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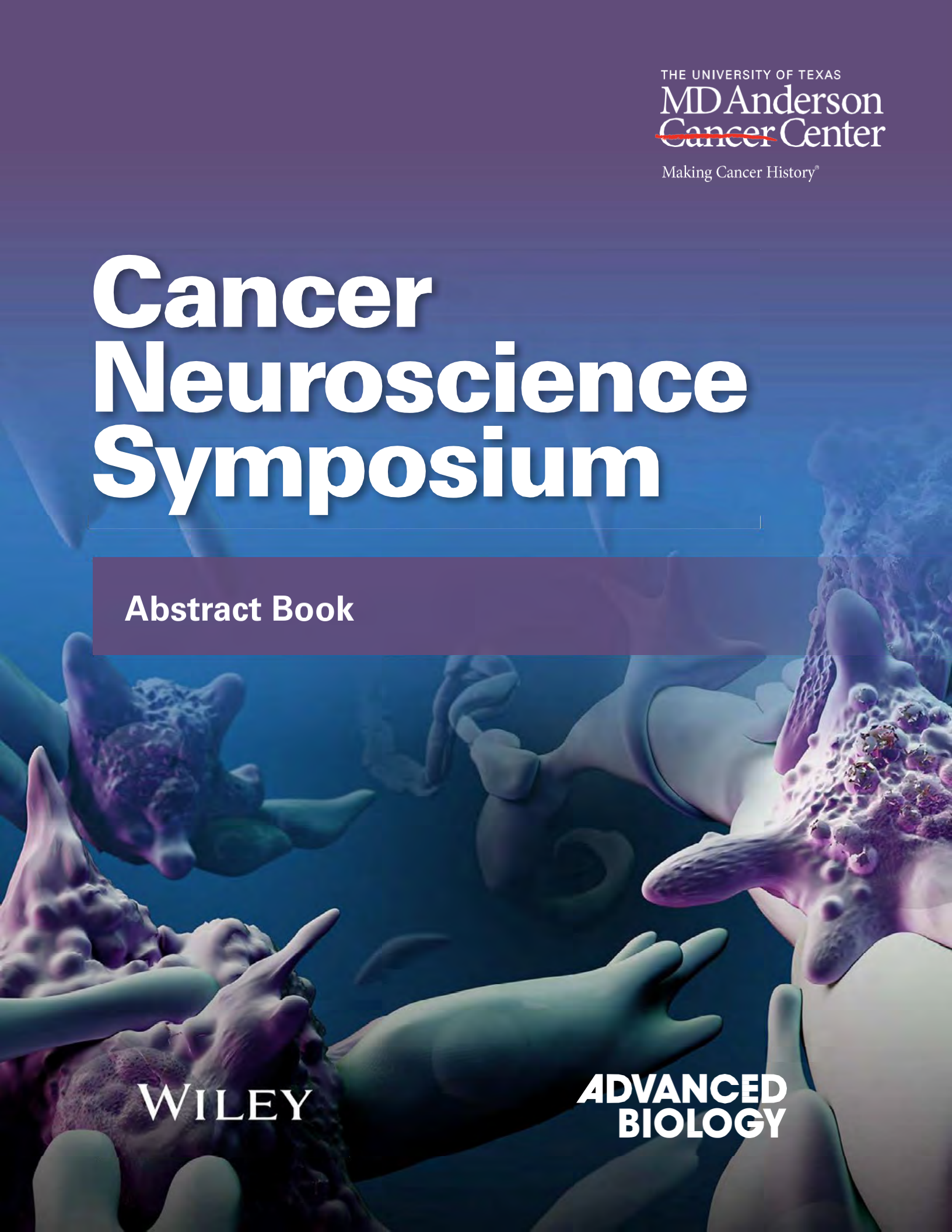
Cancer Neuroscience Symposium

Abstract Book



WILEY

ADVANCED BIOLOGY

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Friday Posters | March 1

WILEY

ADVANCED BIOLOGY

Friday Abstract 1

TRPV1+ sensory innervation as a novel driver of ovarian cancer progression

Matthew Knarr*[1], Katherine Cummins[1], Dusan Racordon[1], Hunter Reavis[1], Timothy Lippert[1], Ryan Hausler[1], Priyanka Rawat[1], Suyeon Ryu[2], Jamie Moon[2], Dave Hoon[2], Roger Greenberg[1], Paola Vermeer[3], Ronny Drapkin[1]

[1]Perelman School of Med. Univ. of Pennsylvania, Philadelphia, PA,[2]Saint John's Cancer Institute, Santa Monica, CA,[3]Sanford Research Institute, Sioux Falls, SD

Introduction

A primary challenge currently faced in ovarian cancer (OVCA) treatment is that patient prognoses remain poor despite current therapeutic interventions. Overall survival for OVCA patients with advanced disease is <30%, and most patients recur within 5 years. As such, there is a critical need for new therapies that can overcome OVCA chemoresistance and produce meaningful increases in patient survival. Recent efforts that have targeted the tumor microenvironment (TME), such as immune checkpoint inhibitors, have been successful in somecancers but have limited therapeutic benefit when used to treat OVCA. Thus, new TME targeting therapies must be developed that can be used to effectively treat OVCA patients. A novel TME component ripe for therapeutic targeting are the nerve fibers that infiltrate tumors.

Recent studies in several cancers have shown that tumor innervation can promote tumor growth/metastasis. However, in ovarian cancer the role of innervation in promoting cancer progression remains a gap in knowledge. Here we show that Transient Receptor Potential cation channel subfamily V member 1 (TRPV1)+ sensory innervation plays a significant role indriving ovarian cancer progression in part via the secretion of the neuropeptide nociceptin.

Methods

We performed IHC staining to determine the extent of TRPV1+ nerve infiltration in OVCA vs normal reproductive tissue in patients. We utilized a syngeneic mouse model of ovarian cancer metastasis, where mouse OVCA cells were injected intraperitoneally, to explorethe functional role of TRPV1+ sensory nerves and nociceptin in OVCA. TRPV1 sensory nerveswere ablated using TRPV1 driven expression of diptheria toxin alpha (DTA) or were activated pharmacologically using capsaicin.

Results

Analysis of patient samples showed that TRPV1+ sensory innervation is much higher in ovarian tumors vs benign reproductive tissue. Ablation of TRPV1+ sensory nerve fibers *in vivo* caused reduced tumor burden and prolonged survival in our OVCA mouse models.

Stimulation of TRPV1+ sensory nerves with capsaicin accelerated OVCA growth and decreasedsurvival in tumor bearing mice. Pathway analysis of WT vs TRPV1-DTA tumors identified diminished levels of nociceptin within DTA tumors. Treatment of tumors with recombinant nociceptin accelerated OVCA growth, suggesting nociceptin as one of the factors secreted by TRPV1+ sensory nerves to drive OVCA progression.

Conclusions

Our results establish TRPV1+ sensory innervation as a novel driver of OVCA growth/metastasis and a potential therapeutic target for OVCA treatment.

Significance to cancer neuroscience field

Our data add to a growing body of evidence that sensory nerves are pro-tumorigenic in multiple cancer types and could be therapeutically targeted for cancer treatment.

Friday Abstract 2

Enhanced locus coeruleus response to stress in primary breast adenocarcinoma

Nikolas Holland, Adrian Gomez, Jeremy Borniger
Cold Spring Harbor Laboratory, Cold Spring Harbor, NY

Sympathetic innervation of the tumor microenvironment (TME) has been associated with faster progression of multiple cancer types including breast adenocarcinoma. Despite this, the impact of primary breast cancer in the periphery on the Locus coeruleus (LC), a major brain region which modulates the sympathetic nervous system (SNS) is not understood. Moreover, the impact of breast cancer on LC activation due to acute stress is unknown. To characterize this influence, we used the Fos:TRAP2 transgenic mouse line to identify expression of the immediate early gene, cFos, in brain regions during acute restraint stress before and after orthotopic E0771 breast cancer development. We found that significantly more LC neurons express cFos in the presence of primary breast cancer over their pre-tumor internal baseline, suggesting the presence of the tumor further sensitizes the LC to acute stress. The mechanism underlying this LC dysregulation may be mediated by peripheral neurons innervating the TME. To investigate the relationship between the LC and the primary tumor via these peripheral neurons, we injected pseudo rabies virus (PRV), a robust neural tracer, into developing E0771 tumors. We found that PRV is expressed in the LC in the days following intra-tumor administration, suggesting a polysynaptic connection between the LC and the TME. Administration of PRV into healthy mammary gland also resulted in PRV expression in the LC, suggesting that this polysynaptic connection is present in tumor-free mice, and is maintained as the tumor develops. These findings begin to characterize a putative bi-directional relationship between the LC and primary breast adenocarcinoma that can exacerbate the CNS response to stress and in-turn accelerate progression of the disease via polysynaptic TME innervation.

Friday Abstract 3

Peripheral nerve subtype dynamics in radiotherapy-treated PDAC

Ella Perrault, Nicole Lester, Hannah Hoffman, William Hwang
Harvard University, Boston, MA

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive and lethal cancer associated with a high frequency of tumor innervation and perineural invasion (PNI). PNI, the invasion of cancer cells within or surrounding nerves, is associated with tumor metastasis, therapeutic resistance, and poor clinical outcomes. Previous literature has shown that nerve subtypes contribute to distinct tumor microenvironments (TME). However, it is unknown how tumor innervation and nerve subtype distribution are impacted by standard-of-care cancer treatment such as adjuvant radiotherapy (RT), which is frequently given in the context of PNI. Our study aims to characterize the composition of peripheral nerve subtypes throughout tumorigenesis and investigate the peripheral nervous system's role in radioresistance. In PDAC, sympathetic nerves may contribute to a protumoral TME through increased angiogenesis, immune suppression, and norepinephrine signaling. Since overall nerve incidence is asso ciated with aggressive and treatment-resistant tumors, we hypothesize RT increases sympathetic nerveinnervation in the PDAC TME.

Methods

We explanted tumor-bearing pancreata from KPCT transgenic mice to investigate the histopathological profiles of sympathetic nerves during tumor progression (8, 12, 18 weeks age) and 48 hours after receiving various doses of single-fraction RT (0, 2, 5, 12 Gy). Immunofluorescence (IF) images of tumor-bearing or control pancreata (non-tumor-bearing littermates) stained for PanCK and tyrosine hydroxylase were analyzed for intratumoral nerve density by confocal microscopy.

Results

Preliminary findings reveal increased sympathetic nerve density in late-stage PDAC compared to mid- and early-stage PDAC and control tissue. We completed treatment with varying doses of RT to a cohort of approximately 10 mice per dose, and IF-based nerve quantification isongoing.

Conclusions

Our preliminary findings indicate that sympathetic nerve involvement changes throughout PDAC progression. Analysis of sympathetic nerve involvement in RT-treated tumors is ongoing. We are expanding our IF-based quantification to include parasympathetic and sensorynerves to assess the potential remodeling of nerve subtypes by RT. We will also characterize nerve subtypes in liver and lung metastases, and we aim to validate preclinical findings in our patient cohorts.

Significance to the cancer neuroscience field

Tumor innervation and perineural invasion are associated with worse patient outcomes. Our research will identify nerve subtype dynamics (i.e., density, distribution) in PDAC and how these innervation patterns are modulated by RT, a therapy often utilized to address PNIclinically. Our findings will be significant to scientists interested in the interplay among nerve subtypes in pathology, as well as clinicians aiming to identify novel targets to improve patient outcomes for this devastating disease.

Friday Abstract 4

Validation of TXNIP pathway in developing of chronic oxaliplatin-induced peripheral neuropathy

Junwei Du[1,2], Leland C. Sudlow[2], Kiana Shahverdi[2], Haying Zhou[2], Matthew D. Wood[4], Shamim Mollah [3], Mikhail Y. Berezin[2]

[1]Institute of Materials Science and Engineering, [2]Mallinckrodt Institute of Radiology, [3]Department of Genetics, [4]Division of Plastic and Reconstructive Surgery, Washington University School of Medicine in St. Louis.

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) afflicts millions of cancer patients, presenting as a common, debilitating side effect of treatment. Acute symptoms emerge within hours to days of chemotherapy, and in severe cases, develop into chronic neuropathy causing persistent pain after treatment ends. Underlying mechanism of chronic CIPN has not been fully elucidated. Finding an effective diagnostictool and treatment or prevention strategy for chronic CIPN remains a major challenge, with the identification of a new target being a top-priority unmet need.

Method

Animal model of oxaliplatin triggered CIPN was developed by weekly injection of oxaliplatin for 8 weeks. Behavior studies including cold allodynia, nerve conduction velocity (NCV), and locomotor activity were utilized to quantify CIPN symptoms mice. Bulk RNA-seq from the isolated dorsal root ganglia (DRG) and developed bioinformatics tool Inter Variability Cross-Correlation Analysis (IVCCA) was performed to identify novel pathways. The results were confirmed by different assays (TEM, immunohistochemistry, etc) and pharmacological intervention.

Results

Mice treated with a dosage of oxaliplatin equivalent to the human dose exhibited CIPN symptoms similar to those seen in patients. Analysis of RNA-seq from the mice's DRG showed that the drug influenced pathways associated with ROS (reactive oxygen species) inflammation. Bioinformatics analysis with IVCCA pinpointed the TXNIP pathway as a major player in controlling these ROS and inflammatory responses. The pathway was only activated in the DRG and not in other organs. This pathway was further confirmed by evidence of increased levels of plasma TNF-α and IL-6 cytokines, as well as abnormalities in nerve structure and damaged fibers and mitochondria in the sciatic nerve. By inhibiting the TXNIP pathway, the painful CIPN symptoms in the mice were reduced.

Conclusion

Our study unveils the critical role of the TXNIP pathway in governing the surge of ROS and inflammation within the DRG of mice treated with oxaliplatin that leads to the chronic pain. Both in vitro and in vivo evidence underscore the potential of this inflammatory pathway as a strategic target for imaging and therapeutic intervention.

Significance to the cancer neuroscience field

Peripheral neuropathy is one of the most severe side effects of chemotherapies while no preventive strategy or treatment is available. Our study might guide the development of novel imaging methods and therapies to alleviate pain in millions of cancer patients and cancer survivors.

Friday Abstract 5

Neuronal distribution in colorectal cancer: associations with clinicopathological parameters and survival

Maartje Massen[1], Glenn Rademakers[1], Meike S. Thijssen[1,2], Musa Idris[1,3], Kim A.D. Wouters[1], Jaleesa R.M. van der Meer[1], Nikkie Buekers[1], Desirée Huijgen[1], Iryna. V. Samarska[1], Matty P. Weijenberg[5], Piet A. van den Brandt[5], Manon van Engeland[1], Marion. J. Gijbels[1,4], Werend Boesmans[1,2], Kim M. Smits[1*], Veerle Melotte[1,3*]

[1]Department of Pathology, GROW – School for Oncology and Reproduction, Maastricht University Medical Center, Maastricht; The Netherlands [2]Biomedical Research Institute (BIOMED), Hasselt University, Hasselt; Belgium [3] Department of Clinical Genetics, Erasmus University Medical Center, Rotterdam; The Netherlands [4]Department of Medical Biochemistry, Amsterdam Cardiovascular Sciences: Atherosclerosis & Ischemic Syndrome; Amsterdam Infection and Immunity: Inflammatory diseases; Amsterdam UMC location University of Amsterdam, Amsterdam; The Netherlands [5]Department of Epidemiology, GROW - School for Oncology and Reproduction, Maastricht University, Maastricht; The Netherlands. *These authors contributed equally to this work

Introduction

Over the last years, insights in the cancer neuroscience field increased rapidly and a potential role for neurons in colorectal carcinogenesis has been recognized. However, knowledge on the neuronal distribution, subtypes, origin and associations with clinicopathological characteristics in human studies is scarce.

Methods

In this study, colorectal tumor tissues from the Netherlands Cohort Study on diet and cancer (n=490) and an in-cohort validation population (n=529) were immunohistochemically stained for the pan- neuronal markers neurofilament (NF) and protein gene product 9.5 (PGP9.5) to study the association between neuronal marker expression and clinicopathological characteristics. In addition, tumor and healthy colon tissue were stained for neuronal subtype markers and their immunoreactivity in colorectal cancer (CRC) stroma was analyzed.

Results

NF and PGP9.5 positive nerve fibers were found within the tumor stroma and were mostly characterized by the neuronal subtype markers vasoactive intestinal protein (VIP) and neuronal nitric oxide synthase (nNOS), suggesting that inhibitory neurons are the most prominent neuronal subtype in CRC. NF and PGP9.5 protein expression were not consistently associated with tumor stage, sublocation, differentiation grade and median survival. NF immunoreactivity was associated with a worse CRC-specific survival in the study cohort (p=0.025), independent of other prognostic factors (HR=2.31; 95% CI 1.33-4.03; p=0.003), but these results were not observed in the in-cohort validation group. PGP9.5 on the other hand, was associated with a worse CRC-specific survival in the in-cohort validation (p=0.046) but not in the study population. This effect disappeared in multivariate analyses (HR=0.81; 95% CI 0.50-1.32; p=0.393) indicating that this effect was dependent on other prognostic factors.

Conclusion

This study demonstrates that the tumor stroma of CRC patients mainly harbors inhibitory neurons and that NF as a single marker is statistically significantly associated with a poorer CRC-specific survival in the study cohort. This finding however needs future validation.

Significance to the cancer neuroscience field

Knowledge on the role of neurons in the context of CRC is still limited and mainly studied using in vitro and in vivo models. To our knowledge, this is the first large human study using tissue from a well characterized cohort studying an association between a neuronal marker and survival in CRC.

Friday Abstract 6

Exploring the interplay between neuropeptide signaling and age-onset multiple myeloma inthe bone marrow microenvironment.

Silvia Vicenzi, Anna Rapp, Joshua Hartman, Alison Kochersberger, Aeowynn Coakley, JenniferGarrison, Leslie Crews
University of California at San Diego, San Diego, CA.

Introduction

Multiple myeloma (MM) is a fatal plasma cell neoplasm characterized by the uncontrolled regeneration of malignant stem-like cells in the protective and inflammatory bone marrow microenvironment (BMM). The underlying molecular mechanisms remain poorly understood, as no single initiating oncogene exists. One intriguing candidate is the nervous system that innervates and controls the BMM. Neuropeptides have recently emerged as crucial regulators of tumor initiation and progression, and they can act as autocrine, paracrine, endocrine, or released by the peripheral nervous system. Given that neuropeptides were shown to interact with several cell types and cytokines within the tumor microenvironment, I hypothesized that neuropeptidesare responsible for creating a permissive BMM for the onset and progression of MM.

Methods & Results

To address this hypothesis, I first investigated the CZ CELLxGENE Discover dataset that revealed the expression of neuropeptides and their receptors in several cell types of the human BMM. For example, I detected the expression of over 100 neuropeptide/receptor systems throughout the healthy BMM human tissue as well as in the presence of B-cell non-Hodgkin lymphoma, another tumor originating in the B-cell lineage. Next, I screened a publicly available transcriptomic database (Keats lab) of 66 human MM cancer cell lines, revealing the presence and abundance of neuropeptide/receptor systems in most of the screened cell lines. Following up on this, I exposed MM cell lines H929, RPMI-8226, and U266 to selected neuropeptides in combination with MM standard-of-care drugs lenalidomide and bortezomib and measured their proliferative and apoptotic responses. Interestingly, acute exposure of H929 cells to neuropeptides protected them against lenalidomide, giving them an advantage and resistance to the drug. On the other hand, somatostatin exposure was synergistic with bortezomib-induced cytotoxicity, suggesting neuropeptides exert different functions based on distinct drug-induced downstream signaling cascades.

Conclusions

Although preliminary, these data support the hypothesis that neuropeptides could act as paracrine factors in MM cancer cells originating in the BMM. Given that curative treatment for MM remains an unmet and significant need, neuropeptides and their receptors could act as crucial anticancer targets and novel biomarkers for MM prevention and treatment.

Significance to the cancer neuroscience field

This study is the first evidence for the role of neuropeptides in the context of MM, suggesting a neural regulation of immune function as well as cancer initiation and progression in the BMM. This project aspires to unravel the bi-directional communication of the neural-immune axis in the BMM underlying the onset and progression of MM.

Crosstalk between sensory nerves and tumor cells drives metastasis in breast cancer

Hanan Bloomer, Savannah Parker, Thanh T Le, Tolulepe Adewumi, Wesley Clawson, Michael Levin, Madeleine J. Oudin[1].

[1]Department of Biomedical Engineering, Tufts University, Medford, MA 02155

Introduction: Compared to healthy breast tissue, breast tumors exhibit an increased density of peripheral nerves, which is associated with higher histological grade, lymph node metastasis, and advanced clinical staging. We have recently shown that sensory nerves can induce changes in gene expression in triple-negative breast tumor cells to drive contact-dependent tumor cell invasion and metastasis. How breast tumor cells increase sensory innervation and how tumor cells impact properties of sensory nerves remains unknown. Here, we investigate how tumor cells impact sensory nerves, and dissect the role of TRPV1, a non-selective cation channel present on sensory nerves involved in neural growth and regeneration.

Methods: We injected DiI dye into the 4th left mammary gland of healthy and tumor bearing mice, and isolated the dorsal root ganglia (DRG) along the spinal cord to identify the origin of tumor nerves. We isolated primary sensory neurons from the DRG of adult female wild-type and Trpv1-/- female mice mice and plated them alone, with conditioned media (CM) from MDA-MB-231 (231) cells, a human triple negative breast cancer cell line, or directly with 231 cells, or in 3D hydrogels We used commercially available high-density multielectrode arrays (MEAs) to measure electrical activity and burst behavior of primary mouse sensory neurons.

Results: The DiI labeling experiments revealed that mammary gland tumors in mice are innervated by nerves originating from discrete areas in the spinal cord. Compared to DRG cultured alone, MDA-MB-231 conditioned media or direct co-culture increased the number of primary neurites extending from DRG cell bodies, the maximum diameter of DRG neurites and neurite bundling. Further, using 3D hydrogels, we found that tumors cells increase axon extension of DRG spheroids. Using MEAs, we found that neurons with TNBC cells showed bursts that were significantly longer, with more individual action potentials and a shorter time period between action potentials. Knockout of *Trpv1* abrogated these effects, suggesting that TRPV1 stimulation drives breast cancer cell-mediated neuronal changes. We then performed RNA sequencing of co-cultures and identified changes in gene expression in neurons associated with migration and development, and an enrichment in genes regulated by c-Fos and c-Jun, transcription factors that drive neural growth and regeneration, which we validated by immunofluorescence.

Conclusions: These studies describe a novel effect of breast tumor cells on sensory innervation, nerve morphology and electrical activity mediated by *Trpv1*-driven activation of c-Fos and c-Jun in neurons.

Relevance to cancer neuroscience field: These studies shed light on the mechanisms by which tumor cells drive increased innervation, via effects on neuronal morphology, gene expression, electrical activity and firing.

Friday Abstract 7

Epigenome Dysregulation in NF1-Associated Malignant Peripheral Nerve Sheath Tumors

Biji Chatterjee[1,2], Veena Kochat[1,2], Suresh Satpati[1], Sharon M Landers[2], Angela D Bhalla[2], Keila E. Torres[1,2], Kunal Rai[1]

[1]Department of Genomic Medicine, [2]Department of Surgical Oncology, TheUniversity of Texas MD Anderson Cancer Center, Houston, TX

Introduction

Malignant Peripheral Nerve Sheath Tumors (MPNSTs) pose a formidable challenge in the realm of cancer due to their propensity for recurrence and resistance to conventional therapies like chemotherapy and radiation. These aggressive tumors predominantly affect individuals with neurofibromatosis type 1 (NF1), often driven by mutations in the NF1 gene and genetic abnormalities within the Polycomb Repressor Complex 2 (PRC2), involving SUZ12 and EED. Intriguingly, in MPNSTs with PRC2 mutations leads the absence of a repressive histone mark and a simultaneous increase in an activating mark linked to gene activation. The gene 5'- methylthioadenosine phosphorylase (MTAP) is frequently deleted in MPNSTs. This deletion disrupts a metabolic pathway, leading to the accumulation of 5'-methylthioadenosine (MTA), which selectively inhibits PRMT5, a critical protein involved in various cellular processes**.** We aimed to determine how these epigenome imbalance leads to alterations in cell fates in MPNST cells.

Methods

Our approach involves utilizing histone mass spectrometry and RNA sequencing data for validation. We examined patterns of various histone modification marks within MPNST cells by CUT&RUN, immunohistochemistry and immunofluorescence. We conduct proliferation, clonogenicity, and invasion assays, to revels therapeutic potential of certain inhibitors.

Results

In MPNSTs carrying NF1 mutations and showing deficiencies in MTAP and PRC2, there's a loss of gene-silencing marks and a simultaneous increase in gene-activating marks. Thisdisrupts normal gene activity and results in abnormal cellular behavior, underscoring the intricatenature of MPNSTs

Conclusion

Our research unravels the intricate mysteries surrounding MPNSTs, shedding light on their unique genetic and epigenetic alterations. Moreover, MPNSTs present a unique treatment challenge due to mutations in these genes which disrupt fundamental cellular processes. These findings not only deepen our understanding of MPNST biology but also pave the way for the discovery of novel therapeutic targets and strategies tailored to the specific characteristics of thesechallenging tumors.

Significance to the cancer neuroscience field

Our research is at the forefront of establishing a crucial link between NF1-associated MTAP deficiency, PRC2 mutations, and the epigenomic dysregulation of chromatin states in MPNSTs. We meticulously profile chromatin states and comprehensively characterize functional enhancers, paving the way for precise and effective therapies tailored to these tumors' unique characteristics. This journey into uncharted territory holds promise for instilling hope in those facing the challenges of MPNSTs and related conditions. Our goal is to illuminate the intricate molecular mechanisms driving MPNST pathogenesis, deepening our understanding and offering prospects for novel therapeutic targets and strategies.

Friday Abstract 9

Cancer-induced Pain in an Orthotopic Malignant Peripheral Nerve Sheath Tumor (MPNST) MouseModel

Khalil Ali Ahmad[1], Ibdanelo Cortez[1], Irshad Khushboo[1], Kechen Ban[1], Anand Singh[1], Sami Mohd Rasheed[1], Kendal Willcox[1], Peter M Grace[1], Angela Hirbe[2], Andrew J Shepherd[1], and Yuan Pan[1.3]
[1]Department of Symptom Research, the University of Texas MD Anderson Cancer Center, Houston TX [2]Division of Oncology, Department of Internal Medicine, Washington University School of Medicine, St.Louis, MO.
[3]Department of Neuro-Oncology, the University of Texas MD Anderson Cancer Center, Houston TX

Introduction

Cancer pain can occur at any stage of the disease development and many cancer patients experience moderate to severe pain. Despite advances in cancer treatment, pain management remains limited. Pharmacotherapy of cancer pain has relied mostly on therapeutic approaches in other pain conditions; however, the mechanisms underlying cancer pain may be distinct and require new treatment strategies. Animal models have provided insights into the mechanisms of cancer pain, which is thought to result from complex interactions between tumor cells, the immune system, and the nervous system. Malignant peripheral nerve sheath tumors (MPNST) are highly aggressive soft-tissue sarcomas arising in peripheral nerves. Patients with MPNSTs often experience pain but little is known about the mechanisms by which MPNST induces pain. This study aims to characterize pain behaviors and the underlying molecular mechanisms in murine MPNST models and to identify novel therapeutic targets.

Methods

Behavioral, cell culture and immunohistochemistry methods were performed. MPNST cancer pain model was developed by implanting the mouse MPNST cells into the sciatic nerves of either male or female mice. Primary mouse dorsal root ganglion (DRG) neuronal cell cultures were prepared for Calciumimaging experiments.

Results

Mouse MPNST cell line formed tumors within the sciatic nerve following implantation. Mechanical allodynia, thermal hyperalgesia and spontaneous pain were observed in MPNST-bearing female and male mice after one week of inoculation compared to the sham groups. In addition, MPNST-conditioned medium altered calcium influx and c-FOS expression in primary cultured mouse DRG neurons,suggesting that MPNST cells secrete factors that change DRG neuron activity.

Conclusions

Our data demonstrated that MPNST induces pain in the nerve where the tumor grows. Future studies will further characterize the pain behaviors in the MPNST model and determine the cellular and molecular mechanisms.

Significance to the cancer neuroscience field

This study provides a valuable model for enhancing ourknowledge of how cancer pain develops and the development of new therapeutic strategies.

Friday Abstract 10

Individualized MRI Neuromodulation Targeted Towards the Alleviation of Radiation-Induced-Cranial-Neuropathyin Head and Neck Cancer.

T. Dorina Papageorgiou[1,2,3,6,7,8], Anthony Allam[1,4], Duong Huynh[1], Rasoul Hekmati[1], Sandy Reddy[4], Peyton Presto[1,11],Emmanouil Froudarakis[2,5], Erich M. Sturgis[7,9], Katherine A. Hutcheson,[10,11]

[1] Department of Psychiatry, Baylor College of Medicine, Houston, U.S.A. [2] Department of Neuroscience, Baylor College of Medicine, Houston, U.S.A. [3] Department of Physical Medicine & Rehabilitation, Baylor College of Medicine, Houston, U.S.A. [4] School of Medicine, Baylor College of Medicine, Houston, U.S.A. [5] Institute of Molecular Biology and Biotechnology, FORTH, Crete, Greece [6] Department of Electrical and Computer Engineering, Rice University, Houston, U.S.A. [7] Center for Space Medicine, Baylor College of Medicine, Houston, U.S.A. [8] Dan L. Duncan Comprehensive Cancer Center, Baylor College of Medicine, Houston, U.S.A. [9] Dept of Otolaryngology-Head and Neck Surgery, Baylor College of Medicine, Houston, U.S.A. [10] Dept of Head and Neck Surgery, Division of Surgery, M.D. Anderson Cancer Center, U.S.A [11] Department of Pharmacology and Neuroscience, Baylor College of Medicine, Houston, U.S.A.

Introduction

Our long-term goal is to strengthen motor and sensory cortical networks that regulate swallowingand tongue motor sensory control (TMSC) through our individualized fMRI neuromodulation, termed iNM **(U.S. Patent No.16/954,256**) to alleviate radiation-induced cranial neuropathy (RICN) in head and neck cancer (HNC) patients, for which there is no standard of care treatment. fMRI measures the magnitude and spatial extent of oxy-(O_2)-to-deoxy-genated hemoglobin [Hb]. iNM: 1. is a non-invasive, precision-medicine intervention with 1mmanatomical and functional precision; and 2. is guided by reinforcing or inhibiting the HbO2 intensity and extent ofeach patient's unique brain network, as opposed to relying on complete self-regulation of the HbO2 intensity. Here we wanted to assess if iNM can strengthen TMSC and swallow networks.

Methods

Healthy subjects (n=30) underwent iNM and control-NO iNM conditions in a 2-day study. Each participant's individualized TMSC and swallow cortical selectivity was delineated and targeted for iNM. Support vector machine (SVM) classified cortical tongue direction and swallow patterns versus tongue-at-rest under iNM and control. We quantified the HbO2 magnitude for each network's areas separately, by determining the area under the curve (AUC), variance and the association between brain states and physiological responses of TMSC and swallow via dynamic causal modeling (DCM).

Results

The mechanisms associated with iNM are: 1. 45% increase in the AUC's HbO2 magnitude ($p<0.001$); 2. 14% decrease in the BOLD's intensity variance ($p<0.01$); and 3. 20% increase in spatial network expansion ($p<0.001$). DCM uncovered 95% of the trials as iNM dominant driven versus 76% of the control trials): 1. 71% motor-to-motor (M1, motor cerebellum, basal ganglia) and 63% motor-to-sensory; 2. 63% sensory-to-sensory (intraparietal lobule, insula-claustrum, sensory cerebellum); and 3. 76% sensorimotor-to-attention-memory connectivities.

Conclusion

iNM establishes spatiotemporal causality between swallow and TMSC networks, which can serveas clinical biomarkers for the alleviation of RICN.

Significance to the cancer neuroscience field

HNC is the sixth most prevalent malignancy. Seventy percent of HNC is oropharyngeal cancer (OPC), resulting from human papillomavirus (HPV), the most common HPV- related malignancy in the US. Radiation, the mainstay OPC treatment can induce neuropathy along the lower cranial nerves with a 10-15% incidence, resulting in dysphonia, dysphagia, loss of taste, tongue fibrosis and atrophy (causing loss of motor control). RICN besides leading to impaired quality of life, it can even lead to mortality due to aspiration. Although clinical trials show that steroids (NCT04151082) and gabapentin (NCT03747562) temporarily reduce pain, their adverse effects comprise treatment tolerance and adherence. Thus, we need effective treatments!

Friday Abstract 11

Neurological Manifestations of Hemophagocytic Lymphohistiocytosis in Cancer Patients: The MDAnderson Cancer Center Experience

Ashley Aaroe, Sudhakar Tummala, Anne Kleiman, Anuj Patel, Monica Loghin, Rutu Patel, Laura Corkin, Merry Chen, Karin Woodman, Nazanin Majd, Carlos Kamiya-Matsuoka, Chirag B. Patel, Vinay Puduvalli, Naval Daver, Sattva Neelapu
Department of Neuro-Oncology, the University of Texas MD Anderson Cancer Center, Houston TX

Introduction

Hemophagocytic lymphohistiocytosis (HLH) can be complicated by both central and peripheral nervous system involvement. Neurological HLH in patients with cancer has not been fully characterized given the rarity of such cases.

Methods

A retrospective review of the electronic medical record (EMR) at MD Anderson Cancer Center (MDA) was conducted with IRB approval and identified 66 patients from 2015-2023 seen by the inpatient and outpatient consultative neurology services with documentation of suspected HLH. Structured data, clinical note text, and laboratory results were abstracted and analyzed via the Palantir Foundry platform, part of the Context Engine Data Management System at MDA. Suspected HLH was determined upon review of the following data elements: pathology results demonstrating hemophagocytosis, germline genetic testing including variants associated with HLH, the clinical presence of splenomegaly or fever, and laboratory markers including cytopenia, hyperferritinemia, elevated soluble interleukin 2, or low or absent natural killer cell activity.

Results

Each case was reviewed to identify patients with pathological evidence of hemophagocytosis identified at MDA (N=13), documented confirmed HLH at an outside institution (N=4), or germline genetic testing at MDA containing variants associated with HLH (N=6). The most common reason for consultation was encephalopathy (N=38) followed by seizure (N=9), generalized weakness (N=7), cranial neuropathy (N=4), peripheral neuropathy (N=3), syncope (N=3), vision change (N=3), abnormal/aggressive behavior (N=2), aphasia/language disturbance (N=2), and asymptomatic abnormal brain imaging (N=2). 5 patients had two reasons for consultation. Two patients were identified as having acute ischemic stroke on imaging, and two had multicompartment intracranial hemorrhage. Three patients had electrodiagnostic evidence of axonal neuropathy, two of these were thought to have axonal variant Guillain-Barré syndrome.

Conclusions

Patients with suspected HLH may present with a variety of neurological symptoms. Work isongoing to analyze patients by HLH-2004 criteria and review electrophysiologic, imaging, and cerebrospinal fluid measures.

Significance to the cancer neuroscience field

Describing the neurological manifestations of HLH in a cancer-specific context will add to our understanding of the interactions between the immune and nervous systems. Of specific interest, patients with cancer are increasingly being treated with immune effector cell (IEC) based therapies, which have been described in association with an HLH-syndrome (IEC-HS). Further analysis of data will seek to clarify distinctions between IEC-HS and immune effector cell associated neurotoxicity (ICANS).

Friday Abstract 12

Characterizing sex differences in HPV negative cancer

Sarah Barclay
University of South Dakota, Sanford Health
University of South Dakota, Vermillion, SD

Introduction

It is now widely accepted that peripheral solid tumors are infiltrated by nerves. This infiltration of malignancies by nerves is referred to as tumor innervation. The Vermeer lab studies tumor innervation primarily in head and neck squamous cell carcinoma (HNSCC) using a syngeneic cell line representing a mutationally-induced form of the disease; these cells are called MOC2-7 cells. In addition to defining the molecular consequences of tumor-infiltrating nerves on disease, the lab also focuses on their influence on behavior. This is important as cancer patients have a significantly higher incidence of depression and anxiety as compared to the population at large.

Methods

To assess the impact of tumor-infiltrating nerves on disease, MOC2-7 cells were orthotopically implanted into the mouse oral cavity and tumor growth, innervation, survival, and cancer-associated behavioral changes were analyzed. In humans, males are more susceptible to head and neck cancers than females, thus few studies have analyzed this disease using female animals. This project characterized tumor growth, innervation, and cancer-associated behavioral changes in female mice and compared them to their male counterparts.

Results

We found that MOC2-7 tumors grow significantly slower in females. Surprisingly, tumors were also significantly more innervated in females. However, there were no differences in behavioral decline between tumor-bearing males and females.

Conclusion

These findings suggest that nerve recruitment may differ between males and females. Future directions include defining these differences as well as investigating the impact of chemotherapy and radiotherapy on tumor innervation and behavior for both sexes.

Significance to the cancer neuroscience field

Head and neck cancer patients often receive the same treatment regardless of sex. From our studies, it is clear that sex has an influence on tumor growth and innervation. It is possible that this disease responds to treatment differently depending upon the patient's sex. Therefore, it is important that we, as a field, continue to study this disease in the female population.

Friday Abstract 13

Sensory neurons promote breast cancer metastasis *via* anextracellular RNA/ TLR7 signaling axis

Veena Padmanaban[1], Isabel Keller[1], Benjamin N. Ostendorf[1], Sohail F. Tavazoie[1] [1]Laboratory of Systems Cancer Biology, The Rockefeller University, New York, NY, USA

Introduction

Breast cancer represents a significant global health challenge, with an incidence rate of one in eight women. The paramount cause of mortality in these cases is metastasis, a process involving complex interactions between the tumor and its surrounding stroma. Peripheral nerves are now recognized as key players within the tumor microenvironment, with recent evidence demonstrating their requirement for gastric and prostate tumor initiation. The role for neurons in altering the immune milieu of tumors is also emerging. While nerves have been visualized in breast tumors, their role in breast cancer metastasis remains poorly characterized. Moreover, immune-independent, cancer cell-intrinsic mechanisms by which neurons regulate tumorigenesis are unexplored.

Methods and results

Careful examination of almost a dozen murine and human models revealed that breast tumors are universally innervated by sensory nerves. Significantly, metastaticmammary tumors were substantially more innervated than non-metastatic, isogenic tumors. Usingthree-dimensional co-culture systems, we demonstrated that primary sensory neurons from dorsal root ganglia (DRG) of mice enhanced the growth, invasion, and colony forming potential of cancer cell spheroids. *In vivo* co-transplantation and pharmacological denervation studies revealed a requirement for sensory nerves in tumor growth and metastasis of multiple breast cancer models. Conditioned medium from DRG neurons (DRG-CM) phenocopies the co-culture– suggesting that secreted factors mediate the pro-metastatic effects of sensory neurons. While addition of DNase or heat inactivation of DRG-CM had little effect, RNase A (single strand RNA (ssRNA)-specific) abolished its metastasis-promoting effects; this implies that ssRNAs within DRG-CM are pro-metastatic. Consistently, addition of ssRNA mimetics into the culture medium promotes cancer spheroid invasion and proliferation. Intra-tumoral delivery of RNase A significantly inhibits tumor growth and metastasis. Furthermore, depletion of the ssRNA receptor,TLR7 in breast cancer cells abrogates tumor growth and metastasis. Unexpectedly, sensory neuron-dependent TLR7 signaling occurs in a non-canonical, MyD88-independent, immune cell- independent manner. This ssRNA induced *Tlr7* gene expression signature associated with reduced breast cancer survival outcomes in two independent patient cohorts. Taken together, these data present a model in which sensory nerves innervating primary breast tumors drive metastatic colonization via an extracellular RNA/ TLR7 signaling axis.

Conclusion

Conceptually, our work implicates sensory neurons as drivers oftumor invasion, growth, and metastasis in breast cancer. We uncovered an immune-independent, tumor-intrinsic, and metastasis-associated transcriptional response upon neuronally-induced TLR7 activation in breast cancer cells.

Significance

Such molecular characterizations of the interplay between peripheral nerves and cancer cells could provide therapeutic opportunities to target the neuro- cancer axis to curb metastatic disease.

Friday Abstract 14

Histone H3.3 mutant-derived pediatric diffuse gliomas Multi-omicand Cross-species heterogeneity characterization

David Rincon, Fernandez Pacheco

California School of Health Sciences, Anaheim, CA

Introduction

Brain tumors are the leading cause of solid-tumor-related deaths among children. These tumors are now categorized by WHO as separated from adult brain tumors and based on their distinct molecular features, including K27M and G34R mutations in the histone H3.3. These tumors, despite similar mutational landscapes, differ significantly in their development and location, resulting in fast-growing diffuse midline gliomas and slower-developing diffuse hemispheric gliomas, respectively.

To address the limitations of current cancer modeling technologies, we developed Mosaic Analysis using Dual Recombinase-mediated cassette exchange (MADR). This technology offers precise single-copy transgenesis, enabling the generation of murine gliomas that closely resemble their human counterparts. We aimed to characterize the internal heterogeneity of H3.3 mutant pediatric brain tumors at the single-cell level, comparing them to H3.3 WT tumors, and validating these findings using human datasets to uncover developmental processes responsible for the divergent evolution of these tumors.

Methods

MADR technology was applied to target neuron progenitor cells of P1-2 pups to generate endogenous tumors that shared driver oncogenes signatures ($Pdgfra^{D842V}$, $Trp53^{R270H}$), only varying in the mutations carried at H3.3 (K27M/G34R/WT). Tumors were analyzed by scRNAseq, snATACseq, scISOseq, and Cut&Tag as well as exploited to generate organoids and 2D cultures.

Results and conclusions

scRNAseq and snATACseq analyses revealed striking similarities in the transcriptional and epigenetic profiles of the three tumor variants, as well as in their internal heterogeneity, results that correlate with those obtained from patient-derived human datasets. However, a transcription-dynamic-centered analysis using RNA-Velocity unveiled novel, stable, transcription profiles including Myeloid-like and Neuron-like programs, which showed a differential prevalence in each model. Specifically, neuron-like cells were almost exclusively found in K27M tumors and the Myeloid-like transcriptional program was linked to differential regulon-networks enhanced in G34R tumors.

Copy number variation analysis uncovered greater clonal divergence within G34R tumors correlating with the known genomic instability of G34R tumors. Long-read-based scISOseq analysis discriminated between models highlighting the role of splicing on their differential development. Finally, the epigenetic effects of these mutations were explored with Cut&Tag analysis uncovering differential genomic-targeting of the mutant histones altering transcription factors regulatory-networks.

Significance to the cancer neuroscience field

The present study emphasizes the importance of understanding the internal heterogeneity of pediatric gliomas for the development of personalized therapies. We have extensively characterized the global and specific heterogeneity among these tumors, including the primary role of the epigenetic alterations promoted by H3.3 mutations in their evolution.

Friday Abstract 15

Distinct tumor architectures and microenvironments for the initiation of metastasis in thebrain

Siting Gan[1, 8], Danilo G. Macalinao[1, a], Sayyed Hamed Shahoei[1], Lin Tian[1, b], Xin Jin[2, 3], Harihar Basnet[1, c], Catherine Bibby[1], James T. Muller[4], Pranita Atri[5], Evan Seffar[5], Walid Chatila[5], Ali Karacay[6], Pharto Chanda[6], Anna-Katerina Hadjantonakis[4], Nikolaus Schultz[5], Edi Brogi[6], Tejus A. Bale[6], Nelson S. Moss[7], Rajmohan Murali[6], Dana Pe'er[8, 9] and Joan Massagué[1, *] Corresponding author

[1] Cancer Biology and Genetics Program, Sloan Kettering Institute, Memorial Sloan Kettering Cancer Center, NY, USA [2] Westlake Laboratory of Life Sciences and Biomedicine, Hangzhou, Zhejiang Province, China [3] Research Center for Industries of the Future, School of Life Sciences, Westlake University,Hangzhou, Zhejiang Province, China [4] Developmental Biology Program, Sloan Kettering Institute, Memorial Sloan Kettering Cancer Center, NY, USA [5] Computational Oncology Service, Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, NY, USA [6] Department of Pathology and Laboratory Medicine, Memorial Hospital, Memorial Sloan Kettering Cancer Center, NY, USA [7] Department of Neurological Surgery, Memorial Sloan Kettering Cancer Center, , NY, USA [8] Computational and Systems Biology Program, Sloan Kettering Institute, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA [9] Howard Hughes Medical Institute, NY, USA

Introduction

Brain metastasis is an ominous form of cancer progression and the most common malignancy in the central nervous system. Despite poor prognosis in patients, it is a highly inefficient process at the cellular level, hinging on the initial survival, microenvironment adaptation, and outgrowth of disseminated cancer cells. Prior research has mostly focused on advanced macrometastatic lesions, leaving the crucial early stages of brain colonization obscure.

Methods

To address this knowledge gap, we examined two prevalent sources of cerebral relapse, triple-negative and HER2+ breast cancers (TNBC and HER2BC). To analyze incipient brain metastases in mouse models and human tissue samples, we employed a set of interdisciplinary techniques, spanning from 3D imaging of cleared whole brain hemispheres to single-cell transcriptomics of tumor microenvironment (TME) cells, spatially enriched by a metastatic niche labeling reporter.

Results

The two tumor types aggressively colonize the brain with distinct tumor architectures and stromal interfaces. TNBC predominantly forms perivascular sheaths with diffusive contact with astrocytes and microglia. In contrast, HER2BC mainly forms compact spheroids driven by autonomous tenascin C (TNC) production, segregating stromal cells to the periphery. These colony-initiating architectures evoke differential Alzheimer's disease-associated microglia (DAM) responses and engagement of the GAS6 receptor AXL. TNBC metastasis-associated microglia cells are largely restricted to the stage 1 DAM state, while the HER2BC ones progress towards the AXL+ stage 2 DAM state, triggered substantially by tumor-derived TNC that also drives spheroidal colonization. While a GAS6/AXL autocrine loop promotes TNBC brain metastasis, GAS6 overabundance can potentiate the capacity of AXL+ microglia to eliminate cancer cells in HER2BC colonies.

Conclusion

Our work unveils two modes of metastatic colonization adopted by prevalent subtypes of breast cancer and other cancers to commence brain relapse. The two modes present unique tumor architectures in mouse models and clinical samples of micrometastatic disease, closely linked to differences in tumor-ECM interactions, autocrine growth mechanisms, and engagement of a highly reactive stroma to gain advantage.

Significance to the cancer neuroscience field

Our findings suggest that the various aspects of subtype-specific colonization initiation modes are important determinants in the progression and potentially the treatment of brain metastasis. We uncover specific signals and therapeutic opportunities of the DAM phenotype, which we identify as a conserved, prominent feature of the TME, revealing a connection between brain metastases and neurodegenerative diseases. These insights motivate future systematic investigations into howdifferent cancer types and DAM stages influence each other in various clinically relevant contexts.

Friday Abstract 16

Hyperbaric Oxygen Treatment for Chemotherapy-Related Cognitive Impairment: A Focus on Cellular Senescence.

Oanh T.P. Trinh, Paapa Mensah-Kane, Helen Shi, Nathalie Sumien.
University of North Texas Health Science Center.
Corresponding author: Oanh Trinh (oanhtrinh@my.unt.edu)

Introduction

"Chemobrain" is a prevalent condition affecting approximately 75% of cancer patients, characterized by impaired attention, learning and memory retention during cancer treatments.
Chemotherapy-related cognitive impairment (CRCI), a subtype of chemobrain, can persist for up to 20 years post-treatment, significantly diminishing the daily quality of life for survivors and caretakers.
Although chemotherapy exposure is implicated in accelerating brain aging and functional declines, there is limited research on the mechanistic impact of chemotherapy on brain functions, with chronic inflammation, oxidative stress, and cellular senescence emerging as potential contributors to CRCI. Additionally, few interventions have been explored to mitigate CRCI, prompting investigation into hyperbaric oxygen therapy (HBOT) as a potential treatment. HBOT has demonstrated neuroprotective effects in conditions such as Alzheimer's disease, traumatic brain injury, and stroke. My research project seeks to elucidate the mechanism by which chemotherapy accelerates brain aging and whether HBOT can alleviate CRCI.

Hypothesis

Hyperbaric oxygen treatment will reverse cognitive impairments associated with chemotherapy exposure.

Methods

Adult C57BL/6 mice were exposed to a weekly cocktail of chemotherapeutics (methotrexate and 5-fluorouracil i.p.) for three weeks to induce CRCI. Simultaneously, half of the mice underwent daily HBOT sessions (2.4 ATM for 90 minutes). Cognitive, motor, and affective functions were assessed. Serum and brain regions were analyzed for markers of central and systemic inflammation, oxidative stress, and cellular senescence to study the pathways involved in the predicted beneficial effect of HBOT.

Results

Preliminary findings reveal HBOT's effectiveness in reversing cognitive impairments induced by low-dose chemotherapy in domain- and
sex-dependent manners. Ongoing studies, including evaluating higher chemotherapy doses and biochemical parameters, are underway.

Conclusion

Hyperbaric oxygen emerges as a potentially effective therapy for CRCI, reversing low-dose chemotherapy-induced cognitive impairments.

Significance to the cancer neuroscience field

The outcomes of this study will elucidate the mechanistic underpinnings of CRCI and provide preclinical information on the potential of HBOT to mitigate CRCI, thus paving the way for the development of interventions addressing other cancer treatment-induced impairments. With increasing cancer survival rates and survivors' life expectancies, it is important to identify interventions to reduce the cognitive impacts of chemotherapy on cancer survivors.