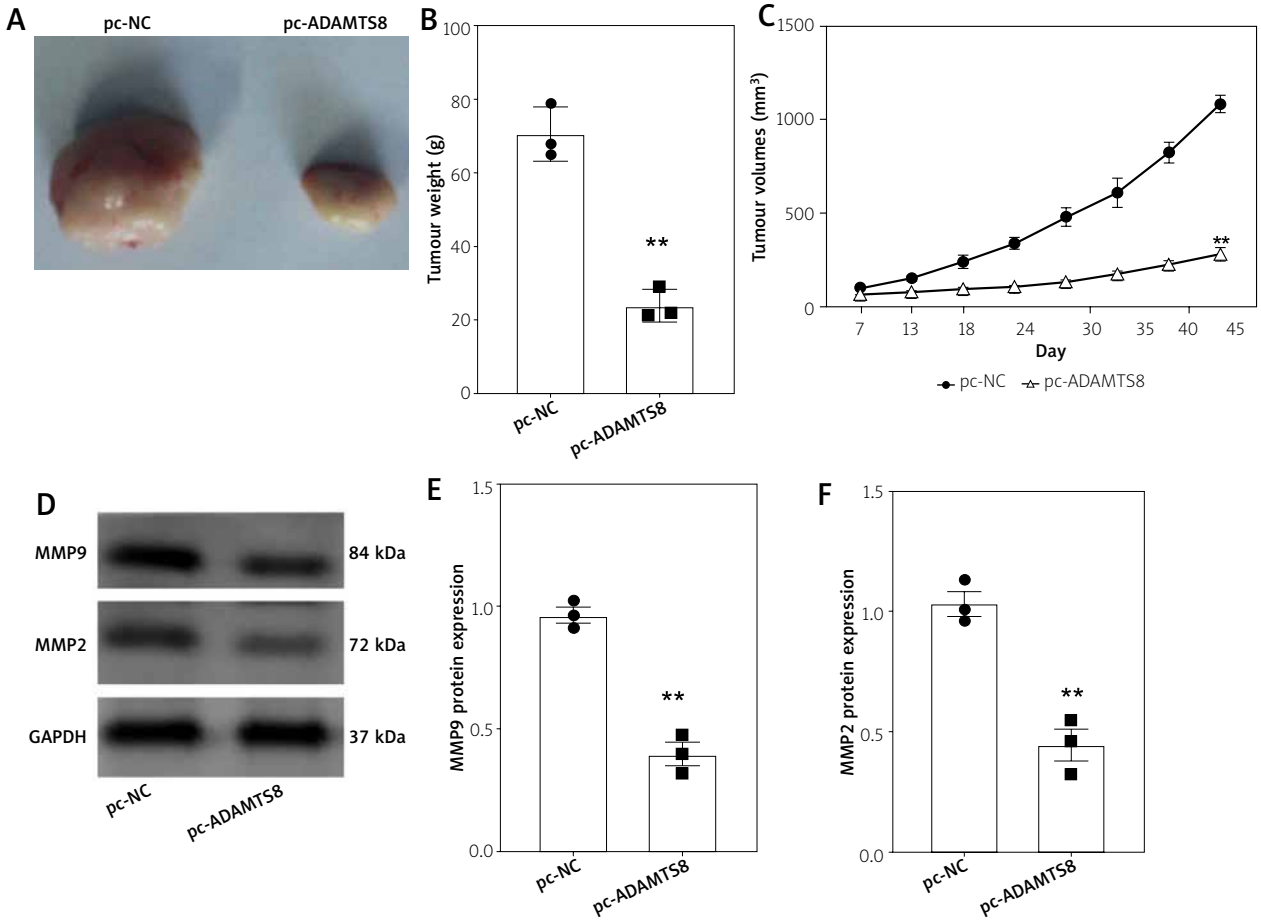


Fig. 4. The upregulation of ADAMTS8 suppresses the glioma growth *in vivo*. **A**) The tumour sample from each group. **B**) Tumour weight (g). **C**) The growth curve of tumour volumes. **D, E**) Western blot for MMP2/9 analysis in tumour tissues. $^{**}p < 0.03$.

and MMP9 and its downregulation could promote the secretion (Fig. 3J, Suppl. Fig. 2M, N).

The upregulation of ADAMTS8 suppresses the glioma growth *in vivo*

After the injection of stable transfected cells into the nude mice, results confirmed that the overexpression of ADAMTS8 inhibited the tumour growth in nude mice (Fig. 4A-C). In addition, MMP2 and MMP9 protein expression levels in tumour tissues were inhibited in the pc-ADAMTS8 group (Fig. 4D-F).

Discussion

Glioma is a considerably complicated disease and so far, there have been various genes reported to be involved in the modulation of the pathogenesis. It was recently discovered that MXRA8, matrix remodelling-associated protein 8 expression was higher in glioma and higher expression in glioma was correlated with lower survival rates; downregulation of MXRA8 could inhibit the glioma cell growth through regulating the ferroptosis and immune microenvironment [34]. HMGA1 was revealed to be upregulated in glioma and modulate the cell survival, invasion and migration *via* PI3K/Akt/c-Jun pathway [26]. ARPC1B, actin-related protein 2/3 complex subunit 1B, was revealed to facilitate the invasion, migration and the EMT in glioma cells and promote intracranial tumour growth [18]. Further, ARPC1B was discovered to regulate the tumour microenvironment in the co-culture model of macrophage and glioma cells [18]. Previously, ADAMTS8 was reported to be downregulated in brain tumours [11]. Apart from this, there is no further study on the role of ADAMTS8 in glioma. In this study, we disclosed that ADAMTS8 was inhibited in glioma, and higher ADAMTS8 expression in glioma patients was correlated with better overall survival and disease-free survival, particularly in primary glioma patients, suggesting that clinically, ADAMTS8 expression might act as a prognostic biomarker for glio-

ma patients. Therefore, we studied the regulatory function of ADAMTS8 in glioma cells and confirmed that ADAMTS8 overexpression could suppress the cell proliferation, invasion and migration and promote the cell apoptosis. Further, we also validated the suppressive role of ADAMTS8 in glioma growth in nude mice.

Glioma malignancy is correlated with the tumour infiltration and tumour microenvironment. The cell invasion enables glioma cells to escape from the original tumour site, resulting in metastasis [5]. The degradation of extracellular matrix is of importance in tumour infiltration and development in microenvironment [4,5,7,27,28]. The dense extracellular matrix is a natural obstacle for the infiltrating cells and in order to go through, proteases are secreted, including the matrix metallopeptidases (MMPs) and proteases like a disintegrin and metalloproteinases (ADAMs) [12]. MMP2 and MMP9 play important roles in degrading the extracellular matrix components and thereby effecting on the migration and invasion of glioma cells [8,9,12,19,22,23,31]. In addition, MMP2 and MMP9 were revealed to be associated with higher recurrence in glioma patients [39]. In this study, we reported that ADAMTS8 was not only negatively correlated with MMP2 and MMP9 in glioma tissues, but also capable of inhibiting MMP2 and MMP9 secretion in glioma cells and tumours in xenograft models, suggesting that ADAMTS8 might play its suppressive role in glioma through inhibiting secretion of MMP2 and MMP9.

On the other hand, epithelial-mesenchymal transition (EMT), featuring the loss of epithelial characteristics like cell-cell adhesion and gain of mesenchymal traits including the increase of invasion and migration, is widely involved in malignancy of various cancers [36]. Apart from the epithelial protein marker E-cadherin, mesenchymal marker Vimentin, transcriptional factors like snail are correlated with the EMT-like features in glioma [21]. In addition, MMPs like MMP2 and MMP9 are actively involved with the EMT regulation [3,28]. In this study, we found that ADAMTS8 could inhibit the EMT-like features in glioma, perhaps *via* suppression of MMP2 and MMP9.

Conclusions

Taken together, this study reports that higher ADAMTS8 expression in glioma patients was correlated with better prognosis and ADAMTS8 might inhibit the glioma development *via* regulating MMP2 and MMP9.

Supplementary figures are available on journal's website.

Disclosure

The authors report no conflict of interest.

References

1. Aiman W, Rayi A. Low grade gliomas. StatPearls Publishing LLC., Treasure Island (FL) 2022.
2. Armstrong TS, Dirven L, Arons D, Bates A, Chang SM, Coens C, Espinasse C, Gilbert MR, Jenkinson D, Kluetz P, Mendoza T, Rubinstein L, Sul J, Weller M, Wen PY, van den Bent MJ, Taphoorn MJB. Glioma patient-reported outcome assessment in clinical care and research: A response assessment in neuro-oncology collaborative report. Lancet Oncol 2020; 21: e97-e103.
3. Asuthkar S, Nalla AK, Gondi CS, Dinh DH, Gujrati M, Mohanam S, Rao JS. Gadd45a sensitizes medulloblastoma cells to irradiation and suppresses MMP-9-mediated EMT. Neuro Oncol 2011; 13: 1059-1073.
4. Bissell MJ, Radisky D. Putting tumours in context. Nat Rev Cancer 2001; 1: 46-54.
5. Chen YF, Shih PC, Kuo HM, Yang SN, Lin YY, Chen WF, Tzou SJ, Liu HT, Chen NF. TP3, an antimicrobial peptide, inhibits infiltration and motility of glioblastoma cells via modulating the tumor microenvironment. Cancer Med 2020; 9: 3918-3931.
6. Choi GC, Li J, Wang Y, Li L, Zhong L, Ma B, Su X, Ying J, Xiang T, Rha SY, Yu J, Sung JJ, Tsao SW, Chan AT, Tao Q. The metalloprotease ADAMTS8 displays antitumor properties through antagonizing EGFR-MEK-ERK signaling and is silenced in carcinomas by CpG methylation. Mol Cancer Res 2014; 12: 228-238.
7. Cuddapah VA, Robel S, Watkins S, Sontheimer H. A neurocentric perspective on glioma invasion. Nat Rev Neurosci 2014; 15: 455-465.
8. Demuth T, Berens ME. Molecular mechanisms of glioma cell migration and invasion. J Neurooncol 2004; 70: 217-228.
9. Dong C, Li X, Yang J, Yuan D, Zhou Y, Zhang Y, Shi G, Zhang R, Liu J, Fu P, Sun M. PPFIBP1 induces glioma cell migration and invasion through FAK/Src/JNK signaling pathway. Cell Death Dis 2021; 12: 827.
10. Dunn JR, Panutsopulos D, Shaw MW, Heighway J, Dormer R, Salmo EN, Watson SG, Field JK, Liloglou T. METH-2 silencing and promoter hypermethylation in NSCLC. Br J Cancer 2004; 91: 1149-1154.
11. Dunn JR, Reed JE, du Plessis DG, Shaw EJ, Reeves P, Gee AL, Warnke P, Walker C. Expression of ADAMTS-8, a secreted protease with antiangiogenic properties, is downregulated in brain tumours. Br J Cancer 2006; 94: 1186-1193.
12. Giese A, Westphal M. Glioma invasion in the central nervous system. Neurosurgery 1996; 39: 235-250.
13. Gokce A, Gokce EC, Sunguroglu A. Role of Adamts-1 in pleomorphic xanthoastrocytoma tumor cells progression. Turk Neurosurg 2021; 31: 731-739.
14. Held-Feindt J, Paredes EB, Blömer U, Seidenbecher C, Stark AM, Mehdorn HM, Mentlein R. Matrix-degrading proteases ADAMTS4 and ADAMTS5 (disintegrins and metalloproteinases with thrombospondin motifs 4 and 5) are expressed in human glioblastomas. Int J Cancer 2006; 118: 55-61.
15. Huang H, Yu X, Han X, Hao J, Zhao J, Bebek G, Bao S, Prayson RA, Khalil AM, Jankowsky E, Yu JS. Piwil1 regulates glioma stem cell maintenance and glioblastoma progression. Cell Rep 2021; 34: 108522.
16. Li L, Yuan S, Zhao X, Luo T. ADAMTS8 is frequently down-regulated in colorectal cancer and functions as a tumor suppressor. Biochem Biophys Res Commun 2020; 524: 663-671.
17. Li Y, Yang X, Sun J, Zhao Y, Zhou Q, Hua B. ADAMTS8 expression is a potential prognostic biomarker for postoperative metastasis in lymph node-negative early-stage invasive breast carcinoma patients. Pharmgenomics Pers Med 2021; 14: 1701-1713.

18. Liu T, Zhu C, Chen X, Wu J, Guan G, Zou C, Shen S, Chen L, Cheng P, Cheng W, Wu A. Dual role of ARPC1B in regulating the network between tumor-associated macrophages and tumor cells in glioblastoma. Oncoimmunology 2022; 11: 2031499.
19. Liu X, Chen JY, Chien Y, Yang YP, Chen MT, Lin LT. Overview of the molecular mechanisms of migration and invasion in glioblastoma multiforme. J Chin Med Assoc 2021; 84: 669-677.
20. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, Hawkins C, Ng HK, Pfister SM, Reifenberger G, Soffietti R, von Deimling A, Ellison DW. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro Oncol 2021; 23: 1231-1251.
21. Mahabir R, Tanino M, Elmansuri A, Wang L, Kimura T, Itoh T, Ohba Y, Nishihara H, Shirato H, Tsuda M, Tanaka S. Sustained elevation of Snail promotes glial-mesenchymal transition after irradiation in malignant glioma. Neuro Oncol 2014; 16: 671-685.
22. Matthews RT, Gary SC, Zerillo C, Pratta M, Solomon K, Arner EC, Hockfield S. Brain-enriched hyaluronan binding (BEHAB)/brevican cleavage in a glioma cell line is mediated by a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) family member. J Biol Chem 2000; 275: 22695-22703.
23. Mentlein R, Hattermann K, Held-Feindt J. Lost in disruption: role of proteases in glioma invasion and progression. Biochim Biophys Acta 2012; 1825: 178-185.
24. Nakada M, Miyamori H, Kita D, Takahashi T, Yamashita J, Sato H, Miura R, Yamaguchi Y, Okada Y. Human glioblastomas overexpress ADAMTS-5 that degrades brevican. Acta Neuropathol 2005; 110: 239-246.
25. Pan Z, Zhao R, Li B, Qi Y, Qiu W, Guo Q, Zhang S, Zhao S, Xu H, Li M, Gao Z, Fan Y, Xu J, Wang H, Wang S, Qiu J, Wang Q, Guo X, Deng L, Zhang P, Xue H, Li G. EWSR1-induced circNEIL3 promotes glioma progression and exosome-mediated macrophage immunosuppressive polarization via stabilizing IGF2BP3. Mol Cancer 2022; 21: 16.
26. Que T, Zheng H, Zeng Y, Liu X, Qi G, La Q, Liang T, Li Z, Yi G, Zhang S, Li J, Nie J, Tan JE, Huang G. HMGA1 stimulates MYH9-dependent ubiquitination of GSK-3β via PI3K/Akt/c-Jun signaling to promote malignant progression and chemoresistance in gliomas. Cell Death Dis 2021; 12: 1147.
27. 27.Quesnel A, Karagiannis GS, Filippou PS. Extracellular proteolysis in glioblastoma progression and therapeutics. Biochim Biophys Acta Rev Cancer 2020; 1874: 188428.
28. Rajesh Y, Banerjee A, Pal I, Biswas A, Das S, Dey KK, Kapoor N, Ghosh AK, Mitra P, Mandal M. Delineation of crosstalk between HSP27 and MMP-2/MMP-9: A synergistic therapeutic avenue for glioblastoma management. Biochim Biophys Acta Gen Subj 2019; 1863: 1196-1209.
29. Serrano-Garrido O, Peris-Torres C, Redondo-García S, Asenjo HG, Plaza-Calonge MDC, Fernandez-Luna JL, Rodríguez-Manzaneque JC. ADAMTS1 supports endothelial plasticity of glioblastoma cells with relevance for glioma progression. Biomolecules 2020; 11: 44.
30. Sheng J, He X, Yu W, Chen Y, Long Y, Wang K, Zhu S, Liu Q. p53-targeted lncRNA ST7-AS1 acts as a tumour suppressor by interacting with PTBP1 to suppress the Wnt/βcatenin signalling pathway in glioma. Cancer Lett 2021; 503: 54-68.
31. Viapiano MS, Hockfield S, Matthews RT. BEHAB/brevican requires ADAMTS-mediated proteolytic cleavage to promote glioma invasion. J Neurooncol 2008; 88: 261-272.
32. Weller M, Le Rhun E. How did lomustine become standard of care in recurrent glioblastoma? Cancer Treat Rev 2020; 87: 102029.
33. Wu Z, Shi Y, Ren S, Ju Y, Hu Y, Wu J. ADAMTS8 inhibits progression of esophageal squamous cell carcinoma. DNA Cell Biol 2020.
34. Xu Z, Chen X, Song L, Yuan F, Yan Y. Matrix remodeling-associated protein 8 as a novel indicator contributing to glioma immune response by regulating ferroptosis. Front Immunol 2022; 13: 834595.
35. Zhang K, Tian R, Wang G, Zhang J, Ma H, Hu X, Xi J, Wang G. ADAMTS8 inhibits cell proliferation and invasion, and induces apoptosis in breast cancer. Onco Targets Ther 2020; 13: 8373-8382.
36. Zhang N, Ng AS, Cai S, Li Q, Yang L, Kerr D. Novel therapeutic strategies: targeting epithelial-mesenchymal transition in colorectal cancer. Lancet Oncol 2021; 22: e358-e368.
37. Zhang Y, Hu K, Qu Z, Xie Z, Tian F. ADAMTS8 inhibited lung cancer progression through suppressing VEGFA. Biochem Biophys Res Commun 2022; 598: 1-8.
38. Zhao M, Zhang Y, Jiang Y, Wang K, Wang X, Zhou D, Wang Y, Yu R, Zhou X. YAP promotes autophagy and progression of gliomas via upregulating HMGB1. J Exp Clin Cancer Res 2021; 40: 99.
39. Zhou W, Yu X, Sun S, Zhang X, Yang W, Zhang J, Zhang X, Jiang Z. Increased expression of MMP-2 and MMP-9 indicates poor prognosis in glioma recurrence. Biomed Pharmacother 2019; 118: 109369.