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Program and Abstracts
(Plenaries, Orals and Posters)

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GLIOBLASTOMA STEM CELLS EXPRESS NON-CANONICAL PROTEINS AND EXCLUSIVE MESENCHYMAL-LIKE OR NON-MESENCHYMAL-LIKE PROTEIN SIGNATURES

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Glioblastoma's (GBM) origin, recurrence and resistance to treatment are driven by GBM cancer stem cells (GSCs). Existing transcriptomic characterisations of GBM classify the tumours to three subtypes: classical, proneural, and mesenchymal. The comprehension of how expression patterns of the GBM subtypes are reflected at global proteome level in GSCs is limited. To characterise protein expression in GSCs, we performed in-depth proteogenomic analysis of patient-derived GSCs by RNA-sequencing and mass-spectrometry proteomics. We identified and quantified over 10,000 proteins in two independent GSCs panels, and propose a GSC-associated proteomic signature (GSAPS) that defines two distinct morphological conditions; one defined by a set of proteins expressed in non-mesenchymal - proneural and classical - GSCs (GPC-like), and another expressed in mesenchymal GSCs (GM-like). The expression of GM-like protein set in GBM tissue was associated with hypoxia, necrosis, recurrence, and worse overall survival in GBM patients.

In a proof-of-concept proteogenomic approach, we discovered 252 non-canonical peptides expressed in GSCs, i.e., protein sequences that are variant or derive from genome regions previously considered protein-non-coding. We report new variants of the heterogeneous ribonucleoproteins (HNRNPs), which are implicated in mRNA splicing. Furthermore, we show that per-gene mRNA-protein correlations in GSCs are moderate and vary compared to GBM tissue.

GLIOBLASTOMA TUMOROIDS: OVERVIEW AND CHALLENGES

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With the increasing role of the microenvironment on tumor growth, appropriate pre-clinical models are needed to develop promising therapeutic strategies and to promote bench to bedside transfer. Tumoroids aim to reconstitute a tumor in a dish for a long-term culture. In the 1990's a brain tumoroid model was first developed but abandoned in favor of simpler models such as cell lines until 2016 when the development of this model again emerged to get closer to the real tumor. The current challenge of this model, in the context of glioblastoma, is to preserve the heterogeneity of the cell composition, in particular the cancer stem cells and the microenvironment. In the GlioME team, we are successfully developing tumoroids based on the culture of small tumor pieces to preserve the organization and the cellular composition of the tumor (vessels, immune cells, tumor stem cells). To monitor the stability of the model over time, we compare the cellular composition of cultured tumoroids to the parental tumor by immunohistochemistry and flow cytometry. In parallel, we are standardizing our approach to perform drug screening and to move towards a personalized medicine.

SERUM EXTRACELLULAR VESICLE-DERIVED CIRCHIPK3 AND CIRCSMARCA5 ARE TWO NOVEL DIAGNOSTIC BIOMARKERS FOR GLIOBLASTOMA MULTIFORME

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Glioblastoma multiforme (GBM) is the most frequent and deadly human brain cancer. We propose the use of serum extracellular vesicle (sEV)-derived circular RNAs (circRNAs) as highly stable, minimally invasive biomarkers for GBM diagnosis. EVs were isolated by size exclusion chromatography from sera of 23 GBM and 5 grade 3 glioma (GIII) patients, and 10 unaffected controls (UC). The expression of two candidate circRNAs (circSMARCA5 and circHIPK3) was assayed by droplet digital PCR. CircSMARCA5 and circHIPK3 were significantly less abundant in sEVs from GBM patients with respect to UC (-2.15 and -1.92 fold, respectively) and GIII (−1.75 and −1.4 fold, respectively). Receiver operating characteristic curve (ROC) analysis, based on the expression of sEV-derived circSMARCA5 and circHIPK3, allowed to distinguish GBM from UC (AUCs = 0.823 (0.667–0.979) and 0.855 (0.704 to 1.000), with a 95% confidence interval (CI), respectively). Multivariable ROC analysis, performed by combining the expression of sEV-derived circSMARCA5 and circHIPK3 with preoperative neutrophil to lymphocyte (NLR), platelet to lymphocyte (PLR) and lymphocyte to monocyte (LMR) ratios (three known diagnostic and prognostic GBM markers) allowed an improvement in the GBM diagnostic accuracy (AUC 0.901 (0.7912 to 1.000), 95% CI). Our data suggest sEV-derived circSMARCA5 and circHIPK3 as good diagnostic biomarkers for GBM, especially when associated with preoperative NLR, PLR and LMR.

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THE INFLUENCE OF VALPROIC ACID ON TOTAL DNA METHYLATION LEVEL IN GLIOBLASTOMA CELL LINES

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Valproic acid (VPA) is a first-line antiepileptic drug for glioblastoma (GBM) patients. There is also some evidence it improves the clinical outcome in those patients. However, the exact mechanism of VPA action is vague. Temozolomide (TMZ) is a first-line chemotherapeutic in GBM. Epigenetics offers a connection between genetic and environmental factors that influence the development of the disease. The best-characterized epigenetic mark is 5-methylcytosine (m5C) in DNA. The aim of that project is to show the effects of VPA administration on the total DNA methylation level. Using the nucleotide post-labeling method, we analyzed the total amount of m5C in DNA of GBM (T98G, U118, U138), cancer (HeLa) and normal (HaCaT) cell lines treated with VPA, and a combination of VPA and with TMZ. We adjusted the VPA doses to the ones achieved in the central nervous system during treatment. We observed dose-dependent changes in the total DNA methylation in neoplastic cell lines and the lack of such effect in a normal cell line. VPA alone produced a clear dose-dependent increase in total DNA methylation in GBM