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The compression of brain tissue by a tumor mass is believed to be a major cause of the clinical symptoms seen in patients. However, the biological consequences of these physical stresses on the brain tissue are unknown. Using clinical imaging and preclinical studies, we discovered that a subgroup of primary and metastatic brain tumors, classified as nodular based on the growth pattern, exert compressive solid stress on the surrounding brain tissue, leading to a decrease in local vascular perfusion, as well as neuronal death and impaired function. We demonstrated a causal link between solid stress and neurological dysfunction, by applying and removing cerebral compression, mimicking the mechanics of tumor growth and surgical resection respectively. Finally, we showed that treatment with lithium reduced solid stress-induced neuronal death and improved motor coordination in mice. Our results indicate that brain tumor-generated solid stress impairs neurological function in patients and show lithium as a potential therapeutic intervention to counter these effects.

BSCI-11. STROMAL PLATELET DERIVED GROWTH FACTOR RECEPTOR-B (PDGFRB) PROMOTES BREAST CANCER BRAIN METASTASIS

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Stromal platelet-derived growth factor receptor-beta (PDGFRβ) has emerged as an actionable mediator of breast tumor-stromal communication. As a receptor tyrosine kinase, PDGFRβ is activated by its ligand, PDGFB, which is released by neighboring tumor epithelium and endothelium. However, how PDGF signaling mediates breast cancer (BC) initiation, progression, and metastasis remains unclear. To evaluate PDGFRβ in this disease, we developed a mouse model of stromal-specific PDGFRβ activation using the *Fsp-cre* transgene previously published by our group. Mesenchymal-specific activation of PDGFRβ promotes preferential experimental brain metastasis of PDGFB-expressing mammary tumor cells when injected intravenously and accelerates intracranial tumor growth of these cells. Mammary tumor cells expressing low levels of PDGFB do not exhibit a similar increase in brain metastases in PDGFRβ mutant mice. To our knowledge, this is the first example where genetic manipulation of the stroma leads to an increased incidence of BCBM. Our pre-clinical data suggests that primary breast tumors that express high PDGFB could preferentially metastasize to the brain. To test this in patients, we analyzed PDGFB protein expression in a tissue microarray comprised of HER2-positive and triple negative BC primary tumors. While high PDGFB did not correlate with site-independent metastatic recurrence, it was prognostic of brain metastasis, mirroring our mouse data. Our findings suggest that high primary tumor PDGFB expression defines a subset of BC patients predisposed to brain metastases. These patients may benefit from therapeutic intervention of PDGFRβ signaling. To test this preclinically, we treated mice harboring intracranial tumors with the PDGFR-specific inhibitor, crenolanib. Excitingly, crenolanib treatment significantly inhibited the brain tumor burden in these mice. Combined, our findings (1) advocate that primary tumor expression of PDGFB is a novel prognostic biomarker for the development of BCBM and (2) support clinical trial evaluation of PDGFR inhibitors for the prevention and treatment of BCBM.

BSCI-12. COMPREHENSIVE GENOMIC ANALYSIS OF BRAIN METASTASES FROM MULTIPLE CANCER TYPES

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PURPOSE: Brain metastases occur in approximately 8–10% of patients with cancer, and the incidence has increased over the past decades. The most common primary tumors responsible for brain metastases are lung cancer, melanoma, renal cell carcinoma (RCC), breast cancer and colorectal cancer. The precise mechanisms by which genomic and transcriptional abnormalities drive the formation of brain metastases remain unclear. Here, we conducted comprehensive genomic and transcriptional analysis with paired primary tumor tissue (or extracranial metastasis tissue) and brain metastasis tissue using whole-exome sequencing (WES), mRNA-Seq and global methylation profiling. METHODS: Frozen, paired brain metastasis tissue and primary tumor tissue (or extracranial metastasis tissue) and white blood cells were acquired from RCC (n=12), breast cancer (n=17), lung cancer (n=15) and melanoma (n=14) patients, followed by extraction of DNA and RNA. WES and mRNA-Seq were performed on the Illumina HiSeq4000 platform. For methylation profiling, DNA was analyzed using Illumina Infinium MethylationEPIC Beadchip arrays. RESULTS: Somatic mutations or methylation of *VHL* gene were identified in 81.8% of RCC patients. Gene Set Enrichment Analysis revealed significant enrichment for hypoxia pathway transcripts in RCC brain metastases relative to primary tumors. The most common alterations in breast and lung cancer patients were *TP53* mutations with frequencies of 50.0% and 73.3%, followed by *ERBB2* alterations (43.8%) in breast cancer patients and mutually exclusive alterations of *EGFR* (33.3%) and *KRAS* (26.7%) in lung cancer patients. Mutually exclusive alterations of *NRAS* (42.9%) and *BRAF* (42.9%) were also observed in melanoma patients. Gene expression and epigenetic analysis revealed characteristics of brain metastases depending on primary cancer types. CONCLUSIONS: Comprehensive genomic analysis of brain metastases from four different cancer types revealed that brain metastasis tissues have unique genomic, transcriptional and epigenetic profiles according to histopathology groups. Therefore, the therapeutic strategies should be designed based at least in part on tumor histiogenesis.

BSCI-13. TUMOR-SPECIFIC TGLI1 TRANSCRIPTION FACTOR MEDIATES BREAST CANCER BRAIN METASTASIS VIA ACTIVATING METASTASIS-INITIATING CANCER STEM CELLS AND ASTROCYTES IN THE TUMOR MICROENVIRONMENT

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Breast cancer is the second leading cause of brain metastases in women; patients with breast cancer brain metastasis (BCBM) survive only 6–18 months after diagnosis. Mechanisms for BCBM remain unclear, which contributes to ineffective treatments and dismal prognosis. Truncated glioma-associated oncogene homolog 1 (tGLI1) belongs to the GLI1 family of zinc-finger transcription factors and functions as a tumor-specific gain-of-function mediator of tumor invasion and angiogenesis. Whether tGLI1 plays any role in metastasis of any tumor type remains unknown. Using an experimental metastasis mouse model, via intracardiac implantation, we showed that ectopic expression of tGLI1, but not GLI1, promoted preferential metastasis to brain. Conversely, selective tGLI1 knockdown using tGLI1-specific antisense oligonucleotides led to decreased brain metastasis of intracardially inoculated breast cancer cells. Furthermore, intracranial implantation mouse study revealed tGLI1 enhanced intracranial colonization and growth of breast cancer cells. Immunohistochemical staining of patient samples showed that tGLI1, but not GLI1, was increased in lymph node metastases compared to matched primary tumors, and that tGLI1 was expressed at higher levels in BCBM specimens compared to primary tumors. Whether tGLI1 plays any role in radioresistance is unknown; we found radioresistant BCBM cell lines and patient specimens expressed higher levels of tGLI1 than radiosensitive counterparts, and that tGLI1 promotes radioresistance. Since cancer stem cells (CSCs) are highly metastatic and radioresistant, we examined whether tGLI1 promotes BCBM and radioresistance through activating CSCs. Results showed that tGLI1 transcriptionally activates stemness genes CD44, Nanog, Sox2, and OCT4, leading to stem cell activation. Furthermore, we observed that tGLI1-positive CSCs strongly activated and interacted with astrocytes, the most abundant brain tumor microenvironmental cells known to promote tumor growth, *in vitro* and *in vivo*. Collectively, our findings establish a novel role of that tGLI1 plays in promoting breast cancer preferential metastasis to brain, radioresistance, and astrocytes in the metastatic niche.

BSCI-14. SYNTHETIC METASTATIC BRAIN DISEASE MRI IMAGES CREATED USING A GENERATIVE ADVERSARY NETWORK TO OVERCOME DEEP MACHINE LEARNING CHALLENGES IN HEALTHCARE

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Deep Machine Learning (DML) in commercial applications such as recognizing animal species in photographs occurred through analyzing large volumes of public data. To achieve similar success in brain tumor imaging, additional factors must be addressed such as the need to follow strict regulatory protocols, work with limited datasets, and protect patient privacy. Generative adversary network (GAN) restricted to intracranial disease is one possibility to overcome these challenges and enable training on small annotated datasets to synthesize new samples. Large fabricated brain metastases (BM) training datasets derived from patient MRI using GAN models may enable DML of BM MRI studies. METHOD: We randomly selected 82 glioma