Neuro-Oncology Advances 3:iii1–iii26, 2021.
doi:10.1093/noajnl/vdab071

NEURO-ONCOLOGY ADVANCES

THE SOCIETY FOR NEURO-ONCOLOGY, AND THE AANS/CNS SECTION ON TUMORS: 3RD ANNUAL CONFERENCE ON BRAIN METASTASES

Abstract Categories and Codes
BSCI – Basic Science
TRLS – Clinical Trials
LMD – Leptomeningeal Disease
THER – Medical Therapy (Chemotherapy and Immunotherapy)
MLTI – Multimodality
OTHR – Other
RADI – Radiation
SURG – Surgery

BASIC SCIENCE

BSCI-01. SMALL RNASEQ ANALYSIS OF MICRORNAS IN BRAIN METASTASIS

Radim Jancalek[1], Frantisek Siegl[2], Jiri Sana[2,3], Simona Sidorova[2], Marek Vecera[2], Karolina Trachtova[2], Michal Hendrych[4], Vaclav Vybihal[5], Martin Smrcka[5], Marketa Hermanova[4], Tomas Kazda[6], Ondrej Slaby[2,3]; [1]Department of Neurosurgery, St, Anne's University Hospital Brno, Brno, Czech Republic, [2]Central European Institute of Technology (CEITEC), Masaryk University, Brno, Czech Republic, [3]Department of Pathology, University Hospital Brno, Brno, Czech Republic, [4]Department of Pathology, St. Anne's University Hospital Brno, Brno, Czech Republic, [5]Department of Neurosurgery, University Hospital Brno, Brno, Czech Republic, [6]Clinic of Radiation Oncology, Masaryk Memorial Cancer Institute, Brno, Czech Republic

MicroRNAs (miRNAs) are a well-known subclass of short non-coding RNAs responsible for posttranscriptional gene silencing and have been described as dysregulated in many cancers. They have also been shown to be both specific diagnostic, prognostic, and predictive biomarkers as well as therapeutic targets. Therefore, specific miRNA expression patterns of BMs of various origins could serve as a promising diagnostic tool for determining both the original tumor and the prognosis in patients with BMs of unknown origin. For identifying significantly dysregulated miRNAs among BMs (n = 90) with various origin and non-tumor brain tissues (n = 12), small RNAseq analyses were used. cDNA libraries were prepared using QIAseq miRNA Library Kit and purified by Qiaseq beads. The final sequencing analyses were performed by Next 500/550 High Output v2 Kit-75 cycles using the NextSeq 500 instrument. For miRNA mapping and analysis, Miraligner and MirBase were used. Bioinformatic analysis of obtained sequencing data identified 472 significantly dysregulated miRNAs (logFc>2, adj.p-value<0.05) between BM and non-tumor samples. The comparison of BMs origin from lung BMs (n = 26) with other BMs revealed 132 significantly dysregulated miRNAs, mainly miR-4662a-5p, miR-1179, miR-211-5p, miR-146a-5p, and miR-194-5p. The most significantly dysregulated miRNAs in breast BMs were miR-4728-3p, miR-211-5p, miR-184, miR-365b-5p, and miR-2115-3p. In BMs originating from melanoma, miR-200c-3p, miR-141-5p, miR-200b-5p, miR-514a-3p, and miR-200b-3p showed the most aberrant expression. We have demonstrated that miRNA profiling could be a potent tool for the partition of brain metastases based on their origin. We found that miRNA signatures corresponding to particular origins are rather distinct from the profiles of the rest of BMs. Our results suggest that after validation, miRNA profiling can be used to identify the origin of brain metastases and potentially for the refinement of the diagnosis.

Supported by the Ministry of Health of the Czech Republic, grant nr. NV18-03-00398.

BSCI-02. METPLATFORM IDENTIFIES BRAIN METASTASIS VULNERABILITIES AND PREDICTS PATIENT RESPONSE TO THERAPY

Lucía Zhu[1], Carmen Blanco-Aparicio[1], Luca Bertero[2], Riccardo Soffietti[2], Tobias Weiss[3], Javier Muñoz[1], Juan Manuel Sepúlveda[4], Michael Weller[3], Joaquín Pastor[1], Manuel Valiente[1]; [1]Spanish National Cancer Research Center, Madrid, Spain, [2]University and City of Health and Science Hospital, Turin, Italy, [3]University Hospital Zurich, Zurich, Switzerland, [4]Hospital Universitario Doce de Octubre, Madrid, Spain

The diagnosis of brain metastasis involves high morbidity and mortality and remains an unmet clinical need in spite of being the most common tumor in the brain. Exclusion of these cancer patients from clinical trials is a major cause of their limited therapeutic options. We report a novel drug-screening platform (METPlatform) based on organotypic cultures which allows identifying effective anti-metastasis agents in the presence of the organ microenvironment. By applying this approach to brain metastasis, we identified heat shock protein 90 (HSP90) as a promising therapeutic target for CNS dissemination. DEBIO-0932, a blood-brain barrier permeable HSP90 inhibitor, shows high potency against mouse and human brain metastases from different primary origin and oncogenomic profile at clinically relevant stages of the disease, including a novel model of local relapse after neurosurgery. Furthermore, *in situ* proteomic analysis of brain metastases treated with the chaperone inhibitor revealed non-canonical clients of HSP90 as potential novel mediators of brain metastasis and actionable mechanisms of resistance driven by autophagy. Combined therapy using HSP90 and autophagy inhibitors showed synergistic effects compared to sublethal concentrations of each monotherapy, demonstrating the potential of METPlatform to design and test rationale combination therapies to target metastasis more effectively. Finally, we have exploited METPlatform as "avatars" to show that brain tumor PDOCs predict response of the corresponding patient to standard of care, thus proving the potential of METPlatform for improving personalized care in cancer. In conclusion, our work validates METPlatform as a potent resource for metastasis research integrating drug-screening and unbiased omic approaches that is fully compatible with human samples and questions the rationale of excluding patients with brain metastasis from clinical trials. We envision that METPlatform will be established as a clinically relevant strategy to personalize the management of metastatic disease in the brain and elsewhere.

BSCI-03. ADAPTATION OF COLORECTAL CANCER CELLS TO THE BRAIN MICROENVIRONMENT: THE ROLE OF IRS2

Inbal Greenberg[1,2], Anat Klein[1], Rachel Grossman[1], Ethan Sokol[3], Eilam Yeini[2], Paula Ofek[2], Ronit Satchi-Fainaro[2], Bertrand Liang[4], Hadas Reuveni[5], Tami Rubinek[1,2], Ido Wolf[1,2]; [1]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, [2]Tel Aviv University, Tel Aviv, Israel, [3]Massachusetts Institute of Technology, MA, USA, [4]Purple Biotech Ltd., Rehovot, Israel, [5]TyrNovo Ltd., Rehovot, Israel

Colorectal cancer (CRC) reflects the fourth most frequent etiology of brain metastasis (BM). Yet, molecular mechanisms supporting it are unknown. We aimed to explore drivers enabling adaptation of CRC cells to the brain and decipher mechanisms facilitating the process. We analyzed the FoundationOne database, which contains genomic alterations data of cancer-related genes in over 16,000 human CRC primary and metastasis samples. Increased prevalence of IRS2 gene amplification was observed in 13% of BM, compared to only 3% of primary tumors or other metastatic sites. IRS2 is a cytoplasmic adaptor mediating effects of insulin and IGF-1 receptors and is involved in more aggressive behavior of different cancer types. In agreement with the genomic data, immunohistochemistry of human clinical samples showed increased expression of IRS2 protein in BM. We constructed an *in-vitro* system mimicking the brain microenvironment using cultured human astrocytes or their conditioned media. Under these conditions, IRS2-overexpressed CRC cells survived better and formed larger 3D spheres. IRS2-silenced CRC cells showed a mirror image. Moreover, in an intracranial CRC BM mouse model, IRS2-overexpressed cells generated larger brain lesions, while silencing IRS2 dramatically decreased tumor outgrowth and extended survival. Interestingly, transcriptomic analysis revealed enrichment of oxidative phosphorylation (OXPHOS) and Wnt/β-catenin pathways by IRS2. Indeed, IRS2-expressing cells showed increased mitochondrial activity and glycolysis-independent viability. Furthermore, IRS2-expressing cells had increased β-catenin transcriptional activity. Interestingly, β-catenin or IRS2 inhibition (using NT219) in IRS2-expressing cells decreased their viability, β-catenin transcriptional activity, and OXPHOS gene expression, suggesting involvement of IRS2 in modulating OXPHOS through β-catenin. β-catenin is known to confer 5-FU resistance; consequently, we showed that combination of 5-FU and NT219 worked in synergy, inhibited the formation of BM, and extended animal survival. These data reveal the unique genomic profile of CRC BM and suggest IRS2 inhibition as a novel target for treatment of these patients.

BSCI-04. TUMOR-EDUCATED PLATELETS PROMOTE BREAST CANCER BRAIN METASTASIS AND THERAPEUTIC RESISTANCE

Elie Tabet, Bakhos Tannous; Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

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/micro-