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Identification of MGMT promoter methylation as a specific lipid metabolism biomarker, reveals the feasibility of atorvastatin application in glioblastoma

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Abstract

Background

Glioblastoma is one of the deadliest tumors, and limited improvement in managing glioblastoma has been achieved in the past decades. The unmethylated promoter area of 6-O-Methylguanine-DNA Methyltransferase (MGMT) is a significant biomarker for recognizing a subset of glioblastoma that is resistant to chemotherapy. Here we identified MGMT methylation can also work as a specific biomarker to classify the lipid metabolism patterns between methylated and unmethylated glioblastoma and verify the potential novel therapeutic strategy for unmethylated MGMT glioblastoma.

Methods

Liquid Chromatograph Mass Spectrometer has been applied for non-targeted metabolome and targeted lipidomic profiling to explore the metabolism pattern correlated with MGMT promoter methylation. Transcriptome has been performed to explore the biological differences and the potential mechanism of lipid metabolism in glioblastoma samples. In vivo and ex vivo assays were performed to verify the anti-tumor activity of atorvastatin in the administration of glioblastoma.

Results

Multi-omics assay has described a significant difference in lipid metabolism between MGMT methylated and unmethylated glioblastoma. Longer and unsaturated fatty acyls were found enriched in MGMT-UM tumors. Lipid droplets have been revealed remarkably decreased in MGMT unmethylated glioblastoma. In vivo and ex vivo assays revealed that atorvastatin and also together with temozolomide showed significant anti-tumor activity, and atorvastatin alone was able to achieve better survival and living conditions for tumor-hosting mice.

Conclusions

MGMT promoter methylation status might be a well-performed biomarker of lipid metabolism in glioblastoma. The current study can be the basis of further mechanism studies and implementation of clinical trials, and the results provide preclinical evidence of atorvastatin administration in glioblastoma, especially for MGMT unmethylated tumors.

Introduction

Glioma is one of the most common malignancies in the central nervous system (CNS), which has been classified from grade I to grade IV according to World Health Organization (WHO) criteria. Among them, glioblastoma (GBM) is the deadliest type that with a poor prognosis. The standard care, radiotherapy, and concomitant chemotherapy with temozolomide after surgical resection, for glioblastoma patients only achieves a median survival time of only 15.3 months [1]. Efforts to improve the administration of glioblastoma patients by scientists have had limited survival benefits for patients since 2005. To develop novel therapies or strategies for glioblastoma, it is necessary to further understand the tumor and its subtypes from the aspects of tumor molecular biology, metabolism, microenvironment, and clinical characteristics. 6-O-Methylguanine-DNA Methyltransferase (MGMT) promoter methylation is a significant clinical marker for glioma patients, which has been applied for the identification of potential temozolomide-sensitive patients [[1], [2], [3]]. Unmethylated MGMT subset of GBM, all with isocitrate dehydrogenase (IDH) wildtype allele referring to the latest guideline [4], has been exploited to bearing forlorn overall survival of merely 10.0 months with radiotherapy plus temozolomide and 7.9 months with radiotherapy alone [5]. The updated criteria of glioma classification led to the re-definition of GBM, which excludes all IDH mutated grade IV primary tumors bearing better clinical outcomes. This makes it more challenging to develop novel treatments for GBM since we are facing one much more malignant subset of glioma and other limitations in the study (shortage in tumor samples for instance).

Metabolic reprogramming is one of the most significant markers of tumor that alters the energy supply, cell proliferation, tumor immunity, and remodeling of the microenvironment in the tumor context [[6], [7], [8]]. Different metabolic pattern also refers to sub-populations of tumors. We therefore aimed to explore the metabolic features of GBM subsets determined by MGMT promoter methylation status (PMS) for a further understanding of biological characteristics represented by the epigenetic status of MGMT. Our findings revealed metabolism differences between MGMT promoter unmethylated (MGMT-UM) and MGMT promoter methylated (MGMT-M) subsets, especially for lipids metabolism. Fatty acyls and sterol lipids were revealed to be the hub differential metabolite between MGMT-M and MGMT-UM GBMs. Following the clue of lipid metabolism, we then find out that lipid droplet, a storage condition of lipid, has also been significantly degraded or consumed in MGMT-UM GBMs. Evidence of transcriptome also supports that the lipid droplet lipolysis pathway is up-regulated in MGMT-UM GBMs. A pilot study on exploring lipid-control agents was then performed, and we found that atorvastatin showed tremendous therapeutic potential in the administration of GBM, especially for MGMT-UM, which suggests a possible future avenue for treating glioma.

Section snippets

Clinical characteristics of samples and quality control of LC-MS based analytical processes

To investigate the metabolic features of GBM, we enrolled 42 IDH-wildtype GBM patients who were diagnosed following the newest WHO (World Health Organization) 2021 criteria of GBM definition. 18 and 24 patients were identified as MGMT-M and MGMT-UM, respectively. The threshold for recognizing MGMT promoter methylation is 10%, in accordance with clinical practice. To ensure the balance of the sample grouping, all clinical and molecular features between MGMT-M and MGMT-UM were statistically…

Discussion

Glioblastoma is one of the deadliest tumors that bring forlorn prognosis to patients. Administrations of GBM have achieved limited improvement in survival time in the past years. The launch of the 5th edition of WHO criteria of glioma diagnosis [4] marks one step forward in a more specific classification of glioma, which is fundamental for recognizing the subtypes of glioma and predicting the respective prognoses. Methylation of the promoter region of MGMT is one critical clinical biomarker for …

Sample enrollment

All samples were collected at Beijing Tiantan Hospital from September 2021 to March 2022. Those patients with occupation observed in post-Gadolinium (Gd) T1-weighted magnetic resonance imaging (MRI) were tentatively included. Intraoperative sampling of the core area of the tumor was accomplished for rapid pathological assay using the frozen section, and tumors with lower-grade features of pathology were excluded. A sampling of tumor tissue and peri-tumor tissue, size as 1X1X1 (cm), was…

Abbreviations

CNS
: central nervous system…

WHO
: World Health Organization…

GBM
: glioblastoma…

MGMT
: 6-O-Methylguanine-DNA Methyltransferase…

PMS
: promoter methylation status…

MGMT-UM
: MGMT promoter unmethylated…

MGMT-M
: MGMT promoter methylated…

MRI
: magnetic resonance imaging…

LC-MS
: liquid chromatograph mass spectrometer…

MTBE
: methyl tert-butyl ether…

CCK-8
: Cell Counting Kit-8…

SPF
: specific pathogen free…

PCA
: Principal Component Analysis…

PLS-DA
: Partial Least Squares-Discriminant Analysis…

VIP
: Variable Importance Projection…

GO
: Gene Ontology…

GSEA
: Gene Set…

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Consent for publication

Not applicable.…

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CRediT authorship contribution statement

Zhaonian Hao: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Jiejun Wang:** Writing – review & editing, Writing – original draft, Software, Investigation, Formal analysis, Data curation. **Yifan Lv:** Resources, Investigation, Data curation. **Weiqi Wu:** Resources, Investigation, Data curation. **Shaodong Zhang:** Resources, Investigation. **Shuyu Hao:** Resources, Data curation. **Junsheng Chu:** Resources, Data curation. **Hong**…

Declaration of competing interest

The authors declare that they have no competing interests.…

Acknowledgments

Not applicable....

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