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12th International Conference on

CANCER STEM CELLS AND ONCOLOGY RESEARCH

July 18-19, 2019 | Valencia, Spain

CANCER STEM CELLS 2019



SCIENTIFIC TRACKS & ABSTRACTS

DAY 1

DAY 1 SESSIONS

JULY 18, 2019

Cancer Stem Cells | Stem Cells | Stem Cell Research

SESSION CHAIR

Adam Frosh
Lister Hospital, United Kingdom

SESSION INTRODUCTION

Title: Cancer Stem Cells dedifferentiation as the cornerstone of tumor relapse and disease progression

Carlos FD Rodrigue, University of Coimbra, Portugal

Title: Drug resistant stem cells in cellular models for molecular subtypes of breast cancer

Nitin Telang, Palindrome Liaisons Consultants, USA

Title: ERG enhancer-based reporter identifies leukemia cells with elevated leukaemogenic potential driven by ERG-USP9X feed-forward regulation

Nasma Aqaqe, Tel Aviv University, Israel

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Carlos FD Rodrigues et al., J Med Oncl Ther 2019, Volume 4

CANCER STEM CELLS DEDIFFERENTIATION AS THE CORNERSTONE OF TUMOR RELAPSE AND DISEASE PROGRESSION

Carlos FD Rodrigues[1,2,3], Eurico Serrano[1,2], Patrícia Albuquerque[1,4], Luís Almeida[1,4] and **Maria Carmen Alpoim[1,2,5]**
[1]Center for Neuroscience and Cell Biology (CNC), University of Coimbra, Portugal
[2]Center of Investigation in Environment, Genetics and Oncobiology (CIMAGO), University of Coimbra, Portugal
[3]Centro Hospitalar do Baixo Vouga, Portugal
[4]Faculty of Pharmacy (FFUC), University of Coimbra, Portugal
[5]Department of Life Sciences, University of Coimbra, Portugal

Cancer stem cells (CSCs) are the orchestrators of the intricate communication pathways hijacked by tumors to overcome the inefficiency of the invasion-metastasis cascade. Their plasticity and boosted defense mechanisms permits their survival to the current therapeutic regimens, thus retaining the potential to drive tumor relapse. After observing that the malignant human bronchial epithelial RenG2 cells dedifferentiated following culture in the subcutaneous mouse lumbar region, co-cultures of mice lumbar fibroblats with RenG2 cells were established and the conditioned media was studied. Results showed Interleukin-6 (IL-6), Granulocyte colony-stimulating factor (G-CSF) and Activin-A were the mediators of the aforementioned intercellular communication process, which prompted the study of the individual role of each cytokine and of exosomes in the overall process. To this end the same co-cultures were reproduced in the presence of combinations of specific cytokine-communication blockers and exosome-mediated communication inhibitors. Whenever exosome's release was blocked, dedifferentiation was abrogated. Additionally, only IL-6 and Activin-A were endowed with the potential to orchestrate dedifferentiation, as when at least one of these cytokines was present a stem cell population developed inside RenG2 cells. G-CSF only maintained CSC's undifferentiated phenotype, as a larger pool of CSCs was attained whenever this cytokine and either IL-6 or Activin-A was present. The attained results implicated IL-6 and Activin-A in the formation of CSCs by dedifferentiation and G-CSF as a potent keeper of the dedifferentiation status. The scavenging of these cytokines from the tumor microenvironment presents a new avenue for therapeutic intervention aiming CSCs ablation and metastasis abrogation.

BIOGRAPHY

Carlos FD Rodrigues has been graduated from the University of Coimbra, Portugal as both Medical Doctor and a Biologist. He holds a PhD in Biomedicine and Experimental Biology and a Master in Medicine from the same university. Currently he is taking his specialization in Internal Medicine in the Centro Hospitalar do Baixo Vouga, Portugal while continuing his research both at his Hospital in Aveiro and at the Center for Neuroscience and Cellular Biology in Coimbra, Portugal.

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Nitin Telang, J Med Oncl Ther 2019, Volume 4

DRUG RESISTANT STEM CELLS IN CELLULAR MODELS FOR MOLECULAR SUBTYPES OF BREAST CANCER

Nitin Telang
Palindrome Liaisons Consultants, USA

Study rationale global expression profiling of differentially expressed genes in breast cancer has provided scientifically robust rationales for molecular classification of breast cancer subtypes and for targeted treatment options. Chemo-endocrine therapy combined with pathway selective small molecule inhibitors represents common treatment of choice. However, this option is frequently associated with emergence of drug resistant stem cells that favor progression of therapy resistant disease. This limitation emphasizes development of cancer stem cell models that are capable of identifying testable therapeutic alternatives against drug resistant stem cells. Experimental approach experiments on cellular models for Luminal A, HER-2 enriched and triple negative breast cancer subtypes were designed to isolate and characterize stem cell phenotypes resistant to clinically relevant chemo-endocrine therapeutics and examine the mechanistic efficacy of natural products on drug sensitive and drug resistant phenotypes. Study outcome parental MCF-7 (Luminal A), 184-B5/HER (HER-2 enriched) and MDA-MB-231 (Triple negative) cells exhibited progressive growth in the presence of cytotoxic concentrations of Tamoxifen (TAM), Lapatinib (LAP) and Doxorubicin (DOX), respectively. Long-term treatment with these drugs favored emergence of drug resistant TAM-R, LAP-R and DOX-R phenotypes. These resistant cells exhibited up regulated expression of stem cell specific tumor spheroid formation and CD44 (cellular) and Oct-4 and NANOG (molecular) markers. Treatment of drug sensitive and resistant cells with select nutritional herbs, vitamin A derivative and natural terpenoid induced inhibition of tumor spheroid formation and down regulated expression of CD44, Oct-4 and NANOG. Study conclusions present cancer stem cell models provide a novel approach to identify natural products as testable alternatives for stem cell targeted therapy of chemo-endocrine therapy resistant breast cancer.

BIOGRAPHY

Nitin Telang obtained his PhD in Developmental Biology from University of Poona, India in 1974, followed by post-doctoral training in the USA during 1976-1985. He has served as attending Biochemist at Memorial Sloan-Kettering Cancer Center, New York during 1985-1991, as an Associate Professor at Cornell University Medical College, New York during 1991-2004, and as Senior Scientist and Director, Carcinogenesis a Prevention Laboratory at Strang Cancer Prevention Center, New York during 2004-2007. His research on preclinical models for genetically predisposed breast and colon cancer has been funded through US Department of Defense Breast Cancer Research Program and through US National Cancer Institute. His current research interests are in the fields of preclinical oncology, cancer stem cell biology and anti-cancer lead compound efficacy.

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Nasma Aqaqe-Tibi et al., J Med Oncl Ther 2019, Volume 4

ERG ENHANCER-BASED REPORTER IDENTIFIES LEUKEMIA CELLS WITH ELEVATED LEUKAEMOGENIC POTENTIAL DRIVEN BY ERG-USP9X FEED-FORWARD REGULATION

Nasma Aqaqe-Tibi, Muhammad Yassin, Abed Alkader Yassin, Eitan Kugler, Eric R Lechman, Olga I Gan, Amanda Mitchell, John E Dick, Shai Izraeli and **Michael Milyavsky**
Tel Aviv University, Israel

Acute leukaemia is a rapidly progressing blood cancer with low survival rates. Unfavorable prognosis is attributed to the insufficiently characterized subpopulation of leukemia stem cells (LSCs) that drive chemo resistance and leukemia relapse. Here authors utilized a genetic reporter which enables stemness assessment to enrich and functionally characterize LSCs. They revealed heterogeneous activity of the ERG+85 enhancer based fluorescent reporter in human leukemias. Cells with high reporter activity (tag BFP High) exhibited elevated expression of stemness and chemo-resistance genes, demonstrated increased clonogenicity and resistance to chemo and radio-therapy as compared to their tag BFP Neg counterparts. Moreover, tag BFP high enriched fraction was capable of regenerating the original cellular heterogeneity and demonstrated increased invasion ability. Most importantly, tag BFP High fraction was enriched for leukemia initiating cells in a xenograft assay. They also identified USP9X deubiquitinase enzyme as a novel ERG transcriptional target that sustains ERG+85 positive cells. Therapeutic targeting of USP9X led to the preferential inhibition of the ERG-dependent leukemias. In summary, they have developed a new strategy to characterize LSCs and propose ERG targeting via USP9X inhibition as a potential anti-leukaemia treatment.

BIOGRAPHY

Nasma Aqaqe-Tibi is a fourth year PhD student at Tel-Aviv University, currently working on characterization of gene regulatory networks responsible for human leukemia cells regeneration after genotoxic stress at Dr Milyavsky lab.

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DAY 2

DAY 2 SESSIONS

JULY 19, 2019

Cancer Stem Cells | Stem Cells | Stem Cell Research

SESSION CHAIR

Adam Frosh
Lister Hospital, United Kingdom

SESSION INTRODUCTION

Title: Living with cancer

Xu Chen, Ashford University-University of the Rockies, USA

Title: Effects of selected plant polyphenols on SIRT gene expression and antitumor activity in cultures of colorectal cancer cells

Helena Moreira, Wroclaw Medical University, Poland

Title: Novel DNA methylation in GBM

Tao P Wu, Baylor College of Medicine, Houston

Title: Salinomycin as potent drug to target CSCs

Divya Sivanesan, Indian Institute of Technology (IIT) - Madras, India

Title: Clinical experience in advanced cancer with dendritic cells loaded with autologous stem cell antigens

Robert O Dillman, AIVITA Biomedical Inc., USA

Title: Acquisition and augmentation of cancer stem cell-like properties in polymer thin film-induced tumour spheroids

Sangyong Jon, Korea Advanced Institute of Science and Technology, Korea

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Xu Chen, J Med Oncl Ther 2019, Volume 4

LIVING WITH CANCER

Xu Chen
Ashford University-University of the Rockies, USA

During the last four decades, cancer rates over all went up. Among them, thyroid cancer rate went up even more. Because thyroid cancer has a high survival rate, every year, more people are living with this cancer. During the cancer remission time, every day practice, such as the food you eat, water you drink, a small walk, social support or mental status can be key factors in cancer survival. To understand these key factors, this researcher went through thousands of threads in Yahoo Thyroid cancer long term survivor support group and summarized the possible best practices in thyroid cancer long term survival. Also, this researcher will tentatively discuss the reasons behind different people's various reactions towards the same treatments.

BIOGRAPHY

Xu Chen holds a BA in Biology and MS in Exercise Science from The College of St. Scholastica. Currently, she is working on her Doctor of Psychology through Ashford University. Besides being a student, she is a performing actor around Boston area.

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Helena Moreira et al., J Med Oncl Ther 2019, Volume 4

EFFECTS OF SELECTED PLANT POLYPHENOLS ON SIRT GENE EXPRESSION AND ANTI-TUMOR ACTIVITY IN CULTURES OF COLORECTAL CANCER CELLS

Helena Moreira, Anna Szyjka, Katarzyna Pelc, Magdalena Żuk and **Anna Kulma**
Wroclaw Medical University, Poland

Colon cancer stem cells (CSC) play critical role in the resistance of colorectal cancers to radiotherapy/chemotherapy, metastasis and relapse. Author's compared the effects of plant polyphenols, Celastrol and Resveratrol on human colon cancer cell lines: Sensitive to cytotoxic drugs (LOVO) and doxorubicin resistant (LOVO/DX). Both polyphenols caused cell-cycle arrest at S phase in LOVO and LOVO/DX cells. Resveratrol exerted a strong proapoptotic effect against LOVO cells, but it does not affect the viability of LOVO/DX cells. Celastrol caused an increase (up to 50%) in the percentage of cells in apoptosis in both LOVO and LOVO/DX cells, which correlated with decreased expression of BRCA1 and PPAR genes. Importantly, Celastrol and Resveratrol inhibited the functional activity of multidrug resistance proteins (MDRs). Resveratrol increased the expression of SIRT 1, 2 and 3 genes whereas Celastrol strongly increased the expression of SIRT 1 and decreased SIRT 3 gene expression, in both LOVO and LOVO/DX cells. Expression of the SIRT 6 gene was increased by Celastrolin LOVO/DX cells (depending on concentration), while resveratrol did not affect gene expression of this sirtuin in LOVO/DX cells. In conclusion, the effect of tested polyphenols on sirtuin gene expression may have different influence on the progression of colon cancer. According to literature data, the increase in SIRT 1 expression may potentiate and SIRT6 may inhibit the progression of colon cancer. Because celastrol and resveratrol have significant pro-apoptotic effects and they inhibit cell cycle progression and block the function of multidrug resistance proteins in both types of colon cancer cells, they concluded that the antitumor effect of these polyphenols occurs through multiple mechanisms of action and is largely unrelated to their effects on sirtuin gene expression.

BIOGRAPHY

Helena Moreira is Assistant Professor at the Department of Basic Medical Science of the Faculty of Pharmacy at the Medical University of Wroclaw, Poland. She completed her Doctoral studies at the Institut Gilbert-Laustriat at Department Physicochimie des Interactions Cellulaires et Moléculaires in Strasbourg in France where she was working on the molecular mechanisms of TNF-α secretion, a key cytokine in chronic inflammation. She is deeply interested in research on cancer treatment, especially in studying the anti-cancer mechanisms of various natural plant polyphenols. Her research interest mainly focus on cancer stem cells in colorectal cancer. She has a strong laboratory experience, including in cell culture and flow cytometry.

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Tao P Wu et al., J Med Oncl Ther 2019, Volume 4

NOVEL DNA METHYLATION IN GBM

Tao P Wu[1], Qi Xie[2], Jeremy Rich[2] and **Andrew Xiao[3]**
[1]Baylor College of Medicine, USA
[2]University of California San Diego, USA
[3]Yale University, USA

Genetic drivers of cancer can be disregulated through epigenetic modifications of DNA. Although the critical role of DNA 5-methylcytosine (5mC) in the regulation of transcription is recognized, the functions of other non-canonical DNA modifications remain obscure. Here, authors report the identification of novel N6-methyladenine (N6-mA) DNA modifications in human tissues and implicate this epigenetic mark in human disease, specifically the highly malignant brain cancer glioblastoma. Glioblastoma markedly up regulated N6-mA levels, which co-localized with heterochromatic histone modifications, predominantly H3K9me3. N6-mA levels were dynamically regulated by the DNA demethylase ALKBH1, depletion of which led to transcriptional silencing of oncogenic path ways through decreasing chromatin accessibility. Targeting the N6-mA regulator ALKBH1 in patient-derived human glioblastoma models inhibited tumor cell proliferation and extended the survival of tumor bearingmice, supporting this novel DNA modification as a potential therapeutic target for glioblastoma. N6-mA also response to hypoxia stress and hypoxia respond genes were regulated by ALKBH1. Collectively, author's results uncover a novel epigenetic node in cancer through the DNA modificationN6-mA.

BIOGRAPHY

Tao P Wu has completed his PhD in 2008 from University of Chinese Academy of Sciences, China. He is the Assistant Professor of Baylor College of Medicine, USA. He has over 20 publications including one Nature article and one Cell article and his publication H-index is 9.

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Divya Sivanesan et al., J Med Oncl Ther 2019, Volume 4

SALINOMYCIN AS POTENT DRUG TO TARGET CSCS

Divya Sivanesan, Raj Pranap Arun and **Rama Shanker Verma**
Indian Institute of Technology (IIT) - Madras, India

Cancer relapse has been an issue in oncology research for more than few decades but author hasn't reached at a solution yet. Their study aims at avoiding the recurrence by making conventional therapies more efficient with adjunct treatment. Cancer stem cells (CSCs) is the root cause for drug/chemo-resistance as these cells have characteristic properties of stem cells, they are quiescent and are highly invasive. Recent research article explored various chemical compounds though high-throughput screening which would selectively target CSCs. Salinomycin is the reported potent drug and we decided to further investigate the same. Colorectal cell lines DLD1, SW620 and breast cancer cell lines MCF7, MDA-MB-231 cells were used for the study. These cells were exposed repeatedly to radiation dosage or treated with IC50 concentration of 5-Flurouracil (5-FU) to generate resistant cell line. Levels of stemness markers like SOX2, KLF4, OCT4 etc. and epithelial-to-mesenchymal (EMT) markers like Snail1, Zeb1, E-cadherin, N-cadherin etc., were observed and were compared with that of untreated cells. There was a significant up regulation in stemness and EMT pathway at transcriptional as well as at protein level which was evaluated through real-time PCR and western blot, immune cytochemistry respectively. At as low concentration of salinomycin as 2μM, these markers were down regulated and functional assays like colony forming assay and flow cytometry analysis of CD133 and CD44-CSC markers corroborated the same. Thus, salinomycin could be potent drug to target CSCs avoid secondary tumor formation. Further understanding of the target mechanism could help us improve the current treatment method.

BIOGRAPHY

Divya Sivanesan is a PhD scholar working in Stem Cell and Molecular Biology laboratory under the guidance of Prof Rama Shanker Verma, Biotechnology Department, IIT Madras. She is final year student and has two publications.

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Robert O Dillman, J Med Oncl Ther 2019, Volume 4

CLINICAL EXPERIENCE IN ADVANCED CANCER WITH DENDRITIC CELLS LOADED WITH AUTOLOGOUS STEM CELL ANTIGENS

Robert O Dillman
AIVITA Biomedical Inc., USA

Tumor initiating cells, including cancer stem cells and their early progenitors are a desirable target for cancer therapy but hard to target with chemotherapy and radiation therapy and hard to target with tumor-specificity using targeted therapies. Immunologic vaccines directed to tumor stem cells have shown promise in animal models. Our approach has been to utilize autologous tumor antigens (ATA) derived from short-term cell lines. Such cells have phenotypic markers shared with stem cells, produce tumors of the parental histology in animals and contain many non-synonymous mutations that may encode for neo-antigens. Author's early work focused on irradiated tumor cells as a tumor cell vaccine (TCV) and was associated with a 29% 5-year survival rate in patients with metastatic melanoma. Then they turned to autologous dendritic cells (DC) loaded with ATA from irradiated tumor cells (DC-ATA). 5-year survival rates of 33% were observed in patients with metastatic renal cell cancer and 50% in patients with metastatic melanoma. Next a randomized trial confirmed the superiority of the DC-ATA approach compared to TCV in metastatic melanoma with more than a doubling of median survival from 20 to 43, and a 70% reduction in the risk of death. Toxicity was minimal in all of these studies. A major limitation of these trials was that it typically took three to four months to establish successful cell lines, and only about 50% of tumor samples resulted in cell lines; in contrast, DCs were reliably derived from peripheral blood mononuclear cells. More recently they converted to using serum free media to encourage tumor-spheres that favor tumor stem cells and establish short-term cell lines in four weeks. So far this approach has been associated with greater than 90% success in various tumor types including glioblastoma, ovarian cancer, melanoma, hepatocellular cancer, sarcoma and squamous cell cancers of the neck and vulva. At the time of treatment, DC-ATA are suspended in granulocyte-macrophage colony stimulating factor and injected subcutaneously weekly for three weeks, then monthly at weeks 8, 12, 16, 20 and 24. DC-ATA. Multi-institutional phase II trials are in progress: A double-blind randomized phase II trial in patients with a primary diagnosis of stage 3 or 4 ovarian cancer and a single-arm phase II trial in patients with newly diagnosed glioblastoma that can be at least partly resected surgically. Trials are also in development for patients with metastatic melanoma and locally advanced hepatocellular cancer.

BIOGRAPHY

Robert O Dillman is Chief Medical Officer of AIVITA Biomedical. Earlier he served as Vice President of Oncology at Caladriu's Biosciences Inc. (formerly Neostem Inc.), a leading development and manufacturing partner to the cell therapy industry. From May 2014 to January 6, 2016 he also served as Member of Caladriu's Melanoma Scientific Advisory Board. He has served as the Executive Medical Director of the Hoag Hospital Institute for Research and Education, in Newport Beach, California, a position he has held since 2011.

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Sangyong Jon et al., J Med Oncl Ther 2019, Volume 4

ACQUISITION AND AUGMENTATION OF CANCER STEM CELL-LIKE PROPERTIES IN POLYMER THIN FILM-INDUCED TUMOUR SPHEROIDS

Sangyong Jon, Minsuk Choi, Seung Jung Yu, Yoonjung Choi, Yumi Lee, Junhyuk Song, Daeyoup Lee and **Sung Gap Im**
Korea Advanced Institute of Science and Technology, Korea

Although cancer stem cells (CSCs) are thought to be responsible for tumour recurrence and resistance to chemotherapy, CSC-related research and drug development have been hampered by the limited supply of diverse, patient-derived CSCs. Here, author's developed a functional polymer thin film (PTF) platform that promotes conversion of cancer cells to highly tumorigenic three-dimensional (3D) spheroids without the use of biochemical or genetic manipulations. Culturing various human cancer cells on the specific PTF, poly (2, 4, 6, 8-tetravinyl-2, 4, 6, 8-tetramethyl cyclotetrasiloxane) (pV4D4), gave rise to numerous multicellular tumour spheroids within 24 hours, with high efficiency and reproducibility. Cancer cells in the resulting spheroids showed an enormous increase in the expression of CSC-associated genes and acquired dramatically increased drug resistance compared with 2D monolayer-cultured controls. These spheroids also showed greatly enhanced xenograft tumour forming ability and metastasis capacity in nude mice. By enabling the generation of tumorigenic spheroids from diverse cancer cells, the surface platform described here will likely contribute to CSC-related basic research and drug development.

BIOGRAPHY

Sangyong Jon received his BS in 1993, MS in 1995 and PhD in 1999 from the Department of Chemistry of KAIST, Korea. Then he moved to the US for his Post Doctorate career in the Department of Chemical Engineering at MIT. After returning to Korea, he joined Gwangju Institute of Science and Technology (GIST) as an Assistant Professor of Life Sciences in 2004. He was promoted to Associate Professor in 2007 and Professor in 2010. He is a Fellow of Korean Biochip Society and Korean Molecular Imaging Society. He has published over 60 papers, numerous chapters, and 30 patents. He sits on the Editorial Board for two peer-reviewed journals and is a regular reviewer for over 30 journals. His research interest lies at the interface of medicinal chemistry, biotechnology, and biomaterials science.

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Note: