targeting TAM/M function warrant evaluation. Such concepts might be evaluated in vivo using the herein established orthotopic mouse model.

BSCI-09. MULTIOMIC SINGLE CELL ANALYSIS REVEALS EMERGING PRINCIPLES OF TUMOR IMMUNE MICROENVIRONMENT INHERENT TO NSCLC BRAIN METASTASES

Lei Wen, Changguo Shan, Da Liu, Cheng Zhou, Linbo Cai; Guangdong Sanjiu Brain Hospital, Guangzhou, China

Brain is one of the most common sites for distant metastasis of lung cancer. Treatment naïve lung cancer patients diagnosed with brain metastasis are left with very limited options. Checkpoint inhibition is a powerful immunotherapy strategy but delivers benefit only to a small population of patients. Here we harnessed the power and resolution of single cell RNA sequencing and single cell TCR/BCR sequencing to investigate the tumor immune microenvironment (TIME) of NSCLC brain metastases. We enrolled treatment naïve lung cancer patients with brain metastasis. The enrolled subjects covered different histology types and driver gene mutation status. We revealed the emerging principles of innate and adaptive immune components inherent to NSCLC brain metastases. We also uncovered several significant intercellular communication patterns that potentiates cancer cell seeding and fosters cancer cell proliferation. Those results served as a starting point to design optimal immunotherapy strategies for advanced lung cancer patients with limited options.

BSCI-10. INVASIVE GROWTH OF BRAIN METASTASES IS DRIVEN BY CANCER CELL-PSTAT3+ REACTIVE ASTROCYTE CROSSTALK

Matthew Dankner[1], Sarah Maritan[1], Rebecca Zhuang[2], Maxime Caron[3], Neibla Priego[4], Manuel Valiente[4], Kevin Petrecca[5], Peter Siegel[1]; [1]Goodman Cancer Research Centre, McGill University, Montreal, QC, Canada, [2]University of British Columbia, Faculty of Medicine, Vancouver, BC, Canada, [3]McGill University Genome Centre, Department of Human Genetics, Montreal, QC, Canada, [4]Spanish National Cancer Research Center (CNIO), Madrid, Spain, [5]Montreal Neurological Institute-Hospital, Department of Neurology and Neurosurgery, Montreal, QC, Canada

BACKGROUND: Brain metastases (BrM) with a highly invasive (HI) histological growth pattern are associated with poor prognosis compared to minimally invasive (MI) masses. Compared to MI lesions, HI BrM form greater contacts with cells in the peritumoral brain, particularly reactive astrocytes (RAs). RAs expressing phosphorylated STAT3 (pSTAT3+RAs) have been shown to promote BrM colonization. Here, we investigate the role of pSTAT3+RAs in promoting invasive growth of HI BrM. METHODS: We performed immunohistochemistry to identify pSTAT3+RAs in HI and MI human and patient-derived xenograft BrM. We assessed how pharmacological STAT3 inhibition or RA-specific STAT3 genetic ablation affected HI and MI BrM growth *in vivo*. scRNA-seq data generated from HI BrM astrocytes were integrated with published RA secretome data to identify STAT3 targets expressed by RAs that may drive invasion. Cancer cell invasion was modeled *in vitro* using a brain slice-tumor co-culture assay. RESULTS: HI BrM display increased pSTAT3-positivity within RAs when compared to MI lesions. Pharmacological STAT3 inhibition with Legasil (Silibinin) or genetic ablation decreased *in vivo* growth of HI, but not MI, BrM. Brain slice cultures treated with STAT3-activating cytokines induced cancer cell invasion, a response that was ablated following STAT3 inhibition. Chi3L1 was identified as a STAT3 target expressed by RAs. Cancer cells treated with recombinant Chi3L1 showed greater invasion into brain slice cultures compared to untreated cells. CONCLUSIONS: pSTAT3+RAs are over-represented in HI BrM, rendering HI BrM preferentially sensitive to STAT3 inhibition. pSTAT3+RAs functionally contribute to BrM invasion within the brain, in part through Chi3L1-mediated activity. This work identifies STAT3 and Chi3L1 as clinically relevant therapeutic targets in management of HI BrM.

BSCI-11. TARGETING PI3K/AKT/MTOR PATHWAY TO PREVENT MELANOMA BRAIN METASTASIS

Cedric Tehranian[1], Laura Fankhauser[1], Patrick N. Harter[2], Colin D. H. Ratcliffe[3], Pia S. Zeiner[2], Julia M. Messmer[1], Dirk C. Hoffmann[1], Katharina Frey[1], Dana Westphal[4], Michael W. Ronellenfitsch[2], Erik Sahai[3], Wolfgang Wick[1,5], Matthia A. Karreman[1,5], Frank Winkler[1,5]; [1]Clinical Cooperation Unit Neurooncology, German Cancer Research Center, Heidelberg, Germany, [2]Frankfurt Cancer Institute, Frankfurt, Germany, [3]Tumour Cell Biology Laboratory, The Francis Crick Institute, London, United Kingdom, [4]Department of Dermatology, Medical Faculty and University Hospital Carl Gustav Carus, TU Dresden, Dresden, Germany, [5]Neurology Clinic and National Center for Tumor Diseases, University Hospital Heidelberg, Heidelberg, Germany

BACKGROUND: Patients developing brain metastasis (BM) still face a poor survival due to limited treatment options. BM prevention using low dose drug schedules could be a more potent strategy with less side effects than treating established BM. This could add a real benefit to the ongoing challenge of facing the frequent BM formation in high-risk malignant melanoma (MM) patients. METHODS: Aiming to study the dynamics of PI3K/Akt/mTOR (PAM) pathway activation during the brain metastatic cascade, *in vivo* molecular imaging with an Akt biosensor was performed. Long-term intravital multiphoton microscopy through a chronic cranial window in mice was employed to investigate timing and effectiveness of PAM pathway inhibition for BM prevention. RESULTS: *In vivo* molecular imaging revealed the activation of PAM pathway as a prerequisite for extravasation of circulating MM cells in the brain. However, established human BM present with heterogeneous activation of the PAM pathway. Moreover, in two MM mouse models, PAM pathway inhibition with the brain-penetrant dual PI3K/mTOR inhibitor GNE-317 resulted in only moderate effects on established BM. In contrast, giving low dose GNE-317 in a preventive schedule successfully reduced growth rate and number of BM in both mouse models. Longitudinal intravital multiphoton microscopy suggests that the first, rate-limiting, steps of BM formation can be effectively targeted by dual PI3K/mTOR inhibition. CONCLUSION: PAM pathway activation is key for the critical early steps of MM metastatic brain colonization. These findings reveal that early PAM pathway inhibition is a promising strategy to prevent the formation of clinically relevant BM.

BSCI-12. INHIBITION OF MELANOMA BRAIN METASTASIS BY TARGETING MIR-146A

Jiwei Wang[1,2], Emma Rigg[2], Taral R. Lunavat[2], Wenjing Zhou[1], Zichao Feng[1], Tuyen Hoang[2], Rolf Bjerkvig[2], Frits Thorsen[1,3]; [1]Department of Neurosurgery, Qilu Hospital of Shandong University and Brain Science Research Institute, Shandong University, Key Laboratory of Brain Functional Remodeling, Shandong, Jinan, China, [2]Department of Biomedicine, University of Bergen, Bergen, Norway, [3]Molecular Imaging Center, Department of Biomedicine, University of Bergen, Bergen, Norway

BACKGROUND: Melanoma has the highest propensity of any cancer to metastasize to the brain, with late-stage patients developing brain metastasis (MBM) in 40% of cases. Survival of patients with MBM is around 8 months with current therapies, illustrating the need for new treatments. MBM development is likely caused by molecular interactions between tumor cells and the brain, constituting the brain metastatic niche. miRNAs delivered by exosomes released by the primary tumor cells may play a role in niche establishment, yet the mechanisms are poorly understood. Here, the aim was to identify miRNAs released by exosomes from melanomas, which may be important in niche establishment and MBM progression. MATERIALS AND METHODS: miRNAs from exosomes collected from human astrocytes, melanocytes, and MBM cell lines were profiled to determine differential expression. Functional *in vitro* validation was performed by cell growth and migration assays, cytokine arrays, qPCR and Western blots. Functional *in vivo* studies were performed after miR knockdown in MBM cell lines. An *in silico* docking study was performed to determine drugs that potentially inhibit transcription of miR-146a to impede MBM development. RESULTS: miR-146a was the most upregulated miRNA in exosomes from MBM cells and was highly expressed in human and animal MBM samples. miR-146a mimics activated human astrocytes, shown by increased proliferation and migration, elevated expression of GFAP *in vitro* and in mouse brain tumor samples, and increased cytokine production. In animal studies, knockdown of miR-146a in MBM cells injected intracardially into mice reduced BM burden and increased animal survival. Based on the docking studies, deserpidine was found to be an effective inhibitor of MBM growth *in vitro* and *in vivo*. CONCLUSIONS: MiR-146a may play an important role in MBM development, and deserpidine is a promising candidate for clinical use.

BSCI-13. MTH1 EXPRESSION IS UPREGULATED IN BRAIN METASTASES OF MALIGNANT MELANOMA

Marco Timmer; Neurosurgery, Cologne, Germany

OBJECTIVE: MuT Homolog1 (MTH1) is an enzyme involved in DNA repair in normal cells and is often up- regulated in cancer cells. The enzyme catalyses the hydrolysis of oxidised dNTPs, to prevent their incorporation into DNA or RNA, resulting in mutations or cell damage/death. Cancer cells can have a high concentration of ROS, due to defective redox regulation. This results in the damage of DNA and oxidises free dNTPS, which in turn leads to mutations in DNA replication or cell death. Identifying MTH1 in brain metastases could present a target for treatment with MTH1-Inhibitors. METHODS: The quantification of MTH1 expression was shown using