Molecular Characteristics of Tumor Infiltrating Front in Glioblastoma : Insights into Molecular Heterogeneity and Implications on Targeted Therapy

Arivazhagan Arimappamagan MS DNB MCh; Kruthika BS; Rose Dawn B; Kondaiah Paturu; Vani Santosh

[Institution]

NATIONAL INSTITUTE OF MENTAL HEALTH AND NEUROSCIENCES (NIMHANS), BANGALORE, INDIA AND

CNS 2016 ANNUAL MEETING San Diego CALIFORNIA SEPTEMBER 24-28, 2016

Introduction

Molecular heterogeneity in GBM is a novel area of research recently. As tumor infiltrating front in GBM is often left behind following tumor decompression, knowledge of its genetic makeup can improve the rationale of potential molecular targets.

Methods

MRI localised biopsies of the tumour core and PBZ were obtained from 25 Glioblastoma patients. The PBZ samples containing 15-30% tumour cells and core samples with predominantly tumour cells along with 8 non-neoplastic brain tissues were selected for a whole Genome Gene Expression Microarray. The list of differentially expressed genes between the tumour core and PBZ as compared to non-neoplastic brain tissue was identified using R Bioconductor. Selected genes were validated using Quantitative Real-Time PCR (qRT-PCR) and IHC.

Learning Objectives

Understand the molecular heterogeneity in GBM and infiltrating front, which can guide future research in target identification.

Results

Unsupervised hierarchical clustering of the genes revealed that the tumour core and PBZ samples showed a varied gene expression profile and clustered into two distinct groups. Around 7123, 5188 and 991 genes were differentially expressed in Core versus Normal, PBZ versus Normal and PBZ versus Core. Novel genes like PBK (role in cell cycle), MELK (stem cell marker) and TOP2A (proliferation marker) were up-regulated in PBZ and tumour core as compared with normal brain and robustly validated on IHC. Pathways involved in cell cycle, immune response, cell-cell adhesion, cell-matrix interaction etc were commonly enriched in Periphery and tumour core compared to normal brain. Some of the novel markers were validated by Real time PCR and IHC.

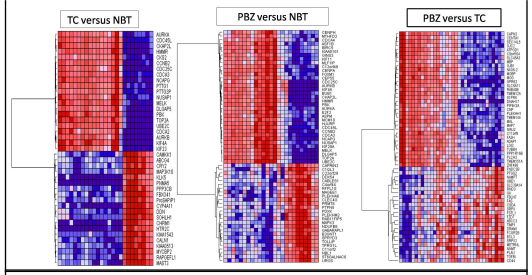
Conclusions

We demonstrate that the key genes involved in tumour cell proliferation, invasion, migration, response to immune system and stemness markers are highly enriched in the PBZ. These genes, probably contribute to the resistance of PBZ

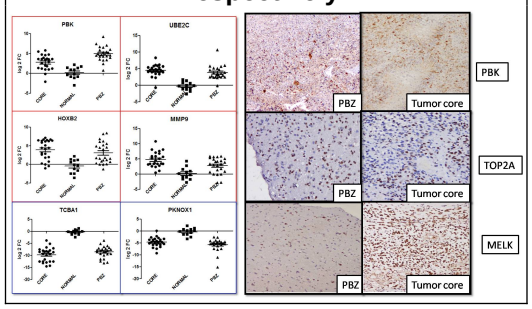
References

1. Verhaak et al. Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. Cancer Cell. ;17(1):98-110 (2010).
2. Houtan Noushmehr et al. Identification of a CpG Island Methylator Phenotype that Defines a Distinct Subgroup of Glioma. Volume 17, Issue 5, Pages 510–522 Cancer Cell (2010).
3. Marusyk A, Polyak K Tumor heterogeneity: Causes and consequences. Biochim Biophys Acta 1805(1):105–117. (2010).
4. Sottoriva et al., Intratumor heterogeneity in human glioblastoma reflects cancer evolutionary dynamics. ;110(10):4009-14 (2013).
5. Annunziato Mangiola et al. Gene expression profile of glioblastoma peritumoral tissue: an ex vivo study. PLoS ONE ; 8(3):e57145 (2013).

Hierarchical clusters for deregulated genes between core versus normal brain tissue, PBZ versus normal brain tissue and core versus PBZ



Validation of selected genes at RNA and protein level using quantitative Real-time PCR and Immunohistochemistry, respectively.



Acknowledgements:

We would like to acknowledge the Department of Biotechnology (DBT) for financial support and Dr.Ruchi Jain, Post-doctoral fellow at the Indian Institue of Science, for her contributions towards Bio-informatics of the Microarray data.