Title

TMOD-15. SPATIOTEMPORAL LOSS OF SMARCB1 IN EARLY NEURAL CREST LINEAGE LEADS TO DIFFERENT MOLECULAR SUBTYPES OF RHABDOID TUMORS

Journal

Neuro-oncology, 21(Suppl 2)

ISSN

1522-8517

Authors

Vitte, Jeremie
Gao, Fuying
Coppola, Giovanni
et al.

Publication Date

2019-04-01

Peer reviewed

Francesca Diomedi Camassei[3], Vinicia Assunta Polito[1], Cristiano De Stefanis [4], Concetta Quintarelli[1], Biagio De Angelis[1], Franco Locatelli[1], Ignazio Caruana[1], and Francesca Del Bufalo[1]; [1]Department of Hematology/Oncology and Cell and Gene Therapy, Bambino Gesù Pediatric Hospital, IRCCS, Rome, Italy, [2]Department of Neuroscience and Neurorehabilitation, Unit of Neurosurgery, Bambino Gesù Pediatric Hospital, IRCCS, Rome, Italy, [3]Department of Laboratories and Immunological Diagnostics, Pathological Anatomy Service, Bambino Gesù Pediatric Hospital, IRCCS, Rome, Italy, [4]Research Laboratories, Bambino Gesù Pediatric Hospital, IRCCS, Rome, Italy

Solid tumours are characterized by a high structural complexity that is difficult to reproduce with common bidimensional (2D) systems. We developed an innovative fibrin-based hydrogel 3D model and tested it as platform to establish primary LGG cultures, otherwise difficult to maintain owing to the activation of senescence pathways. To date, 37 samples were cultured in both 2D and 3D platforms (19 astrocytomas and 18 gangliogliomas), with an average culture duration of 177+13 days, showing that the 3D-culture enables the stabilization of LGG. Whereas in the 2D-culture the cells showed overtime a significant reduction in the average culture days between each passage (average P1-P3:35+6 days; P3-P6: 29+5; >P6: 17+5), suggesting the selection of a peculiar clone, in the 3D-*setting*, we observed a more regular growth (average P1-P3:44+5 days; P3-P6: 64+20;>P6: 48+16). Cell lines identity was confirmed by short tandem repeats (STRs) and the immunohistochemical characterization (H&E, Ki67, tumour and differentiation markers) in 3D cultures revealed phenotype, cellular organization and proliferative rates closer to those observed in the onset samples, as compared to the 2D. We then analyzed the methylation profile and preliminary results suggest that the 2D lines evolve towards different lineages. The analysis of cell senescence using ß-galactosidase assay revealed a lower senescence in the 3D cultures (3D:12,28%+4,3% of the cells vs 2D:50,69%+18,46%; p=0,008). Lastly, we evaluated the responses to radiotherapy by MTS assay, and showed that 2D-cultured cells are more sensitive to treatment than 3D (2D: untreated, 0,0232+0,023, 160 Gy 0,089+0,025; 3D: untreated 0,235+0,09, 160 Gy 0,169+0,08), suggesting an overestimation of the efficacy of such treatment by the 2D-*setting*, therefore reducing the predictive power. The response to chemotherapy and more innovative approaches (i.e. Oncolytic Adenovirus) is currently under evaluation, the preliminary results confirming a similar finding. Overall, the 3D-culture offers an innovative platform for biological and therapeutic studies.

TMOD-15. SPATIOTEMPORAL LOSS OF *SMARCB1* IN EARLY NEURAL CREST LINEAGE LEADS TO DIFFERENT MOLECULAR SUBTYPES OF RHABDOID TUMORS

Jeremie Vitte[1], Fuying Gao[2], Giovanni Coppola[2], Alexander R. Judkins[3], and Marco Giovannini[1]; [1]Department of Head and Neck Surgery, David Geffen School of Medicine at UCLA and Jonsson Comprehensive Cancer Center (JCCC), University of California Los Angeles, Los Angeles, CA, USA, [2]Semel Institute for Neuroscience & Human Behavior and Department of Psychiatry and Biobehavioral Sciences, University of California Los Angeles, Los Angeles, CA, USA, [3]Department of Pathology and Laboratory Medicine, Children's Hospital Los Angeles, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

Rhabdoid tumor predisposition syndrome 1 (RTPS1) results from inactivation of the tumor-suppressor *SMARCB1*, a core component of the BAF (hSWI/SNF) complex. Rhabdoid tumors (RTs) are a highly malignant group of neoplasms that usually occur in children less than 2 years of age, which have no effective medical treatment. We discovered that the myelin protein zero (P0) gene serves as a lineage marker to trace the developmental origin of RT neoplastic cells. Ablating *Smarcb1* in the $P0^{+}$early neural crest lineage was necessary and sufficient to initiate tumorigenesis in cranial nerves and meninges, faithfully recapitulating histological features and molecular profiles of human RTs. About 65% of P0-CreC;$Smarcb1^{flox/flox}$mice developed tumors between 1.5 and 5 months of age with an overall median survival of 3.2 months. These mice developed aggressive tumors emanating from cranial nerves, meninges, with variable extent of brain invasion, and spinal nerve roots. This genetically engineered mouse model opens the doors for deciphering the origin and evolution of RTs to identify effective therapies.

TMOD-16. A NOVEL ALGORITHM FOR MANAGEMENT OF PEDIATRIC CRANIOPHARYNGIOMA

Mohammed Fouda, David Zurakowski, and Liliana Goumnerova; Boston Children's Hospital, Boston, MA, USA

INTRODUCTION: Pediatric craniopharyngioma is associated with significant long-term morbidities and high rate of recurrence despite the "benign" histopathologic nature of the tumor. Optimal management remains controversial. We propose a novel algorithm for the management of pediatric craniopharyngioma in the context of prevention of recurrence and long-term hypothalamic obesity. METHODS: A cohort study of all pediatric patients diagnosed and managed at Boston Children's Hospital between 1985–2017. Chi-square, Fisher exact tests, logistic regression, and Cox-mantel models were used for the statistical analysis. IRB approval obtained. RESULTS: 90 patients met the inclusion and exclusion criteria (47 males, 43 females). Median age at the time of presentation was 8 years; median follow up was 10 years. 28 (31%) patients developed hypothalamic morbid obesity. 26 (29%) patients had a recurrence. Based on the univariate and multivariable logistic regression analysis for risk factors for the development of hypothalamic morbid obesity and recurrence we identified: 1) age at the time of presentation > 10 yrs. old (P-value 0.023), 2) preoperative obesity (P-value 0.006) and 3) preoperative papilledema (P-value < 0.0001) as significant risk factors for the development of hypothalamic morbid obesity while 1) extent of resection (P-value < 0.0001), 2) fine calcifications (P-value 0.025) and 3) maximum dimension of the lesion > 3.5 cm (P-value 0.008) were independent significant risk factors for recurrence. Based on the likelihood ratio tests and the weight of the risk factors for hypothalamic morbid obesity, we proposed a predictive score to differentiate patients with and without risk for hypothalamic morbid obesity. CONCLUSIONS: Based on these data we developed a novel algorithm for the management of pediatric craniopharyngioma using a new predictive score for hypothalamic morbid obesity and the probability of recurrence.

TMOD-17. DEVELOPMENT AND CHARACTERIZATION OF DIFFUSE INTRINSIC PONTINE GLIOMA MOUSE MODELS GENERATED BY BRAINSTEM IN UTERO ELECTROPORATION

Smruti Patel[1], Rachel Hartley[1], Heather Bear[2], Christine Fuller[2], and Timothy Phoenix[1,2]; [1]University of Cincinnati, Cincinnati, OH, USA, [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Diffuse intrinsic pontine glioma (DIPG) is a universally fatal pediatric cancer arising in the brainstem of children. Their unique brainstem location and pathology, including limited disruption of the blood-brain barrier (BBB), present a significant challenge to treatment. Developing mouse models that accurately reflect the genetic landscape and brainstem location of DIPG will be critical to delineate the role of newly identified mutations in DIPG pathogenesis. Here we describe the efficient generation of DIPG mouse models by targeted transfection of the developing brainstem using in utero electroporation, and characterize the pathological and molecular features associated with PDGFB, Pdgfra, and H3.3 K27M genetic variants. Both PDGFB and $Pdgfra^{D842V}$ expression, in combination dominant negative Trp53 (DNp53), develop fully penetrate high-grade gliomas that display distinct differences in latency, histology, and molecular profiles. Addition of the H3.3 K27M mutation alters gene expression in both PDGFB and PdgfraD842V tumors, but only significantly accelerated $Pdgfra^{D842V}$ tumors in this system, likely due to the already aggressive nature of PDGFB tumors. Compared to PDGFB tumors, PdgfraD842V brainstem tumors maintain BBB function. Paracrine effects of PDGFB expression in the tumor microenvironment are associated with disruption of pericyte-endothelial interactions, extracellular matrix remodeling, and increased angiogenesis and BBB disruption. This DIPG mouse modeling system provides a rapid and flexible *in vivo* platform to perform functional genomic studies to fundamentally advance our understanding of the cellular and molecular basis underlying DIPG, and conduct preclinical studies of molecularly targeted therapies that aim to improve survival rates and outlook for DIPG patients and their families.

TMOD-18. AN INTEGRATED SET OF PEDIATRIC HIGH GRADE GLIOMA RESOURCES FOR TRANSLATIONAL STUDIES

Heba Ijaz, Valerie Baubet, Mateusz Koptyra, Pichai Raman, Lamiya Tauhid, Krutika Gaonkar, Yuankun Zhu, Bo Zhang, Namrata Choudhari, Jamie Galanaugh, Elizabeth Appert, Jennifer Mason, Linnea Cripe, Taylor Lis, Maria Rita Santi, Jay Storm, Angela Waanders, Adam Resnick, and Kristina Cole; Children's Hospital of Philadelphia, Philadelphia, PA, USA

PURPOSE: Pediatric high grade glioma (pHGG) remains a fatal disease. Increasing the number of patient derived tumor models and reagents will encourage research in pHGG and support the translation of basic science research discoveries. This work describes a recent multi-institution initiative to provide such a resource. METHODS: pHGG tumors with associated clinical data were prospectively collected and sequenced through the Children's Brain Tumor Tissue Consortium (CBTTC) and Pediatric Brain Tumor Atlas (PBTA) with data deposited into PedcBioPortal for easy access and visualization. Primary tumor was dissociated and cultured to create both adherent and glioma stem cell lines analyzed by targeted and WGS/RNA sequencing. A tissue microarray (TMA) of primary pHGG tumors was created and examined by immunohistochemistry. RESULTS: The pHGG set included 81 collection events (70 patients, 54% at diagnosis, median age of 11 yrs, 52% female, 43% hemispheric). Analysis of somatic mutations and copy number alterations of known glioma genes were of expected distribution (36% H3.3, 47% TP53, 24% ATRX and 7% BRAF V600E variants). There were rare germline variants in mismatch