seeking 231-BR subclone of MDA-MB-231 TNBC cells, which harbors a loss of PTEN compared to parental cells. Brain metastases were generated in nude mice by intracardiac injection of $1.75x10^5$ 231-BR cells engineered for expression of luciferase, as confirmed by IVIS one week after injection. Mice with brain metastases were treated by tail vein injection of control (PBS, n=7) or DX1 (20 mg/kg, n=7) 3x/week for 4 weeks. Mice were observed for behavior and weights, and brain radiance efficiency was monitored by weekly IVIS to track metastatic tumor growth. PAT-DX1 significantly suppressed growth of brain metastases based on absolute and relative radiance efficiencies in the brain, increased the median survival of the mice from 38 to 52 days ($P< 0.02$), and was well tolerated. These results provide proof of concept for use of a re-engineered autoantibody against brain metastases.

BSCI-05. HOW MICROGLIA, BRAIN RESIDENT MYELOID CELLS, RESPOND TO BREAST CANCER METASTASIS INTO THE BRAIN?

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Brain metastasis from different cancers, including lung, breast, melanoma, colorectal or renal cell carcinoma is relatively common and its frequency increases with a prolonged survival of cancer patients. New anti-cancer therapies frequently fail to reduce metastatic burden. While the important role of tumor-associated macrophages as pro-tumorigenic cells facilitating tissue remodeling, invasion and metastasis is well documented, much less is known about the immune microenvironment of brain metastases and potential mechanisms that mediate interactions of cancer cells with brain immune cells - microglia. Triple-negative breast cancer metastases to the brain were discovered in 46% of patients. We evaluated the abundance and morphology of microglia on sections from breast cancer metastases using immunohistochemistry. We found that microglia cells are activated, surround the breast tumor cells and do not infiltrate the solid tumor. Searching for a potential attractant of microglia, we determined osteopontin levels in six human breast cancer cell lines and found upregulation of osteopontin in transformed cells, with the highest level in the triple-negative MDA-MB-231 cells. MDA-MB-231 cells activated primary murine microglia cultures when co-cultured. Invasion of MDA-MB-231 cells in co-cultures with murine immortalized BV2 microglial cells and human SV40 immortalized microglia was increased, as demonstrated using Matrigel Invasion Assay. Using immunofluorescence we detected osteopontin in cancer cells in human breast cancer metastases. Moreover, we found that minocycline, a clinically used antibiotic, reduces the osteopontin production in human breast cancer cells and the most sensitive cells were MDA-MB-231 cells. Our study shows that metastatic cancer cells may employ microglia to facilitate extravasation and colonization of brain parenchyma. We postulate that osteopontin mediates interactions between microglia and metastatic cancer cells and minocycline may interfere with those interactions. Funding: TEAM TECH CORE FACILITY FNP: Development of comprehensive diagnostics and personalized therapy in neuro-oncology

BSCI-06. FREQUENCY OF BRAIN METASTASIS FROM BREAST AND LUNG CANCER IN THE UNITED STATES -- A POPULATION-BASED ASSESSMENT

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BACKGROUND: Brain metastases (BM) are the most common central nervous system tumor in the United States and occur with increasingly frequency due to improved screening and therapeutics leading to improved survival. Current estimates of frequency of BM vary significantly by cancer site and are typically not population-based. Population-based estimates of incidence have recently become possible due to collection of data on BM identified at diagnosis ("synchronous" BM, SBM). BM may occur at any point after cancer diagnosis. We report our recent population-based estimates of SBM and period incidence of BM (PBM) from breast (BC) and lung cancer (LC). METHODS: Data from Surveillance, Epidemiology, and End Results (SEER, 2010–2016 diagnoses) were used to estimate SBM and linked data from SEER-Medicare (2008–2012 diagnoses for individuals 65+, with 2007–2014 claims) were used to estimate PBM, for BC and LC overall and by BC and LC subtypes. RESULTS: Within the SEER data, 10.9% of LC cases presented with SBM (15.5% in small cell LC [SCLC], and 10.8% in non-small cell LC [NSCLC]); 0.4% of BC cases presented with SBM, 0.7% in triple negative (TNBC), 0.8% for HER2+, and 0.2% for ER+\PR+\HER2-. Within the SEER-Medicare data, 13.5% of LC overall had LBM with 23.1% for SCLC and 15.3% for NSCLC; 1.8% of BC overall had LBM with 4.2% in triple negative (TNBC), 3.1% for HER2+, and 1.1% for ER+\PR+\HER2. CONCLUSION: Frequency of synchronous and period BM varies by originating site as well as subtype. The new SBM variable in SEER allows for estimation of this important statistic, while the SEER-Medicare linked data allows for estimation of PBM, both on a population-level for the US population. These estimates are useful to clinical practice and critical for estimating morbidity and mortality due to BM.

BSCI-07. BONE MARROW T-CELL SEQUESTRATION IN THE SETTING OF BRAIN METASTASES

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INTRODUCTION: Brain metastases remain one of the most dreaded consequences of late stage cancer, yet their incidence has risen as survival from primary cancers has improved. We have recently reported that tumors harbored within the brain, specifically, sequester T-cells within the bone marrow as a novel mechanism of immune evasion. Sequestration results from tumor-imposed loss of S1P1 receptor from the T-cell surface. Stabilization of the receptor on T-cells frees T-cells from sequestration and licenses T-cell activating therapies for intracranial tumors. While this phenomenon was initially uncovered in glioblastoma, its role in promoting immune-evasion in brain metastases remains less clear. METHODS: Blood, bone marrow, and tumors were collected from mice bearing intracranial tumors commonly metastatic to the brain, including lung carcinoma (LLC), melanoma (B16F10), or breast carcinoma (E0771) and analyzed by flow cytometry. T-cell S1P1 levels, as well as total T-cell counts were assessed in each compartment. Correlation analyses were conducted between T-cell counts and S1P1 levels on T-cells in the bone marrow across intracranial and subcutaneous murine tumor models. RESULTS: T-cell lymphopenia and accompanying accumulation of T-cells in the bone marrow were observed in the murine models of lung carcinoma, melanoma, and breast carcinoma, but only when these tumor lines were implanted intracranially. Sequestered T-cells in tumor-bearing mice showed decreased surface S1P1 levels in a manner correlating with their sequestration. CONCLUSION: S1P1-mediated bone marrow T-cell sequestration is a novel mode of cancer-induced T-cell dysfunction in intracranial tumors. Preventing receptor internalization abrogates T-cell sequestration and licenses T-cell activating therapies in glioblastoma. Sequestration is now observed in models of brain metastases. Pharmacologic strategies to stabilize S1P1, reverse sequestration, and restore circulating T-cell numbers are anticipated to improve immunotherapeutic efficacy for brain metastases.

BSCI-09. MECHANISMS OF ENHANCED DRUG DELIVERY IN BRAIN METASTASES WITH FOCUSED ULTRASOUND-INDUCED BLOOD-TUMOR BARRIER DISRUPTION

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Blood-brain/blood-tumor barriers (BBB and BTB) and interstitial transport may constitute major obstacles to the transport of therapeutics in brain tumors. In this study, we examined the impact of focused ultrasound (FUS) in combination with microbubbles on the transport of two relevant chemotherapy-based anticancer agents in HER2-positive breast cancer brain metastases at cellular resolution: the non-targeted chemotherapeutic doxorubicin and the antibody-drug conjugate ado- trastuzumab emtansine (T-DM1). Using an orthotopic xenograft model of HER2-positive breast cancer brain metastasis and quantitative microscopy we demonstrate multifold increases in the extravasation of both agents (7-fold and 2-fold for doxorubicin and T-DM1, respectively) and we provide evidence of increased drug penetration (>100μm vs. < 20μm and 42±7μm vs. 12±4μm for doxorubicin and T-DM1, respectively) after application of FUS as compared to control (non-FUS). Integration of experimental data with physiologically based pharmacokinetic (PBPK) modeling of drug transport reveals that FUS in combination with microbubbles alleviates vascular barriers and enhances interstitial convective transport via increase in hydraulic conductivity. Combination of experimental data and PBPK modeling suggests that FUS in combination with microbubbles increases the endothelial cell transmembrane transport and uptake. PBPK modelling indicates selective increase in transvascular transport of the non- targeted small chemotherapeutic doxorubicin through small vessel-wall pores size with a narrow range (Diameter: 10-50nm). Our work provides a quantitative framework for the optimization of FUS-drug combinations to maximize intratumoral drug delivery and facilitate the development of novel therapeutic strategies against brain metastases.

BSCI-10. NEUROLOGICAL DYSFUNCTION CAUSED BY BRAIN TUMOR-GENERATED SOLID STRESS IS REVERSED BY LITHIUM

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