

22nd Global Annual Oncologists Meeting

May 24-25, 2018 Osaka, Japan

Posters

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The histone methyltransferase G9a as a therapeutic target in colorectal cancer

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Neo-adjuvant Concurrent Chemo-Radiotherapy (CCRT) is a standard treatment of locally advanced Colon Cancer Cell (CRC). In order to maximize efficacy and minimize toxicity, new drugs have been developed and used in combination with CCRT. Recently, it has been shown that G9a plays a role in mediating phenotypes of Cancer Stem Cells (CSCs). This study aimed to characterize G9a as a biomarker in predicting therapy response to prevent overtreatment and adverse effects in CRC patients. The primary tumors from 39 patients who received CCRT for rectal cancer were selected. In vivo tumor xenograft models for tumorigenic properties in immune-deficient mice were developed. In vitro stemness ability was performed by tumor-sphere assays, cell response to anticancer agents and stemness-related genes analysis. Cells survived from radiation treatment and displayed high levels of G9a. A significantly positive correlation was shown between G9a and CSCs marker CD133 in locally advanced rectal cancer patients with CCRT. Knockdown of G9a increased the sensitivity of cells to radiation treatment and sensitized cells to DNA damage agents through PP2A-RPA axis. Taken together, our study theorized that G9a might serve as a novel target in colon cancer, which offers exciting potential in prediction of response to preoperative chemo-radiotherapy in patients with advanced CRC.

Biography

Mei-Ren Pan has completed her PhD from Kaohsiung Medical University, Taiwan. She is currently the Assistant Professor at Graduate Institute of Clinical Medicine, Kaohsiung Medical University.

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Texture analysis predicting EGFR mutation and recurrence in lung adenocarcinoma

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Objectives: We aimed to investigate the discriminative value of texture feature in EGFR mutation of lung adenocarcinoma and prognostic value of texture features using 18Fluorine-Fluorodeoxyglucose (18F-FDG) Positron Emission Tomography/Computed Tomography (PET/CT).

Methods: 63 lung adenocarcinoma patients with preoperative 18F-FDG PET/CT between January 2010 and December 2014 were included. Texture features are extracted automatically by using LIFEx software (University of Paris-Saclay, France), which provided texture features of gray level co-occurrence matrix, neighborhood gray-level different matrix, gray-level run length matrix and gray-level zone length matrix.

Results: Contrast ($p=0.0179$), dissimilarity ($p=0.024$), entropy ($p=0.0097$), HGRE ($p=0.0093$), HGZE ($p=0.0044$), LRHGE ($p=0.0076$), RLNU ($p=0.0249$), SRHGE ($p=0.0105$), SZHGE ($p=0.014$), ZLNU ($p=0.011$), SUVmax ($p=0.0087$), SUVmean ($p=0.0084$), SUVpeak ($p=0.0105$), TLG ($p=0.0138$) were lower in adenocarcinoma with mutant EGFR, while energy ($p=0.102$), homogeneity ($p=0.0318$), LGRE ($p=0.0079$), LGZE ($p=0.0055$), LRLGE ($p=0.0084$), LZLGE ($p=0.037$), SRLGE ($p=0.0059$), SZLGE ($p=0.0417$) were higher in adenocarcinoma of mutant EGFR. Entropy (odds ratio 0.2548, 95% CI 0.09-0.7209, $p=0.01$) was the independent predictor of EGFR mutation. In addition, LRHGE (hazard ratio 1.0017, 95% CI 1.0008-1.0026, $p=0.0002$) predicted the recurrence in lung adenocarcinoma.

Conclusion: Texture features predicted EGFR mutation in lung adenocarcinoma. In addition, LRHGE was an independent predictor of recurrence in patients with lung adenocarcinoma.

Biography

Yun Seong Kim has completed his PhD from Pusan National University and Postdoctoral studies from University of Massachusetts, USA. He is the Director of Pulmonology and Critical Care Medicine in Pusan National Yangsan Hospital. He has published more than 30 papers in reputed journals.

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Effects of fluid shear stress on the malignant characteristics and drug sensitivity of breast cancerChi-Wen Luo¹, Mei-Ren Pan², Ming-Feng Hou^{2, 3} and Hon-Kan Yip¹¹Kaohsiung Chang Gung Memorial Hospital, Taiwan²Kaohsiung Medical University, Taiwan³Kaohsiung Municipal Hsiao Kang Hospital, Taiwan

Introduction & Aim: Recent studies have indicated that the dynamic stresses created by interstitial fluid flow/blood flow play important roles in tissue development, maintenance, function and pathogenesis. Increasing evidences also indicated that dynamic stresses, such as Shear Stress (SS), play roles in tumor cell survival and several malignant characteristics. SS in and around tumor tissue could affect the efficacy of anticancer agent delivery, tumor microenvironment, and metastasis/invasion capacity. In addition, SS also could affect the migration of Circulating Tumor Cells (CTCs) during metastasis. Our previous studies have shown that SS could increase the sensitivity of radiation and induce apoptosis on tumor cell through the inhibition of integrin β 1/FAK pathway. Here, we want to clarify whether FAK also plays roles in controlling chemotherapeutic responsibility and regulating the malignant characteristics after SS stimulation in adherent tumor cells and CTCs.

Materials & Methods: Breast cancer cells (MDA-MB-231, MDA-MB-468 and MCF-7) were used in this study. Cells were seeded onto glass slides pre-coated with fibronectin or in suspension, and then subjected to 0, 1 and 12 dyne/cm² of laminar shear stress for 0-24 hours. Cells were then collected to study the migration/invasion abilities, drug sensitivity and signaling transduction pathway by other assays.

Results: Our data showed that high shear stress (12 dyne/cm²) might inhibit the migration/invasion abilities of adherent and circulating tumor cells but not in low shear stress (1 dyne/cm²). Low shear stress could induce the Mesenchymal-Endothelial Transition (MET) in CTCs. In addition, high shear stress could also increase the cisplatin sensitivity in both adherent and circulating tumor cells. High shear stress could down-regulates FAK, p-FAK, p-AKT expression through integrin β 1. Knockdown of FAK could increase the drug sensitivity and decrease the migration/invasion abilities induced by low shear stress in adherent and circulating tumor cells.

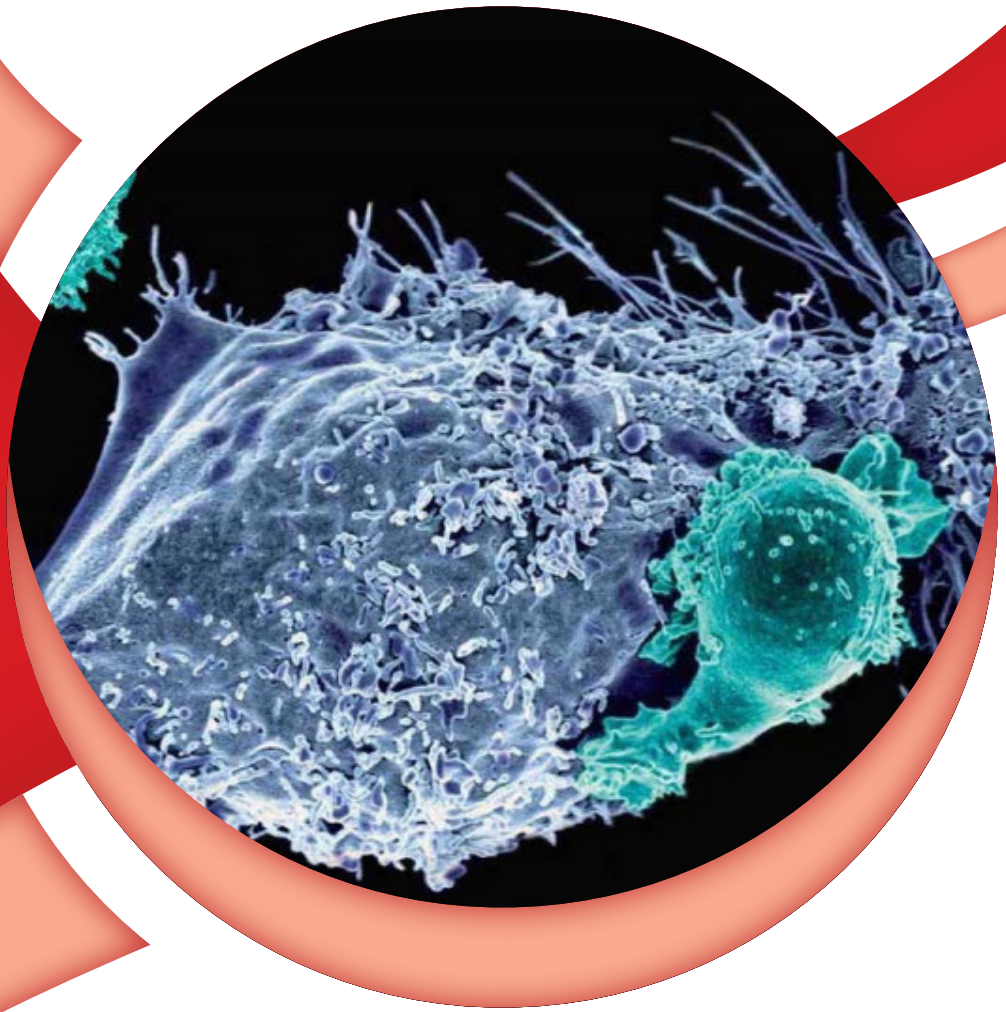
Conclusion: Our results suggest that mechanical forces applied on tumor cells may play important roles in tumor biology and the effects of shear stress could be taken into account in cancer therapy development.

Biography

Chi-Wen Luo has completed his PhD from Tamkang University, Taipei, Taiwan and Postdoctoral studies from National Institute of Cancer Research, National Health Research Institutes, Taiwan. He has been the Assistant Principal Investigator in Department of Pathology, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan. He has published more than 20 papers in reputed journals.

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Accepted Abstracts

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Ameloblastic carcinosarcoma in a 42 year-old female: A case report and literature review

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Ameloblastic or odontogenic carcinosarcoma is an extremely rare mixed malignant odontogenic tumor with only a handful of reported cases published. Histologically, it is characterized by a mixed atypical epithelial and mesenchymal component showing features of malignancy. It is assumed to arise from pre-existing lesions such as ameloblastoma, ameloblastic fibroma and ameloblastic fibrosarcoma. The aggressive clinical behavior of the tumor needs further understanding. The case of an ameloblastic or odontogenic carcinosarcoma in the mandible of a 42 year old female is described herein. The tumor involved the left mandible bony cortices and adjacent soft tissue structures. A surgical resection and reconstruction of the mandible as well as chemotherapy were done. This is the seventh case in literature of this rare tumor. The purposes of this case report are to distinguish it from related diseases and to discuss features of the tumor in the existing literature.

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Fever gone malignant: A case report of squamous cell carcinoma of the renal pelvis initially presenting as renal abscess**Christer Mari F Taclobos, Jeanette Umali and Gregorio Galve**
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The fact that the urothelium normally does not have squamous cells renders the pathogenesis of squamous cell carcinoma of the renal pelvis interesting. We report a 69 year old male who initially presented with persistent fever even with antimicrobial therapy. Patient is known to have nephrolithiasis since three years prior to admission and would experience occasional right flank pain, not compliant to medications prescribed and was lost to follow up. Patient experienced on and off undocumented fever for three weeks. Consult was done wherein ultrasound and computed tomography with contrast of the whole abdomen were requested which pointed to a non-obstructing nephrolithiasis associated with an intra-renal abscess communicating to an abscess of the right hepatic lobe. Nephrectomy was advised however patient was initially undecided thus nephrostomy was done. There was persistence of fever with note of anorexia, abdominal enlargement and generalized body weakness thus patient was readmitted in this institution for further medical and surgical management. Patient had slightly pale conjunctiva. Abdominal examination revealed a nephrostomy tube inserted in the right kidney. Bowel sounds are normoactive with direct tenderness at the right upper quadrant area. A smooth, tender, non-erythematous mass is palpated at the right upper quadrant. There is note of right costovertebral tenderness. Patient was admitted as a case of: (1) Sepsis secondary to right renal abscess and right hepatic lobe abscess and (2) right nephrolithiasis. Patient was immediately referred to the department of general surgery for evaluation and co-management due to intractable leukocytosis associated with persistent fever. Notable were persistent leukocytosis, hypercalcemia and thrombocytosis on laboratory tests. Nephrectomy was done and histopathology report showed squamous cell carcinoma of the right kidney. Squamous renal cell carcinoma is a rare neoplasm which is always associated with long standing renal stone and is always intensive at the time of diagnosis. Aside from renal calculi, infections such as chronic UTI, renal TB, schistosomiasis, vitamin A deficiency, percutaneous nephrostomy and immunosuppression can cause this entity but the main risk factor almost constant in all reported cases of squamous cell carcinoma of the renal pelvis is a history of long standing nephrolithiasis.

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Meta-analysis of promoter methylation in eight tumor-suppressor genes and its association with the risk of thyroid cancerFatemeh Khatami¹, Bagher Larijani¹, Ramin Heshmat¹, Abbasali Keshkar¹, Mahsa Mohammadamoli¹, Ladan Teimoori-Toolabi², Shirzad Nasiri¹ and Seyed Mohammad Tavangar¹¹Tehran University of Medical Sciences, Iran²Pasteur Institute of Iran, Iran

Promoter methylation in a number of Tumor-Suppressor Genes (TSGs) can play crucial roles in the development of thyroid carcinogenesis. The focus of the current meta-analysis was to determine the impact of promoter methylation of eight selected candidate TSGs on thyroid cancer and to identify the most important molecules in this carcinogenesis pathway. A comprehensive search was performed using Pub Med, Scopus and ISI Web of Knowledge databases and eligible studies were included. The methodological quality of the included studies was evaluated according to the Newcastle Ottawa scale table and pooled Odds Ratios (ORs); 95% Confidence Intervals (CIs) were used to estimate the strength of the associations with Stata 12.0 software. Egger's and Begg's tests were applied to detect publication bias, in addition to the Metatrim method. A total of 55 articles were selected and 135 genes with altered promoter methylation were found. Finally, we included eight TSGs that were found in more than four studies (RASSF1, TSHR, PTEN, SLC5A, DAPK, P16, RAR β 2 and CDH1). The order of the pooled ORs for these eight TSGs from more to less significant was CDH1 (OR=6.73), SLC5 (OR=6.15), RASSF1 (OR=4.16), PTEN (OR=3.61), DAPK (OR=3.51), P16 (OR=3.31), TSHR (OR=2.93) and RAR β 2 (OR=1.50). Analyses of publication bias and sensitivity confirmed that there was very little bias. Thus, our findings showed that CDH1 and SCL5A8 genes were associated with the risk of thyroid tumor genesis.

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Discovery of 18 β -glycyrrhetic acid conjugated aminobenzothiazole derivatives as Hsp90-Cdc37 interaction disruptors that inhibit cell migration and reverse drug resistance

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A series of 18 β -Glycyrrhetic Acid (GA) conjugated aminobenzothiazole derivatives were designed, synthesized and evaluated for disruption activity of Hsp90-Cdc37 as well as the effects of *in vitro* cell migration. These compounds exhibited relatively good disruption activity against Hsp90-Cdc37 with IC₅₀ values in low micro-molar range. A docking study of the most active compound 11 g revealed key interactions between 11 g and Hsp90-Cdc37 complex in which the benzothiazole moiety and the amine chain group were important for improving activity. It is noteworthy that further antitumor activity screening revealed that some compounds exhibited better inhibitory activity than the commercial anticancer drug 5-FU and showed potent suppression activity against drug-resistant cancer cells. In particular, compound 11 g appeared to be the most potent compound against the A549 cell line, at least partly, by inhibition of the activity of Hsp90 and apoptosis induction. The treatment of A549 cells with compound 11 g resulted in inhibition of *in vitro* cell migration through wound healing assay and S phase of cell cycle arrested. In addition, 11 g-induced apoptosis was significantly facilitated in A549 cells. Thus, we conclude that GA aminobenzothiazole derivatives may be the potential Hsp90-Cdc37 disruptors with the ability to suppress cells migration and reversed drug-resistant.

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Coronary artery disease after radiation therapy for Hodgkin's lymphoma in a pregnant patient: A case report**Joe Patrick Tiu Jamelo and Ana Ma Nanette Arriola**
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Radiation-associated cardiovascular diseases are increasingly recognized as adverse effects of Hodgkin's Lymphoma (HL) treatment. This case report aims to identify the risk factors for Coronary Artery Disease (CAD) in a symptomatic pregnant patient who had mediastinal irradiation for HL. She later underwent coronary angiogram and Percutaneous Coronary Intervention (PCI). We evaluated a 26-year-old pregnant patient who had been treated for HL by radiation therapy at the age of 19. The total mediastinal dose was 51 Gray (Gy). Patient was evaluated with serial Electrocardiography (ECG) monitoring and troponin I followed by coronary angiography of the coronary arteries. Patient had CAD. Coronary angiogram showed 2-vessel CAD with significant left main coronary artery involvement, which led to PCI of ostial to proximal left main artery. We report a case of a 26-year-old pregnant patient with CAD who had history of HL treated by radiation therapy. Cardiovascular complications like CAD should be kept in mind as a possible complication after radiation therapy. Physicians must be aware of post-radiation cardiac complications, recognize at-risk patients, and screen such patients for symptoms and signs of cardiac disease.

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Delving KS-01 as a novel therapeutic strategy in treating breast cancer

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Cancer cells have an increased need for cholesterol, which is required for cell membrane integrity. Cholesterol accumulation has been described in various malignancies including breast cancer. Cholesterol has also been known to be the precursor of estrogen and vitamin D, both of which play a key role in the histology of breast cancer. Thus, depleting the cholesterol levels in cancer cells is a proposed innovative strategy to treat cancer. Therefore, novel cholesterol depleting compounds are currently being investigated. KS-01 is a cyclic amylose oligomer composed of glucose units. It solubilizes the cholesterol and is proven to be toxicologically benign in humans. This led us to hypothesize that it might deplete cholesterol from cancer cells and may prove to be a clinically useful compound. Our work provides preliminary experimental evidences to support this hypothesis. We identified the potency of KS-01 in vitro against two breast cancer cell lines: MCF-7 (Estrogen positive, ER+), MDA-MB-231 (Estrogen negative, ER-) and compared the results against two normal cell lines: MRC-5 (normal human lung fibroblasts) and HEK-293 (normal human embryonic kidney cells) using cytotoxic, apoptosis and cholesterol based assays. KS-01 treatment reduced intracellular cholesterol resulting in significant breast cancer cell growth inhibition through apoptosis. The results hold true for both ER+ and ER-. These data suggest that KS-01 can prevent cholesterol accumulation in breast cancer cells and is a promising new anticancer agent.

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Metabolic targeting of glioblastoma cells**P Sinha^{1, 3}, S Lawler² and P Chumas³**¹Royal Hallamshire Hospital, UK²Brigham and Women's Hospital, USA³Leeds Teaching Hospitals NHS Trust, UK

Brain tumor account for less than 2% of all primary cancers; however still 1860 new cases of malignant gliomas are diagnosed each year in England and Wales. Standard care of treatment for patients with glioblastoma is surgery followed by adjuvant radiotherapy and chemotherapy. However, glioblastoma is a highly aggressive and infiltrating tumor and in spite of advances in radiotherapy, chemotherapy and surgical technique, there has not been significant improvement in patient survival. As cure for GBM remain elusive, it is important to identify new treatment modalities as well as modify existing therapies to possibly change malignant gliomas from a deadly disease into a chronic one. In this study, we initially investigated the effect of glucose deprivation on adult glioma cell viability. We have shown that glucose deprivation induced glioma cell death in vitro. We have also shown that free radical scavenger N-acetylcysteine and methyl pyruvate suppressed glucose deprivation induced cell death. We have shown that glucose deprivation induced cell death is not mediated by apoptosis, autophagy or necrosis. Glucose deprivation led to energetic and endoplasmic reticulum (ER) stress in glioma cells. We have also shown that hypoxia rescued glucose deprivation induced cell death whereas glutamine withdrawal had no effect on glucose deprivation induced cell death. We have shown that glucose deprivation and hypoxia promotes glioma cell migration. We then showed that metformin significantly enhanced glucose deprivation induced cell death which was not mediated by apoptosis, autophagy, necrosis or oxidative stress. We have also shown that AMPK mimic AICAR also promoted glucose deprivation induced cell death whereas 2-deoxyglucose (2DG) suppressed glucose deprivation induced cell death. We have also shown that metformin potentiated glucose deprivation induced energetic stress whereas it suppressed ER chaperone protein GRP78. We have shown that metformin and 2DG combination led to significant cell death in glioma cells which were caspase independent and not mediated by oxidative stress. Finally we have also showed that metformin potentiated 2DG mediated pAMPK up-regulation whereas it down-regulated 2DG mediated autophagy and ER chaperone protein GRP78 to induce cell death.

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Abrogation of glutathione peroxidase-1 drives EMT and chemoresistance in pancreatic cancer by activating ROS-mediated Akt/GSK3 β /snail signaling**Qingcai Meng, Si Shi, Chen Liang, Jie Hua, Yiyin Zhang, Jin Xu and Xianjun Yu**
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Introduction & Purpose: Pancreatic Ductal Adenocarcinoma (PDAC) remains one of the deadliest cancers worldwide, partly due to tumor chemoresistance. Numerous studies have shown that Glutathione Peroxidase-1 (GPx1) plays various roles in development and progression of multiple tumors. However, its role in pancreatic cancer remains unclear. In this study, we sought to elucidate the function of GPx1 in pancreatic cancer malignancy and gemcitabine (GEM) resistance.

Experimental Design: PDAC tissue microarrays were used to evaluate the correlation between GPx1 expression and clinicopathological features. Cytobiology, molecular biology assays and mouse models were performed to investigate the detailed mechanisms. Finally, RNA-sequencing was performed in the scramble-shRNA and GPx1-shRNA MiaPaCa-2 cells to identify core signaling pathways.

Result: The level of GPx1 expression was negatively associated with Overall Survival (OS) in patients with PDAC. Silencing of GPx1 resulted in an Epithelial-Mesenchymal Transition (EMT) phenotype and increased chemoresistance to GEM in vitro and in vivo. Additionally, activation of Akt/GSK3 β /snail signaling was demonstrated to be involved in this process.

Conclusion: Our results reveal that GPx1 could inhibit EMT and chemoresistance by regulating Akt/GSK3 β /Snail axis in PDAC.

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