environment, serving as a guiding partner for metastasis. This educational program, however, is not well understood. Here, we show that tumor-educated platelets (TEPs) acquire tumor promoting functions and drive breast cancer progression, metastasis to distal sites including the brain, as well as therapeutic resistance. Importantly, TEPs promoted an increased pro-tumorigenic effect on metastatic breast cancer, compared to their wild-type counterpart, leading to epithelial to mesenchymal transition through NF-κB/STAT3 signaling axis via C/EBPβ transcription factor. Our findings point to the important role of TEPs in breast cancer brain metastasis and therapeutic resistance, which could have a major implication in other tumor types, endorsing TEPs as a potential therapeutic target.

BSCI-05. ABL2-HSF1-E2F SIGNALING AXIS PROMOTES LUNG ADENOCARCINOMA BRAIN METASTASIS

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Brain metastases are the most common intracranial tumors in adults and are associated with increased patient morbidity and mortality. Limited therapeutic options are currently available for the treatment of brain metastasis. We have identified an actionable signaling pathway utilized by metastatic tumor cells whereby the transcriptional regulator Heat Shock Factor 1 (HSF1) drives a transcriptional program, divergent from its canonical role as the master regulator of the heat shock response, leading to enhanced expression of a subset of E2F transcription factor family gene targets. We showed that HSF1 is required for survival and outgrowth by metastatic lung cancer cells in the brain parenchyma. Unexpectedly, we identified the ABL2 tyrosine kinase as an upstream regulator of HSF1 protein expression, and showed that the Src-homology 3 (SH3) domain of ABL2 directly interacts with HSF1 protein at a non-canonical, proline-independent SH3 interaction motif. Importantly, knockdown of ABL2 impairs expression of HSF1 protein and HSF1-E2F transcriptional gene targets. Notably, we found that pharmacologic inhibition of the ABL kinases using selective ABL allosteric inhibitors, but not ATP-competitive inhibitors, ablates the physical interaction between ABL2 and HSF1, leading to markedly decreased expression of HSF1, E2F1 and E2F8 proteins in brain-metastatic lung cancer cells, and depletion of HSF1-E2F transcriptional targets. These findings highlight potential differences affecting intra- and inter-molecular protein-protein interactions induced by allosteric versus ATP-competitive kinase inhibitors that have important therapeutic implications. Importantly, the targetable nature of the ABL2-HSF1-E2F signaling network identifies ABL allosteric inhibitors as a potentially effective therapy for the treatment of metastatic lung cancers characterized by high expression of HSF1.

BSCI-06. PHAGE DISPLAY BIOPANNING IDENTIFIES AMOT REGULATING CELL MOTILITY IN BRAIN METASTASIS-INITIATING CELLS

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OBJECTIVE: Metastatic brain tumors (MBTs) are the most common type of malignant brain tumors. Due to the deviation of MBTs from the parental tumors, the effective therapies for primary tumors often are not working in brain metastases. Even more new intracranial lesions were developed though the primary lesion was controlled. The occurrence of brain metastasis-initiating cells (BMICs) suggested the possibility of its spread intracranially. Here we aimed to explore the biological behavior in cell motility of BMICs and understand the potential mechanisms. METHODS: In vitro and in vivo phage display biopanning strategies were used to isolate dodecapeptides that specifically target BMICs by selecting against primary lung cancer cells and normal brain cells. In silico analysis was used to derive specific protein targets in BMICs. Potential targets were narrowed down through analysis in patient databases and verified for their presence in BMIC through RT-PCR. Cell migration and adhesion in BMICs were analyzed using Transwell, scratch, and adhesion assays. Protein expression and cell morphology were detected by immunofluorescence. Immune blot was performed to detect the epithelial-mesenchymal related molecules and explore protein-protein interactions. RESULTS: In silico analysis of BMICs specific peptides revealed Angiomotin (Amot) as a potential target in BMICs. Amot was found to be overexpressed in BMICs compared to primary lung cancer cells. Kaplan-Meier analysis demonstrated Amot was negatively correlated with overall survival among lung adenocarcinoma patients. Knockdown of AMOT in BMICs decreased the capability of cell migration and adhesion, through the downregulation of E-Cadherin. Amot was found to maintain the E-Cadherin in BMICs through reducing ubiquitination of E-Cadherin. Furthermore, the knockdown of E-Cadherin decreased cell migration and adhesion due to the decrease in cdc42 activity. CONCLUSIONS: Amot plays a role in promoting migration and adhesion in BMICs through preservation of E-Cadherin.

BSCI-07. MULTIOMICS CHARACTERIZATION OF BRAIN METASTASES IN MULTIPLE HISTOLOGIES IDENTIFIES ENRICHMENT OF OXIDATIVE PHOSPHORYLATION AS A PROMISING THERAPEUTIC TARGET

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PURPOSE: Brain metastasis (BM) is a lethal complication from systematic malignant tumors, and the incidence is approximately 10–30% of patients with advanced cancer. Extensive genomic analyses with large sample sets and the following functional studies revealed clinically relevant characteristics for BMs. However, these studies have not identified specific abnormalities driving BM in multiple tumor histologies yet. To identify molecular pathogenesis and promising therapeutic targets shared across multiple histologies of BMs, we performed multiomics molecular profiling, along with functional studies using in vitro and in vivo BM models. METHODS: Frozen tissues of patient-matched BMs and primary tumors (or extracranial metastases) from breast cancer (N= 14), lung cancer (N = 14) and renal cell carcinomas (N = 7) patients were carried out whole-exome sequencing, mRNA-Seq and reverse-phase protein array. Paired parental and brain metastatic derivatives of MDA-MB-231 and BT474 were examined to assess findings from the multiomics datasets. SCID/beige mice were inoculated with MDA-IBC3 cells via tail vein injection and administered an oxidative phosphorylation (OXPHOS) inhibitor by oral gavage daily for 96 days. RESULTS: The multiomics molecular profiling identified enrichment of OXPHOS shared across the histologies of BMs. Brain metastatic derivative cell lines also demonstrated enhanced oxidative metabolism, along with the sensitivity to an OXPHOS inhibitor. Moreover, in vivo studies revealed that OXPHOS inhibition significantly impaired the formation of BM, and fresh brain metastatic derivatives from the murine BM model exhibited the higher oxidative metabolism and sensitivity to the OXPHOS inhibitor as with the prior in vitro studies. CONCLUSIONS: Our multiomics characterization of BMs demonstrates heightened oxidative metabolism shared across the multiple histologies, and the OXPHOS inhibition affects more effectively for brain metastatic derivatives rather than the parentals. Further investigation focusing on metabolic abnormalities in BM will likely develop promising therapeutic strategies against BMs.

BSCI-08. *IN VIVO* TWO-PHOTON CHARACTERIZATION OF TUMOR-ASSOCIATED MACROPHAGES AND MICROGLIA (TAM/M) AND CX3CR1 DURING DIFFERENT STEPS OF BRAIN METASTASIS FORMATION FROM LUNG CANCER

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BACKGROUND: Brain metastases represent a common complication of lung cancer and dramatically limit prognosis in affected patients. The influence of tumor-associated macrophages and microglia (TAM/M) and their receptor CX3CR1 on different steps of brain metastasis formation from lung cancer is poorly characterized, but might be of therapeutic relevance. METHODS: We established an orthotopic cerebral metastasis model using CX3CR1-proficient ($CX3CR1^{GFP/wt}$) and -deficient ($CX3CR1^{GFP/GFP}$) mice with green-fluorescent TAM/M. A cranial window was prepared, and intracarotid injection of red-fluorescent Lewis Lung Carcinoma-cells (^{tdt}LLC) was performed two weeks later. Formation of brain metastases was followed by repetitive two-photon laser scanning microscopy. RESULTS: After intracarotid injection, intravascular tumor cells extravasated into the cerebral parenchyma and eventually formed micrometastases (≤50 cells) and mature macrometastases (>50 cells). We observed phagocytosis of extravasated tumor cells by TAM/M during early steps of metastatic growth. Notably, these anti-tumor effects of TAM/M diminished during later steps of metastasis formation and were accompanied by TAM/M accumulation and activation. CX3CR1-deficiency resulted in a lower number of extravasated tumor cells, and only a small number of TAM/M were visualized during early steps of metastasis formation (extravasation, formation of micrometastases) in such mice. In contrast, progression of extravasated tumor cells into micrometastases was more frequently found in CX3CR1-deficient mice. Overall, these mechanisms resulted in a comparable number of mature macrometastases between CX3CR1-deficient and -proficient mice. CONCLUSION: Our findings indicate that unspecific inhibition of CX3CR1 might not be a suitable therapeutic approach to prevent cerebral dissemination of lung cancer cells. Given the close interaction between TAM/M and tumour cells during metastasis formation, other therapeutic approaches