complicated in part by widespread inter- and intratumoural heterogeneity. To characterize this heterogeneity, we performed regional subsampling of primary glioblastomas and derived organoids from these tissue samples. We then performed single-cell RNA-sequencing (scRNA-seq) on these primary regional subsamples and 1-3 matched organoids per sample. We have profiled samples from six tumour sets to date and have obtained sequencing data for 21,234 primary tissue cells and 14,742 organoid cells. While the most apparent differences in gene expression appear to be between individual tumours, we were also able to identify similar cellular subpopulations across tissue samples and across organoids. Importantly, organoids derived from the same tissue sample appeared to be composed of similar cellular subpopulations and were highly comparable to each other, indicating that replicate organoids faithfully represent the original tumour tissue. Overall, our scRNA-seq approach will help evaluate the utility of tumour-derived organoids as model systems for GBM and will aid in identifying cellular subpopulations defined by gene expression patterns, both in primary GBM regional subsamples and their associated organoids. These analyses will allow for the characterization of clonal or subclonal populations that are likely to respond to different therapeutic approaches and may also uncover novel therapeutic targets previously unrevealed through bulk analyses.

Clinical/Translational

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Metabolic profiling of gliomas reveals distinct subgroups of tumors independent of IDH mutation status

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Background: Gliomas are the most common and fatal adult brain tumor with distinct genomic subgroups defined by isocitrate dehydrogenase (IDH) mutation status. Mutations in IDH result in overproduction of the oncometabolite 2-hydroxyglutarate (2HG). The landscape of metabolic changes that define gliomas has not previously been explored. Methods: We performed liquid chromotography-mass spectrometry (LC-MS) to examine over 700 metabolites on 90 fresh-frozen glioma samples (30 IDH-wildtype, 30 IDH-mutant 1p/19q codeleted, 30 IDH-mutant 1p/19q non-codeleted) from our institutional biobank. R and S enantiomers of 2HG were quantified using high pressure liquid chromatography tandem mass spectrometry coupled with a CHIROBIOTIC R column. Genome wide DNA methylation was performed on all tumors using Illumina 850k EPIC array. Unsupervised consensus clustering of differentially expressed metabolites and methylated post-processed probes was performed. Copy number variations were determined based on intensity values of the methylation array. Survival of unsupervised cluster groups was determined using the Kaplan-Meier Estimate. Results: Unsupervised clustering of 689 metabolites revealed 2 distinct subgroups of gliomas associated with recurrence-free survival (RFS, P = 0.021). IDH mutant tumours were found in both cluster groups where as IDH-wildtype tumors were found only in Group 2. Group 2 IDH-mutant tumors had unfavourable PFS, higher R/S-2HG levels, and higher proportion of copy number alterations (4q, 9p, 13q, 17q) compared to group 1 IDH-mutant tumors (P=0.048, P=0.0194, P<0.0001 respectively) compared to group 1 IDH-mutant tumors. (P= p=0.048). Conclusions: Metabolic profiling of gliomas reveals 2 distinct subtypes of IDH-mutant independent of 1p/19q codeletion status with differing survival patterns and large scale chromosomal alterations that may be driven by varying levels of R/S-2HG.

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SESSION EIGHT ~ GLIOMA

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Identifying and prognosticating malignant brain tumors non-invasively using unique metabolomic signatures derived from patient serum and urine samples

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BACKGROUND: Metabolomics technology has the potential to revolutionize how we screen, diagnose, and treat cancer, as well as improve upon existing cancer molecular tests that may not sufficiently capture the complexity of most malignancies. In this study, we explore the clinical potential of metabolomics analysis in the diagnosis and risk-stratification of brain tumors. METHODS: To test the hypothesis that brain tumor type and survival could be predicted with metabolomics, we analyzed the pre-operative serum and urine samples of patients with glioblastoma (GBM), oligoastrocytoma (OA2), meningioma (M1) and compared them to healthy controls. (HC). Sera from immune-deficient NOD-SCID mice xenografted with human GBM brain tumor initiating cells were also studied. RESULTS: Metabolomics analysis of patient samples was able to accurately differentiate GBM, OA2, M1 and HC (p = 2.3 x 10-26). Subsequently, a prediction model developed and validated internally was able to diagnose GBM with a sensitivity of 86.7% and specificity of 93.8%, and distinguish whether a GBM patient possess O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation (p = 7.4 x 10-10). Within the MGMT methylated group, the model was able to predict longevity (p = 3.25 x 10-4). The model was also able to predict survival irrespective of MGMT methylation status (p = 2.9 x 10-6). CONCLUSIONS: In this study, we demonstrate that metabolomic analysis of patient biofluids can identify brain tumors, distinguish brain tumor subtypes, and independently predict MGMT status as well as longevity among GBM patients. Metabolomics analysis may facilitate non-invasive diagnosis of aggressive brain tumours.

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Integration of multiple platforms to discover idh-mutant glioma subtypes

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Purpose: Diffuse gliomas can be divided on the basis of presence or absence of mutation in IDH genes. IDH-mutant diffuse gliomas represent a wide range of clinical outcome, which is not accounted for by current clinical and pathologic parameters. We aim to