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11th International Conference on

CANCER STEM CELLS AND ONCOLOGY RESEARCH

June 11-13, 2018 | Dublin, Ireland

DAY 1

Scientific Tracks & Abstracts

Day 1
SESSIONS

June 11, 2018

Cancer Stem Cells | Breast Cancer Stem Cells | Prostate Cancer Stem Cells | Ovarian Cancer Stem Cells | Pancreatic Cancer Stem Cells | Lung Cancer Stem Cells | Cancer Stem Cells and Metastasis

Session Introduction

Session Chair
Dean Tang
Roswell Park Cancer Institute, USA

Session Co-chair
Wei Qiang Gao
Shanghai Jiao Tong University, China

Title: **Angiogenin and plexin-B2 inhibition sensitizes prostate cancer stem cells to chemotherapy**
Guo-fu Hu, Tufts University, USA

Title: **Phage display library screening identifies novel binding peptides that preferentially target castration-resistant PSA-/lo prostate cancer stem cells**
Kiera Rycaj, Roswell Park Cancer Institute, USA

Title: **Maintenance of cancer stem cells by microRNA**
Qien Wang, The Ohio State University Wexner Medical Center, USA

Title: **Targeting Notch4 in ovarian cancer results in decreased number of cancer stem cells and increased survival when used in combination with cisplatin in pre-clinical models**
Elaine Hurt, MedImmune LLC, USA

Title: **Metakaryotic cancer stem cells are constitutively resistant to x-rays and chemotherapeutic agents but sensitive to many common drugs: First clinical trial shows effectiveness of a metakaryocide against stem cells in human pancreatic tumors**
William G Thilly, MIT, Cambridge, MA, USA

Title: **Molecules targeting cancer stem cells**
Maithili Athavale, Godavari Biorefineries Ltd., India

Title: **hTERThigh Numb-/low state enriches a castration resistant prostate cancer cell subpopulation with tumor initiating capacity**
Helen He Zhu, Shanghai Jiao Tong University, China

Title: **Drug resistant stem cells: Models for targeted therapy of breast cancer**
Nitin Telang, Palindrome Liaisons Consultants, USA

Title: **The constitution of Cancer tissues: The properties and implication of cancer stem cells derived from patients' samples**
Xianming Mo, Sichuan University, China

Title: **Isolation of cancer stem cells from Cancer of Unknown Primary origin (CUP) and generation of a novel *in vivo* model of early, spontaneous and multiple metastases by subcutaneous transplantation**
Federica Verginelli, Candiolo Cancer Institute, Italy

Title: **Integrated analyses identify a poor-prognosis subtype of hepatocellular carcinoma regulated by a core microRNA regulatory circuitry**
Jiangwen Zhang, The University of Hong Kong, China

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ANGIOGENIN AND PLEXIN-B2 INHIBITION SENSITIZES PROSTATE CANCER STEM CELLS TO CHEMOTHERAPY

Guo-fu Hu[1,2], Shuping Li[1], Kevin A Goncalves[1,2] and Baiqing Lyu[1]

[1]Tufts Medical Center, Washington, USA
[2]Tufts University, Medford, USA

Angiogenin (ANG) and its receptor Plexin-B2 (PLXNB2) has recently been shown to dichotomously regulate the stemness of hematopoietic stem and progenitor cells (HSPC). While *ANG* and PLXNB2 preserve quiescence of the primitive stem cells, they promote proliferation of more differentiated progenitor cells. Here we show that ANG-PLXNB2 also dichotomously regulates the properties of cancer stem cells (CSC) and differentiated bulk cancer cells. Prostate CSCs were cloned from PC3, LNCaP, and DU145 cells, and shown to have self-renewal, differentiation, and tumor-initiating capacities. While ANG-PLXNB2 enhance proliferation of differentiated prostate cancer cells, they restrict proliferation of CSCs and promote quiescence through specific cleavage of 5S rRNA. Monoclonal antibodies against both ANG and PLXNB2 were found to mobilize CSC out of quiescence, sensitive them to chemotherapy, and prevent disease relapse.

BIOGRAPHY

Guo-fu Hu, PhD, is currently a Professor of Medicine, Tufts University School of Medicine, and an Investigator at Tufts Medical Center. He received his PhD from Shanghai Institute ofBiochemistry, Chinese Academy of Sciences, and did his postdoctoral training in Beret L. Vallee lab located at the Center for Biochemical and Biophysical Sciences and Medicine, Harvard Medical School. He established his research program first in the Department of Radiology, Brigham and Women's Hospital, and then in the Department of Pathology, Harvard Medical School, where he raised to the rank of Associate Professor of Pathology. He moved to Tufts Medical Center in 2010.

guo-fu.hu@tufts.edu

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PHAGE DISPLAY LIBRARY SCREENING IDENTIFIES NOVEL BINDING PEPTIDES THAT PREFERE NTIALLY TARGET CASTRATION-RESISTANT PSA-/lo PROSTATE CANCER STEM CELLS

Kiera Rycaj[1], John Moore[1], Xin Liu[1], Mikhail G Kolonin[2] and Tang DG[1,3,4]

[1]Roswell Park Cancer Institute, USA
[2]University of Texas Health Science Center at Houston, USA
[3]The University of Texas MD Anderson Cancer Center, USA
[4]Tongji University School of Medicine, China

Androgen deprivation therapy (ADT) is the mainstay treatment for patients with advanced prostate cancer (PCa). Despite an initial response, the majority of patients relapse resulting in castration-resistant prostate cancer (CRPC). Both untreated advanced PCa and CRPC are enriched in phenotypically undifferentiated PCa cell populations that expresses little or no prostate specific antigen (i.e., PSA-/lo). We have demonstrated that the PSA-/lo PCa cell population harbors self-renewing prostate cancer stem cells (PCSCs) that are intrinsically resistant to ADT and can long-term propagate tumors, mediate recurrence, and serve as a cell-of-origin for CRPC (Cell Stem Cell, 2012; Oncotarget, 2015; Clin Cancer Res, 2016; Oncotarget 2016). Consequently, it is important to find therapeutics that can preferentially target these cells. By employing phage display technology, we screened a combinatorial library for peptides that preferentially bind to PSA-/lo LNCaP PCa cells. An initial competitive assay identified the JRM1 peptide that showed slight preferential binding to the PSA-/lo LNCaP cells. With this knowledge, we carried out another screen using an indirect subtraction assay to identify the peptide JRM2, which demonstrated preferential and statistically significant binding to the PSA-/lo LNCaP cells. Fluorophore-conjugated JRM2 could be internalized into cells. When conjugated to a pro-apoptotic peptide, JRM2 specifically inhibited cell proliferation in PSA-/lo PCa cells. Preliminary *in vivo* studies showed tumor-inhibitory effects of the JRM2-killer peptide conjugates. Our findings demonstrate the feasibility of utilizing novel ligand-directed therapeutics to target undifferentiated (AR-)PSA-/lo CRPC cells.

BIOGRAPHY

Kiera Rycaj, PhD, is currently Assistant Professor at the Roswell Park Comprehensive Cancer Center (RPCCC) in Buffalo, NY, USA. She obtained her PhD from the University of Texas M.D Anderson Cancer Center (MDACC) in 2012 Her PhD thesis work focused on the expression and biological functions of HERV-K (Human Endogenous Retrovirus – K) in breast and ovarian cancer (OC) cells. Her work has demonstrated that the HERV-K env protein not only is expressed on the surface of breast cancer and OC cells but also can function as TAA (tumor-associated antigen) to elicit T-cell and antibody responses. She developed HERV-K specific vaccines and demonstrated their utility in killing autologous patient cancer cells. She conducted her postdoc training in Dr. Tang's laboratory during 2012-2015 and her work focused on elucidating prostate cancer (PCa) cell heterogeneity and therapeutically targeting the phenotypically undifferentiated AR-/lo(PSA-/lo) prostate cancer stem cells (PCSCs). Her recent published study on high-throughput screening shows that treatment-reprogrammed castration-resistant PCSCs are AR-PSA- and completely refractory to antiandrogens but remain partially sensitive to inhibitors of BCL-2 and certain kinase. She became a junior faculty in 2015, and her lab has been focusing on elucidating how primary tumor microenvironment regulates functional properties of metastatic PCSCs and on developing novel immunotherapeutic strategies to target undifferentiated, therapy-resistant and metastasis-prone PCa cells.

Kiera.Rycaj@RoswellPark.org

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MAINTENANCE OF CANCER STEM CELLS BY miRNA

Qi-En Wang, Amit Kumar Srivastava, Tiantian Cui, Chunhua Han, Ananya Banerjee, Shuri Cai, Lu Liu, Zaibo Li, Xiaoli Zhang, Selvendiran Karuppalya and **Altaf A. Wanin**
The Ohio State University Wexner Medical Center, USA

Cancer stem cells (CSCs) are considered to play a central role in the cancer progression, metastasis and the development of drug resistance. MicroRNAs (miRNAs) have important roles in regulating CSC properties and are considered to be potential therapeutic targets. Diverse aberrantly expressed miRNAs have been reported in ovarian cancer cells. However, there have been few reports about miRNAs that were associated with stemness and progression of ovarian cancer. In this study, miRNA nano string profiling analysis was performed to screen crucial miRNAs associated with characteristics and maintenance of CSCs in ovarian cancer. We found that miR-328-3p was remarkably upregulated in ovarian CSCs isolated from both ovarian cancer cell lines and primary ovarian tumors compared to their corresponding bulk cancer cells. We further demonstrated that enforced expression of miR-328-3p in ovarian cancer cell lines expanded the population of ALDH+ cells, enhanced their sphere formation ability, as well as increased their tumorigenicity. While inhibition of miR-328-3p limited the ALDH+ cell population, reduced their sphere formation capacity, and decreased their tumorigenicity. The orthotopic ovarian xenograft assay also demonstrated that inhibition of miR-328-3p impedes tumor growth and metastasis. The mechanistic investigation revealed that repressed ERK1/2 phosphorylation in ovarian CSCs, mainly due to reduced level of reactive oxygen species (ROS), contributes to the enhanced expression of miR-328-3p, and the maintenance of CSCs. Finally, we identified DDB2 as a direct target of miR-328-3p. Given our previous finding that DDB2 is capable of limiting the CSC population in ovarian cancers, we conclude that highly expressed miR-328-3p in ovarian CSCs, probably due to repressed ERK1/2 activity, inhibits DDB2 expression, resulting in the expansion of these CSCs. Thus, targeting miR-328 could be exploited to a novel strategy to eradicate CSCs in ovarian cancer.

BIOGRAPHY

Qi-En Wang is an Associatet Professor in the Department of Radiology and Comprehensive Cancer Center at the Ohio State University. Dr. Wang received his Bachelor Degree in Preventive Medicine in Shanxi Medical College in 1992, and obtained his PhD from Beijing Medical University in 1997 in China. Then, Dr. Wang worked as a Lecturer and Associate Professor at Peking University Medical Center for 4 years. During this time, his research was focused on understanding how gene and environmental exposure interact in carcinogenesis. In 2001, He joined Dr. Altaf Wani's laboratory at the Ohio State University in the United States of America to study the mechanism of DNA repair as a Research Associate and Research Scientist. Since 2011, He has become a Tenure-track Assistant Professor at the Ohio State University, and was promoted to Associate Professor with Tenure in 2017.

wang.771@osu.edu

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TARGETING NOTCH4 IN OVARIAN CANCER RESULTS IN DECREASED NUMBER OF CANCER STEM CELLS AND INCREASED SURVIVAL WHEN USED IN COMBINATION WITH CISPLATIN IN PRE-CLINICAL MODELS

Elaine M Hurt, Suneetha B Thomas, Jon Chesebrough, Tim Hummer and **Peter Pavlik**
MedImmune LLC, USA

The Notch pathway plays a central role in the regulation of cellular growth and differentiation. There are 4 known receptors and 5 ligands in this pathway. While all receptors have been shown to be important in tumor biology, Notch4 continues to be implicated as a key mediator of cancer stem cell (CSC) biology. CSC-targeted biologics are an important part of a comprehensive oncology therapeutic strategy due to the role of CSCs in tumorigenesis, therapeutic resistance and patient relapse. Targeting this sub-population of cells is anticipated to lead to more durable patient responses. We have developed a human IgG1 antibody that targets the negative regulatory region of the Notch4 receptor, keeping it in an auto-inhibited state. We have determined Notch4 is expressed by CSCs of many solid tumors and is increased by cisplatin, a commonly used chemotherapy. Furthermore, uur anti-Notch4 antibody inhibits ovarian CSC growth *in vitro* and secondary tumor growth *in vivo*, consistent with depletion of CSCs. Combination of our anti-Notch4 antibody with cisplatin in ovarian tumor models demonstrates a more durable response than cisplatin alone, as expected with a CSC-combination therapeutic approach. Overall targeting Notch4 with an inhibitory antibody demonstrates superior ability, as compared with other Notch pathway inhibitors, to inhibit CSCs in preclinical models.

BIOGRAPHY

Elaine M Hurt received her PhD in Biochemistry, Molecular Biology and Biophysics from the University of Minnesota in 1999 where she studied estrogen receptor signaling cascades. She did her post-doctoral studies at the National Institutes of Health in the laboratory of Dr. Louis Staudt elucidating the molecular mechanisms governing therapeutic responses in lymphoma and multiple myeloma patients. In 2010, She-joined MedImmune to lead their cancer stem cell group. Prior to joining MedImmune, She was a Staff Scientist at the National Cancer Institute, where she focused primarily on identifying and targeting prostate cancer stem cells. In 2014, She became Adjunct Associate Professor in the Department of Biochemistry and Molecular Biology at the University of Maryland. She is the co-inventor on several patents, has been an invited speaker at numerous conferences, and has published over 50 scientific articles.

elaine.hurt@yahoo.com

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METAKARYOTIC CANCER STEM CELLS ARE CONSTITUTIVELY RESISTANT TO X-RAYS AND CHEMOTHERAPEUTIC AGENTS BUT SENSITIVE TO MANY COMMON DRUGS: FIRST CLINICAL TRIAL SHOWS EFFECTIVENESS OF A METAKARYOCIDE AGAINST STEM CELLS IN HUMAN PANCREATIC TUMORS

William G Thilly and **Elena V Gostjeva**
Massachusetts Institute of Technology, USA

After radio- and chemo-therapy human tumors display many dead eukaryotic cells with pyknotic nuclei. But amitotic metakaryotic stem cells with hollow, bell shaped nuclei are unaffected as expected of treatment-resistant cancer stem cells. These same phenomena may be observed *in vitro* using any of many tumor or metastasis-derived cell lines the immortality of which is conferred by the presence of amitotic, metakaryotic cancer stem cells. About 5% of human colonic adenocarcinoma-derived HT-29 cells in exponential growth are immortal metakaryotic stem cells that increase by symmetric amitoses and continuously create mortal mitotic eukaryotic cells by asymmetric amitoses. Two assays for agents/conditions specifically toxic to metakaryotic stem cells have been devised: (a) microscopic recognition of necrotic metakaryotic nuclei and (b) survival of cells forming large immortal colonies visibly containing metakaryotic stem cells *in vitro*. X-rays and chemotherapeutic agents (alkylating agents, antimetabolites and mitocides) have been found to kill eukaryotic cells but not metakaryotic cells at doses commonly used in cancer therapy. In contradistinction, we have shown that multiple classes of common drugs are preferentially cytotoxic to metakaryotic stem cells including NSAIDS, antibiotics and drugs used to treat diabetes, hypertension and other medical conditions. There are reports of the first images demonstrating killing of the preponderance of metakaryotic cancer stem cells in a series of pancreatic tumors by an antibiotic metakaryocide in a clinical trial in progress at the Medical College of Wisconsin (Prof. Susan Tsai, M.D, Principle Investigator). Research plans to identify effective protocols for a series of metakaryocidal drugs are outlined.

BIOGRAPHY

William G Thilly, Sc.D. was born in Port Richmond NY, USA and is now Professor of Genetics, Toxicology and Biological Engineering at MIT. With multiple collaborators he and Dr Gostjeva are exploring the bizarre physiology of metakaryotic stem cells, growing them in cell cultures, and devising means to kill them with drugs and protocols expected to be well tolerated in patients.

thilly@mit.edu

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MOLECULES TARGETING CANCER STEM CELLS

Maithili A Athavale, Sandip Gavade and **Sangeeta Srivastava**
Godavari Biorefineries Ltd., Somaiya Bhavan, India

The aim of the present project was to synthesize novel derivatives of diphylline glycoside of Cleistanthin A (SBGB-0001-000) and to screen them for anticancer activity (by MTT, Soft Agar Assay) and anticancer stem cell activity (by tumorsphere assay) on breast cancer cell lines. In all 70 novel derivatives of SBGB-0001-000 were synthesized and screened for anticancer and anticancer stem cell activity. Out of 70, two derivatives namely, SBGB-0001-014 and SBGB-0001-023 exhibited better anticancer and anticancer stem cell activity compared to standard chemotherapeutic drug Cisplatin. Since, cancer stem cells (CSCs) are subpopulation of cells within the cancer tissues with drug resistance and metastatic properties, these two candidates were further tested for its anticancer stem cell activity on drug (Paclitaxel) resistant population on highly metastatic breast cancer cell line MDAMB231 (with high number of CSCs) compared to standard chemotherapeutic drug Cisplatin and a target drug therapy sunitinib. Our sphere assay results indicate that the candidate molecules have better anticancer stem cell potential, inhibiting spheres at 25 nM compared to Cisplatin and sunitinib. In (figure 1), briefly describes that, our in-vitro data supports the anticancer stem cell effect of two novel candidates on breast cancer cell lines. Further, these candidates do not exhibit any toxic effect on normal cells (peripheral blood lymphocytes) compared to Cisplatin. The molecules show good hepatocyte stability and have been taken further for the preclinical studies like PK-PD, MTD and Xenograft studies.

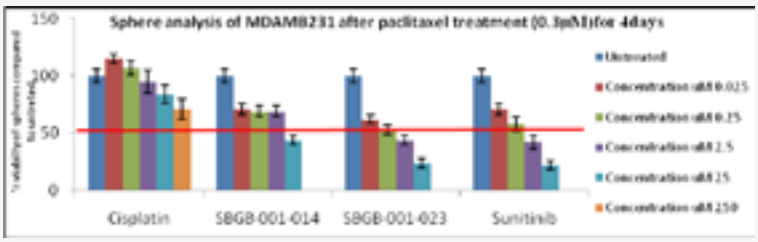

Figure 1: Indicates that the candidate molecules SBGB-0001-014 and SBGB-0001-023 are effective on paclitaxel treated MDAMB231 cells compared to Cisplatin at 25 nM (0.025 µM).

BIOGRAPHY

Maithili A Athavale has completed her PhD from National Institute for Research in Reproductive Health, Mumbai University, India. She has handled various Projects in Research and Development of various Pharma companies. She has publications in national and international journals. Currently, she is working as Senior Manager R&D of Biotech Division, of Godavari Biorefineries Ltd. Her lab is into in-vitro screening of many novel synthetic molecules for anticancer and anticancer stem cell activity on breast, prostate and oral cancer cell lines. The lab has screened and found eight novel molecules having potent anticancer and anticancer stem cell activity. Two of the lead molecules have entered preclinical studies.

maithili.athavale@somaiya.com

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hTERThigh NUMB-/LOW STATE ENRICHES A CASTRATION RESISTANT PROSTATE CANCER CELL SUBPOPULATION WITH TUMOR INITIATING CAPACITY

Helen He Zhu[1, 2]
[1]Ren Ji Hospital, School of Medicine, China
[2]Shanghai Jiao Tong University, China

Castration resistant prostate cancer (CRPC) remains one of the most deadly and incurable cancer types worldwide. Tumor cells in CRPC patient samples display tremendous heterogeneity. Cancer stem cells (CSCs) are proposed to be the driving force in cancer progression and recurrence. Identification of the CSC or prostate cancer cell sub-population with greater castration resistance is a key to the development of targeted anti-CRPC treatment strategies. We report that the hTERThigh PCa cells exhibit CSC properties including stem cell associated gene expression signature, long term tumor propagating capacity, and epithelial-to-mensenchymal transition. hTERThigh CSC cells display distinct cell division modes and can undergo both symmetric division and asymmetric division, as compared to hTERT-/low Pca cells. Numb, an evolutionarily conserved cell fate determinant, tends to segregate into the more differentiating daughter cell during symmetric division and asymmetric division of hTERThigh CSC cells. Further investigation revealed that Numb is down-regulated and negatively correlated with PCa advancement. Functionally, Numb exerted an inhibitory role in xenograft prostate tumor growth and CRPC development via suppression of Notch and Hedgehog signaling. Through a Numb promoter based lentiviral reporter system, we were able to separate Numb-/low Pca cells from Numbhigh cells. Numb-/low PCa cells are smaller and quiescent, preferentially express Notch and Hedgehog downstream and stem-cell-associated genes, and are associated with greater resistance to androgen deprivation therapy. Targeting Notch and Hedgehog signaling with inhibitors can effectively deplete the Numb-/low castration resistant PCa cells. Collectively, these findings provide novel insight into cellular and molecular mechanisms for the development of advanced CRPC and to the development of effective anti-CRPC treatment strategies.

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BIOGRAPHY

Helen He Zhu received her Bachelor Degree from Fudan University, China. She performed her PhD study in Molecular Pathology at School of Medicine, University of California-San Diego and did her postdoctorate training in the Department of Biology, University of California-San Diego. In 2012, She relocated back to China and started to work as an Associate Professor then Professor in Ren Ji Stem Cell Research Center, Ren Ji Hospital at School of Medicine, Shanghai Jiao Tong University. Her current work focuses on 1) adult tissue stem cells from hematopoietic system and prostate in tissue development and tumorigenesis. 2) roles of prostate cancer stem cells in therapeutic resistance and tumor metastasis. Her publication includes first author and corresponding author papers in Blood, PNAS, Gastroenterology, Clinical Cancer Research, Cancer Research and etc.

zhuhecrane@shsmu.edu.cn

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DRUG RESISTANT STEM CELLS: MODELS FOR TARGETED THERAPY OF BREAST CANCER

Nitin Telang
Palindrome Liaisons Consultants, USA

Cancer stem cells represent a subpopulation of the primary cancer that is predominantly characterized by drug resistant phenotypes exhibiting tumorigenic potential. Long-term treatment options lead to emergence of drug resistant cancer stem cells. Relevant models for cancer stem cells facilitate novel experimental approaches that identify efficacy of stem cell targeted therapeutic agents. Experiments in the present study were designed to characterize stem cell models from molecular subtypes of clinical breast cancer.

BIOGRAPHY

Nitin Telang has completed his PhD degree in 1974 from University of Poona, India, and obtained his Post-doctoral training (1976-1985) in the USA at University of Nebraska, American Health Foundation, New York, and Memorial Sloan-Kettering Cancer Center, New York. He served on the Faculty of Memorial Sloan-Kettering Cancer Center, Weill-Cornell Medical College, and Strang Cancer Prevention Center, New York (1986-2007). He serves as the Director of Cancer Prevention Research Program at Palindrome Liaisons Consultants, New Jersey. He has published more than 100 peer-reviewed papers and serves on the Editorial Boards of *International Journal of Oncology, Oncology Reports and BMC-Complementary and Alternative Medicine*.

ntelang3@gmail.com

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THE CONSTITUTION OF CANCER TISSUES: THE PROPERTIES AND IMPLICATION OF CANCER STEM CELLS DERIVED FROM PATIENTS' SAMPLES

Xianming Mo
Sichuan University, China

The growth of cancers depend on the formation of blood vessels that provide the supply of nutrients and oxygen and the nervous system acts as a crucial part of cancer microenvironment. The angiogenesis and vasculogenesis are essential during cancer progression. Recently, several studies have reported that glioblastoma stem cells are able to give rise to tumor vascular endothelial cells (ECs) and vascular pericytes for tumor vascularization. However, there is no evidence to show that the tumor stem cells from other kinds of tumors including carcinoma produce endothelial cells to constitute the functional blood vessels in cancer. In addition, recent evidences have demonstrated that the stimulation of both cancer growth and metastasis by members of nervous system such as neurons. How the nervous system built in cancer tissues is unknown. We transplanted the cancer stem cells that were isolated from the patients with gastric and colorectal carcinoma into nude mice via subcutaneous and intraperitoneal injections to produce human cancer xenografts. Then the innervations, angiogenesis were examined and the origins of the neural cells and endothelial cells were determined in cancer tissues. A single cancer stem cell from the cancer tissues of human patients was able to generate neurons including sympathetic and parasympathetic cells to take part in the nervous system in cancer tissues. Knocking down the neural generating capabilities of the human cancer stem cell inhibited the growth of tumors. Next, we show that cancer stem cells of the human colorectal carcinoma (CoCSCs) give rise to vascular endothelial cells and compose the vasculatures in cancer tissues. NuMA+ EC incorporated blood vessels were functional. Dependent on the biology of cancer stem cell, we identified small molecules to drive the differentiation of the cancer stem cell for restricted cancer grow. Our data demonstrate that neural cells and endothelial cells originated from human cancer stem cells constitute blood vessels and nerve system for the cancer progression in the cancer tissues. The findings are able to guide the development of therapeutic approaches to restrict cancer.

BIOGRAPHY

Xianming Mo is a professor of internal medicine and acts as Director of Laboratory of Stem Cell Biology, State Key Laboratory of Biotherapy, West China Hospital, Sichuan University. He obtained his medicine degree from North Sichuan Medical College. Then he was trained in pathology and accept Master of Medicine in West China University of Medical Science. After obtaining a PhD degree in Peking Union Medical College, He moved to Humboldt-Universität zu Berlin and then to Medical College of Georgia as postdoctoral fellows. Then, he became junior faculty in Medical College of Georgia and senior scientist in Max Delbruck Center for Molecular Medicine. In 2006, he returned back to West China Hospital.

xmingmo@scu.edu.cn

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ISOLATION OF CANCER STEM CELLS FROM CANCER OF UNKNOWN PRIMARY ORIGIN (CUP) AND GENERATION OF A NOVEL *IN VIVO* MODEL OF EARLY, SPONTANEOUS AND MULTIPLE METASTASES BY SUBCUTANEOUS TRANSPLANTATION

Federica Verginelli, D'Ambrosio Antonio, Carollo Rosachiara, Benvenuti Silvia, Senetta Rebecca, Pisacane Alberto, Geuna Elena, Gentile Alessandra, Marsoni Silvia, Balsamo Antonella, Montemurro Filippo, Sapino Anna , Comoglio Paolo M., and **Boccaccio Carla**
Candiolo Cancer Institute, Italy

Cancer of unknown primary origin or CUPs, represent 3-5% of all cancers with a very poor prognosis (overall survival: 9 months). Patients display unpredictable and precocious metastatic dissemination in the absence of a clinically detectable primary lesion. Histologically, CUPs display mostly epithelial morphology but, invariably, they lack expression of lineage markers that allow unambiguous identification of the tissue of origin. Today many efforts are aimed to develop new molecular diagnostic tools to predict the primary tissue and guide to a more rational therapeutic choice. However, the aberrant molecular mechanisms underlying CUP pathogenesis are largely obscure. Here, we show for the first time the isolation and the extensive *in vitro* and *in vivo* characterization of cancer stem cells isolated from CUPs, as cultures named "agnospheres". Specifically, agnospheres are able to grow in suspension and in the absence of growth factors, they express well-known stem cell markers and are endowed with self-renewal ability and long term propagation *in vitro*. They repopulate a tumor when transplanted subcutis in immunocompromised mice at very low number (i.e. as few as 10 cells, stem cells frequency: 5-15%). Most importantly, after subcutaneous transplantation, agnospheres recapitulate the whole metastatic cascade, generating metastases in multiple organs (lung, lymph nodes, thymus...) within a month (estimated metastatic stem cell frequency: 1-2%). For the first time to our knowledge, cancer stem cells have been isolated from CUPs, and phenotypically and functionally characterized. We generated a new cancer stem cell model endowed with extremely high tumor-initiating ability and impressive precocious metastogenic potential in different organs. Agnospheres may represent an unprecedented tool for investigating the molecular mechanisms responsible for the metastatic process in general, and to assess the anti-metastatic effect of approved or new therapeutic compounds.

BIOGRAPHY

Federica Verginelli has accomplished her PhD in Cellular and Molecular Biology at the Tor Vergata University in Rome (Italy), and a 4-years post-doc at the Montreal Neurological Institute (Canada). She is now research associate at the Candiolo Cancer Institute (Italy). She is author of 10 publications that have been cited 297 times, and her publication H-Index is 8.

federica.verginelli@ircc.it

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INTEGRATED ANALYSES IDENTIFY A POOR-PROGNOSIS SUBTYPE OF HEPATOCELLULAR CARCINOMA REGULATED BY A CORE microRNA REGULATORY CIRCUITRY

Jiangwen Zhang, Qingzheng Kang, Yin Tong, Jianlong Sun and Xin-Yuan Guan
The University of Hong Kong, China

Cancer stem cells (CSCs) cause tumor heterogeneity, relapse, and resistance to therapy. The underpinnings of CSCs remain to be elucidated, especially the underlying gene regulatory network. We here conducted integrated analyses and identified a miRNA-regulatory network defining a stemness subtype with poor-prognosis from TCGA hepatocellular carcinoma (HCC) cohort with independent validations. The poor-prognosis subtype was characterized by the signature expression pattern of CSCs orchestrated by two miRNAs and their mRNA targets that formed a core regulatory circuitry (CRC). Within the CRC, miR483-3p bound a complementary sequence on *SOX9* promoter, facilitating the recruitment of RNA polymerase II and STAT3, which was essential for *SOX9* transcription activation. SOX9 can further activate *SOX4* expression. Both *SOX4* and its associated activator lncSOX4 were the direct targets of miR204-5p. *SOX4* and miR204-5p formed double-negative feedback loop through mutual inhibition. The expression level of miR204-5p was tightly modulated by miR483-3p, whose promoter was significantly demethylated in the stemness subtype. Activation of the CRC essential for the self-renewal and maintenance of liver CSCs culminated in downregulation of miR204-5p and upregulation of miR483-3p, *SOX9*, and *SOX4*. Functional significance of the CRC for HCC metastasis and drug resistance was further demonstrated with various *in vitro* and *in vivo* assays.

BIOGRAPHY

Jiangwen Zhang graduated from Johns Hopkins University with PhD He has worked at Harvard University Genome Center as Senior System Biologist for years before joining University of Hong Kong in 2013. His lab has broad interest in genetic and epigenetic regulation in development and diseases. Currently, his lab is focusing on epigenetic regulation of tumorigenesis. His lab employs high through-put 'omics' assays and large scale computation to dissect the gene regulatory network and signaling pathways involved in oncogenesis.

jzhang1@hku.hk

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DAY 2

Scientific Tracks & Abstracts

Day 2
SESSIONS

June 12, 2018

Cancer Stem Cells | Prostate Cancer Stem Cells | Colorectal Cancer Stem Cells | Therapies targeting Cancer Stem Cells | Cancer Genomics & Metabolomics

Session Introduction

Session Chair
Yong Li
University of New South Wales, Australia

Session Co-chair
Maithili A Athavale
Sathgen Biotech, India

Title: **Development of novel miR-129 mimic with enhanced therapeutic potential to eliminate resistant colon cancer stem cells**
Jingfang Ju, Stony Brook University, USA

Title: **Role of miRNAs and YAP in the promotion of colorectal cancer stem cell self-renewal by the tight junction protein claudin-2**
Frederic Hollande, The University of Melbourne, Australia

Title: **Therapeutic stress induced cellular plasticity: A possible new mechanisms of therapeutic resistance in Glioblastoma**
Atique Ahmed, Northwestern University, USA

Title: **Replication stress response in CSCs: Molecular mechanisms and therapeutic implication**
Ilio Vitale, Regina Elena National Cancer Institute, Italy

Title: **Magnetic nanocrystals and magnetic hyperthermia to tackle cancer stem cells**
Teresa Pellegrino, Italian Institute of Technology, Italy

Title: **CD44 variant 6 (CD44v6) as a cancer stem cell biomarker in prostate cancer progression and chemo-/radio-resistance**
Jie Ni, University of New South Wales, Australia

Title: **NFATc2-SOX2 coupling supports cancer stem cells and mediates drug resistance of lung adenocarcinoma**
Maria Pik Wong, The University of Hong Kong, China

Title: **Targeting the multidrug transporter Patched potentiates chemotherapy efficiency *in-vitro* and *in-vivo***
Isabelle Mus-Veteau, Université Côte d'Azur, France

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DEVELOPMENT OF NOVEL miR-129 MIMIC WITH ENHANCED THERAPEUTIC POTENTIAL TO ELIMINATE RESISTANT COLON CANCER STEM CELLS

Jingfang Ju, Andrew Felser, Ning Wu and **Hua Liu**
Stony Brook University, USA

Treatment of advanced stage colorectal cancer remains a clinical challenge associated with resistance to fluoropyrimidine based chemotherapy. There is an urgent need to discover and develop new strategies to enhance treatment efficacy in order to improve outcomes for these patients. Non-coding microRNAs (miRNAs) have important functions as oncogenes or tumor suppressor genes in the regulation of cancer development and progression. Recently, miRNAs have emerged as potential therapeutic options. We have identified miR-129 as tumor suppressor miRNA and potential therapeutic candidate in colorectal cancer. The expression of miR-129 expression is progressively lost in colorectal cancer patients and is an important regulator of apoptosis through the targeting of genes such as BCL-2. miR-129 was also found to enhance 5-flurouracil (5-FU) cytotoxicity *in vitro* and *in vivo*. To further developing miR-129 based novel therapeutics in colorectal cancer, we have designed a modified version of miR-129 to enhance stability and efficacy. The miR-129 mimic is significantly more potent in inhibiting proliferation of a panel of colon cancer cell lines than the native miR-129 precursor. The miR-129 mimic induces profound cell cycle arrest at the G1/S checkpoint. We also demonstrated that the miR-129 mimic retains its target specificity to BCL-2, TS and E2F3 as same as the native miR-129 precursor. More importantly, the miR-129 mimic can eliminate resistant colon cancer stem cells. The therapeutic potential of miR-129 was demonstrated *in vivo* mouse colon tumor models as a potent inhibitor of tumor growth and metastasis. As a result, miR-129 mimic has a great potential to be further developed as a novel therapeutic drug for treatment of advanced colorectal cancer.

BIOGRAPHY

Jingfang Ju is the Professor in the Department of Pathology at Stony Brook Medicine/Stony Brook University. He received his BS degree from the Northeastern University and PhD in molecular biology and biochemistry at the University of Southern California. He completed his post-doctoral research fellowship at Yale Cancer Center, Yale University. Previously he has served as the Senior Scientist and Team Leader of high throughput genomics at a biopharmaceutical company, CuraGen Corporation in Connecticut.

jingfang.ju@stonybrookmedicine.edu

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ROLE OF miRNAS AND YAP IN THE PROMOTION OF COLORECTAL CANCER STEM CELL SELF-RENEWAL BY THE TIGHT JUNCTION PROTEIN CLAUDIN-2

Frederic Hollande
The University of Melbourne, Australia

Colorectal cancer (CRC) is the third most lethal cancer worldwide, often due to post-treatment recurrence driven by a subpopulation of Cancer Stem Cells (CSCs). The tight junction (TJ) protein claudin-2 is overexpressed in human CRC, where it enhances cell proliferation, colony formation and chemoresistance *in vitro*. While several of these biological processes are features of the CSC phenotype, a putative role for claudin-2 in the regulation of these had hitherto not been explored. Here, we identify that elevated claudin-2 expression in stage II/III colorectal tumors is associated with poor recurrence-free survival after 5-FU-based chemotherapy, an outcome in which CSCs play an instrumental role. Using overexpression and/or down-regulation models in patient-derived organoids, primary cells and cell lines, we show that claudin-2 promoted CRC self-renewal *in vitro* and in multiple mouse xenograft models. Claudin-2 enhanced self-renewal of ALDHHigh CSCs and increased their proportion in CRC cell populations, limiting their differentiation and promoting the phenotypic transition of non-CSCs towards the ALDHHigh phenotype. Using Next Generation Sequencing in ALDHHigh cells, we establish that claudin-2 regulated the expression of several microRNAs known to control stem cell signalling. We demonstrate that, among these, miR-222-3p was instrumental for the regulation of self-renewal by claudin-2. We also found that the enhancement of self-renewal by claudin-2 required the activation of YAP, most likely upstream from miR-222-3p. Taken together, our results indicate that overexpression of the TJ protein claudin-2 promotes self-renewal within CRC stem-like cells, suggesting a potential role for this protein as a therapeutic target in CRC.

BIOGRAPHY

Frederic Hollande has completed his PhD in 1994 at the University of Montpellier, France. He worked as a Post-doctoral Research Fellow at the Ludwig Institute for Cancer Research and the University of Melbourne, and was recruited as a Research Fellow by the French National Centre for Scientific Research (CNRS) in 1996. He became Group Leader in 2000 and Head of the Oncology Research Department at the Institute of Functional Genomics (IGF) of Montpellier in 2011. In 2007, he co-founded a Biotech Company (colon cancer therapeutics) and was the Joint-Scientific Director until 2011. He has been an Associate Professor in the Department of Pathology at the University of Melbourne since September 2012. His laboratory is located at the new purpose-built Victorian Comprehensive Cancer Centre in Melbourne. His research interest lies in the study of tumour heterogeneity and the regulation of cancer stem cells in colorectal and other cancers

frederic.hollande@unimelb.edu.au

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THERAPEUTIC STRESS INDUCED CELLULAR PLASTICITY: A POSSIBLE NEW MECHANISMS OF THERAPEUTIC RESISTANCE IN GLIOBLASTOMA

Atique U Ahmed, Jack M Shiremen, Cheol H Park, Fatemeh Atashi, Seamus Caragher, Louisa Warnky, Shivani Baisiwala and **Gina Lee**
Northwestern University, USA

Glioma stem cells (GSCs), a rare population of cancer cells capable of self-renewal, are known to underlie therapeutic resistance in glioblastoma (GBM), the most common and aggressive adult primary brain tumor. Previously, we have shown that the anti-glioma chemotherapy temozolomide (TMZ) initiates remarkable plasticity in glioma cells and promotes the conversion of differentiated glioma cells to therapy resistant GSCs. Our initial investigation indicated that Polycomb group protein EZH2 is critical for this therapy-induced cellular plasticity. Genome-wide chromatin immunoprecipitation (ChIP) in parallel with DNA sequencing analysis (ChIP-seq) revealed 1449 distinct regions enriched for EZH2 binding, specifically at the promoter regions of several key genes including PTPRT, CDK5R2, and Siglec6. Gene expression microarray analysis showed that this binding decreased cognate gene expression in an effort to activate the master transcription factor STAT3, a key molecular factor in promoting the GSC niche. To further investigate this plasticity-based adaptation, we next performed histone 3 lysine 27 acetylation (H3K27ac) enrichment analysis in order to mark the transcriptionally active chromatin state on a genome wide scale before and after exposure to TMZ. A significant number of distal H3K27ac peaks were detected only after chemo- (n = 452) and radiotherapy (n= 1029), indicating that H3K27ac was modified by anti-glioma therapies in a locus-specific manner. Furthermore, a *de novo* motif analysis identified the homeobox TF binding motif (p=0.025) enriched within the H3K27ac peak surrounding sequences during therapy. By combining the transcriptome analysis from patientderived xenograft models and GBM patient data (TCGA) with the H3K27ac enriched marks, we have identified several novel homeobox transcription factors, which may contribute to therapyinduced cellular plasticity and adaptation response. These findings provide new insight into the molecular mechanisms by which epigenetic plasticity regulates the GSC niche and may improve our understanding of how GBM cells resist current treatment modalities.

BIOGRAPHY

Atique U Ahmed is currently appointed as Assistant Professor of Cancer Biology and member of the Lurie Comprehensive Cancer Center, Northwestern University, Chicago IL USA. He received his PhD in Molecular Medicine from Mayo Graduate School, USA. He has over 60 publications that have been cited over 2500 times, and his/her publication H-index is 31 and has been American Cancer Society Scholar.

atique.ahmed@northwestern.edu

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REPLICATION STRESS RESPONSE IN CSCs: MOLECULAR MECHANISMS AND THERAPEUTIC IMPLICATION

Vitale Ilio[1], Manic G[2], Sistigu A[2,3] and De Maria R[3]
[1]University of Rome "Tor Vergata", Rome, Italy
[2]Elena National Cancer Institute, Rome, Italy
[3]Catholic University "Sacro Cuore", Italy

Cancer stem cells (CSCs) are subpopulations of multipotent SCs responsible for the initiation, long-term clonal maintenance, growth and spreading of most human neoplasms, including colorectal cancer (CRC). CSCs reportedly share with embryonic and adult SCs a very robust DNA damage response (DDR), which favors their survival and drives the resistance to endogenous and exogenous genotoxins. Taking advantage of a panel of CRC patient-derived tumorspheres enriched for CSCs (CRC-SCs), we demonstrated that CSCs have high, although heterogeneous, levels of replication stress (RS). By performing genetic and cytogenetic analyses, we provided evidence that RS in CRC-SCs is boosted endogenously by p53 deficiency and the presence of supernumerary chromosomes. We also elucidated the tight, but plastic and multipronged RS response put in place by CSCs to set the threshold of and ensure tolerability to RS, which involves CHK1, PARP and some components of the homologous recombination repair. Of relevance for cancer therapy, we showed that such a robust and efficient response confers to replication-stressed CSCs elevated dependency on specific component(s) such as CHK1. Nonetheless, the redundancy and rewiring potential of RS response also favors the acquisition of resistance to RS-modulating and DNA-damaging regimens. Driven by this paradoxical evidence and based on the levels of RS at baseline, we designed dedicated RS response-targeting strategies with long-term CSC depleting effectiveness.

BIOGRAPHY

Vitale Ilio has received his PhD in 2006 for Molecular Characterization of Mitotic Catastrophe. During his six-year Post-doctoral studies in France, he investigated the role of aneuploidy/tetraploidy in tumorigenesis uncovering surveillance mechanisms surveying cell ploidy (EMBOJ 2010, Science 2012). He currently is a Group Leader and Adjunct Professor in Neurobiology at the University of Rome "Tor Vergata" working on the link between CSCs, chromosomal instability, and tumor immunity. His group recently identified a novel strategy for the depletion of CSCs based on CHK1 inhibition (Gut 2017, Mol Cell 2017). He is the Executive Editor of Molecular and Cellular Oncology, Subject Editor in the Reference Module in Life Sciences and served as Editor for several books. He received the Young Scientist Award from the European Environmental Mutagenesis Society (2013). He is Author of >100 ISI papers (including Science, Nat Med, Nat Rev Mol Cell Biol., Nat Cell Biol). "h" index: 34.

iliovit@gmail.com

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MAGNETIC NANOCRYSTALS AND MAGNETIC HYPERTHERMIA TO TACKLE CANCER STEM CELLS

Teresa Pellegrino, Soraia Fernandes, Sabrina Janoschek, Preethi Bala Balakrishnan and **Matilde Todaro**
Italian Institute of Technology, Italy

The use of heat to reduce tumor mass is very ancient. Nowadays, there are several techniques that allow to precisely focalize the heat in very specific body regions resulting in treatments that are more efficient and minimize side effects. Magnetic nanoparticles can act as heat mediators under external magnetic activation in the so-called magnetic hyperthermia. The field of magnetic hyperthermia has received a renewed interest since the colloidal syntheses by non-hydrolytic methods have revealed several merits over conventional wet chemical hydrolytic processes in terms of controlled size, size distribution and crystallinity. All these parameters together with nanoparticles solubility and state of aggregation can affect structural and magnetic properties of nanomaterials and thus their heat performance. I will first focus on our recent progress on iron-based nanoparticles as heat mediators. Then, I will show our ongoing studies aiming at correlate heat effects on cancer stem cells. I will also report about *in vitro* hyperthermia experiments on primary tumor cells to relate nanoparticle geometry to changes of magnetic hyperthermia performances in tumor cell. Finally, I will show our preliminary *in vivo* studies performed with the aim to combine magnetic hyperthermia and heat-mediated drug release.

BIOGRAPHY

Teresa Pellegrino has received her PhD at the age of 30 years in Chemical synthesis and Nanoscience in 2005 from the University of Bari, Italy. Since 2014 she is tenured team leader of the group of "Nanomaterials for Biomedical Applications" at the Italian Institute of Technology, Genoa, Italy. Her current research interests focus on the development of inorganic nanostructures for drug delivery, magnetic hyperthermia, photo-thermal treatment and radiotherapy applications. She is coauthor of 112 publications in the field of nanoscience, nanomedicine and drug delivery systems that have been cited more than 10000 times, and her H-index is 44.

teresa.pellegrino@iit.it

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CD44 VARIANT 6 (CD44v6) AS A CANCER STEM CELL BIOMARKER IN PROSTATE CANCER PROGRESSION AND CHEMO-/RADIO-RESISTANCE

Jie Ni[1, 2], Paul Cozzi[1, 2], Julia Beretov[1, 2], Joseph Bucci[1, 2], Peter Graham[1, 2] and Yong Li[1, 2]

[1]St. George Hospital, Kogarah, Australia
[2]University of New South Wales, Australia

Prostate cancer (CaP) is the most common cancer in men in western countries, accounting for estimated 161,360 new cases and 26,730 deaths in the US in 2017. Chemo-/radio-resistance is an important reason for CaP progression and metastasis. CD44 is a well-documented cancer stem cell (CSC) biomarker, and one of its variants, CD44 variant 6 (CD44v6) is closely associated with aggressive behaviour and correlates with poor prognosis in a variety of human cancers. Our previous study has demonstrated increased expressions of CD44v6 in metastatic CaP cell lines and human CaP tissues which was associated with CaP progression and chemo-/radio-resistance *in vitro*. However, the role of CD44v6 in CaP progression and therapeutic resistance *in vivo* is still uncertain. The aim of this study was to investigate the role of CD44v6 in CaP development and chemo-/radio-resistance as well as underlying pathways *in vivo*, and find whether it is a suitable therapeutic target for CaP therapy.

BIOGRAPHY

Jie Ni is a Scientific Officer and Hospital Scientist in Department of Radiation Oncology, Cancer Services at St George Hospital, Sydney and Conjoint Lecturer in St George and Sutherland Clinical School, Faculty of Medicine at UNSW Sydney, Australia. He obtained his M.D. and B.A. degrees from China in 2011 as an outstanding graduate and national scholarship awardee and completed his PhD in Faculty of Medicine at UNSW Sydney in 2015. During his PhD candidature he was awarded Prostate and Breast Cancer Foundation Scholarship from 2012-2015, and Outstanding Self-Financed Students Abroad Award of China in 2013. The nature of the degrees has equipped him with a strong background of medical practice, and has involved a great deal of independent basic, translational and clinical research. He has 19 publications (6 as the first-author, 2 invited reviews) on peer-reviewed journals on novel therapeutic modalities and targets on prostate, ovarian, cervical and breast cancers. His publications have been cited more than 480 times with a Scopus h-index of 11 and he constantly publishes in top-ranking journals including Theranostics, Oncotarget, Cell Death and Disease, Prostate, and Cancer Metastasis Reviews. He has been an executive committee member of the Australian Association for Chinese Biomedical Scientists since 2011, a member of American Association for Cancer Research since 2012, European Association for Cancer Research since 2017 and European Society for Medical Oncology since 2017. He is currently co-supervising and mentoring PhD students, ILP students and visiting research fellows, and has served as a reviewer for numerous journals and universities.

jie.ni@health.nsw.gov.au

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NFATc2-SOX2 COUPLING SUPPORTS CANCER STEM CELLS AND MEDIATES DRUG RESISTANCE OF LUNG ADENOCARCINOMA

Maria Pik Wong, Zhijie Xiao, Judy Wai-Ping Yam, Jing Liu, Siqi Wang and **Vicky Pui-Chi Tin**
The University of Hong Kong, China

Cancer stem cells (CSC) are dynamic cancer cell subsets that display enhanced tumor functions and resilience to treatment but the mechanism of CSC induction or maintenance in human lung cancer is not fully understood. Calcium signaling integrates exogenous and endogenous stress stimuli leading to cellular responses that overlap with cancer functions. We investigated the role and mechanisms of the calcium pathway transcription factor NFATc2 in lung CSC, and found NFATc2 enhanced CSC phenotypes including tumorspheres, motility, tumorigenesis, as well as *in vitro* and *in vivo* responses of lung cancer cells to chemotherapy and targeted therapy. In human lung cancers, high NFATc2 expression predicted poor tumor differentiation and adverse patient survivals. Since pluripotency factors can modulate widespread transcriptomic changes through epigenetic reprograming, we investigated their candidacy as mediators of NFATc2 on CSC regulation. We found NFATc2 transactivated SOX2 through a novel 3' enhancer locus, while inhibiting SOX2 in cancer cells that overexpressed NFATc2 led to suppressed CSC functions. Targeting NFATc2-SOX2 coupling provides a novel approach for the long term treatment of lung cancer through TIC elimination.

BIOGRAPHY

Maria Pik Wong is currently working as a professor at the Department of Pathology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR China.

mwpik@hku.hk

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TARGETING THE MULTIDRUG TRANSPORTER PATCHED POTENTIATES CHEMOTHERAPY EFFICIENCY *IN VITRO* AND *IN VIVO*

Isabelle Mus-Veteau[1,4], Anida Hasanovic[1,4], Carmen Ruggiero[1,4], Sara Jung[2], Ida Rapa[3], Marco Volante[3], Constanze Hantel[2] and **Enzo Lalli[1,4]**

[1]Institut de Pharmacologie Moléculaire et Cellulaire, France
[2]Ludwig-Maximilians-Universität, Germany
[3]University of Turin at San Luigi Hospital, Italy
[4]Université Côte d'Azur, France

One of the crucial challenges in the clinical management of cancer is the resistance to chemotherapeutics. We recently demonstrated that the Hedgehog receptor Patched, which is overexpressed in many recurrent and metastatic cancers, is a multidrug transporter for chemotherapeutic agents such as doxorubicin. The present study provides evidences that Patched is expressed in adrenocortical carcinoma (ACC) patients, and is a major player of the doxorubicin efflux and the doxorubicin resistance in the human ACC cell line H295R. We discovered a drug-like molecule which inhibits the doxorubicin efflux activity of Patched, enhances the cytotoxic, pro-apoptotic, antiproliferative and anticlonogenic effects of doxorubicin on ACC cells which endogenously overexpress Patched, and thereby mitigates the resistance of these cancer cells to doxorubicin. Moreover, we report that in mice the combination of this molecule with doxorubicin prevents the development of xenografted ACC tumors more efficiently than doxorubicin alone by enhancing the accumulation of doxorubicin specifically in tumors without obvious undesirable side effect. Our results suggest that the use of an inhibitor of Patched drug efflux in combination with doxorubicin could be a promising therapeutic option for adrenocortical carcinoma, and most likely also for other Patched-expressing cancers.

BIOGRAPHY

Isabelle Mus-Veteau is currently working at the Institut de Pharmacologie Moléculaire et Cellulaire, Sophia Antipolis, Université Côte d'Azur, France

mus-veteau@ipmc.cnrs.fr

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DAY 2

Young Researchers Forum

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TARGETING CRC-SC FOR DIFFERENTIATION – A 3D SCREENING SYSTEM FOR DIFFERENTIATION THERAPIES

Mehreen Ahmed, Roya Babaei-Jadidi and **Abdolrahman S Nateri**
University of Nottingham, UK

Cancer stem-like cells (CSC) are a subpopulation of tumour cells with the extraordinary characteristic of self-renewal and also can replenish themselves. The emerging concept of differentiation therapy advocates that the efficacy of conventional anticancer treatment will increase upon forced differentiation of CSCs. Therefore, follow-up discovery of new drugs will involve selective CSC targeting and allowing them to descend to bulk cancer cells will make them easily targeted by conventional treatment. Currently, there is no known compound(s) that drive colorectal cancer (CRC)-SC differentiation. Moreover, current *in vitro* models fail to comprise tumour heterogeneity and predictive patient outcome in preclinical setting. We attempt to harness a patient relevant *in vitro* screening system to identify small molecule(s) and to cross-examine CRC-SC differentiation. At present, we have identified 4 candidate drugs that have been screened from a library of small molecules consisting of 707 compounds for their differentiation induction potential. For this, we have established a novel methodology to screen small molecule-based drugs targeting 'stemness' properties on live 3D colonospheres derived from CRC cell lines. We have optimized our pilot screening with a clinically relevant HDAC inhibitor and a fluorescent rosamine dye CDy1 in a high throughput plate reader screening (PRS) manner to detect reductions in fluorescence staining on live 3D colonosphere. Our results suggest that compounds that induce differentiation can be identified based on the reduction of CDy1 intensity in 3D colonospheres, backed by immunostaining of stemness and differentiation markers.Our initial screening suggest that 6% of the total compounds might be involved in inducing differentiation in CRC-SC obtained from three CRC cell lines. These compounds were identified based on distinct morphology changes, colonosphere sizes and intensity of CDy1. Further follow up data suggest that three of these compounds antagonize nuclear β-catenin, known to regulate self-renewal at adenoma and carcinoma stages. We have selected 4 compounds based on their ability to suppress colony formation, cell growth, and preliminary effects shown for beta catenin expression. Upon finishing this screening on 3D colonosphere representing CSCs, we have been focusing on identifying the mechanisms of our candidate drugs and how they regulate differentiation on CRC-SC. Using proteomic approach and biochemical analysis, we're currently looking at specific targets for these drugs and to elucidate their mechanisms. Simultaneously, we are also evaluating these drugs on patient derived organoids and tissue explants obtained from both tumour and normal adjacent tissue to investigate drug specificity on CSC vs NSC. The lack of relevant models and suitable screening methodology are two major impediments in CRC drug discovery. This study demonstrates the application of colonospheres in drug screening and could potently characterise the mechanisms involved with defined compounds in CSCs eradication, a major aspect behind cancer recurrence, resistance and mortality. Our studies are underway to identify the targets of candidate drugs and exploring their mechanism on CRC-SC specificity. This would be relevant to decipher the differentiation induction pathways in CRC-SC.

BIOGRAPHY

Mehreen Ahmed is currently persuing her research at the Division of Cancer & Stem Cells, Cancer Biology Unit, Cancer Genetics & Stem Cell Group, School of Medicine, University of Nottingham, UK.

mehreen.ahmed@nottingham.ac.uk

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TARGETING CHK1 FOR ERADICATING COLORECTAL CANCER STEM CELLS

Manic Gwenola[1], Sistigu A [1,2], De Maria R2 and Vitale I[1,3]
[1]Regina Elena National Cancer Institute, Italy
[2]Institute of General Pathology, Catholic University "Sacro Cuore", Rome, Italy
[3]Department of Biology, University of Rome "Tor Vergata", Rome, Italy

The tumor is a dynamic system composed by heterogeneous populations of cells with cancer stem cells (CSCs) at its apex. CSCs drive tumor development and progression, and their efficient targeting is required for tumor eradication. Here, with the aim at identifying novel CSC-targeting strategies, we generated a panel of ~30 CRC patient-derived tumorspheres enriched for CSCs (CRC-SCs). By performing a drug-library screening with a panel of clinically-relevant drugs on CRC-SCs, we identified LY2606368 as a potent anti-CSC agent. Thereafter, we confirmed that LY2606368 was able to kill CSCs from a significant number of patients (~36%), both *in vitro* and *in vivo*. As for its mechanism of action, we demonstrated that LY2606368 inhibits CHK1 leading to perturbation of DNA replication followed by premature mitosis entry and cell death of DNA-damaged cells. Moreover, through (cyto)genetic and phosphoproteomic analyses, we provided evidence that LY2606368-sensitive CRC-SCs display ongoing replication stress response associated with mutation(s) in TP53 and hyperdiploidy. This made these CRC-SCs highly dependent on CHK1 function. Accordingly, experimental increase of endogenous DNA damage or cell ploidy sensitized formerly resistant CRC-SCs to LY2606368. This study provides a strong rationale for biomarker-driven clinical trials with LY2606368 in CRC patients.

BIOGRAPHY

Gwenola Manic received her PhD in 2012 for studying the impact of DNA repair on viral expression. During her first post-doc in Rome she investigated the role of chromosomal instability and replication stress in CSCs and identified CHK1 as a target for eradicating CSCs in colorectal tumors (Gut 2017, Mol Cell 2017). She is now working as a senior scientist on a project investigating the replication stress response in CSCs and the link between chromosome instability and immunogenic potential of CSCs. She is in the editorial board of Frontiers in Oncology. She is author of 26 ISI papers (including Science, Mol Cell and Gut).

gwenola.manic@gmail.com

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DAY 3

Scientific Tracks & Abstracts

Day 3

SESSIONS

June 13, 2018

Cancer Stem Cells and Haematopoietic Stem Cells in Leukaemia | Therapies targeting Cancer Stem Cells | Cancer Stem Cells in Brain Gliomas | Neuro Oncology

Session Introduction

Session Chair
Yong Li
University of New South Wales, Australia

Session Co-chair
Maithili A Athavale
Sathgen Biotech, India

Title: **Testing the resilience of cancer stem cells to magnetic hyperthermia and heat-mediated drug delivery**
Soraia Fernandes, Italian Institute of Technology, Italy

Title: **CDK6-mediated Suppression of CD25 is Required for Self-renewal of LSCs**
Miaofen Hu, Tufts Medical Center, USA

Title: **DOCK4 promotes loss of proliferation in glioblastoma progenitor cells through nuclear beta-catenin accumulation and subsequent miR-302-367 cluster expression**
Thierry Virolle, Institut de Biologie Valrose (iBV), France

Title: **Neurotrophins receptors: New aggressiveness markers in Glioblastoma?**
Barbara Bessette, Université de Limoges, France

Title: **SETMAR in Glioblastoma: Splice variants and feedback network in controlling target genes expression**
Corinne Augé-Gouillou, University of Tours, France

Title: **TGF-β signaling is a novel therapeutic target for treating metastatic cancers acquired by EMT and cancer stemness**
Seong -Jin Kim, Seoul National University, Korea

Title: **Inhibitor of apoptosis proteins determine glioblastomas stem-like cells fate in an oxygen-dependent manner**
Aurélie Tchoghandjian, Axe Marseille Université, France

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TESTING THE RESILIENCE OF CANCER STEM CELLS TO MAGNETIC HYPERTHERMIA AND HEAT-MEDIATED DRUG DELIVERY

Soraia Fernandes, Teresa Pellegrino, Sabrina Janoschek, Preethi B Balakrishnan, Binh T Mai, Giorgio Stassi and **Matilde Todaro**
Italian Institute of Technology, Italy

Cancer stem cells (CSCs) are well known for being responsible for tumor regression and metastasis. In particular, quiescent CSCs, kept at a non-proliferating state, have been identified in many human malignancies as the subcellular tumor type that causes resistance to current chemotherapy. Available chemotherapeutics attack the cells by blocking their division and replication, resulting ineffective for the eradication of those cells that rarely divide. Therefore, an efficient cancer therapy must act also on quiescent CSC in order to avoid tumor relapse. In this study, we have investigated the potential of magnetic hyperthermia in combination with a chemotherapeutic agent (Doxorubicin) to eliminate colorectal CSCs (CR-CSCs), expressing high levels of CD44v6 markers, withdrawn from patient. Preliminary results from our research suggest that these cells are sensitive to heat under certain magnetic hyperthermia conditions. Therefore, we have been exploiting the use of magnetic iron oxide nanocubes (IONCs) developed in our group, loaded or not with doxorubicin, to study their effect on CR-CSCs. We hypothesize that under the severe effect caused by the heat generated by the IONCs, which kills most of the cell population, quiescent CSCs will struggle to survive, thus starting to divide and being more susceptible to the action of the doxorubicin released from the nanocubes. The obtained results using this cell model revealed that the combined effect of doxorubicin and heat might lead to more efficient CSCs elimination, encouraging the use of such smart nanoplatforms for further studies.

BIOGRAPHY

Soraia Fernandes has received her PhD degree, in Natural Sciences from the University of Regensburg (Germany) and in Chemistry and Materials Science and Technologies from the University of Genoa (Italy), in 2016. She is currently a Postdoctoral associate in the research group of Dr. Teresa Pellegrino at the Italian Institute of Technology (Italy). Her research focus is the biological assessment of magnetic nanoparticles as heat mediators and/or drug delivery systems for the development of an effective treatment against cancer.

Soraia.fernandes@iit.it

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CDK6-MEDIATED SUPPRESSION OF CD25 IS REQUIRED FOR SELF-RENEWAL OF LSCS

Miaofen G Hu[1], Nilamani Jena[1, 2], Alexander J Hu[1, 3], Wei Li[1], Jamie K Hu[1, 4] and Richard Van Etten[1,2]

[1]Tufts Medical Center, USA
[2]University of California Irvine, USA
[3]Tufts University School of Medicine, USA
[4]Yale School of Medicine, USA

Despite recent advances in chemotherapy, relapse is frequent, possibly because the available therapies do not eradicate the cells that initiate and sustain the disease *in vivo*, so-called leukemia stem cells (LSCs). Cyclin-dependent kinase 6 (CDK6) regulates cell cycle progression and modulates differentiation of certain cells. It is predominantly expressed in hematopoietic cells and over-expressed in human T-ALL/LBL. To clarify the role of CDK6 in cell cycle control and tumorigenesis, I have generated mice with targeted mutations in Cdk6. These "knock-in" alleles generate hyperactive or inactive kinase subunits that may better mimic hyperactivation of CDK6 in tumor cells or model pharmaceutical inhibition of CDK6, respectively. We have found that CDK6 is required for initiation and maintenance of T-ALL leukemia and lymphomagenesis induced by constitutively active Notch/Myr-AKT. Pharmacologic inhibition of CDK6 kinase induces CD25 expression, cell cycle arrest, and apoptosis in mouse and human T-ALL. Ablation of Cd25 in a K43M background restores Notch-induced T-leukemogenesis, with disease that is resistant to CDK6 inhibitors *in vivo*. Moreover, loss of Cd25 in a K43M background restore the ability of LSCs to self-renew. These data support a model whereby CDK6-mediated suppression of CD25 is required for initiation of T-ALL by activated Notch1, and CD25 induction mediates the therapeutic response to CDK6 inhibition in established T-ALL. These results both validate CDK6 as a molecular target for therapy of this subset of T-ALL and suggest that CD25 expression could serve as a biomarker for responsiveness of T-ALL to CDK4/6 inhibitor therapy.

Figure. A working model of the role of CDK6 in T-ALL. In response to stimuli, increased expression of cyclin D1 and CDK6 leads to increased CDK6 activation, while Notch1 and AKT1 are also independently activated in parallel. Notch1 further activates CDK6 via upregulation of CDK6 and/or by increased cyclin D3 protein, while AKT1 activates CDK6 through the stabilization of cyclin D2. Once activated, CDK6 can phosphorylate pRB, resulting in its inactivation. CDK6, along with ERK and CDK1 can also phosphorylate RUNX1 thereby promoting RUNX1 proteolytic degradation. On a different molecular path, phosphorylation of FOXM1 by CDK6 stabilizes FOXM1, which in turn promotes methylation of the GATA3 promoter, decreasing GATA3 expression and the subsequent recruitment to the CD25 proximal promoter region. CD25 expression is consequently reduced and T-ALL develops. Devoid of CDK6 protein/kinase activity, pRB and RUNX1 remain active, which suppress the tumorigenesis in CD25-independent manner. Contrastingly, without CDK6, FOXM1 is in its inactive state, leading to CD25 upregulation. Overall, T-ALL is suppressed by FOXM1 inactivity, and by increasing RUNX1, pRB, GATA3, and CD25 expression or activity.

BIOGRAPHY

Miaofen G Hu has completed her PhD from Boston University School of Medicine and post-doctoral studies from Harvard University School of Medicine. She has been Assistant Professor at TUFTS medical Center since 2011. She has published 24 papers in reputed journals. Her most significant research accomplishments thus far include creating a CDK6 mouse model, discovering the role of CDK6 as a common mediator of Notch1 and AKT1 signaling pathways, establishing the potential therapeutic role of CDK6 in T cell malignance, revealing the function of CDK6 kinase activity in negatively regulating the conversion of fat-storing cells into fat-burning cells.

mhu@tuftsmedicalcenter.org

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DOCK4 PROMOTES LOSS OF PROLIFERATION IN GLIOBLASTOMA PROGENITOR CELLS THROUGH NUCLEAR BETA-CATENIN ACCUMULATION AND SUBSEQUENT miR-302-367 CLUSTER EXPRESSION

Thierry Virolle [1,2,3], David Nicolas Debruyne[1,2,3], Laurent Turchi[1,2,3,5], Fanny Burel-Vandenbos[1,2,3,4], Mohamed Fareh[1,2,3], FabienAlmairac[1,2,3],Virginie Virolle[1,2,3], Dominique Figarella-Branger[6,7,8], Nathalie Baeza-Kallee[6,7], Patricia Lagadec[1,2,3], Valérie kubiniek[9], Philippe Paquis[1,2,3,5], Denys Fontaine[5], Marie-Pierre Junier[10,11,12] and **Hervé Chneiweiss[10,11,12]**

[1]Université Côte d'Azur, France
[2]CNRS, France
[3]Inserm, France
[4]Service d'Anatomopathologie, Hôpital Pasteur, France
[5]Service de Neurchirurgie, Hôpital Pasteur, France
[6]Aix Marseille Université, France
[7]INSERM, France
[8]Departement de Pathology, CHU de la Timone, France
[9]Laboratory of Solid Tumors Genetics, University Hospital of Nice, France
[10]CNRS Neuroscience Paris Seine – IBPS, France
[11]Inserm, France
[12]University Pierre and Marie Curie, Neuroscience Paris Seine – IBPS, France

Glioblastomas (GBM) are lethal primitive brain tumours characterized by a strong intra-tumour heterogeneity. We observed in GBM tissues the coexistence of functionally divergent micro-territories either enriched in more differentiated and non-mitotic cells or in mitotic undifferentiated OLIG2 positive cells while sharing similar genomic abnormalities. Understanding the formation of such functionally divergent micro-territories in glioblastomas (GBM) is essential to comprehend GBM biogenesis, plasticity and to develop therapies. Here we report an unexpected anti-proliferative role of beta-catenin in non-mitotic differentiated GBM cells. By cell type specific stimulation of miR-302, which directly represses cyclin D1 and stemness features, beta-catenin is capable to change its known proliferative function. Nuclear beta-catenin accumulation in non-mitotic cells is due to a feed forward mechanism between DOCK4 and beta-catenin, allowed by increased GSK3-beta activity. DOCK4 over expression suppresses selfrenewal and tumorigenicity of GBM stem-like cells. Accordingly in the frame of GBM median of survival, increased level of DOCK4 predicts improved patient survival.

BIOGRAPHY

Thierry Virolle is a Research Director (permanent position) at Institut National de la Santé et de la Recherche Médicale (INSERM), Head of the Team Cancer Stem Cell Plasticity and Functional intra-tumor Heterogeneity at the Institute of Biologie Valrose (iBV). He is Co-Founder of the French National Sud Cancer Stem Cell Network, SUNRiSE dedicated to the study of cancer stem cell.

Virolle@unice.fr

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NEUROTROPHINS RECEPTORS: NEW AGGRESSIVENESS MARKERS IN GLIOBLASTOMA?

Barbara Bessette[1], G Bégaud[1], S Saada[1], N Vedrenne[1], E Deluche[1,2], S Pinet[1], S Jawhari[1], A Boukredine[1], K Durand[1,2], S Robert[1,2], M O Jauberteau[1], S Battu[1], M Verdier[1] and F Lalloué[1]

[1]Université de Limoges, France
[2]CHU Limoges, France

Glioblastoma (GBM) is the worst brain tumor with therapeutic resistance and recurrence due to its strong cell heterogeneity, which relies on cancer stem-like cells' presence. Tumor aggressiveness is associated to cancer cell adaptation to their environment: autophagy process enhancement, the increase of growth factors signaling such as neurotrophins (TrkB/BNNF and TrkC/NT3), microenvironment modulation by mesenchymal stem cells (MSC). The high level of hypoxia commonly encountered in GBM is counterbalanced by the tumor autophagic capability and growth factors signaling activation. We demonstrated that an increase of autophagy precedes TrkC/NT3 pathway activation in GBM cells. Enhancement of both TrkC and NT-3 followed by the increase of p38MAPK phosphorylation, suggesting the occurrence of a survival loop that was also underlined in patient's tumors. However, the double inhibition of autophagy and TrkC signaling was the only one able to bring cells apoptosis. The ability of cancer cells, to shape tumor environment through exosomes release could explain the spreading of "therapeutic resistance" to neighboring cells. The "stemness" properties loss showed in YKL-40-silenced cells can be reversed by TrkB-containing exosomes provide by native cells. This process contributes to restore cell proliferation and to promote endothelial cell activation. In a xenograft model, TrkB-depleted exosomes from YKL-40-silenced cells inhibits tumor growth *in vivo*. Our recent works showed changes in MSC behavior "aggressiveness" by the GBM cell "secretion", following irradiations suggesting a putative link with neurotrophin receptor. Our data suggest that neurotrophin and their receptors could be considered as new relevant diagnosis biomarkers and potential therapeutic targets in glioblastoma.

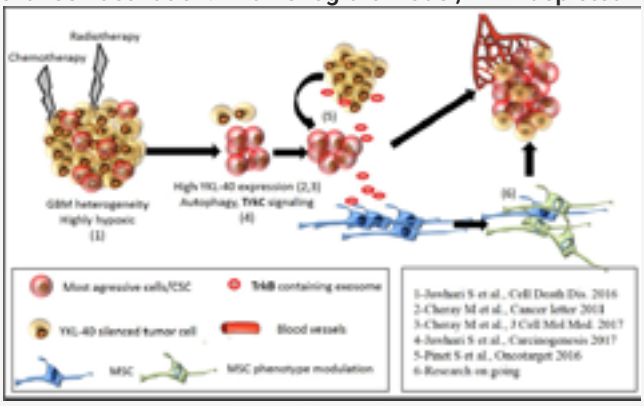

Figure: GBM aggressiveness modelization

BIOGRAPHY

Barbara Bessette received her PhD degree in Neuroscience and oncology from the University of Limoges, France in 2006. She worked one year in Paris on pediatric brain tumors and the characterization of cancer stem cells in these tumors. She followed her post-doctoral experience by collaborating and working for 3 years on GLIADYS project with IDD-Biotech (International Drug Development Biotech), specialized in monoclonal antibodies production in Lyon, France. The project consisted to develop new therapeutics for gliomas. During this project, she develops partner relationship with Oncomedics (CRO specialized in Individualized tumor response tests). She is currently a full-time assistant Professor at the University of Limoges in the Department of Physiology and she leads research into HCP-CAPTur team. Her current research activity focuses on cancer stem cells in glioblastoma and the role of neuropeptides in their therapeutic resistance capacity. One of the workpackages leaders in SUMCASTEC (H2020 European Project) she participates to determine cancer stem cell electromagnetic signature in glioblastoma and medulloblastoma.

barbara.bessette@unilim.fr

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SETMAR IN GLIOBLASTOMA: SPLICE VARIANTS AND FEEDBACK NETWORK IN CONTROLLING TARGET GENES EXPRESSION

Corinne Auge Gouillou[1], Sylvaine Renault[1], Jérôme Jaillet[1], Murielle Genty[1], Edouard Coudert[1], Oriane Lié[1] and **Ilyess Zemmoura[2]**

[1]University of Tours, France
[2]CHRU of Tours, France

SETMAR is a chimeric protein, acting as a house-kipping genome guardian in healthy cells. In a recent work [i], we demonstrate that SETMAR expression increases in GBM where different splice variants are produced depending on the stage of the cells: stem cells express a small hyper-stable SETMAR (sm-SETMAR) whereas differentiated cells express a large form known as the "regular" SETMAR enzyme (r-SETMAR). The only difference between both SETMAR proteins originates from the lack of the SET domain on the sm-SETMAR, due to exon-exclusion during pre-mRNA maturation. As a result sm-SETMAR is devoid of any methyl-transferase activity, preventing chromatin modifications and regulations usually assign to r-SETMAR. In contrast, both proteins are still able to promote DNA repair by NHEJ, albeit sm-SETMAR is less effective. Our current works hypothesis that sm-SETMAR may contribute to confer cancer stem cells properties of chimio- and radio-resistance, in addition to alter their normal epigenetic profile. Because SETMAR originates from a mobile genetic element, the human genome contains of thousands of SETMAR DNA binding sites that are in fact fossils of the original transposon. They together constitute a regulatory network. The characterization of target genes differentially regulated by the one or other one of the SETMAR proteins through this network during GBM biogenesis is under progress.

BIOGRAPHY

Corinne Auge Gouillou has completed her PhD at the Pasteur Institute of Paris in 1993 and postdoctoral studies from Tours University. She has been leading her research team for over 15 years and published more than 25 papers in reputed journals. She is very strongly involved in teaching and pedagogy, especially for young students who arrive at the University. She has been serving as a referee for many journals, and led a French network dedicated to mobile DNA.

auge@univ-tours.fr

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TGF-β SIGNALING IS A NOVEL THERAPEUTIC TARGET FOR TREATING METASTATIC CANCERS ACQUIRED BY EMT AND CANCER STEMNESS

Seong-Jin Kim
Seoul National University, Korea

TGF-β is a multifunctional cytokine involved in diverse cellular functions, including cell growth and immune responses. TGF-β signaling has emerged as a key architect of the microenvironment in poor-prognosis cancers. Disseminated tumor cells show a strong dependency on a TGF-β-activated stromal during the establishment and subsequent expansion of metastasis. TGF-β also has a positive role on the cancer stem cell (CSC) population promoting or sustaining stemness of the pool of CSCs in diverse types of malignancy. Since TGF-β signaling is dysregulation most of human cancers, thus affecting the overall progression to malignancy, TGF-β signaling has been considered a potentially novel therapeutic target for treating resistance acquired by emptying the TGF-β signaling pathway, TGF-β receptor I kinase inhibitors have shown promise in blocking the TGF-β-mediated tumor progression and metastasis and enhancing antitumor immunity in nonclinical animal models. Vactosertib, a TGF-β receptor I kinase inhibitor, has shown significant preclinical antitumor efficacy in a range of in vivo metastatic and orthotopic xenograft models and has completed phase 1 clinical trials in USA. Recent molecular classification of gastrointestinal cancer has identified a poor-prognosis transcriptional subtype associated with mesenchymal traits and genes upregulated by TGF-β in stromal cells are robust predictors of cancer recurrence and metastasis. This observation warrants the development of anti-TGF-β therapies for the treatment of poor-prognosis cancers with TGF-β response signature.

BIOGRAPHY

Seong-Jin Kim is currently working as a professor at the PrecisionMedicine Research Center at the Advanced Institute of Convergence Technology, Seoul National University, Korea.

jasonsjkim@gmail.com

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INHIBITOR OF APOPTOSIS PROTEINS DETERMINE GLIOBLASTOMAS STEM-LIKE CELLS FATE IN AN OXYGEN-DEPENDENT MANNER

Aurélie Tchoghandjian
Axe Marseille Université, France

Smac mimetics (SMs) are inhibitor of apoptosis proteins (IAPs) antagonists. In glioblastomas (GBs), SMs can trigger apoptotic and non-apoptotic processes1, 2, 3. As GBs are highly hypoxic, we investigated SM GDC-0152 effect in GB stem-like cells according to oxygen level. We showed that in an environment rich in oxygen (normoxia), GDC-0152 induced loss of stem-cell properties. Unexpectedly, in an environment deprived of oxygen (hypoxia), it triggered apoptosis and decreased cell proliferation. Analysis of Serine-Threonine Kinases activation upon GDC-0152 treatment revealed involvement of different signaling pathways according to oxygen level. In normoxia, NF-κB pathway was activated and in hypoxia, GDC-0152 efficacy was ATR- and TNFα-dependent. This work shows that GDC-0152 triggers anti-tumoral effects whatever the tumoral oxygen pressure, therefore SMs appear as promising molecules in GBs treatment.

BIOGRAPHY

Aurélie Tchoghandjian is currently working in INP – Institut de Neurophysiopathologie, Axe Marseille Université, France

aurelie.tchoghandjian@univ-amu.fr

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STUDY OF CELL REPROGRAMMING IN A MURINE MODEL: FOLLOW-UP OF RADIO-INDUCED CANCEROUS STEM CELLS AND VALIDATION OF THE CYTOKINES INVOLVED

Bidan Nadege
Inserm, France

Many solid cancers are thought to be organized hierarchically with a small number of cancer stem cells (CSCs) able to re-grow a tumor while their progeny lacks this feature. This CSCs are associated with radioresistance. Recent studies have revealed that noncancer stem cells may undergo dedifferentiation subsequently obtaining the phenotype and functions of CSCs. Indeed, ionizing radiation reprogrammed differentiated breast cancer cells into induced cancer stem cells (iCSCs). This mechanism of reprogramming can contribute to relapse. CSCs and iCSCs cannot be distinguished, because they share the same stem cell-like properties. Breast CSCs can be isolated based on their high ALDH1 activity, and iCSC studies require sorting of ALDH1-negative cells. These studies are therefore limited to *in vitro* experiments. *In vivo* reprogramming studies require to design a CSC and iCSC identification system. We compared different promoters for the use of CSC reporters. To do so, we built expression vectors with mNeptune fluorophore expression controlled by different sizes ALDH1A1 and NANOG promoters. We validated the CSC reporter capability using RTPCR expression, flow cytometry and functional assay analyses. Indeed, mNeptunepos cells have an overexpression of stemness-related genes (Oct3/4, Sox2 and Nanog), as well as an increase of mammosphere forming capacity and tumorigenicity, compared to mNeptuneneg cells. We also observed an enrichment for mNeptunepos cells after ionizing radiation and a radiation-induced reprogramming of mNeptuneneg cells into mNeptunepos cells. Our observations on CSC reporters showed that the 900 pb sequence of ALDH1A1 promoter seems to be the best choise for a CSC reporter. Based of this first study, we selected this promotor andgenerated a multigene tracing expression vector to distinguish CSC from iCSC at given time points. This vector contains sequence of CSC reporter, TetON system for inducible CRE expression, CRE recombinase/loxP sites system and mNeptune fluorophore. We are currently validating this vector for it use *in vitro* before to generate transgenic mice model for CSC and iCSC reporter. This vector will be a tool for future studies investigating *in vivo* reprogramming mechanism.

BIOGRAPHY

Bidan Nadege is currently persuing her research at Inserm, France.

nadege.bidan@inserm.fr

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IN-VIVO AND *IN-VITRO* IMPACT OF miR-21 AND miR-126 IN THE SUPPRESSION OF METASTASIS AND INVASION IN BREAST CANCER

Sina Taefehshokr[1], Ehsan Mikaili[1], Sahand Fattahi[1], Farzad Rahimi[1], Reza Vaezi[1] and **Peyman Keyhanvar[2]**

[1]Islamic Azad University, Iran
[2]Iran University of Medical Sciences, Iran

The aim of this study was to investigate the effect of miRNA-21 and miRNA-126 inhibition on metastasis and invasion in both MDA-MB231, MDA-MB468 as well as the MCF-7 breast cancer cell lines and five week old female C57BL/6 mice. Following the cloning of miRNA-21 and miRNA-126 into vectors, their expressions were determined before treatment with constructs of miR-21 and miR-126 in cancer cell lines and normal breast cells. Then miRNA-21 and miRNA-126 were transfected to the cell-lines and the expression was assessed after 48 hours. Moreover, levels of migration and invasion were determined in cell-lines. These experiments performed in five-week old female C57BL/6 mice. The results showed that miRNA-21 expression before the transfection of miRNA-21 construct was decreased 4, 70 and 100 times in MCF-7, MDA-MB468 and MDA-MB231 cell lines, respectively, in comparison to normal breast cells; but after the transfection of miR-21 construct, expression of miRNA-21 was increased 100 times. Furthermore, invasion and migration decreased by 15 and 10 times in MDAMB-468. All modifications in miRNA-126 were low in comparison to miRNA-21. The results of the *in vivo* experiments were approximately the same as *in vitro* experiments. It suggests that the use of miRNA-21 is highly efficient than miRNA-126 in the inhibition of metastasis and invasion in breast cancer. Our study enhanced our conception about miR-21 and miR-126 and its roles in identification and therapy of breast cancer.

BIOGRAPHY

Sina Taefehshokr is a self-motivated, dedicated and first top DVM student in the faculty with solid background in Cell Biology, Oncology and Immunology research. She has published more than 15 papers both in Farsi and English in several journals. She had six both oral and poster presentations in international and national conferences. She can implement several research skills including Immunology, Molecular Biology, Tumor, Protein, Histology and Animal Handling Techniques. She has worked as a Lab Demonstrator/Teaching Assistant and Honorary Research Assistant at Stem Cell and Regenerative Medicine Institute, Tabriz University of Medical Sciences.

Sinataefehshokr@gmail.com

Note: