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

43

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

***Nassiri F**, Nejad R, Yasheng M, Torchia J, Aldape K, Zadeh G.*
farshad.nassiri@mail.utoronto.ca

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.

1535 - 1620
SESSION EIGHT ~ GLIOMA

07

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

D Yusuf, AD Singh, R Shaykhutdinov, J Wen, P Forsyth, HJ Vogel, JG Cairncross, AM Weljie, JC Easaw.
dimas.yusuf@alumni.ubc.ca

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.

46

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Integration of multiple platforms to discover idh-mutant glioma subtypes

Yasin Mamatjan, Farshad Nassiri, Severa Bunda, Fabio Moraes, Kenneth D. Aldape, Gelareh Zadeh. ymaimait@uhnres.utoronto.ca

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

identify clinically and biologically relevant subgroups within IDH-mutant gliomas to gain a deeper insight into finer sub-classification. Methods: We used 412 IDH-mutant glioma samples that were profiled by The Cancer Genome Atlas (TCGA) Research Network, utilising methylation/mRNA datasets to identify subtypes with unique molecular signatures. We applied a Similarity Network Fusion (SNF) on individual platforms and their integrations. Results: SNF approach split glioma into four groups. The integrated RNA/methylation subtype produced a highly prognostic groups that predict survival (p-value=0.003) compared to mRNA and methylation alone. We observed a high degree of correlation between integrative subtypes and somatic mutations. Groups 1&4 had higher TERT promoter mutations (35% and 16%, respectively) compared to groups 2&3. Groups 1&4 showed increased TERT expression (34% and 14% respectively), and high percentage of TP53 and ATRX mutations. Multivariate analysis after adjusting for confounding factors including grade and age showed prognostic factors associated with survival (HR=3.2, p-value=0.001) in group 4 versus others. Conclusions: The results indicate that clinically relevant alterations exist within IDH-mutant gliomas that could stratify patients for treatment. Interestingly, group 4 showed high expression of HOX genes (18/18) (p-value=0.01) and higher methylation of Hox genes (21) (p-value=0.01) compared to others. Higher expression of specific Hox genes were associated with worse survival.

49

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Dianhydrogalactitol (VAL-083) reduces glioblastoma tumor progression in vivo, upon bevacizumab-induced hypoxia

A Golebiewska, A Oudin, A Steino, JA Bacha, DM Brown, S Niclou. asteino@delmarpharma.com

Standard-of-care for glioblastoma (GBM) includes surgery, radiation and temozolomide. Nearly all tumors recur and 5-year survival is less than 3%. Unmethylated promoter status O6-methylguanine-DNA-methyltransferase (MGMT) is a validated biomarker for temozolomide-resistance. Second-line treatment with bevacizumab has not only failed to improve survival, but has also been shown to induce intratumor hypoxia and increased chemoresistance. VAL-083 is a bi-functional DNA-targeting agent that readily crosses the blood-brain barrier. VAL-083 targets N7-guanine, causing DNA double-strand breaks and cancer cell-death in GBM cancer stem cells (CSCs) and non-CSCs, independent of MGMT. To investigate the in vivo anti-tumor effect of VAL-083+bevacizumab, we used an orthotopic GBM T16 PDX model. All mice carried MGMT-unmethylated, temozolomide-resistant recurrent GBM tumors detected by MRI 35 days post-implantation. Tumor progression was measured by MRI on days 49 and 56, and was calculated for the entire study (day 35 vs. 56) and for the last 7 days (day 49 vs. 56). Mice were grouped into control, bevacizumab, VAL-083, and VAL-083+bevacizmab. VAL-083 treatment started 3 days after bevacizumab treatment to ensure induction of hypoxia. Results: Tumors were significantly smaller in VAL-083-treated mice both compared to control (-83%, $p<0.001$) and compared to bevacizumab-treated (-75%, $p<0.001$) mice. Additionally, analysis of tumor growth in-time showed significantly reduced tumor progression for VAL-083+bevacizumab compared to VAL-083 alone ($p<0.01$). Conclusions: These results show strong in vivo anti-tumor efficacy of VAL-083 against MGMT-unmethylated, recurrent GBM. This effect was further augmented in combination with bevacizumab, providing rationale of clinical investigation of VAL-083+bevacizumab in GBM.

1720-1805 SESSION NINE | TOP SCORING ABSTRACTS

29

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Unraveling molecular drivers of brain cancers at the clinical setting

D. Wong, Y. Shen, A. B. Levine, T. Hoon Lee, E. Pleasance, M., Jones, B. Thiessen, B. Toyota, C.M, J. Laskin, S. Jones, M. A Marra, S. Yip. derekwong90@gmail.com

Brain tumor behavior is driven by aberrations in the genome and epigenome. Many of these changes, such as IDH mutations in diffuse low-grade glioma (DLGG), are common amongst the same class of tumour and can be incorporated into the diagnostic criteria. However, any given tumor may have other, less common genomic aberrations that are essential for its biological behavior and may inform on underlying aberrant cellular pathways, and potential therapeutic agents. Precision oncology is a genomics-based approach which profiles these alterations to better manage cancer patients and has established itself within the practice of oncology and is slowly making its way into neuro-oncology. The BC Cancer‟s Personalized OncoGenomics (POG) program has profiled 16 adult tumours originating from the central nervous system using whole genome and transcriptome analysis (WGTA), for the first time, within a meaningful clinical timeframe/setting. As expected, primary genomic drivers were consistent with their respective diagnoses, though secondary drivers were found to be unique to each tumour. Although these analyses did not result in altered clinical management for these patients, primarily due to availability of drug or clinical trials, they highlight the heterogeneity of secondary drivers in cancers and provide clinicians with meaningful biological information. Lastly, the data generated by POG has highlighted the frequency and complexity of novel driver fusions which are predicted to behave similarly to canonical driver events in their respective tumours. The information available to clinicians through POG has provided paramount knowledge into the biology of each unique tumour.

59

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Microglia and macrophages display heterogeneous phenotypes in IDH-mutant and -wildtype glioblastomas

Candice C. Poon, Runze Yang, Tanveer Sheikh, Katherine Liu, Susobhan Sarkar, V. Wee Yong, John J. Kelly. ccpoon@ucalgary.ca

Background: CNS innate immune cells, microglia and macrophages (MMs), are the largest component of the inflammatory infiltrate in glioblastoma (GBM). They initially participate in tumor surveillance, but are subverted by GBM. Immunotherapies have proven incredibly successful in cancers