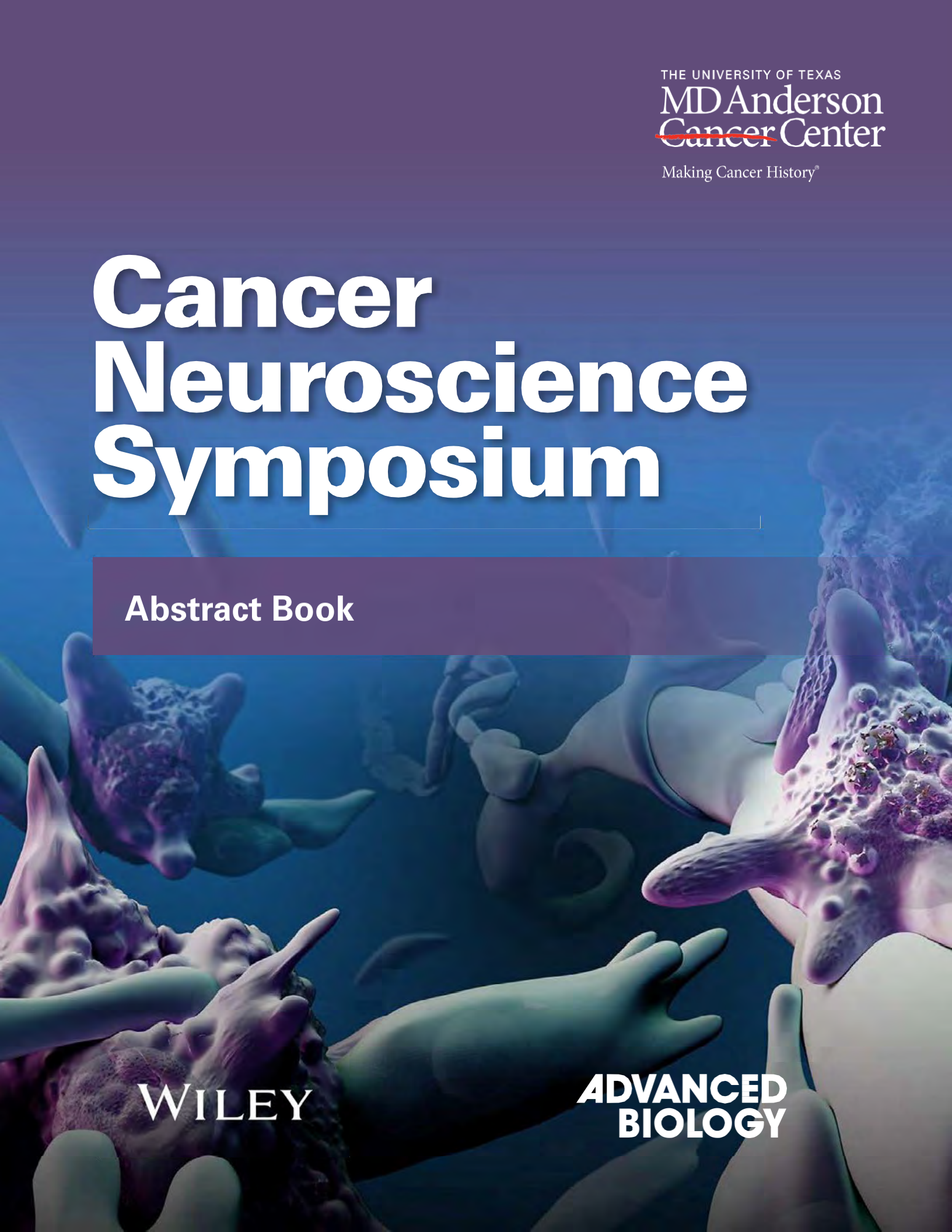
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Cancer Neuroscience Symposium

Abstract Book



WILEY

ADVANCED BIOLOGY

Friday, March 1st 2024, 12:00 – 1:00pm			
Poster	**Title**	**Authors**	**Affiliation**
1	TRPV1+ sensory innervation as a novel driver of ovarian cancer progression	Matthew Knarr, Katherine Cummins, Dusan Racordon,…,Ronny Drapkin	Pennsylvania University
2	Enhanced locus coeruleus response to stress in primary breast adenocarcinoma	Nikolas Holland, Adrian Gomez, Jeremy Borniger	Cold Spring Harbor Laboratory
3	Peripheral nerve subtype dynamics in radiotherapy-treated PDAC	Ella Perrault, Nicole Lester, Hannah Hoffman, William Hwang	Harvard University
4	Validation of TXNIP pathway in developing of chronic oxaliplatin-induced peripheral neuropathy	Junwei Du, Leland C. Sudlow, Kiana Shahverdi,…,Mikhail Y. Berezin	Washington University
5	Neuronal distribution in colorectal cancer: associations with clinicopathological parameters and survival	Maartje Massen, Glenn Rademakers, Meike S. Thijssen,…,Veerle Melotte	Maastrich University
6	Exploring the interplay between neuropeptide signaling and age-onset multiple myeloma in	Silvia Vicenzi, Anna Rapp, Joshua Hartman,…,Leslie Crews	University California San Diego
7	Epigenome Dysregulation in NF1-Associated Malignant Peripheral Nerve Sheath Tumors	Biji Chatterjee, Veena Kochat, Suresh Satpati,…,Kunal Rai	MD Anderson Cancer Center
8	Crosstalk between sensory nerves and tumor cells drives metastasis in breast cancer	Hanan Bloomer, Savannah Parker, Thanh T Le, Tolulepe Adewumi,…, Madeleine J. Oudin	Tufts University
9	Cancer-induced Pain in an Orthotopic Malignant Peripheral Nerve Sheath Tumor (MPNST) Mouse Model	Khalil Ali Ahmad, Ibdanelo Cortez, Irshad Khushboo,…,Yuan Pan	MD Anderson Cancer Center
10	Individualized MRI Neuromodulation Targeted Towards the Alleviation of Radiation-Induced-Cranial-Neuropathy in Head and Neck Cancer	T. Dorina Papageorgiou, Anthony Allam, Duong Huynh,…,Katherine A. Hutcheson	Baylor College of Medicine
11	Neurological Manifestations of Hemophagocytic Lymphohistiocytosis in Cancer Patients: The MD Anderson Cancer Center Experience	Ashley Aaroe, Sudhakar Tummala, Anne Kleiman,…,Sattva Neelapu	MD Anderson Cancer Center
12	Characterizing sex differences in HPV negative cancer	Sarah Barclay	University of South Dakota, Sanford Health
13	Sensory neurons promote breast cancer metastasis via an extracellular RNA/ TLR7 signaling axis	Veena Padmanaban, Isabel Keller, Benjamin N. Ostendorf, Sohail F. Tavazoie	Rockefeller University
14	Histone H3.3 mutant-derived pediatric diffuse gliomas Multi-omic and Cross-species heterogeneity characterization	David Rincon Fernandez Pacheco	California School of Health Sciences
15	Distinct tumor architectures and microenvironments for the initiation of metastasis in the brain	Siting Gan, Danilo G. Macalinao, Sayyed Hamed Shahoei,…,Joan Massagué	Memorial Sloan Kettering Cancer Center
16	Hyperbaric Oxygen Treatment for Chemotherapy-Related Cognitive Impairment: A Focus on Cellular Senescence	Oanh Trinh, Paapa Mensah-Kane, Helen Shi, Nathalie Sumien.	University of North Texas

17	Deciphering Neurodevelopmental Origins of Pediatric Brain Tumors using Single Cell Genomics	Ashmitha Rajendran, Siobhan S. Pattwell	University of Washington
18	Cognitive impairment precedes other neurological symptoms as an early symptom of glioma in mice	B Milutinovic, SK Singh, LM Phillips,…,F Lang	MD Anderson Cancer Center
19	Evaluating the therapeutic potential of novel NTRK agonists in high-risk neuroblastoma	David Johnson, Thomas Schlichthaerle, Natasha Edma,…,Siobhan Pattwell	Seattle Children's Hospital
20	Elucidating the spatial association of tumor microbiome and tumor transcriptome in metastatic brain tumors	Golnaz Morad, Ashish V. Damania, Brenda Melendez,…,Jennifer A. Wargo	MD Anderson Cancer Center
21	Glioma-neuronal circuit integration is modulated by interleukin-6	Thiébaud Picart, Andy Daniel, Saritha Krishna, Shawn Hervey-Jumper	University of California San Francisco
22	Chemotherapy-induced long-term deficits in high-order neurocognitive and sensorimotor function in juvenile mice	Anand Kumar Singh, Renae Bertrand, Rajasekaran Mahalingam,…,Yuan Pan	MD Anderson Cancer Center
23	Self and Proxy Symptom Reporting in Patient-Caregiver Dyads Coping with a Primary Brain Tumor: The Role of Psychosocial Function in Rating Agreement	Kennedy Leonard; Stella Snyder; Shiao-Pei Weathers,…,Meagan Whisenant	MD Anderson Cancer Center
24	A multidimensional model analysis to dissect the impact of brain metastasis on neuronal communication	Masmudi-Martín M.*, Sanchez-Aguilera A., Navas-Olive A,…,Valiente M.	Centro Nacional de Investigaciones Oncológicas
25	A CRISPR/Cas9-Based Assay for High-Throughput Studies of Cancer-Induced Innervation	Sapthala Loku Galappaththi, Brenna Katz, Patrick H. Howze IV,…,Simon Grelet	University of South Alabama
26	Diroximel fumarate reverses doxorubicin-induced cognitive and sensorimotor deficits and associated loss to synaptic protein, microglia phenotypic transition, and myelin damage in mice	Anand Kumar Singh, David Ruiz, Mohd Sami Ur Rasheed, Thomas D. Avery,…,Peter M. Grace	MD Anderson Cancer Center
27	Developing a physical activity intervention for survivors of adolescent and young adult central nervous system tumors	Eduardo Gonzalez Villarreal, Emily C. LaVoy, Tamara E. Lacourt,…, Maria C. Swartz	MD Anderson Cancer Center
28	Elucidating the role of triggering receptor expressed in myeloid cells 2 (TREM2) in glioblastoma	Mekenzie M. Peshoff, Pravesh Gupta, Shivangi Oberai,…,Krishna P. Bhat	MD Anderson Cancer Center

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Cancer Neuroscience Symposium

Friday Posters | March 1

WILEY

ADVANCED BIOLOGY

Friday Abstract 17

Deciphering Neurodevelopmental Origins of Pediatric Brain Tumors using Single Cell Genomics

Ashmitha Rajendran[1,5], Siobhan S. Pattwell[1,2,3,4]
[1]Ben Towne Center for Childhood Cancer Research, Seattle Children's Research Institute, Seattle, WA, USA.
[2]Department of Pediatrics, University of Washington School of Medicine, Seattle, WA, USA.
[3]Human Biology Division, Fred Hutchinson Cancer Center, Seattle, WA, USA
[4]Molecular Medicine and Mechanisms of Disease, University of Washington, Seattle, WA, USA
[5]Biomedical Informatics and Medical Education, University of Washington School of Medicine, Seattle, WA, USA

Introduction

A growing body of evidence has shown that many pediatric brain tumors have embryonic origins with driving aberrations arising in precursor cells associated with neurodevelopment. These linked patterns, however, are not fully understood yet and the genetic mechanisms involved in fetal and embryonic brain development still require additional modeling especially with the advent of big data and single cell technologies. We hypothesize that expanding on existing neurodevelopmental and pediatric brain cancer atlases using single cell RNA sequencing integrative approaches will allow us to 1- create a comprehensive cellular meta-analysis of human neurodevelopment and 2- identify the neurodevelopmental genetic programs involved in pediatric brain cancerprogression.

Methods

Here, we use conventional and novel approaches for single cell RNA sequencing analysis---proposing new methods for cell identification and gene module creation rooted in probabilistic topic models and information theory. We use scRNAseq across 20 datasets in mouse and 5 in human resulting in over 5 million cells across both species. The datasets are individually analyzed using natural language processing techniques and conventional single cell RNA sequencing data analysis approaches to mark cell lineages across developmental time. Subsequently, these atlases are overlaid with single cell RNA sequencing from several pediatric brain cancer datasets to identify contributing cellular lineages.

Conclusion

In this work, we identify gene sets and cellular lineages putatively linked to the transient cell lineages in human fetal and embryonic brain development and possible genetic contributions to specific pediatric brain tumors. Additionally, we validate a geneset creation and cell ID characterization method using unsupervised natural language processing approaches for single cell RNA sequencing.

Significance to the cancer neuroscience field

In this project, we develop a meta-atlas of human brain development with single cell RNA sequencing. We develop and propose using unsupervised methods to derive cell type lineages across developmental time and associated genesets. These genesets across time are used with single cell RNA sequencing from pediatric brain cancers to highlight possible neurodevelopmental contributing effects. These analyses are anticipated to contribute to our understanding of cellular and genetic dynamics involved in embryonic and fetal brain development and uncover novel insight into the origins of pediatric cancer.

Friday Abstract 18

Cognitive impairment precedes other neurological symptoms as an early symptom of glioma in mice

B Milutinovic[1], SK Singh[1], LM Phillips[1], A Shepherd[2], P Grace[2], F Lang[1]

[1] Department of Neurosurgery, MD Anderson Cancer Center Houston Texas 77030 USA

[2] Department of Symptom Research, MD Anderson Cancer Center Houston Texas 77030 USA

Introduction

Gliomas represent 70–80% of central nervous system (CNS) tumors. High-grade glioma patients have impairments in cognitive domains, including executive functions, memory, attention, and language may be observed. Lower cognitive ability and depression symptoms are also related to shorter survival. We hypothesize that, in mouse model of orthotopically implanted glioma, cognitive impairment presents an independent symptom of glioma, that can be observed by specialized testing.

Methods

For assessment of survival and neurological symptoms, mouse GSC-005 (50.000 cells/3 µL) were injected into the right striatum of C57bl mice (male, 10-week-old, n=10) using stereotactic guided surgery (AP:+ 1.0; ML: + 2.0; and DV: − 3.5). Mice were monitored for glioma-specific neurological symptoms (seizures and shaking), as well as weight loss, reduced mobility, hunched position, and ruffled coat. Animals were sacrificed when moribund. For assessment of cognitive function, mouse GSC-005 (50.000 cells/3 µL) were injected into the striatum of C57bl mice (male, 10-week-old, n=15), as previously. Cognitive function was assessed using Novel Object Place Recognition Test (NOPRT) 21 days after tumor injection. To quantify preference for novelty, time spent exploring novel and familiar objects were recorded and discrimination index (DI) was calculated. Animals were sacrificed after completion of testing and brains were collected for histological assessment.

Results

Median survival of orthotopic glioma-bearing mice was 47 days. Seizures were observed in 2/10 animals, coinciding with the appearance of hunched position and ruffled coat. In cognitive testing cohort, on day 21, animals showed normal activity, no seizures were detected, no difference in weight between glioma- bearing and control animals was observed. In NOPRT test, glioma-bearing showed DI significantly reduced compared to control animals (0.3942 vs. 0.01053, $p<0.001$). Tumors collected upon completion of testing showed circumscribed morphology, there was little to no compression of the ventricles and no compression of the hippocampus. Mechanism underlying cognitive impairment may be inferred throughanalysis of RNA sequencing of hippocampi and this data will be discussed.

Conclusions

Reduced DI in glioma-bearing animals indicates impaired spatial and learning memory. In our orthotopicmouse glioma model, cognitive impairment precedes onset of other symptoms. This may be the result of remodeling of neuronal circuits involved in performing specific cognitive tasks.

Significance to the cancer neuroscience field

Understanding mechanisms underlying glioma-related remodeling of neural circuits is a major interest in cancer neuroscience. Elucidating the mechanism involved in this remodeling is essential in designing strategies to manage glioma symptoms.

Friday Abstract 19

Evaluating the therapeutic potential of novel ntrk agonists inhigh-risk neuroblastoma

David Johnson, Thomas Schlichthaerle**,** Natasha Edma, David Baker, Siobhan Pattwell
Seattle Children's Hospital, Seattle, WA

Introduction

Neuroblastoma is the most common extra-cranial tumor diagnosed in children within the first two years of their lives. Although low-risk and intermediate -risk neuroblastoma patients have a survival rate of 90-95%, high-risk neuroblastoma patients have a survival rate of approximately 50%. To improve the survival rate in high-risk patients, our group focuses on tropomyosin receptor kinases (TRKs); a family of tyrosine kinases that have been heavilyimplicated in crucial developmental processes, such as differentiation, that are typically hijacked in cancer. Using de novo agonists specifically designed against TrkA, our group is investigating the fundamental biological role of TrkA receptors in mediating tumorigenesis in neuroblastoma.

Methods

We used immunoblotting, RNA-sequencing, Celltiter Glo, and Incucyte (Neurotrack) to quantify the effects of modulating TrkA activity.

Results

Preliminary results show that our TrkA agonist increase pERK activity and causes a significant decrease in TrkA expression in several neuroblastoma cell lines. Phenotypically, we observe that neuroblastoma cell line SK-N-SY5Y(SY5Y), lose their neuroblast-like phenotype and begin to exhibit significant neurite outgrowth when treated with TrkA agonists. Using retinoic acid(RA) as a positive control for neurite elongation, our results show that TrkA agonists have similarefficiency to RA when causing neurite elongation. Although TrkA agonists don't affect proliferation, when using CellTiter Glo, we saw an increase in cell viability, suggesting that our TrkA agonists may increase metabolic activity in our neuroblastoma cells given this assay quantifies ATP.

Conclusion

Constitutive activation of TrkA via de novo designed TrkA agonists in our neuroblastoma cell lines, leads to significant decrease in TrkA expression which we hypothesize is due to internalization and degradation of TrkA once activated. Moreover, our results suggest that activation of TrkA in SY5Y cells, which is typically used in neuronal differentiation studies, significantly increases neurite elongation with similar efficiency to that of RA, which is currentlyused for treating neuroblastoma. Our results suggest that modulating TrkA activity via highly specific agonists may provide new insight into therapies for neuroblastoma and potentially, othercancers.

Significance to cancer neuroscience field

Our research provides, for the first time: (1) a TrkA agonist specifically designed to bind and activate TrkA receptors, (2) show that activating TrkA with our agonists cause neurite elongation in SY5Y cells with similar efficiency as RA, thereby providing novel insight and potential into a new differentiation mechanism via TrkA activationin neuroblastoma, and ultimately, (4) highlighting a new avenue for treating neuroblastoma.

Friday Abstract 20

Elucidating the spatial association of tumor microbiome and tumor transcriptome in metastatic brain tumors

Golnaz Morad, Ashish V. Damania, Brenda Melendez, Matthew C. Wong, Pranoti Sahasrabhojane, Sarah B. Johnson, Nadim J. Ajami, Sherise D. Ferguson, Jennifer A. Wargo
Department of Surgical Oncology, MD Anderson Cancer Center Houston Texas 77030 USA

Introduction

Metastatic brain tumors are associated with significant morbidity and mortality. Themicrobiome has emerged as a novel hallmark of cancer, with a prominent role in tumor immunity and response to treatment. However, the role of the microbiome in brain tumors, and in particular brain metastasis, is largely unknown. We hypothesize that distinct microbial communities are associated with alterations in the tumor microenvironment in metastatic brain tumors.

Methods

To evaluate the role of different microbial communities in brain metastasis, matched stool, saliva, and tumor samples were collected prospectively from patients with metastatic braintumors who underwent surgical tumor resection at the University of Texas MD Anderson Cancer Center. Stool and saliva samples were sequenced via metagenomic shotgun sequencing and tumor samples were analyzed through 16S rRNA sequencing. The tumor microbiome was furthercharacterized through confocal and electron microscopy and culture techniques. Lastly, we conducted digital spatial profiling using the GeoMx® platform (NanoString Inc.) to determine the spatial association of the tumor microbiome with tumor and immune transcriptome.

Results

Our computational and experimental analyses demonstrated that bacterial signals could be detected in metastatic brain tumors and exhibit an intracellular localization. Interestingly, we found that the tumor microbiome in brain metastasis tumors was composed of oral bacterial taxabut had limited overlap with the gut microbiome. Our digital spatial profiling analysis demonstratedthat tumor areas with high bacterial reads were associated with innate-immune mediated anti- bacterial responses, suggesting the functionality of intra-tumoral bacteria in metastatic brain tumors.

Conclusion

Overall, our clinical study demonstrates that the brain metastasis tumormicroenvironment can harbor bacterial signals and that the tumor microbiome can be associated with immune modulation in the brain microenvironment.

Significance to the cancer neuroscience field

Our study offers a new perspective on the dynamic interaction between cancer, microbiome, and the brain microenvironment and can informfuture mechanistic and translational studies to improve the outcome of brain tumor patients.

Friday Abstract 21

Glioma-neuronal circuit integration is modulated by interleukin-6

Thiébaud Picart, MD, PhD[1, 2] Andy Daniel, PhD[1], Saritha Krishna, PhD[1], Shawn Hervey-JumperMD[1]

1. Glial tumor Neuroplasticity Research, Dr Shawn Hervey-Jumper lab, Department of Neurological Surgery, UCSF, San Francisco, CA, USA
2. Department of Neurosurgery, Hospices Civils de Lyon, Lyon, France

Introduction

The pleiotropic cytokine interleukin-6 (IL6) is involved in several pro- and anti-inflammatory signaling cascades. IL6 promotes local immunosuppression, tumor progression, and is negatively associated with overall survival in animal and human cell line models of glioblastoma. Although IL6 is also known to contribute to neuronal network remodeling following focal brain injury, notably through the regulation of GAP43 expression, and increase synaptogenesis during development, its contribution to glioma-induced circuit remodeling is poorly understood. Few studies have evaluated the effects of IL6 using primary patient-derived glioma and may therefore not recapitulate *in vivo* conditions in patients. Here, we investigated the neuromodulatory potential of IL6 to influence glioma-induced circuit remodeling using primary patient-derived glioma samples.

Methods

The transcriptomic profiles and *IL6* expression were compared in regions of high (HFC) and low (LFC) intratumoral functional connectivity originating from primary glioblastomas using bulk and single-cell RNA sequencing. IL6 and GAP43 expression was also assessed by immunofluorescence in a panel of gliomas of various grade, in HFC and LFC regions. Mouse embryonic cortical neurons and primary patient-derived glioblastoma cells were cultured separately or together. Neuronal activity was assessed for cells cultures on microelectrode arrays, using weighted mean firing rate (WMFR), network burst frequency (NBF), and synchrony index (SI). The effects of exogenously applied recombinant human IL6 and pharmacological inhibition using the humanized IL6 receptor antibody tocilizumab on neuronal activity and tumor connectivity were monitored over time.

Results

The expression profile of IL6 and GAP43 was different in samples originating from HFC and LFC regions. *In vitro*, coculture with neurons modified the expression profile of IL6 and GAP43 by tumors cells. Consistent with clinical findings, neuronal hyperexcitability was observed in the pre- treated co-culture conditions compared to the neuron-only condition. At different concentrations,exogeneous IL6 decreased WMFR and NBF, while increasing SI in neuronal networks. In co- culture conditions however, there were divergent concentration-dependent effects of IL6 on WMFR and NBF whereas SI was reliably suppressed. In pre-treated co-culture conditions, tocilizumab application also resulted in reduced SI.

Conclusion

These findings suggest that the expression of IL6 may depend on the functional connectivity status.IL6-signaling induces neuromodulatory effects on glioma-neuronal circuits in a concentration- dependent manner. Future studies are needed to understand how IL6-dependent mechanisms differentially impact neuronal firing and network synchrony.

Significance to the cancer neuroscience field

A better understanding of mechanisms regulated by IL6-signaling could help to design new therapeutic options likely to improve oncological and functional outcomes.

Friday Abstract 22

Chemotherapy-induced long-term deficits in high-order neurocognitive and sensorimotor function in juvenile mice

Anand Kumar Singh[1], Renae Bertrand[1], Rajasekaran Mahalingam[1], Khalil Ali Ahmad Kasm[1], Yuan Pan[1]

[1]Department of Symptom Research, University of Texas MD Anderson Cancer Center, Houston TX USA

Introduction

Because of major advancements in cancer treatment methods especially chemotherapy, 85% of children with cancer are predicted to survive for 5 years or more. However, chemotherapy can cause long-term health problems when childhood cancer survivorsenter adulthood, lasting for months and years (known as *late effects*). The neurocognitive features of these *late effects* (chemobrain) include trouble in concentrating, memorizing, and decreased processing speed, and results in lower IQ and academic achievement, poor hand-eye coordination, and slower development over time. Despite such a negative impact on the quality of life of cancer-surviving children, the mechanism is poorly understood and there is no FDA- approved drug to prevent or cure these side effects. To gain a better understanding of the mechanism underlying chemotherapy-induced cognitive impairments, we are developing a pre-clinical model using carboplatin in juvenile mice to study long-term neurological defects.

Method

Using our juvenile mouse model, we have tested the capacity of different doses of carboplatin (30, 60, and 90 mg/kg) and its long-term effect on cognitive and sensorimotor function. We have also carried out single nuclear RNA sequencing (RNAseq) of hippocampal tissue to identify cell types, genes, and potential molecular pathways involved in the neurotoxicity.

Results

Our preliminary data demonstrated dose-dependent deficits in executive and sensorimotor function 7-9 weeks after carboplatin administration in the mice of both sexes. Single nuclear RNAseq of the hippocampus showed changes in the glial cell number as well as genes associated with oxidative phosphorylation and neurodegeneration at early and late time points.

Conclusion

Juvenile exposure to carboplatin leads to long-term deficits in high-order neurocognitive and sensorimotor functions. The behavioral deficits could be due to early and late changes in pathways associated with oxidative phosphorylation and changes in the glial cells.

Significance to the cancer neuroscience field

The current study established a preclinical modelthat can be leveraged to mechanistically understand the long-term neurocognitive side effects of chemotherapy during childhood. Our study aims to identify potential targets to prevent and/or cure the neurotoxic effects of cancer treatment in pediatric patients.

Friday Abstract 23

Self and Proxy Symptom Reporting in Patient-Caregiver Dyads Coping with a Primary Brain Tumor: The Role of Psychosocial Function in Rating Agreement

Kennedy Leonard[1]; Stella Snyder[2]; Shiao-Pei Weathers[3]; Eduardo Bruera[4]; Kathrin Milbury[1]; MeaganWhisenant[1]

[1]Department of Behavioral Science, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA; [2]Department of Psychology, School of Science, Indiana University-Purdue University at Indianapolis; [3]Department of Neuro-Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA; [4]Department of Palliative, Rehabilitation and Integrative Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Introduction

Patients with glioma experience high levels of symptom burden. Without open communication, caregivers rely on their perceptions of the patient's symptom burden to guide the type of support and care they provide to the patient. Caregiver characteristics may be important for accurately perceiving patient symptoms. We examined the associations between symptom agreement and patient and caregiver perceived illness communication, depressive symptoms, and QOL.

Methods

Cross-sectional measures were collected prior to randomization as part of the baseline assessment of a feasibility randomized controlled trial seeking to pilot-test a yoga intervention for patients with glioma and their caregivers (n = 67 dyads). Here, we report on the agreement of proxy symptom burden reporting (MDASI-BT) and its association with patient and caregiver depressive symptoms (CES-D), illness communication (CICS), and QOL (SF-36). Inter-correlations coefficients were used to test for congruence in symptom scores. Bivariate correlations were calculated to examine the association between psychosocial function variables and symptom agreement. Dyadic level associations between symptom agreement and QOLwere examined using multi-level modeling.

Results

Thirty-nine percent of patients (93% non-Hispanic White; mean age=47 years; 84% Grade III-IV) and 49% of caregivers (90% non-Hispanic White; mean age=51 years) endorsed clinical levels of depression (paired t =.74, p=.46). ICCs of patient and caregiver proxy ratings were significant (except cognitive and GI subscales) ranging from small to moderate coefficients (.09 - .50). Clinically significant disagreement was found for all means scores of the MDASI-BT subscales except for GI symptoms and general symptoms. Patient illness communication was associated with agreement in overall symptom severity (r=-.27, p=.03) and affective symptom subscale (r=-.34, p<.01). Caregiver illness communication (r=-.33, p<.01) and depressive symptoms (r=.46, p<.0001) were associated with symptom interference agreement. Caregiver overestimation of patient symptom severity was associated with poor caregiver physical QOL, while underestimation was associated with poor patient physical and mental QOL and poor caregiver mental QOL.

Conclusions

The psychosocial context of the family plays an important role in the accuracy of proxy symptom reporting. Moreover, inaccurately understanding patients experience is related to poor QOL for both patients and caregivers, which points to the importance of symptom management interventions involving family caregivers.

Significance to the cancer neuroscience field

Typical symptom management guidelines are often insufficient for patients with brain tumors making new interventions that improve QOL imperative for this population. This study suggests that involving family caregivers to increase accuracy of proxy symptom reporting may increase QOL for patients andcaregivers.

Friday Abstract 24

A multidimensional model analysis to dissect the impact of brain metastasis on neuronal communication

Masmudi-Martín M.[1]*, Sanchez-Aguilera A.[2], Navas-Olive A. [2], Baena P. [1], Hernández- Oliver C. [1], Priego N. [1], Cordón-Barris L. [1], Alvaro-Espinosa L. [1], García S. [1], Martínez S. [1], Lafarga M. [3], RENACER[4], Lin MZ.[5], Tezanos P. [2], Muela P. [2], Cintado E. [2], Trejo JL. [2],Al-Shahrour F. [1], Menendez de la Prida L. [2], Valiente M. [1]

Spanish National Cancer Research Center (CNIO), Madrid, Spain[1], Instituto Cajal. CSIC,Madrid, Spain[2], University of Cantabria- IDIVAL, Santander, Spain[3], Red Nacional de Metástasis Cerebral[4], Stanford University, Stanford, CA[5]

*Corresponding / presenting author.

Introduction

A high percentage of patients with brain metastases frequently develop neurocognitive symptoms, however understanding how brain metastasis co-opt the function of neuronal circuits beyond the mass effect remains unknown.

Methods

We tested different pre-clinical models of brain metastasis from various primarysources and oncogenic profiles by applying a multidimensional modelling of brain functional analysis including *in vivo* electrophysiology recordings, computational analysis,transcriptomics and behavioural tests.

Results

We dissociated the heterogeneous impact on brain function that we detected in our pre-clinical models; which correlated with failures in specific behavioral tests; fromthe homogeneous inter-model tumor size. In contrast, we report a potential underlying molecular program responsible for impairing neuronal crosstalk in a model-specific manner. Additionally, measurement of various brain activity readouts matched with machine learning strategies predict the presence of metastases and the subtype.

Conclusion

We demonstrated that pre-clinical models of brain metastasis recapitulate neuronal impact heterogeneity showing that a molecular signature is enriched in modelsimposing high neural impact where failures in specific behavioral tests were also seen. Inaddition, altered brain activity patterns suggest the possibility to exploit them as novel biomarkers.

Significance to the cancer neuroscience field

We envision that our findings not only increase our knowledge on the molecular basis of neurocognitive impairment associatedwith brain metastases but they are also the first step towards new therapeutic strategies to prevent or stop the decline in quality of life associated with these symptoms.

Friday Abstract 25

A CRISPR/Cas9-Based Assay for High-Throughput Studies ofCancer-Induced Innervation

Sapthala Loku Galappaththi* [1,2], Brenna Katz [1,2], Patrick H. Howze IV [1,2], Gregory Hoover [1,2] and Simon Grelet [1,2]

[1] Biochemistry and Molecular Biology, College of Medicine, University of South Alabama, Mobile, AL 36688, USA [2] Mitchell Cancer Institute, The University of South Alabama, Mobile, AL 36604, USA
*Presenting author: sl1822@jagmail.southalabama.edu

Introduction

The *in vitro* quantification of cancer-induced axonogenesis and neuronal differentiation has traditionally been limited to morphometric techniques measuring the changes in neuronal morphology such as neurite length, branches, or number. While these methods have been effective in studying cancer-induced axonogenesis, they are not adapted for large screening approaches and do not easily apply to direct nerve-cancer coculture. Therefore, there is a recognized need for more efficient approaches that could facilitate the study of neuronal morphology changes at a larger scale, particularly for examining the mechanisms of cancer innervation to identify therapeutic targets.

Methods

To advance this area of research, we have applied CRISPR/Cas9 technology to create a streamlined high-throughput assay of neuronal precursor differentiation. Using homology-independent targeted insertion (HITI), we tagged the tubulin **ββββ**3 general marker of neuronal differentiation with the GFP fluorophore in PC12 and N2A neuronal differentiation models. This tagging approach allows for the fluorescence-based observation of neuronal differentiation in any fluorescent-based platform and allows for high-throughput analysis.

Results

We conducted co-culture experiments with breast cancer cells of various phenotypes to assess the impact of cancer cells on neuronal maturation, reflective of the nerve-cancer crosstalk established during cancer innervations. We have shown that breast cancer cells that undergo a transition from Epithelial to Mesenchymal phenotypes (EMT transition) are preferentially driving the cancer-induced differentiation of the neuronal precursors, suggesting the role of EMT in promoting cancer aggressivity through increased cancer innervation. The novel use of the tubulin **ββββ**3-GFP tagging system enabled us to quickly quantify these changes across millions of cells and to screen various biological conditions, surpassing the capabilities of traditional microscopic and morphological methods. Our findings suggest a critical role of EMT in promoting cancer aggressivity through increased cancer innervation.

Conclusion

The assay we have developed will contribute to the field of cancer neuroscience by offering a streamlined, unbiased method that complements traditional microscopic analysis. It enables the observation of neuronal differentiation *in vitro* at a scale that was not previously feasible. By facilitating the study of a larger number of cells, and by allowing studies in direct nerve-cancer cocultures, the method provides a means to potentially identify trends and patterns that warrant further investigation. Our results indicate that this assay could serve as a stepping stone for more comprehensive studies into the mechanisms of cancer-induced neuronal differentiation.

Diroximel fumarate reverses doxorubicin-induced cognitive and sensorimotor deficits and associated loss to synaptic protein, microglia phenotypic transition, and myelin damage in mice

Anand Kumar Singh[1], David Ruiz[1], Mohd Sami Ur Rasheed[1], Thomas D. Avery[2], Dion J. L. Turner[2], Andrew D. Abell[2], Peter M. Grace[1]

[1]Laboratories of Neuroimmunology, Department of Symptom Research, and the MD Anderson Pain Research Consortium, University of Texas MD Anderson Cancer Center, Houston, USA

[2]ARC Centre of Excellence for Nanoscale BioPhotonics (CNBP), Institute for Photonics and Advanced Sensing (IPAS), Department of Chemistry, The University of Adelaide, Adelaide, Australia

Introduction: Cancer survivorship has increased due to the success of chemotherapy treatments, with an estimated 18.1 million survivors in 2022 in the US alone and projected to increase by 24.4%, to 22.5 million, by 2032. However, chemotherapy treatments often carry long-lived neurotoxic side effects. Commonly affected domains include memory, executive function, attention, processing speed, and psychomotor function, colloquially known as chemotherapy-induced cognitive impairment (CICI) or ‘chemobrain’. There are no FDA-approved treatments for these deficits which dramatically reduce quality of life, persisting years into survivorship. Since doxorubicin induces oxidative stress and inflammation in the brain, and Nrf2 being an endogenous master regulator of genes involved in the antioxidant metabolism and anti-inflammation proven, we have tested the efficacy of systemic Nrf2 activator, diroximel fumarate (DRF) in our recently developed chemobrain mouse model.

Method: Doxorubicin (5 mg/kg/week, Pfizer, New York, NY) was diluted in sterile phosphate-buffered saline (PBS) and treated for 4 weeks, one injection i.p. each week. DRF, 89 mg/kg, oral) was dissolved in 2% methylcellulose and administered daily, starting one week after doxorubicin treatment and continuing throughout the cognitive and sensorimotor behavioral tests. Two weeks after the completion of doxorubicin treatment, mice were tested for cognitive behavior and sensorimotor function followed by tissue collection for biochemical assays.

Result: DRF reverses doxorubicin-induced deficits in executive function, spatial and working memory, fine motor, and grip strength deficits in both sexes. In the brain, DRF reverses doxorubicin-induced loss of synaptic proteins, microglia phenotypic transition, and myelin damage.

Conclusion: Our results highlight the critical role of systemic DRF activation in reversing doxorubicin-induced cognitive impairments, motor incoordination, and associated structural and phenotypic changes in the brain.

Significance to the cancer neuroscience field: Since Nrf2 agonists are already being used to combat remitting-relapsing multiple sclerosis, our results underline the importance of the use of DRF in reversing the neurotoxic effects of cancer treatment.

Friday Abstract 27

Developing a physical activity intervention for survivors of adolescent and young adult central nervous system tumors

Eduardo Gonzalez Villarreal[1], Emily C. LaVoy[2], Tamara E. Lacourt[1], Grace Waterman[1], Elizabeth Pan[1,3], Michael Roth[1], Shiao-Pei Weathers[1], Jinbing Bai[4], Tricia Z. King[5], Jian Wang[1],Maria C. Swartz[1]

[1]UT MD Anderson Cancer Center [2]University of Houston [3]Rice University [4]Emory University [5]Georgia State University

Background

Up to 45% of survivors of adolescent and young adult (AYA; 15-39 years old at diagnosis) central nervous system (CNS) tumors experience cognitive impairment (CI).Physical activity (PA) is a promising approach to mitigate CI. However, <50% of AYA survivors meet recommended PA levels.

Purpose

To design a feasible and engaging PA intervention (i.e., using active video games [AVG]) to improve survivorship outcomes for the AYA CNS population.

Methods

Guided by the Adaptome framework, we aimed to adapt the behavioral coaching materials and PA components of an existing virtual PA intervention using AVG for survivors of AYA CNS tumors. We recruited 16 survivors of AYA CNS tumors and 16 clinical providers to participate in online semi-structured focus groups, each with a minimum of four participants and lasting ~60 minutes each. Two research assistants conducted thematic analysis on feedback from focus groups; themes and subthemes were generated.

Results

AYA participants (n=16) ranged from ages 19-38 (mean age: 25.8±5.5) at the time of the focus group. Most participants (62.5%) were white, 25% were Hispanic or Latino, and 12.5% identified as “other race.” Thematic analysis resulted in 19 subthemes under five levels of adaptation based on the Adaptome framework The following top themes were identified under each level of adaptation: ‘target audience’: providing flexibility in the exergame intervention; ‘service setting’: 1) accounting for barriers and 2) screening for activity levels; ‘mode of delivery’: 1) inclusivity, 2) benefits of virtual delivery, and 3) social facilitation; ‘cultural adaptations’: 1) motivation, 2) careful selection of images and topics, 3) community building, and 4) mental health awareness; ‘core components’: 1) a variety of activities and 2) clinical integration. Each of the themes listed above was found in at least 10 participant quotes.

Conclusion

Qualitative analysis findings indicate that program adaptation needs to occur at all five levels of the Adaptome framework. Key recommendations included maximizing program inclusivity, incorporating motivational techniques, and providing various exercise options. The future direction will be to focus on implementing the adapted exercise intervention.

Friday Abstract 28

Elucidating the role of triggering receptor expressed in myeloid cells 2 (TREM2) inglioblastoma

Mekenzie M. Peshoff, Pravesh Gupta, Shivangi Oberai, Rakesh Trivedi, Minghao Dang,Hiroshi Katayama, Joy Gumin, Brittany C. Parker Kerrigan, Frederick F. Lang, Jason T. Huse, Linghua Wang, Karen C. Dwyer, Krishna P. Bhat
UT MD Anderson Cancer Center, Houston, TX

Introduction

Although lymphoid-targeting immunotherapies have revolutionized treatment for other solid tumors, these strategies have yielded disappointing results for glioblastomas (GBMs), which instead exhibit an abundance of myeloid cells. While emerging immunotherapies aim to reprogram these cells, they have highly complex functions that can either support or inhibit tumor growth based on cues from their microenvironment. One critical myeloid regulator, triggering receptor expressed on myeloid cells 2 (TREM2), has been implicated in a variety of cancers and neurological diseases, making it a target of keen interest in GBM.

Methods

We characterized TREM2 in myeloid cell subpopulations in human gliomas using transcript- and protein-level analyses of both internal and external datasets. By employing two distinct mouse models, we examined the role of Trem2 on tumor progression and immune function in murine gliomas. Furthermore, we designed a method of tracking phagocytosis of glioma cells *in vivo* and employed *in vitro* assays to gain a mechanistic understanding of TREM2 signaling.

Results

We found that TREM2 does not correlate with immunosuppressive pathways in GBM; rather, TREM2 is strongly associated with phagocytosis in both human and mousegliomas. While Trem2 deficiency was found to be dispensable for gliomagenesis, $Trem2^{+}$ myeloid cells display enhanced tumor uptake compared to $Trem2^{-}$ cells. Finally, we demonstrate a mechanism by which TREM2 mediates phagocytosis via Syk signaling.

Conclusion

These results indicate that unlike in other cancers, TREM2 is not associated with immunosuppression in gliomas. Instead, our data uncover TREM2 as an important phagocytic immunomodulator in gliomas that may be exploited as a potential therapeuticstrategy for brain tumors.

Significance to the cancer neuroscience field

Although TREM2 has been widely studied in peripheral cancers and neurological disorders, its role in GBM is just beginning to emerge. Only a handful of studies have reported on TREM2 in brain tumors with contradictory results, suggesting that TREM2 plays a highly complex, context-dependentrole in gliomas that needs to be further explored. Therefore, our work investigating the function of TREM2+ myeloid cells in gliomas will help further our understand of this criticalmyeloid regulator in brain tumors.