Abstract Book

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April 13-15, 2023, | Sercotel Sorolla Palace, Valencia, Spain

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The nuclear translocation of ERK as a therapeutic target for cancer

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Abstract

A hallmark of MAPK signaling is the nuclear translocation of some of its components, which is necessary for their physiological/pathological functions. We have shown that the prevention of the nuclear translocation of ERK inhibits nucleus-dependent processes and pathologies without affecting the cytoplasmic activities of the kinase, and therefore, this inhibition has less side effects or resistance development than the currently used drugs. Our studies established that the nuclear translocation of ERK is mediated by Imp7. Prevention of the interaction between the two proteins blocks the nuclear ERK translocation, and as a consequence, inhibits the growth of some cancers. We developed a peptide and a small molecule that are able to inhibit the interaction and showed that they are effective in preventing melanoma, pancreatic, triple negative breast, and other cancers. One of the drugs was shown to be completely abolish the growth of melanoma, and demonstrated much lower acquired resistance than a clinically used Raf inhibitor termed vemurafenib. In the lecture, I will describe our recent studies on the regulation of the nuclear ERK translocation, and how can our finding be used as a new strategy to combat cancer.

Biography:

RonySeger, Professor

Prof. Rony Seger became a group leader in the Weizmann Institute of Science in 1994 promoted to full professor full professor in 2007, and was the head of the department of Biological Regulation (2011-2017). His research group is interested in MAPK and AKT signaling and in particular in the subcellular localization of their components. Recently, the group elucidated the distinct mechanisms of nuclear translocation of ERK and p38/JNK, which are used as anti-cancer and inflammation targets. Dr. Seger published more than 230 papers, supervised more than 80 research students and post-docs, and received many prizes and awards.

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Retinoic acid receptor signaling pathway is regulated by all-trans retinoic acidin Merkel cell carcinoma cells

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Abstract

The biological activity of retinoids, which are active metabolites of vitamin A, is mainly mediated by retinoic receptors, which are ligand-dependent transcription factors that belong to the superfamily of steroid/thyroid hormone nuclear receptors. Retinoid signaling regulates crucial cell differentiation genes whose dysregulation can lead to carcinogenesis.A strong antitumor activity of all-trans retinoic acid (ATRA) by modulating the retinoic pathway has been proved in different carcinoma histotypes. However, the effect of this molecule in Merkel cell carcinoma (MCC), a rare but aggressive skin neoplasm of viral origin in 80% of cases, is unknown. Herein, we explored transcriptionally the retinoic signaling pathway in Merkel cell polyomavirus (MCPyV)-positive/-negative MCC cells by Profiler PCR array. Then, we investigated the antineoplastic effect of ATRA in MCC cells and in control human fibroblasts. The antineoplastic effect of ATRA was evaluated by testing MCC cell proliferation, migration and clonogenicity. Upon treatments, apoptosis/cell death and cell cycle were evaluated byAnnexin-V/PI and TALI assays, respectively. Apoptotic and retinoic pathway genes were then evaluated by Profiler PCR array and by western blot (WB) analysis.ATRA treatment led to a strong reduction in MCC cell proliferation, migration and clonogenicity, while promoting cell cycle arrest and apoptosis/cell death, with a more pronounced effect in MCPyV-positive cells. A significant overexpression of pro-apoptotic markers in ATRA-treated MCC cells compared to untreated cells was determined through gene expression array and WB. Neither phenotypic nor molecular effects were found in ATRA-treated fibroblast control cells. Several retinoic signaling genes, includingBMP2, FOXA1, MAFB, OLIG2, UCP1 and RBP4, resulted as differentially expressed in ATRA-treated MCC cells compared to untreated cells. Our findings suggest that ATRA presents an antineoplastic activity in MCC cellsby modulatingretinoic receptor pathway.

Biography:

John Charles Rotondo, PhD, Principal Investigator, University of Ferrara.My scientific interests are focused on understanding the molecular dysregulations in human tumors. I have obtained a PhD degree in 2015 the "Biomedical Sciences" program at the University of Ferrara. After two years aspost-docat the University of Ferrara,I worked about one and a half years as post-doc at the International Agency for Research on Cancer in Lyon, France, and at the German Cancer Research Center, Freiburg, Germany. Then, Ihave obtained research founds and I returned in Italy in the University of Ferrarato work on oncology-related projects.

A Stress-Induced Bias in the Reading of the Genetic Code inEscherichia coli

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Abstract

Escherichia coli mazEF is an extensively studied stress-induced toxin-antitoxin (TA) system. The toxin MazF is an endoribonuclease that cleaves RNAs at ACA sites. Thereby, under stress, the induced MazF generates a stress-induced translation machinery (STM), composed of MazF-processed mRNAs and selective ribosomes that specifically translate the processed mRNAs. Here, we further characterized the STM system, finding that MazF cleaves only ACA sites located in the open reading frames of processed mRNAs, while out-of-frame ACAs are resistant. This in-frame ACA cleavage of MazF seems to depend onMazF binding to an extracellular-death-factor (EDF)-like element in ribosomal protein bS1 (bacterial S1), apparently causing MazF to be part of STM ribosomes. Furthermore, due to the in-frame MazF cleavage of ACAs under stress, a bias occurs in the reading of the genetic code causing the amino acid threonine to be encoded only by its synonym codon ACC, ACU, or ACG, instead of by ACA.

Biography:

PROF. HANNA ENGELBERG-KULKA was born in Vienna, Austria. She completed her MSc degree and Degree-Ph.D on the subject (Studies on streptomycin-dependent bacteria) at Hebrew University, Jerusalem, Israel and She is a Member, of the Executive Committee of the Board of Governors, Hebrew University, from 1994-2000 Chairperson, Dept of Molecular Biology, Institute of Microbiology, she was honored with the EMET prize on Genetics and The Ilanit-Kazir Prize awarded once in 3 years by the Israel Society of Experimental Biology (FISEB). This award is given to Hanna Engleberg Kulka for her pioneering research that led to the discovery of bacterial PCD and its mode of signaling, the identification of a communication factor, and The Ulizky Prize of the Israel Society of Microbiology for Excellency in microbiological research. She published 115 publications in first-class journals. Also, she is an Invited speaker for International Scientific Meetings; for the last 28 years, Her research areas are Molecular biology, Microbial genetics, biochemistry, and physiology Since 1996

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Human epithelial cell clonogenic potential is regulated by hsa-microRNA-1249-3p/homeobox A13 axis

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Abstract

The role for microRNA (miRNAs) molecules in regulating epithelial cell adhesion mechanisms has partially been uncovered. Hsa-miR-1249-3p is dysregulated in several cancers, including hepatocellular and breast carcinomas. However, its function in human epithelial cells is unknown. The purpose of this study was to functionally investigate the effect of hsa-miR-1249-3p on the clonogenic potential of human epithelial cells and explore the possible underlying molecular mechanism of action. Additional epithelial cell processes such as proliferation, migration and apoptosis were investigated. DdPCR was used to evaluate the hsa-miR-1249-3p expression in epithelial cell lines HaCaT and NCTC and in control cervical carcinoma cell lines SiHa, CaSki and HeLa. Then, the hsa-miR-1249-3p mimic, inhibitor and negative/positive controls were transfected onto HaCaT cells. Upon transfections, cell proliferation, clonogenicity, migration and apoptosis were assessed by WST, clonogenic, wound healing and western blot assays, respectively. Hsa-miR-1249-3p resulted as overexpressed in HaCaT and NCTC cells, respectively, compared to cervical carcinoma cells. Hsa-miR-1249-3p resulted as undetectable in miR-inhibitor HaCaT condition, while being strongly overexpressed miR-mimic HaCaT, compared to untreated cells. Hsa-miR-1249-3p knockdown modestly favored cell proliferation and migration potential in HaCaT cells, without perturbing apoptosis. Contrariwise, a strong clonogenic effect was detected in hsa-miR-1249-3p-inhibited HaCaT cells. Furthermore, in silico analyses identified the oncogene Homeobox A13 (HOXA13) as a hsa-miR-1249-3p downstream target. Mechanistically, hsa-miR-1249-3p inhibition prompted the up-regulation of HOXA13 transcript in HaCaT cells. Our data indicate that hsa-miR-1249-3p can target HOXA13 to regulate the clonogenic potential of HaCaT cells. These data will allow the development of further investigations aimed in studying the role of has-miR-1249-3p/HOXA13 axis in epithelial cell clonogenic potential, such as evaluating the relationship between this miRNA/target gene axis and its downstream genes β-catenin, c-Met, and c-Jun which have been reported to be implicated in cell-cell adhesion pathways.

Biography.

Chiara Mazziotta, Ph.D., post-doctoral fellow.

I am a post-Doc, awarded of a three-year fellowship from the "Italian Foundation for cancer research" (AIRC), in the Laboratories of Cell Biology and Molecular Genetics, Department of Medical Sciences, University of Ferrara, Ferrara, Italy.

In 2018, I discussed my experimental thesis entitled "Adult mesenchymal stem cells employed to investigate an innovative biomaterial: identification of osteogenic genes and microRNAs" for the master's degree in biotechnology for the Environment and Health. Then, I was enrolled as a Ph.D. student in the Molecular Medicine course, and I presented my Ph.D. thesis in June 2022. During these years, I mainly worked in different projects, including (i) molecular oncology; (ii) regenerative medicine/bone regrow and (iii) epigenetics of stem cells.

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Specific features of Arabidopsis glutathione peroxidases in ROS processing, redox homeostasis and signaling

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Abstract

Glutathione peroxidases (GPXs) are key antioxidant enzymes in mammals. Plants contain GPX-like (GPXL) proteins, which are thiol-based peroxidases catalyzing the reduction of H2O2 or hydroperoxides to water or alcohols by electrons derived from reduced glutathione (GSH) or thioredoxin (TRX). In contrast to animal GPXs, the plant enzymes are non-seleno monomeric proteins that generally utilize TRX more effectively than GSH but can be a putative link between the two main redox systems. Their most known functions are the conversion of lipid hydroperoxides into less toxic compounds, the maintenance of membrane integrity, and involvement in the regulation of the redox homeostasis, altering the thiol/disulphide balance. However, recent evidence suggests that GPXs not only can protect cells from stress-induced oxidative damages but are crucial components of plant development and growth. Estimation of their species-specific functions revealed their important signaling function due to locally fine-tuning the ROS level and redox homeostasis or modifying activity of interacting regulatory proteins. Arabidopsis thaliana possesses eight isoenzymes located in different plant's organelles and having various roles in redox-dependent processes. To reveal their physiological function we investigated the growth, levels of reactive oxygen species, activity of antioxidant mechanisms, expression of AtGPXL genes and some transcription factors in Atgpxl1-8 insertion mutants under abiotic stresses. Our results confirmed that AtGPXLs are involved in the maintenance of the ROS homeostasis.Mutation in one of their coding genes can affect the ROS levels, vitality, and glutathione redox potentials both in seedlings and adult plants. While AtGPXLs were generally down-regulated in mutants, several stress-inducible transcription factor genes were up-regulated, especially after applying osmotic stress. More detailed characterization was performed on Atgpxl2, -3,-4 and -5 mutants and AtGPXL5-overexpressing plants. In short, we have shown that these non-heme ROS-scavengers are involved in different signaling network and connect redox processes to development of plants.

Biography:

J. Csiszár, Associate Professor at the Department of Plant Biology, University of Szeged (Hungary).
Her main research interest is the effect of abiotic stresses on physiological and molecular processes of different plant species. She is the leader of the Plant Molecular Biology group. They focus on the relation between the antioxidant mechanisms, redox status, and growth.Especially the glutathione and glutathione-related enzymes, like glutathione peroxidases (GPXLs) and glutathione transferases (GSTs) are estimated. One of their research programs targets the adaptation of a recently developed redox-sensitive GFP (roGFP2) fluorescent probe to monitor the redox state in living plants or tissues. Currently, they investigate the role and regulation of specific GPXL and GST enzymes in Arabidopsis and tomato roots.

The response to DNA damage induced by the keto-enol insecticide Movento® 240SC in Drosophila melanogastergermarium depends on the ATM-Chk2 signaling pathway.

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Abstract

Movento®240SCis a new systemic insecticide thatbelongsto the keto-enol pesticides derived from tetronic and tetramic acids. However,the DNA damage response (DDR) pathways in keto-enol genotoxicity have not been characterized, and few studies have reported genotoxic effects in non-target organisms. Cellular responses to DNA damage are mainly coordinated by two kinase signaling cascades: ATM-Chk2, which isactivated by DNA double-strand breaks (DSBs),and ATR-Chk1, activated by single-stranded DNA (SSD).These pathways regulate cell cycle arrest, DNA repair, and apoptosis. Most DDR genes studied in mammals are found in Drosophila melanogaster, and the major pathways appear highly conserved. The Drosophila ATM homolog (tefu), ATR (mei-41), Chk2 (lok), and Chk1 (grp) areessential for DDR and cell cycle checkpoint signaling. The present study characterized the DDR response after Movento® 240SC exposure. Drosophilamutant females with specific loss of function of the DDR genes ATMtefu, ATRmei-41, Chk1grp/Chk2lok,and Chkgrp, and wildtype Oregon-R flieswere exposed to sublethal concentrations (0.0, 11.2, 22.4, 37.3 mg/L) of Movento®240SC in food. After exposure, we quantified by immunofluorescence confocal microscopy the expression of γH2AX (an early chromatin modification after DNA damage) in the germarium ofDrosophila DDR mutants and wildtype Oregon-R flies. The expression of γH2AX in the germarium of the DDR mutants (ATMtefu, Chk1grp/Chk2lok) exposed to Movento®240SC(11.2, 22.4, 37.3 mg/L) was significantly higher than inthe wildtype strain. However, DDR mutant strains (ATRmei-41and Chkgrp) showed no significant increases in DNA damage compared to the wildtypestrain. Our study is the first to elucidate that the loss of function of ATM-Chk2 kinases significantly increases DNA damage induced by the keto-enol insecticide Movento®240SC. Our study reveals that Movento®240SC induces DNA damage (DSBs)in Drosophila germarium cells and that DDR depends on the activation of the ATM-Chk2 kinases signaling pathway.

Biography:

Berenyce González Marín, Doctoral student.

PhD student in the Environmental Toxicology laboratory at the Institute of Atmospheric Sciences and Climate Change of the National Autonomous University of Mexico, Mexico. Her professional experience focuses on using mutant and transgenic strains of Drosophila melanogasterto identify molecular mechanisms, genes, and proteins involved in the response to damage induced by environmental pollutantexposure. She is the director of Droso@LatAm, an international network for collaborative scientific dissemination between Latin American countries and the University of Manchester in the U.K. She is also one of the youngest tutors and teachers at UNAM; she has directed undergraduate theses and currently teaches Developmental Biology to undergraduate Biology students.

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Targeting the ATR/CHK1 pathway re-sensitizes olaparib-resistant BRCA2MUT ovarian cancer cells via induction of caspase-mediated apoptosis

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Abstract

Olaparib is a first-in-class poly(ADP-ribose) polymerase inhibitor commonly used to treat a multitude of tumors including ovarian cancer. Despite the clinically meaningful benefits of olaparib for the treatment of ovarian cancer, the emergence of resistancepresents a major obstacle in achieving long-term efficacy in some patients.Here we investigated the synergistic antitumor activity of olaparib combined with inhibitors of ATR (ceralasertib) and CHK1 (MK-8776) kinases in established BRCA2MUThigh-grade serous ovarian cancer cell line with resistance to olaparib. Next-generation sequencing revealed that ovarian cancer cells with BRCA2truncating mutation (c.4965C>G, Y1655*) acquire resistance to olaparib during selection in the presence of increasing doses of the drug, partially due to restoration of full-length BRCA2 via secondary reversion mutation. Furthermore, we showed that inhibitors of the ATR/CHK1 pathway re-sensitize resistant ovarian cancer cells to olaparib resulting in inhibited proliferation, ability to form colonies, and cellular metabolic activity.The addition of inhibitors of ATR or CHK1 kinases promotes apoptosis synergistically activated by caspase-3 and -7. Our study highlights that combination treatment offers the potential to combat acquired resistance to olaparib in BRCA2MUT ovarian cancer cells.This research was funded by the Polish National Science Centre (Project grant number: Sonata Bis 2019/34/E/NZ7/00056).

Biography:

Łukasz Biegała, Ph.D. Student.

Łukasz Biegała is a Ph.D. Student in the Department of Medical Biophysics at the University of Lodz, Poland. He earned his Master of Science degree in Molecular Biotechnology and Industrial Biochemistry at Lodz University of Technology in 2019. His research interests includethe molecular biology of cancer and new targets for diseasetreatment. He has investigatednew potential insulin secretion modulators in pancreatic cells. He has also developed his skills in the R&D department of a pharmaceutical company, where he participated in the development of therapeutic biosimilar monoclonal antibodies for thetreatment of autoimmune diseases and types of cancer.His current work focuses on identifying and understanding key pathways involved in acquired resistance to a small-molecule inhibitor olaparib in ovarian cancer. Moreover, he elucidates the rationale for the combination treatment employing inhibitors of the ATR/CHK1 pathway to re-sensitize ovarian cancer cells to olaparib.

Flexibility of Telomerase in Binding the RNA template and DNA telomeric repeat

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Abstract

Telomeres at the ends of chromosomes protect these DNA ends from degradation, fusion and shortening. Telomeres are composed of hundreds of G-rich telomeric repeating units. The telomeric unit is synthesized by telomerase, which consists of a specialized reverse transcriptase, TERT, and telomerase RNA (TER) subunit containing a short template region (10-20 nt). TERTcan repeatedly and processively reuses the short RNA template to synthesize many telomericrepeats through repeated translocations of the template after each unit synthesis, which is called Repeat Addition Processivity (RAP). However, the RAP mechanism isunclear. In 2015, a DNA hairpin model proposed that RNA template is translocated together with a transient looped-out telomeric DNA primer, which depends on the TERT specific cavity adjacent to the active site. In this study, I tested this model using biochemical and structural approaches. I showed that only TERT, not other reverse transcriptase (RT), can bind a DNA looped-out bulge 2 bp upstream from the DNA 3' end. To support the cavity and primer loop-out hypothesis, I showed that reducing the cavity size by amino-acid mutations decreases the catalytic rate of the looped-out DNA primer, but not a normal fully base-paired primer. I also discovered a new function of TBE (Template Boundary Element). TBE is a downstream RNA duplex defining 5' boundary of the template. I determined a ternary complex of TERT-RNA/DNA-incoming nucleotide at 2 Å resolution, and the structure reveals that the downstream RNA/DNAhybrid (equivalent to TBE) interacts with TERT to stably template/primer in the catalytic site, thus enhancing the TERT catalytic activity.We suggest that TBE plays threeroles: marking the template 5' boundary, facilitating the template transfer by stabilizing the looped-out primer/template pair, and enhancing catalytic rate of TERT. Based on these results, I have revised the DNA hairpin model.

Biography:

Woo SukChoi (First name: Woo Suk, Last name: Choi), Research Fellow in NIDDK/NIH.
I graduated from Korea University with a B.S. in Life Sciences and a M.S in Biochemistry, and I earned my Ph.D. in Biochemistry and Structural Biology at the Stony Brook University in 2016. I have worked as a postdoctoral fellow in NIDDK / NIH since 2017. My research areas are biochemistry/molecular biology and structural biology using X-ray crystallography and Cryo-EM. I studied protein degradation mechanism (N-end rule pathway) during M.S. and mitochondrial transcription initiation mechanism during Ph.D. Since the postdoctoral research, I have studied various DNA repair/maintenance mechanisms such as telomere biogenesis and translesion synthesis.

Taguchi and cancerous tumor, how? Why?

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Abstract

Cancer biology involves complex dynamics and interactions between cells and the tissue environment. Mathematical modeling and computer simulation can provide a powerful instrument for considering this complexity. Agent-based modeling is a particular discrete hybrid modeling method. Because of their ability to model heterogeneity of cancerous tumors, this modeling has particular importance. For proposing this kind of model need important features that influence on the agents. there are more features that effect on tumor growth. Therefore, the existence of a method that helps in choosing the most effective features will be valuable.for the first time we used Taguchi method to get the most effective features of the six important features that influence on cancer stem cells growth. we used the Taguchi results for proposed an agent-based model of cancer stem cells growth process.first explain a brief history of Taguchi method and its applications and then answer this main question: why the Taguchi method can be a suitable features selection method in cancer computational model?

Biography:

Mina Lagzian, Ph.D. Candidate in Electrical engineering branch of control Department of Electrical Engineering of Islamic Azad University, Mashhad branch. she graduated with a master's degree in Applied mathematics from the Ferdowsi University of Mashhad. During this level, she researched mathematical applications in medicine and did a project on the mathematical applications in blood sugar control. An article from this research has also been published. After graduating, continue my education in the Electrical Engineering branch of power. First, she research the field of the brain and then the mathematical modeling of disease and continued my research on the application of mathematics and engineering in medicine and the treatment and control of the disease. she published three articles in this field. Now a days focus on mathematical modeling of cancer disease and proposed models that can predict cancer growth and control it. she hopes that her research can help to control and treatment of cancer disease.

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Selective GSK3β inhibition mediates an Nrf2-independent anti- inflammatory microglial response

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Abstract

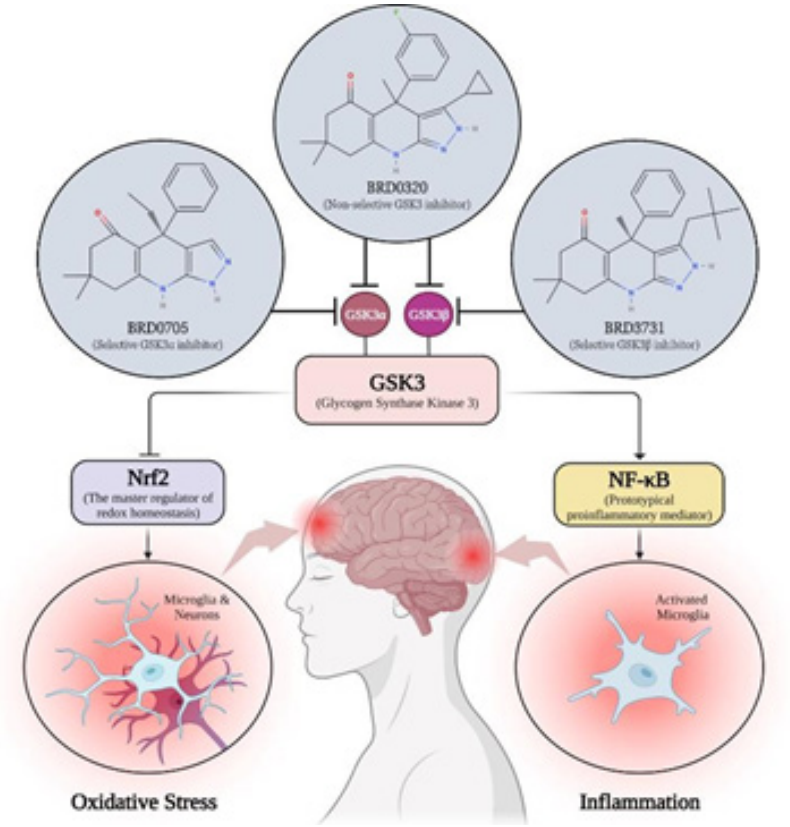
Glycogen Synthase Kinase 3 (GSK3) is associated with the proinflammatory phenotype of microglia and has been shown to act in concert with nuclear factor kappa B (NF-κB). GSK3 is also a suppressor of nuclear factor erythroid 2-related factor 2 (Nrf2), the principal regulator of redox homeostasis. Agreeing with the oxidative paradigm of aging, Nrf2 is often deregulated in parainflammatory and neurodegenerative diseases. In this study, we aimed to explore a multimodal disease-modifying utility of GSK3 inhibition, beyond neuronal proteopathologies, Furthermore, we aimed to underscore the difference in therapeutic value between the two GSK3 paralogs by isoform-selective chemical inhibition.

The anti-inflammatory effects of paralog-selective GSK3 inhibitors were evaluated as a function of the reductive capacity of each to mitigate LPS-induced activation of SIM-A9 microglia. The Griess method was employed to detect the nitrate-lowering capacity of selective GSK3 inhibition. Real-time PCR was used to assess post-treatment expression levels of pro-inflammatory markers and antioxidant genes; pro- inflammatory cytokines were assayed by ELISA. Nuclear lysates of treated cells were examined for Nrf2 and NF-κB accumulation by immunoblotting. Finally, to infer whether the counter-inflammatory activity of GSK3 inhibition was Nrf2-dependent, DsiRNA-mediated knockdown of Nrf2 was attempted.

Results from our experiments reveal a superior anti-inflammatory and anti-oxidative efficacy for GSK3β-selective inhibition, compared to GSK3α-selective and non-selective pan-inhibition; hence use of selective GSK3β inhibitors is likely to be more propitious than non-selective dual inhibitors administered at comparable doses. Moreover, our results suggest that the anti-inflammatory effects of GSK3 inhibition is not Nrf2 dependent.

Keywords:

GSK3; paralog selectivity; microglia; neuroinflammation; neurodegenerative diseases; oxidative stress; Nrf2; NF-κB



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Clinical characteristics and oncological outcomes of recurrent adult granulosa cell tumor of ovary: a retrospective study of seventy patients

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Abstract

Objective

To describe the clinicopathological characteristics of recurrent adult granulosa cell tumor (AGCT) and identify the risk factors of recurrence.

Methods

Seventy recurrent AGCT patients treated in Peking Union Medical College Hospital between 2000-2020 were retrospectively reviewed. The primary outcomes were overall survival (OS) and recurrence times, and the secondary outcomes was disease status at last follow-up. The Kaplan-Meier (KM) analysis, univariate and multivariate Cox proportional hazard analysis, and the Prentice, Williams and Peterson counting process (PWP-CP) model were adopted.

Results

The median PFS1(PFS at fist recurrence) was 63.5 months (range 5-375), and the median OS was 164 months (range 39-424). PFS1≤60 months was the independent risk factor of OS(HR 14.240, 95% confidence interval[CI] 1.661~122.051, P=0.015). It demonstrated that PFS1≤60 months(HR 4.607, 95%CI 2.359~9.1000, P<0.001) and PFS2≤33.5 months (HR 2.296, 95%CI 1.248~4.255, P=0.008) were independent risk factors of repeated recurrence, and that transabdominal operation(at initial treatment, HR 0.311, 95%CI 0.159~0.608, P=0.001) and single lesion recurrence (at first relapse, HR 0.376, 95%CI 0.143~0.987, P=0.047) were independent protective factors of repeated recurrence. PWP-CP analysis showed that laparoscopic operation (at each operation) could significantly increase recurrence times (P=0.002, HR=3.441), and R0 operation could significantly decrease recurrence times (P<0.001, HR<0.001). And PFS1≤60 months(HR 3.282, P=0.002) and PFS2≤33.5 months (HR 2.651, P=0.004) were independent risk factors of CR, and that transabdominal operation(at initial treatment, HR 0.406, 95%CI 0.192~0.860, P=0.019) and single lesion recurrence (at first relapse, HR 0.406, P=0.023) were independent protective factors of CR.

Conclusion

PFS1≤60 months was the independent risk factor of OS, multiple recurrence, and CR at last follow up. PFS2>33.5 months, transabdominal operation and single lesion recurrence were independent protective factors of multiple recurrence and CR. And Transabdominal operation and R0 operation could significantly decrease recurrence times.

Biography

Yu Gu, a postgraduate of Department of Obstetrics and Gynecology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College.The major research interest is immunotherapy of gynecological oncology.Her research has been published in Modern Pathology, Frontiers in Oncology, and serving as a reviewer of Frontiers in Pharmacology, Frontiers in Oncology, Clinical Inhabitation.

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Cell Therapies: A Promising Approach to Tackle Severe SARS-CoV-2 in those with Malignancy

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Abstract

According to the World Health Organization, there is a 17.9% increased risk for cancer patients to develop severe SARS-CoV-2 due to their immunocompromised status. Despite active malignancy portending a poorer prognosis, those in remission had an increased risk of severe COVID-19 compared to non-cancer patients. Given the limited pathogenic information between severe SARS-CoV-2 and cancer, we (1) developed a model to explain the interplay between the two conditions (2) highlight the efficacy of promising cell therapies based on clinical trial evidence.

Severe SARS-CoV-2 causes multi-organ injury and dysfunction through IL-6-mediated inflammation and hypoxic-induced metabolic changes leading to increased IL-6 production and apoptosis. Malignancy induces cell death through hypoxia-induced cellular metabolic alterations resulting in an upregulation of IL-6 release, which is responsible for propagating inflammation and tumorigenesis. In this model, infection with severe SARS-CoV-2 and malignancy results in increased IL-6 production leading to enhanced systemic injury as compared to either alone.

Currently, there are limited effective therapeutic interventions against severe SARS-CoV-2. Due to its complex nature, we propose the use of combination therapies that can control the systemic inflammation induced by this condition, while halting viral replication. One approach is the use of mesenchymal stem cells (MSCs), which have demonstrated over a 90% overall survival and 100% survival in patients younger than age 85 within a month after treatment with efficacy lasting over 6 months. MSCs possesses regenerative, antiviral, and immunomodulatory properties that can inhibit viral replication, while dampening the cytokine response with resulting systemic inflammation and injury Thus, cancer patients can quickly contain SARS-CoV-2 with limited interruptions to their treatment schedule.

In conclusion, MSCs have demonstrated clinical efficacy, safety, and tolerability in patients with severe SARS-CoV-2 given their ability to target disease pathogenesis at multiple steps within the pathway. Given their limited drug interactions and side-effects, MSCs are a viable approach to contain SARS-CoV-2 with limited interruptions to their treatment regimens.

Biography:

Yan Leyfman, MD.

Dr. Yan Leyfman has been recognized as one of the top international researchers in oncology by the American Society of Hematology and American Society of Clinical Oncology (ASCO). He has contributed to the development of several anti-cancer therapies that have recently entered clinical trials and new treatment recommendations of care. During the COVID-19 pandemic, he was recruited as the Director of the Immunology Division of the Global COVID-19 Taskforce, which produced one of the first mechanisms for SARS-CoV-2 and COVI-Flu.His successes have been recognized by the Goldwater Research Foundation, NY Times, and Harvard Medical School. Most recently, he has been recognized as a 2021 & 2022 Hero in Healthcare for research contributions to cancer & COVID-19 at the Lymphoma, Leukemia & Myeloma Congress and amongst the top 6 early career scientists for 2022 in recognition of his contributions to cell and immunotherapy with a 2023 PhacilitateAdvanced Therapies Young Scientist Award.

Molecular and biochemical mechanism of cannabidiol in the management of endometriosis

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Abstract

Endometriosis is usually associated with inflammation and chronic pelvic pain. This paper focuses the attention on the anti-inflammatory, anti-oxidant and analgesic effects of cannabidiol (CBD) and on its potential role in endometriosis. We employed an in vivo model of endometriosis and administered CBD daily by gavage. CBD administration strongly reduced lesions diameter, volume and area. In particular, it was able to modify lesion morphology, reducing epithelial glands and stroma. CBD showed anti-oxidant effects reducing lipid peroxidation, the expression of Nox-1 and Nox-4 enzymes. CBD restored the oxidative equilibrium of the endogenous cellular defense as showed by the SOD activity and the GSH levels in the lesions. CBD also showed important antifibrotic effects as showed by the Masson trichrome staining and by downregulated expression of MMP-9, iNOS and TGF-beta. CBD was able to reduce inflammation both in the har-vested lesions, as showed by the increased Ikb-alpha and reduced COX2 cytosolic expressions and reduced NFkB nuclear localization, and in the peritoneal fluids as showed by the decreased TNF-alpha, PGE2 and IL-1beta levels. CBD has important analgesic effects as showed by the reduced mast cells recruitment in the spinal cord and the reduced release of neuro-sensitizing and pro-inflammatory mediators. In conclusion, the collected data showed that CBD has an effective and coordinated effects in endometriosis suppression.

Biography:

Dr. Ramona D'Amico has completed the bachelor's degree in biological sciences and a master's degree in biology at the University of Messina in 2016. Dr. Ramona D'Amico has completed her PhD in Applied Biology and Experimental Medicine in the year 2020 by University of Messina. Additionally, she worked at Health Science Research Centre, Whiteland College, University of Roehampton in London (UK) and performed postdoctoral studies at University of Messina. She worked as researcher for studies on preclinical pharmacology activities (in vitro primary cultures and in vivo experimental models), for the Epitech Group; she is also a research fellow in Biochemistry at Messina University. Now she is a Researcher at the University of Messina. She has published more than 70 articles in reputed journals about biochemistry, oxidative stress and pharmacology. Her research is involved in preclinical studies for the discovery of new biochemical markers. Dr. Ramona D'Amico have knowledge about animals research, biochemical and molecular biology, immunohistochemical and immunofluorescence analysis.

Discovering the effects of fisetin on NF-κB/NLRP-3/Nrf-2 molecular pathways in a mouse model of vascular dementia

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Abstract

Vascular dementia (VaD) is the second cause of dementia, after Alzheimer's disease. The majority of people affected by VaD have cognitive deficits, partly owing to the cerebral hypoperfusion-induced ischemia, endothelial dysfunction, oxidative stress, and neuroinflammation. Natural products are drawing the increasing attention for the treatment of neuroinflammatory diseases. The aim of study was to investigate the molecular pathways underlying the protective effects of fisetin, a flavonoid present in many fruits and vegetables, in a mouse model of VaD induced by repeated ischemia-reperfusion (IR) of the total bilateral carotid artery. Here, we found that VaD caused brain injury, lipid peroxidation and neuronal death in the hippocampus as well as astrocyte and microglial activation, reduced BDNF neurotrophic factor expression together with behavioral alterations. In addition, VaD induced activation of inflammasome components (NLRP-3, ASC and caspase 1) and their downstream products (IL-1β and IL-18) release and promotes activation of apoptotic cell death. Fisetin attenuated histological injury, malondialdehyde levels, inflammasome pathway activation, apoptosis, as well as increased BDNF expression, reduced astrocyte, microglial activation and cognitive deficits. In conclusion, the protective effects of fisetin could be due to the inhibition of ROS-induced activation of NF-κB/NLRP3 inflammasome together with the activation of antioxidant Nrf2/HO-1 suggesting a possible crosstalk between these molecular pathways.

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Physiological and Biochemical Changes in NRF2 Pathway in Aged Animals Subjected to Brain Injury

Marika Cordaro

Department of Biomedical Dental and Morphological and Functional Imaging.

University of Messina.

Abstract

Background/aims:
Oxidative stress plays a key role in aging, which in turn represents a substantial risk factor for brain injuries. The aim of the present study was to investigate the differences in physiological and biochemical changes in the brain during injury-related inflammation and oxidative stress, comparing young and old mice.

Methods:
Young and old mice were subjected to focal cerebral ischemia induced by transient middle cerebral artery occlusion or to traumatic brain injury performed by a controlled cortical impactor. At the end of both experiments, mice were sacrificed 24h after injuries and brains were collected to perform biochemical analysis.

Results:
In both ischemic stroke and traumatic brain injury, aging has not only led to damage-induced worsening of motor function and behavioural changes but also increased of infarct area compared to young animals. Moreover, aged mice show increased evidence of oxidative stress and reduced antioxidant capacity when compared to younger animals, as demonstrated by Nrf2-Keap1 signalling pathway and lower expression of antioxidant enzymes, such as HO-1, SOD-1 and GSH-Px. Additionally, brain tissues collected from elderly mice showed an increased IκB-α degradation into the cytoplasm and consequently NF-κB translocation into the nucleus, compared to young mice subjected to same injuries. The elderly mice showed significantly higher levels of iNOS and CoX-2 expression than the young mice, as well as higher levels of inflammatory cytokines such as TNFα, IL-1β, and IL-6 after MCAO and TBI.

Conclusion:
Preserving and keeping the NRF-2 pathway active counteracts the onset of oxidative stress and consequent inflammation after ischemic and traumatic brain insult, particularly in the elderly. Not only that, NRF-2 pathway could represent a possible therapeutic target in the management of brain injuries.

Keywords:
Nrf2; Oxidative stress; Aging; Inflammation; Brain injuries.

Biography:

Dr Marika Cordaro graduated in Biology at the University of Messina in 2015. She has completed his PhD in- "Applied Biology and Experimental Medicine" at the Department of Biological and Enviromental Sciences at University of Messina, Italyin the year 2017. She is a young researcher in physiology, with particular interest in cell physiology and molecular mechanism underlyng inflammation. In particular, Dr Cordaro, during her research activity, produced about 134 articles that attest a diffuse interest in the field of inflammation and oxidative stress neurological disorder-related. She also interest endocrine disruptors and in its role in neurological deficits.Her research is involved in preclinical studies for the discovery of physiological cellular response that could be used as new potential therapeutic targets. Dr. Cordaro have knowledge about animals research, behavioral alterations, biochemical and molecular biology and immunohistochemical analysis. Additionally, she has been serving as an editorial board member of several cited journal.

The Effects of Dictyostelium PP2A/B56 and Superoxide Dismutase C (SodC) on the Ingestion and the Killing of Live Bacteria Klebsiella aerogenes.

Victor Osorio-Castillo and Lou W. Kim

Florida International University, USA

Email: *vosor008@fiu.edu,*

Abstract

Nowadays, multidrug-resistant bacteria are a critical risk to public health. An effective innate immune response for the elimination of pathogens is phagocytosis. Dictyostelium discoideum is an excellent model organism to study this response. In Dictyostelium, the receptor fAR1 mediates the chemotaxis, phagocytosis of bacteria, and the activation of PKB and ErkB proteins. These proteins are regulated by the phosphatase 2A (PP2A) subunit B56. Our laboratory has investigated two pathways that affect PKB: SodC/Ras/PI3K/PKB and PP2A/B56/PKB. The present study aims to determine the effect of SodC/Ras/PI3K/PKB, and PP2A/B56/PKBpathways and PKB and ErkB proteins in the bacterial ingestion and inactivation of live bacteria Klebsiella aerogenes. In this study JH10 (wild type), sodC-, Ax3 (wild type), and psrA- (knockout B56) cells were used. Phagocytosis assays and killings assays were performed in the presence or absence of LY294002 using 2 x 106 Dictyostelium cells and 2 x 104 Bacteria. Further western blots in the presence or absence of the PI3K inhibitor LY294002 were performed for cell lines Ax3 and psrA- using Anti-MAPK and Anti-pPKB antibodies. psrA-significantly increased its engulfment and bactericidal activity compared with WT cells(AX3) ($P<0.01$). After the LY294002 treatment, psrA- cells significantly decrease their bactericidal activity ($P<0.05$). The level of phospho-PKBA in psrA-after an LY294002 treatment was statistically significant ($P<0.009$). The phospho-Erk2 activity after LY294002 treatment psrA- and Ax3 cells showed an insignificant increase ($P>0.36$ and $P>0.1$).

In conclusion, PP2A/B56 is essential for properly regulating the uptake and elimination of Klebsiella aerogenes.

Biography:

Victor David Osorio Castillo is a senior student of Biochemistry Ph.D. at Florida International University. He is working at Dr. Lou Kim's lab. Victor Osorio-Castillo completed his college degree in biological sciences at the "Universidad autónoma de Yucatán" in 2017. He is a Maya native American student interested in public health and protein interactions.

Chronic Exposure to Vinclozolin Induced Fibrosis Mitochondrial Dysfunction, Oxidative Stress and Apoptosis in Mice Kidney

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University of Messina.

Abstract

Vinclozolin is one of the most used fungicides in the control of fungi in fruits, vegetables, and ornamental plants. The effects of its exposure on different organs have been described, but information regarding its relevance to vinclozolin-induced nephrotoxicity is largely missing. This study focuses on the potential mechanism of vinclozolin-induced nephrotoxicity. CD1 male mice were administered vinclozolin (100 mg/kg) by oral gavage for 28 days. Vinclozolin administration decreased body weight over the treatment period and at the end of the experiment, increased the ratio of kidney weight to body weight and increased serum urea nitrogen and creatinine contents. Vinclozolin also induced histopathological alterations, including tubular dilatation and necrosis and impaired the integrity of the renal-tubular architecture and kidney fibrosis. The analyses conducted showed that vinclozolin administration altered the mRNA levels of mitochondrial function-related proteins (SIRT3, SIRT1, PGC-1α, TFAM, NRF1, VDAC-1, and Cyt c) and oxidative stress (increased lipid peroxidation and decreased total antioxidative capacity, catalase, and superoxide dismutase activities, glutathione levels, and glutathione peroxidase activity) in the kidneys. Furthermore, vinclozolin induced toxicity that altered Nrf2 signalling and the related proteins (HO-1 and NQO-1). Vinclozolin administration also affected both the extrinsic and intrinsic apoptotic pathways, upregulating the expression of proapoptotic factors (Bax, Caspase 3, and FasL) and downregulating antiapoptotic factor (Bcl-2) levels. This study suggests that vinclozolin induced nephrotoxicity by disrupting the transcription of mitochondrial function-related factors, the Nrf2 signalling pathway, and the extrinsic and intrinsic apoptotic pathways.

Keywords:

persistent organic pollutants, vinclozolin, kidney impairments, mitochondrial disfunction, apoptosis

Biography:

Dr. Roberta Fusco has completed her PhD in Applied Biology and Experimental Medicine by University of Messina and Yale University School of Medicine and postdoctoral studies from University of Messina. She worked as researcher for studies on preclinical pharmacology activities (in vitro primary cultures and in vivo experimental models) for the Epitech Group, biological pharmacology company. Now she is an Assistant Professor at the University of Messina. She has published more than 90 articles (H index 36) in reputed journals about biochemistry, oxidative stress and pharmacology.

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Actaea Racemosa L. Rhizome Protect Against MPTP-induced Neurotoxicity in Mice by Modulating Oxidative Stress and Neuroinflammation.

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Abstract
Parkinson's disease (PD) is a dopaminergic neuron-related neurodegenerative illness. Treatments exist that alleviate symptoms but have a variety of negative effects. Recent research has revealed that oxidative stress, along with neuroinflammation, is a major factor in the course of this disease. Therefore, the aim of our study was to observe for the first time the effects of a natural compound such as Actaea racemosa L. rhizome in an in vivo model of PD induced by neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). For the study, mice received four injections of MPTP (20 mg/kg) for the induction of PD. Starting 24 h after the first administration of MPTP we treated mice with Actaea racemosa L. rhizome (100 mg/kg) daily for seven days. Our findings clearly demonstrated that Actaea racemosa L. rhizome treatment decreases oxidative stress by activating redox balance enzymes such as Nrf2/HO-1. We also demonstrated that Actaea racemosa L. rhizome is capable of modulating inflammatory indicators involved in PD, such as IκB-α, NF-κB, GFAP and Iba1, thus reducing the degeneration of dopaminergic neurons and motor and non-motor alterations. To summarize, Actaea racemosa L. rhizome, which is subject to fewer regulations than traditional medications, could be used as a dietary supplement to improve patients' brain health and could be a promising nutraceutical choice to slow the course and symptoms of PD.

Keywords:
dietary supplement; neurodegeneration; neuroinflammation; redox balance

Biography:
Rosalba Siracusa is a "Senior" researcher in Clinical Biochemistry and Clinical Molecular Biology; Department of Chemical, Biological, Pharmaceutical and Environmental Sciences, University of Messina. Rosalba Siracusa is PhD in Applied Biology and Experimental Medicine at the University of Messina. She has a Specialization in Clinical Pathology and Clinical Biochemistry. He graduated in Biology at the University of Messina in 2013. She works at the University of Messina from 2014. Dr. Siracusa has collaborated with more national and international experts. She has completed her "Visiting Scientist" at Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA, USA. She has published more than 100 articles in reputed journals on the biochemical evaluation of food science and nutrition.

The Effects of Dictyostelium PP2A/B56 and Superoxide Dismutase C (SodC) on the Ingestion and the Killing of Live Bacteria Klebsiella aerogenes.

Victor Osorio-Castillo and Lou W. Kim

Florida International University, USA

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Abstract

Nowadays, multidrug-resistant bacteria are a critical risk to public health. An effective innate immune response for the elimination of pathogens is phagocytosis. Dictyostelium discoideum is an excellent model organism to study this response. In Dictyostelium, the receptor fAR1 mediates the chemotaxis, phagocytosis of bacteria, and the activation of PKB and ErkB proteins. These proteins are regulated by the phosphatase 2A (PP2A) subunit B56. Our laboratory has investigated two pathways that affect PKB: SodC/Ras/PI3K/PKB and PP2A/B56/PKB. The present study aims to determine the effect of SodC/Ras/PI3K/PKB, and PP2A/B56/PKBpathways and PKB and ErkB proteins in the bacterial ingestion and inactivation of live bacteria Klebsiella aerogenes. In this study JH10 (wild type), sodC-, Ax3 (wild type), and psrA- (knockout B56) cells were used. Phagocytosis assays and killings assays were performed in the presence or absence of LY294002 using 2 x 106 Dictyostelium cells and 2 x 104 Bacteria. Further western blots in the presence or absence of the PI3K inhibitor LY294002 were performed for cell lines Ax3 and psrA- using Anti-MAPK and Anti-pPKB antibodies. psrA-significantly increased its engulfment and bactericidal activity compared with WT cells(AX3) ($P<0.01$). After the LY294002 treatment, psrA- cells significantly decrease their bactericidal activity ($P<0.05$). The level of phospho-PKBA in psrA-after an LY294002 treatment was statistically significant ($P<0.009$). The phospho-Erk2 activity after LY294002 treatment psrA- and Ax3 cells showed an insignificant increase ($P>0.36$ and $P>0.1$).

In conclusion, PP2A/B56 is essential for properly regulating the uptake and elimination of Klebsiella aerogenes.

Biography:

Victor David Osorio Castillo is a senior student of Biochemistry Ph.D. at Florida International University. He is working at Dr. Lou Kim's lab. Victor Osorio-Castillo completed his college degree in biological sciences at the "Universidad autónoma de Yucatán" in 2017. He is a Maya native American student interested in public health and protein interactions.

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p66Shc Enhances Reactive Oxygen Species (ROS) Production in Mediating Advanced Cancer Progression and Metastasis

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Abstract
Oxidant species including Reactive oxygen species (ROS) play a vital role in mediating diverse cellular signaling. Upon growth factor treatments, oxidant species are elevated and cell growth is stimulated; aberrant elevation of oxidant species can oxidize vital molecules and enhance the initiation and progression or apoptosis of cancer cells. While there are numerous reports on ROS in cancer progression, the specific oxidase/pro-oxidant protein and its mechanism of clinical relevance in cancer progression remain enigma.
We made a seminal observation on p66Shc, a pro-ROS protein, that plays a role in cancer progression. p66Shc is a member of Src homologue and collagen (Shc) homologue family and involved in regulating mammal longevity as well as oxidative stress. It can enhance ROS production by interacting with Cytochrome C in mitochondria and via Rac 1 with NAD(P)H oxidases (NOXs) in cytosol. We discovered p66Shc protein enhances ROS production which mediates steroid action on cell growth and supports the progression of advanced cancer progression. In prostate cancer (PCa) archival specimens, p66Shc protein is significantly higher in cancerous cells than in adjacent non-cancerous cells. In cell lines, p66Shc protein level correlates with cell growth. Transfection of the wild type p66Shc cDNA, but not its redox-inactive mutant, via oxidant species production increases the tumorigenicity of androgen-sensitive PCa cells and those cells obtain the castration-resistant phenotype, a lethal disease. Conversely, knockdown p66Shc reverses androgen sensitivity and suppresses tumorigenicity. In summary, p66Shc protein levels are elevated in many cancer cells, e.g., prostate, colon, breast and ovarian, and regulates their tumorigenicity. Hence, p66Shc and its downstream signaling molecules can serve as therapeutic targets for treating this patient sub-population.

Keywords:
p66Shc, Reactive Oxygen Species (ROS), Steroid Hormones, Signal Transduction, Cancer Progression, Cancer Metastasis

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The role of SATB1 in non-small cell lung cancers and its association with EGFR expression

Natalia Glatzel-Plucinska

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Abstract

Lung cancer is one of the most frequently diagnosed neoplasms and the leading cause of cancer-related mortality worldwide. Its predominant subtype is non-small cell lung cancer (NSCLC), which accounts for over 80% of the cases. Surprisingly, the majority of lung cancer-related deaths are caused not by a primary tumour itself, but by its metastasis to distant organs. Therefore, it becomes especially important to identify the factors involved in lung cancer metastatic spread. Special AT-rich binding protein 1 (SATB1) is a nuclear matrix protein that mediates chromatin looping and plays the role of global transcriptional regulator. During the past decade, it has received much attention as a factor promoting tumour invasion. In breast, colorectal and prostate cancers, SATB1 has been shown to influence the epithelial-mesenchymal transition (EMT) process, which is thought to be crucial for cancer metastasis. The aim of this study was to analyse the possible correlations between the expression of SATB1 and major EMT-associated proteins in NSCLC clinical samples. Additionally, the impact of EMT induction in NSCLC cell lines on SATB1 mRNA expression was also investigated. Immunohistochemistry was used to assess the expression of SATB1, SNAIL, SLUG, Twist1, E-cadherin, and N-cadherin in 242 lung cancer clinical samples. EMT was induced by TGF-β1 treatment in the A549 and NCI-H1703 lung cancer cell lines. Changes in gene expression profiles were analyzed using real-time PCR and Droplet Digital PCR. SATB1 expression was positively correlated with the expression of SNAIL ($R=0.129$; $P=0.045$), SLUG ($R=0.449$; $P<0.0001$), and Twist1 ($R=0.264$; $P<0.0001$). Moreover, SATB1 expression significantly increased after in vitro EMT induction in A549 and NCI-H1703 cell lines. The results obtained may point to the role of SATB1 as one of the regulators of EMT in NSCLC.

Keywords:

SATB1, special AT-rich binding protein 1, NSCLC, adenocarcinoma, LSCC, EMT, non-small cell lung carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, epithelial-mesenchymal transition, metastasis

Biography:

Dr Natalia Glatzel-Plucinska has a master's degree in molecular biology and a PhD in medical sciences. She works as a reseracher at the Wroclaw Medical University. She has experience in molecular biology, cell culture, flow cytometry, and digital image analysis. In her research, she focuses mainly on the molecular basis of cancer progression and metastasis. Her recent studies concern the role of SATB1 and Haspin expression in non-small cell lung cancers. Additionally, she is involved in research on breast's cancer adoptive immunotherapy. She is a co-author of 22 papers and participates in numerous research projects.

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Molecular biomarkers and Lymph node metastatic spread: experience of HASSAN II university hospital of FES.

Fatima El agy[1,2*], Sanae el Bardai[2], Laila Bouguennouch[3], Nada Lahmidani[4], Mohammed El Abkari[4], El Bachir Benjelloun[5], Abdelmalek Ousadden[5], Khalid Maazaz[5], Imane Toughrai[5], SidiAdil Ibrahimi[5], Zineb Benbrahim[6], Laila Chbani[1,2].

Abstract

Lymph node metastasis is an important prognostic and predictive factor for colon cancer.Although the molecular mechanisms inducing Lymph nodes metastasis spread are currently unknown.We aim in this study to highlight the effect of KRAS, and NRAS mutations, and microsatellite instability phenotype (MSI) on LN count and LN metastasis spread in CC in our population. 210 patients were enrolledin this study, clinicopathologic data wereobtained from the patient's medical records and pathologyreports. For molecular analysis, DNA was extracted from formalin-fixed, paraffin-embedded (FFPE) colon cancer samples. KRAS (exon 2, 3 and 4) and NRAS (exon 2, 3, and 4) mutations were detected by Sanger sequencing and pyrosequençing technology. Micro satellite instability (MSI) status was determined by immune histochemistry for MLH1, MSH2, MSH6 and PMS2 proteins.Statistical analysis was performed using the IBM SPSSStatistic 21. KRAS and NRAS mutations were found in 36.7% and 2.9% of 210 patients, respectively. KRAS exon 2 mutations were identified in 76.5% of the cases and rare mutations in 7,4% of all cases.According to our results, the mean number of removed lymph nodes was significantly lower in colon cancer with KRAS exon 2 mutations($P<0.001$), NRAS mutations ($P=0.04$)and rareRAS mutations($P=0.007$). Although, it was significantly higher in microsatellite instability tumors. The mean number of metastatic lymph node was significantly higher in KRAS exon 2($P=0.003$) and KRAS codon 13 mutated tumors ($P=0.02$). MSI tumors harbors lower rates of metastatic lymph nodes. Patients with KRAS and KRAS codon 13 mutations showed shorter Relapse free survival. Although, MSI phenotype did not affect relapse free survival. Our findings show that KRAS exon 2 and especially KRAS codon 13 mutations are associated with metastatic lymph nodes spread and a worse relapse free survival.

Keywords:

colon cancer. Lymph nodes.Biomarkers. Relapse free survival.

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Functional and structural characterization of the Ta0887 lipase from the archaeon Thermoplasmaacidophilum.

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Leticia Santos

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Abstract

Thermoplasmaacidophilum is a thermoacidophilic archaeon belonging to the archaeal domain archaea. It grows at a temperature of 59°C and a pH between 0.5 and 2. The cells of Thermoplasma species possess irregular shapes due to the absence of a cell wall. T. acidophilum possesses a circular chromosome of 1.56 million base pairs, which we have completely sequenced. The study ofT. acidophilum molecules has been key in the elucidation of three-dimensional protein structures and molecular mechanisms because of the simplicity of its molecules when compared againsteukaryotic molecules, in addition to the relevance in their stability over wide ranges of temperature and pH, thus biotechnological advantages.Ta0887 is phylogenetically classified as a triacylglycerol lipase. This study involves the cloning of the gene, its heterologous overexpression, elucidation of its biochemical characteristics, three-dimensional structural modeling through crystallographic studies to determine the active sites responsible for lipase activity and substrateselectivity or preference for its potential use in the biotechnology industry.

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Evaluation of driver mutations in EGFR and KRASin non-small cell lung cancer and the correlation with program death ligand-1 expression in Iranian patients

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Abstract

Lung cancer is a fatal disease worldwide with greater than 1 million deaths each year and therefore, detection of mutations in cancer driver genes is useful for choosing the appropriate chemotherapy. The frequency of EGFR and KRAS mutations is ethnicity-dependent, however there is lack of data on these mutations and correlation with PDL-1 expression in Iranian patients.

In this study we have analyzed the mutations of EGFR and KRAS gene in thousand patients with lung cancer and then, the association of PD-L1 expression with clinicopathological parameters has been assessed. For detecting mutations, the EGFR exons 18-21 and KRAS exon 2wereanalyzed by pyrosequencing. PDL-1 expression was assessedby using immunohistochemistry.

EGFR mutations were found in 262 patients (26.2%) and were considerably more often found in females (36.2% vs. 20.4%, p=0.001). Interestingly, most EGFR mutations were identified in adenocarcinomas. KRAS mutations were found in 67 patients (6.7%) who 47 of them were males (7.42 vs. 5.45, p=0.021). We also found three patients who had concomitant mutations in EGFR and KRAS and six patients carried two mutations in EGFR The overall frequency of PD-L1 protein expression was found to be 46.4% (302/650) and we found a statistically significant correlation between higher PD-L1 expression and the presence of EGFR gene mutations in the high grade tumors (p=0.001).

Our results further support the biological significance of EGFR/KRAS-mediated signaling pathways in lung cancer and also raise this possibility that EGFR signaling is somehow involved in expression of PD-L1 in lung cancer.

Keywords:

EGFR; KRAS; PD-L1; non-small cell lung cancer

Biography:

Zahra Abrehdari-Tafreshi is a Ph.D at the University of Tehran. She received a bachelor's degree and master degree in Cell and molecular biologyfrom science and research university of Tehran. She is interested in research of cell and molecular biology and cancer biology.

Ehsan Arefian is a Ph.D at the TarbiatModaresUniversity. He received a bachelor's degree and master degree in biologyfrom university of Tehran. He is interested in virology and cancer biology.

Seyed Mahmood Arabnajafi is a Ph.D at the University of Oxford University. He received a bachelor's degree and master degree in biologyfrom university of Tehran. He is interested in cancer biology and wnt signaling.

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Peripheral and central vascular function alterations caused by unilateral adrenalectomy in rats and effects of BPC 157 pentadecapeptide.
Author name A, Author Name B and Author name C

Authors
Ivan Maria Smoday1, Luka Kalogjera1, Vlasta Vukovic1, Katarina Oroz1, Hrvoje Vranes1, Predrag Sikiric1

Organizations
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Abstract
Background
Small blood vessels and the endothelium have an essential role in maintaining homeostasis of circulation. When their dysfunction occurs, early signs of progressive shock become evident. These changes occur in a variety of noxious procedures. Unilateral adrenalectomy (uADX) is a procedure used in experimental and human contexts. Pentadecapeptide BPC 157 (BPC157) has been shown to have potent cytoprotective effects by modulating minor blood vessels and protecting the endothelium. We described the role of BPC157 on small blood vessel functioning and endothelial maintenance in acute phases of uADX,

Methods
Deeply anesthetized male Wistar rats (200-250g) were submitted to left uADX. Acute effects in 15 min, 5h and 24h after surgery and pretreatment with 1 mL saline (control animals) or 1 mL of BPC-157 pentadecapeptide (BPC157) solution (1ng/L or 1ug /L) applied intraperitoneally were described with ECG, pathoanatomical, pathohistological, invasive blood pressure measurement and thrombosis evaluation in major blood vessels.

Results
As time passed, more prominent signs of vascular failure-related phenomena were evident. Major veins, brain and heart became more congested. Venous pressure rose while aortic pressure fell. ECG showed progression of disturbances as prolonged QTc interval. PHD assessment showed progressed signs of hemorrhage, congestion, and/or thrombosis centrally (brain) and peripherally (viscera, heart, lungs). Cytoprotection with BPC157 showed a beneficial effect by counteracting the above-mentioned pathologies. Macroscopically and histologically, the remnant adrenal gland was pronouncedly hyperemic with BPC157 treatment, while the control group had an initial physiological hyperemia that converted into congestion.

Discussion/Conclusion

uADX causes a vascular failure-induced peripheral and central syndrome similarly to other noxious procedures. Cytoprotection by BPC157 had a curative role on the syndrome. These findings have meaningful clinical implications for acute uADX as thrombosis, hematoma, and hemorrhages present the main complications of this procedure in humans which could be antagonized with agents such as BPC157. Also, acute compensation phases of the remnant adrenal gland have been modified with BPC157, which further elaborates the role of blood vessels on this elusive physiological response. Gene expression analysis (aVEGF, bFGF, PDGF, iNOS and eNOS), NO and oxidative radical levels in the remnant adrenal gland, brain, and stomach will further elaborate these findings.

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Natural Flavonoids Inhibit Cancer Stem Cells and CD73, delay Tumor Growth and Increase Infiltrating CD8+ T Cells in Triple-Negative Breast Cancer

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Abstract

Intellectual disability is characterized by a significant impaired intellectual and adaptive functioning, affecting approximately 1 to 3% of the population, which can be caused by a variety of environmental and genetic factors. In this respect, de novo heterozygous HECW2 variants were associated recently with neurodevelopmental disorders associated to hypotonia, seizures, and absent language. HECW2 encodes an E3 ubiquitin-protein ligase that stabilizes and enhances transcriptional activity of p73, a key factor regulating proliferation, apoptosis, and neuronal differentiation, which are together essential for proper brain development.

Here, using whole exome sequencing, we identified a homozygous nonsense HECW2 variant: c.736C>T; p.Arg246* in a proband from a Moroccan consanguineous family, with developmental delay, intellectual disability, hypotonia, generalized tonico-clonic seizures and a persistent tilted head.

Thus this study describes the first homozygous HECW2 variant, inherited as an autosomal recessive pattern, contrasting with former reported de novo variants found in HECW2 patients.

Keywords:

HECW2, whole exome sequencing, homozygous nonsense mutation, autosomal recessive pattern, neurodevelopmental delay, intellectual disability.

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