Therapeutic Implications Of Transcriptome Sequencing In Aggressive Meningiomas

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Background:
We sought to establish the genomic landscape of clinically aggressive meningiomas (CAMs) with recurrence-free survival less than 5 years.

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 Gene Set 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.