ferent tissues, including the brain, bone, and lung. While 20 OR transcripts were differentially expressed in distant metastases, OR5B21 displayed high expression in all three metastatic sites with respect to the primary tumor, especially in brain metastasis with 13 fold higher than the primary site. Metastatic clones showed distinguishing higher invasion biological characteristics compared to parental cells in vivo and in vitro. Knockdown of OR5B21 significantly decreased the invasion and migration of MDA-MB-231 Brain-seeking metastatic cell as well as metastasis to different organs, including the brain, while overexpression of OR5B21 had the opposite effect. Mechanistically, OR5B21 expression was associated with epithelial to mesenchymal transition through the STAT3/NFkB/CEBPβ signaling pathway. We propose OR5B21 (and potentially other ORs) as a novel oncogene contributing to breast cancer brain metastasis and a potential target for adjuvant therapy.

TAMI-05. FATTY ACID SYNTHESIS IS REQUIRED FOR HER2+ BREAST CANCER BRAIN METASTASIS

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Brain metastases are refractory to therapies that control systemic disease in patients with human epidermal growth factor receptor 2-positive breast cancer and the brain microenvironment contributes to this therapy resistance. Nutrient availability can vary across tissues, therefore metabolic adaptations required for brain metastatic breast cancer growth may introduce liabilities that can be exploited for therapy. Here we assessed how metabolism differs between breast tumors in brain versus extracranial sites and found that fatty acid synthesis is elevated in breast tumors growing in the brain. We determine that this phenotype is an adaptation to decreased lipid availability in the brain relative to other tissues, resulting in site-specific dependency on fatty acid synthesis for breast tumors growing at this site. Genetic or pharmacological inhibition of fatty acid synthase reduces human epidermal growth factor receptor 2-positive breast tumor growth in the brain, demonstrating that differences in nutrient availability across metastatic sites can result in targetable metabolic dependencies.

TAMI-06. TUMOR CELL-DERIVED CYTOKINE EXPRESSION CHANGES ASSOCIATED WITH BRAIN METASTASIS IN A SYNGENEIC MOUSE MODEL OF BREAST CANCER

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Breast cancer is the most common malignancy in women in the United States, and brain metastases occur in almost a third of patients with metastatic dissemination. Immunoediting is a critical component of metastatic tumor cell elimination, and tumor clones that develop immune-escape mechanisms are associated with progression and metastatic dissemination. We hypothesized that breast cancer brain metastatic cells harbor immunomodulatory cytokine expression changes that promote an immunosuppressive environment to avoid immune cell-mediated elimination. To study this, a syngeneic mouse model of metastatic breast cancer was used. A brain metastatic line derived from the 4T1 breast cancer parental cell line was created by serially selecting brain metastatic populations of cells after intracardiac injection (4T1 BrM). A gene-expression analysis using an 800-gene cancer immunology-specific microarray panel was performed comparing the 4T1 parental and 4T1 BrM lines. 4T1 BrM cells demonstrate gene expression changes promoting immunosuppression including significant upregulation of IL18 and Lgals9 (Galectin-9) and downregulation of CD40, IL2rg, CCL2, and EOMES. When compared to 4T1 parental lines, the 4T1 BrM line demonstrated decreased expression of CCL2 and increased expression of GM-CSF on a cytokine array, corresponding to results obtained from gene expression analysis. These results suggest tumor-intrinsic cytokine expression changes that may mediate an immunosuppressive environment.

TAMI-07. TUMOR-EDUCATED PLATELETS GUIDE BREAST CANCER BRAIN METASTASIS AND PROMOTE THERAPEUTIC RESISTANCE

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BACKGROUND: Platelets have been shown to play an important role in systemic and local tumor modulation. Once encountered by tumor cells, platelets are educated to collect and release pro-tumor factors in the tumor/microenvironment, serving as a guiding partner for metastasis. This educational program, however, is not well understood. METHODS: Wild-type platelets (WTPs) were isolated from blood of healthy humans or mice, whereas tumor-educated platelets (TEPs) were isolated from blood of breast cancer patients or from tumor-bearing donor mice. The tumorigenic and modulatory effect of these two types of platelets on breast cancer was examined *in-vitro* and *in-vivo*. RESULTS: Here, we show that TEPs acquire tumor promoting functions and drive breast cancer progression, metastasis to distal sites specifically 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, promoting epithelial to mesenchymal transition through NF-κB/STAT3 signaling axis via C/EBPβ transcription factor. CONCLUSION: 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.

TAMI-08. THE CCL2-CCR2 ASTROCYTE-CANCER CELL AXIS IN TUMOR EXTRAVASATION AT THE BRAIN

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Although brain metastases are common in cancer patients, little is known about the mechanisms of extravasation across the blood-brain barrier (BBB), a key step in the metastatic cascade that regulates the entry of cancer cells into the brain parenchyma through its selective endothelial barrier. Progress in this area has been impeded by challenges in conducting high spatio-temporal resolution imaging in vivo and isolating factors and cellular interactions directly contributing to extravasation rather than cancer survival and proliferation in the brain tissue. To address these limitations, we engineered a three-dimensional in vitro BBB microvascular model with endothelial cells derived from induced pluripotent stem cells, brain pericytes, and astrocytes, into which we perfused cancer cells to recapitulate their circulation and extravasation at the BBB. With this platform, we revealed that astrocytes play a major role in promoting cancer cell transmigration via their secretion of C-C motif chemokine ligand 2 (CCL2). We found that this chemokine promoted the chemotaxis and chemokinesis of cancer cells via their C-C chemokine receptor type 2 (CCR2), with no significant changes in vascular permeability. These findings were validated in vivo, where CCR2-deficient cancer cells exhibited significantly reduced cancer cell arrest and transmigration in mouse brain capillaries. Our results attest to the translational value of our BBB-on-a-chip model and reveal that the CCL2-CCR2 astrocyte-cancer cell axis plays a fundamental role in extravasation and consequently metastasis to the brain.

TAMI-09. INTRAOPERATIVE MICRODIALYSIS AS A FEASIBLE PLATFORM FOR METABOLIC AND PHARMACODYNAMIC BIOMARKER DISCOVERY

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BACKGROUND: Progress for gliomas is slowed in part by the paucity of mechanistic feedback during treatment with experimental therapies. Access to extracellular tumor pharmacodynamic biomarkers could provide an avenue to accelerate progress. We have initiated a program of intra-operative microdialysis to accelerate biomarker discovery and to identify candidate outcome measures for translational therapies. METHODS: Intraoperative microdialysis was performed with M-dialysis 100kDA catheters and 107 variable rate pumps under an IDE. Four IDH-mutant and two IDH-WT lesions were studied intraoperatively with 3 divergently placed catheters. Microperfusate (artifical CSF+ 3% dextran) was perfused at 2uL/min and collected in 20 min increments. Paired CSF was also obtained when accessible. A parallel cohort of nude mice bearing human IDH-mutant, IDH-WT, or sham intracranial xenografts (n=6-12) underwent intratumoral microdialysis. A pilot murine study of intracranial drug delivery was performed via concurrent microdialysis during convection-enhanced delivery (CED) of saline or the IDH-inhibitor AG120. RESULTS: Microdialysate from IDH-mutant intracranial xenografts revealed >100 differentially abundant metabolites compared to sham or IDH-WT tumors, including D2-HG (21x) and MTA(18x), p< 10^-5. The most significantly abundant metabolite was DMA (4x, p< 10^-10). 15-1000uM D2HG was recovered from intra-operative human IDH-mutant tumors and 1-2uM from normal brain adjacent to IDH-WT gliomas and < 1uM in all IDH-WT samples. Forty metabolites differentiated enhancing tumor from adjacent brain in 3/3 paired human samples including upregulated Aminoacyl-tRNA biosynthesis and downregulated purine metabolism. Serial aliquots of microdialysate during saline CED yielded steady D2-HG levels whereas CED with AG120 yielded undetectable D2-HG within 6 hours. CONCLUSION: The extracellular metabolic landscape of glioma is diverse, dynamic and reflects tumor