CNS 2018 ANNUAL MEETING
HOUSTON, TEXAS
OCTOBER 6-10, 2018

Therapeutic Implications of Molecular Profiling of Aggressive Meningiomas

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Introduction

Meningiomas are the most common primary brain tumor in adults, and while most are considered to be benign (WHO grade I), there are clinically aggressive meningiomas (CAMs) with recurrence-free survival less than 5 years and evidence of disease lethality within 7 years that warrant special consideration. Herein, we sought to establish the genomic landscape of CAMs.

Methods

DNA and RNA was extracted from 88 fresh-frozen meningioma samples from our institutional biobank. DNA methylation was performed using Illumina 850k EPIC array and bulk RNA sequencing was performed using HiSeq2000 platform. Unsupervised clustering of differentially methylated post-processed probes was performed. Differential expression at the gene level was computed and quasi-likelihood F test was used to determine the differentially expressed genes and ranked using fold changes. Enrichment Analysis (GSEA) was used to perform pathway analysis. Potentially druggable targets based on gene expression analysis was explored using the Drug-Gene Interaction Database.

Results

Unsupervised clustering of DNA methylation data revealed 3 distinct subgroups of meningiomas that were associated with recurrence-free survival independent of tumour grade ($P < 0.001$). Pathway analysis of differential gene expression between CAMs and benign meningiomas revealed upregulation of genes involved in cell proliferation, cell motility, and cell cycling pathways. Pathways implicating oncogenes such as FOXM1 and MYC were also upregulated in CAMs compared to benign meningiomas. Tumours with a predominant hypoxic profile were identified and found to have significantly worse recurrence free survival compared to non-hypoxic tumours ($P < 0.035$). Using the Drug-Gene Interaction Database, we identified 17 potential druggable targets based on differential gene expression of CAMs compared to benign meningiomas that can be further explored in the setting of clinical trials

Conclusions

CAMs harbour distinct genomic drivers of oncogenesis as compared to benign meningiomas with targets that are currently druggable. Future clinical trials should explore the therapeutic efficacy of targeting drivers of oncogenesis in CAMs

Learning Objectives

By the conclusion of this session, participants should be able to: 1) Describe the importance of DNA methylation profiling in meningiomas, 2) Describe the transcriptomic pathways that differentiate aggressive meningiomas from benign meningiomas, and 3) Identify a potential druggable targets that can be further explored in the setting of clinical trials

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