Prognostic value of metabolic alterations in saliva and plasma of glioblastoma patients

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INTRODUCTION

- Glioblastoma (GBM) is an aggressive type of tumor arising from the central nervous system (1).
- GBM remains an incurable disease despite current standard of care, with survival rate of approximately 15 months from diagnosis (2).
- GBM prognosis is mainly assessed by imaging techniques which may result in misinterpretation of treatment response.
- There are no clinically validated biomarkers to monitor treatment response in GBM.
- The use of metabolomics is a promising tool to address this clinical need.
- We hypothesized that metabolites and lipids isolated from blood and saliva of patients could predict clinical outcomes in newly diagnosed GBM patients.
- Here, we aim to isolate metabolites and lipids from GBM patients and study their prognostic value during therapy.

METHODS

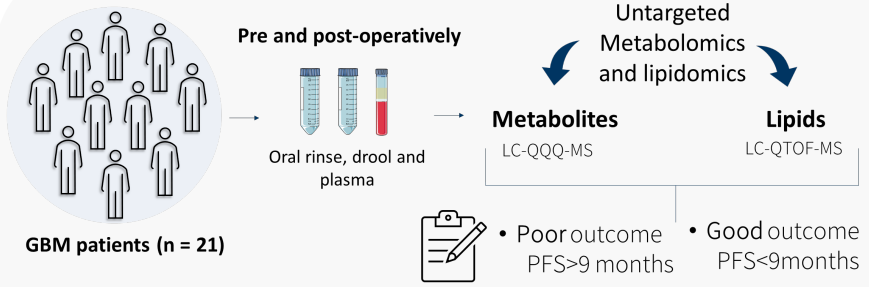

Fig 1. Saliva (unstimulated, oral rinse) and plasma samples were collected from 21 newly diagnosed GBM patients pre and post-operatively. Metabolomic and lipidomic profiles were analysed using LC-QqQ-MS and LC-QTOF-MS. GBM patients were classified according to clinical outcomes (progression-free survival (PFS)>9 months or PFS≤9 months, respectively). Univariate and multivariate statistical analyses were performed using MetaboAnalyst.

RESULTS

Metabolites and lipids identified in GBM patients

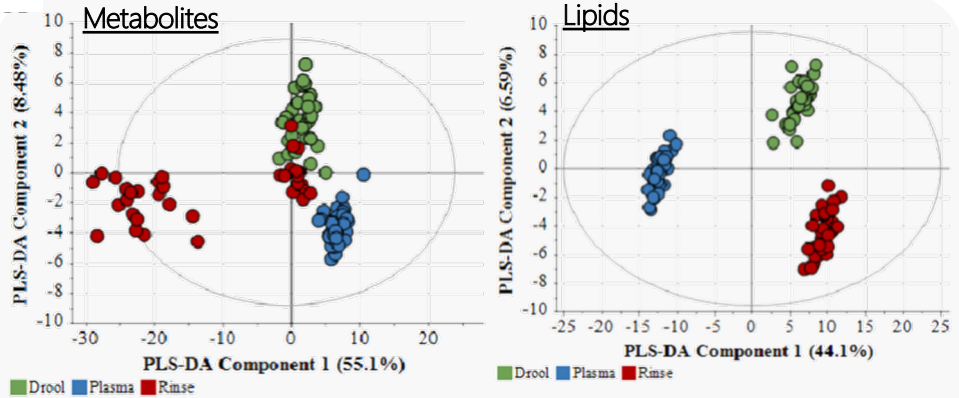

Fig 2. PLS-DA dataset for the metabolic and lipidomic profiles of various samples derived from glioblastoma patients. Spread of samples indicated by score scatter plot, with ellipse representing 95% confidence interval

- 151 and 197 statistically significant metabolites and lipids, respectively, were identified across all biofluids in GBM patients.

Correlation of lipids with clinical outcome

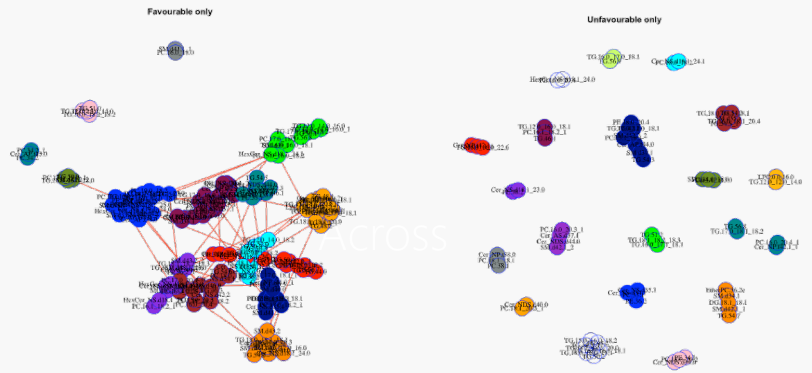

Figure 3. Graphical assessment using the Graphical LASSO. Across all body fluids, patients with unfavourable outcomes showed a more heterogeneous expression of lipids with less association between markers compared to favourable outcomes. Patients with favourable outcomes present a more homogeneous network with connected clusters of lipids.

Metabolic pathway	Total Compounds (Stat Q)	FDR
Purine metabolism	65 (16.29)	6.47E-56
Aminoacyl-tRNA biosynthesis	48 (21.58)	2.39E-33
Pyrimidine metabolism	39 (13.44)	9.21E-37
Alanine, aspartate and glutamate metabolism	28 (12.81)	2.29E-30
Amino sugar and nucleotide sugar metabolism	37 (12.34)	1.26E-25
Pentose phosphate pathway	22 (10.89)	2.71E-19

Table 1.Major metabolic pathways, determined by the Statistical Q value (Go) and total hits observed across all samples from glioblastoma patients.

CONCLUSIONS

Our results suggest that salivary and plasmatic metabolic alterations in GBM have the potential to be utilised as minimally invasive prognostic biomarkers. However, studies with larger cohorts are still warranted.

REFERENCES

1. Ostrom QT, Gittleman H, Liao P, Vecchione-Koval T, Wolinsky Y, Kruchko C, et al. CBTRUS Statistical Report: Primary brain and other central nervous system tumors diagnosed in the United States in 2010-2014. Neuro Oncol. 2017.
2. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJB, et al. Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma. New England Journal of Medicine. 2005.
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