Close Window

Title: Circadian Rhythms and Diurnal Profiles of Salivary Alpha Amylase in Women with Breast Cancer [2015]

Authors: Christy Albert[1] Trevor Stantliff[1] Liz Cash[2] Sandra Sephton[1] Psychological and Brain Sciences[1] and James Graham Brown Cancer Center[2] 2015

Keywords: breast cancer, alpha amylase, circadian disruption, autonomic activity, activity rhythms, circadian clock, actigraphy, biorhythms

Abstract:

Approximately 1 in 8 U.S. women will develop an invasive breast tumor during the course of her life. Numerous biological processes, including those responsible for tumor suppression, are organized into a hierarchy of phase coupled genetic oscillators incorporating auto-regulatory transcription-translation feedback loops. Circadian disruptions affecting the HPA axis correspond to disruptions in activity rhythms and lead to tumor promoting environments. While this knowledge has led to novel interventions benefiting cancer patients, circadian disruptions involving the autonomic system and its effect on activity rhythms has not been fully explored. Sixty breast cancer patients awaiting surgery provided saliva samples over the course of three days. Saliva samples were analyzed for alpha amylase, a surrogate biomarker for SNS activity, using kinetic assay technique. Data was then log transformed and diurnal slopes were calculated. Additionally, participants wore an actigraphy watch, which measures activity levels in one minute epochs. Using Action 4 software, actigraphy data was translated into rest/activity rhythm variables via auto-correlation, a technique used to show how one minute epochs on day 1 correlate with one minute epochs on subsequent days. Hierarchical linear regression models showed no significance ($p>.05$) between circadian activity rhythms (autocorrelation coefficient) and salivary alpha amylase diurnal profile slopes. After controlling for age, stage, and income; models with circadian activity rhythms as a predictor showed no significance ($p>.05$) while models with amylase slope as a predictor became significant, with income as the only significant predictor to these models. Funding was provided by National Cancer Institute grant R25-CA134283.

Public Link: http://ocrss.louisville.edu/clients/hscro/conspectus/searchview.php?ID=4451

Close Window

Title: Optimizing IHC for Cisplatin Treated Tissue [2015]

Authors: Marisa Bohn Levi Beverly Leah Siskind Other[1] and Medicine[2] 2015

Keywords: lung cancer, immunohistochemistry

Abstract:

Cisplatin is a platinum-based chemotherapeutic drug used today for the treatment of many different types of cancer. Although cisplatin is successful initially, its efficacy is impeded by the development of resistance during treatment. Many factors contribute to this development of resistance, such as the DNA repair mechanisms of damaged cells. Identification of specific proteins that contribute to these unique DNA repair pathways of cisplatin treated tissue may lead to the development of rational novel therapies for cisplatin resistant cancer. Immunohistochemistry has become an indispensable technique in understanding the histopathology of cisplatin treated tissues, identifying proteins and noting the differences between their levels of expression in cisplatin treated tissues vs. non-treated tissues can offer insight into the pathological mechanisms of cisplatin and potentially improve current chemotherapeutic strategies.

This research was supported by the NCI R25-CA 134283 grant and the University of Louisville.

Public Link: http://ocrss.louisville.edu/clients/hscro/conspectus/searchview.php?ID=4455

Close Window

Title: Intra-operative navigation of a three-dimensional needle localization system for precision of irreversible electroporation needles in locally advanced pancreatic cancer [2015]

Authors: Logan Bond[1] Robert Martin[1] Surgery[1] 2015

Keywords: Pancreatic adenocarcinoma

Abstract:

Introduction: Irreversible electroporation (IRE) uses multiple needles and a series of electrical pulses to create pores in cell membranes and cause cell apoptosis. One of the demands of IRE is the precise needle spacing required. Intraoperative 2D ultrasound (iUS) is currently used to measure inter-needle distances but requires significant expertise. This study evaluates the potential of 3D image guidance for placing IRE needles and calculating needle spacing.

Methods: A prospective clinical evaluation of a 3D needle localization system (Explorer™) was evaluated from April 2012 through June 2013 in consecutive patients who had IRE for unresectable pancreatic adenocarcinoma. 3D reconstructions of patients' anatomy were generated from preoperative CT images, which were aligned to the intra-operative space.

Results: Thirty consecutive patients with locally advanced pancreatic cancer were treated with IRE. The needle localization system added an average of 6.5 minutes to each procedure. The 3D needle localization system increased surgeon confidence and reduced needle placement time.

Conclusion: IRE treatment efficacy is highly dependent on accurate needle spacing. The needle localization system evaluated in this study aims to mitigate these issues by providing the surgeon with additional visualization and data in 3D. The Explorer™ system provides valuable guidance information and inter-needle distance calculations.

Supported in part by National Cancer Institute grant R25-CA134283.

Public Link: http://ocrss.louisville.edu/clients/hscro/conspectus/searchview.php?ID=4250

Close Window

Title: Small Molecule Inhibition of Choline Kinase-α Decreases Proliferation of Non-Small Cell Lung Cancer [2015]

Authors: Andrew Bratton[1] Jason Chesney[2] Sucheta Telang[3] Biology[1] Medical Oncology/Hematology[2] and Neonatology[3] 2015

Keywords: choline kinase, lung cancer, Kennedy pathway, phospholipid

Abstract:

Non-small cell lung cancers (NSCLC) exhibit significantly elevated steady state levels of phosphocholine relative to adjacent normal lung tissue. The overexpression of phosphocholine in malignant cells is largely due to the activity of the Ras and PI3K signaling cascades, which stimulate the production of the enzyme choline kinase-α (ChKα) via the Rho GTPases. ChKα executes the first committed step in the Kennedy pathway that allows for the biosynthesis of phosphatidylcholine, which serves as the major phospholipid constituent of cellular membranes and a substrate for the production of phosphatidic acid for subsequent growth factor signaling. In previous studies, we found that selective silencing of ChK expression abrogated the expression of phosphocholine which, in turn, decreased phosphatidylcholine, phosphatidic acid and signaling through the MAPK and PI3K/AKT pathways and led to a marked decrease in anchorage-independent survival of cancer cells in soft agar and in athymic mice. We have now examined the effects of a small molecule inhibitor of ChKα (CK1) in a series of NSCLC cell lines and found that CK1 leads to a dose dependent decrease in their proliferation. Current experiments are ongoing to define the mechanism of the decrease in proliferation and to further explore the effects of CK1 in NSCLC. Supported in part by National Cancer Institute grant R25-CA134283.

Public Link: http://ocrss.louisville.edu/clients/hscro/conspectus/searchview.php?ID=4477

Close Window

Title: Radioprotective Effects of Ferritin [2015]

Authors: Phillip Burkhardt Lilibeth Lanceta Patricia Soucy[3] Chi Li[4] John Eaton[4] Arts & Sciences[1] Other[2] Bioengineering[3] and Pharmacology and Toxicology[4] 2015

Keywords: Ferritin, LET Radiation, Iron, D3T

Abstract:

The National Aeronautics and Space Administration (NASA) has its sights set on a manned Mars mission, a mission requiring up to three years of space travel. Astronauts will be exposed to substantial radiation. Prolonged exposure to linear energy transfer (LET) radiation, emitted from our sun and other stars, damages DNA and kills cells partly through iron-dependent reactions. In a recent study, Haro *et al*. (PLOS ONE 7:11/e48841, 2012) selected for human myeloid leukemia HL60 cells resistant to low energy LET and found >12-fold reduction in expression of Iron Regulatory Protein-1 (IRP-1), an important negative regulator of ferritin synthesis. As an intracellular iron storage protein up-regulated by IRP-1 decrease, ferritin is a likely mediator of radioresistance. Increased cellular ferritin may lead to radioresistance through decreasing radiation-induced, iron-mediated, Fenton chemistry and DNA damage from low energy LET radiation. Given that exposure of astronauts to radiation in space during a Mars expedition is likely to lead to a 10-15% increase in cancer risk, pharmacologic strategies to increase ferritin expression might provide a measure of protection. Our research indicates that treatment with the compound 1,2-dithiole-3-thione (D3T), known to induce ferritin, leads to radioprotection of cells. This treatment has promise as a radio-protectant. A related compound, Oltipraz, is currently an FDA approved medication.

This research was supported by the National Cancer Institute grant R25-CA134283.

Public Link: http://ocrss.louisville.edu/clients/hscro/conspectus/searchview.php?ID=4068

Close Window

Title: The Interplay between Aging and Lung Inflammation / Remodeling in Lung Cancer Progression [2015]

Authors: Aneesha Carter[1] John Greenwell[2] Edilson Torres-González[3] Glenn Vicary[2] Jeff Ritzenthaler[3] Jesse Roman[3] Biology[1] Pharmacology and Toxicology[2] and Medicine[3] 2015

Keywords: Lung cancer, Inflammation, Tissue remodeling, aging, Fibroblast, Lung tumor

Abstract:

Lung cancer is the leading cause of cancer-related deaths in the world. Although new information about lung cancer is developing at an increasing pace, its 5-year survival rate remains at a bleak 15%. In addition, most lung cancers develop in elderly people with chronic lung disease characterized by chronic inflammation and tissue remodeling. Thus, we hypothesize that aging and lung inflammation/remodeling act in concert to promote lung cancer progression. *In vitro* studies indicated that fibroblast-conditioned media promotes LLC cell proliferation and protects against Cisplatin induced cell death. This suggests that products derived from stromal cells influence lung cancer. Using the xenograft model, we found that untreated aging mice developed more lung metastases than young mice. We then turned our attention to the effects of bleomycin. When tumors were implanted in bleomycin-treated animals, the size of the subcutaneous tumors were similar ($p = 0.2$). As before, aging animals treated with bleomycin developed more metastases when compared to young mice. Importantly, bleomycin treatment further enhanced the number of metastases in the aging mice when compared to untreated aging animals ($p=0.0002$). Our studies suggest that age-dependent host factors influence lung cancer progression, and that lung fibroblasts might be responsible for some of these events. Importantly, based on studies in the bleomycin model, we conclude that lung inflammation and tissue remodeling enhance pulmonary metastasis in the aging lung, but not in the young lung, thereby indicating interplay between lung aging and inflammation/remodeling in experimental tumor progression. Partially supported by National Cancer Institute grant R25-CA134283.

Public Link: http://ocrss.louisville.edu/clients/hscro/conspectus/searchview.php?ID=4358

Close Window

Title: Effect of Arylamine N-acetyltransferase 1 Knockout by CRISPR/Cas 9 on Doubling Time in MDA-MB-231, MCF-7, & ZR-75-1 Breast Cancer Cell Lines [2015]

Authors: Maggie Chang[1] David Hein[1] Marcus Stepp[1] Mark Doll[1] Pharmacology and Toxicology[1] 2015

Keywords: NAT1, Breast Cancer, CRISPR/Cas 9, Knockout, Doubling Time, Enzyme Activity, PABA Activity Assay

Abstract:

Human arylamine *N*-acetyltransferase 1 (NAT1) is found in almost all tissues and is overexpressed in breast cancers. Previous studies have shown great variation in NAT1 activity among various breast cancer cell lines with MDA-MB-231 < MCF-7 <<< ZR-75-1. We hypothesize that human NAT1 has a role in cancer cell progression and that knockout of arylamine *N*-acetyltransferase 1 (NAT1) will increase the doubling time of MDA-MB-231, MCF7 and ZR breast cancer cell lines. Human NAT1 activity was measured in parent MDA-MB-231, MCF-7, and ZR-75-1 breast cancer cell lines before (parent cell line) and after NAT1 knockout by CRISPR/Cas 9. PABA NAT1 activities in the parent breast cancer cell lines were in the order MDA-MB-231 < MCF-7 <<< ZR-75-1 but were below the limit of detection in each of the breast cancer cell lines following NAT1 knockout. Significant changes in doubling time in the MDA-MB-231 or MCF-7 knockout clones relative to the parent cell line were not observed. The ZR-75-1 NAT1 knockout cell line showed nearly a 2-fold increase in doubling time compared to the parent, but this did not reach statistical significant perhaps due to small sample size. Since the ZR-75-1 breast cancer cell line has the highest NAT1 activity compared to other cell lines, our results suggest the effect of NAT1 knockout on doubling time is more pronounced in breast cancer cells with high levels of NAT1 activity. Further investigations are needed to confirm this hypothesis. This work was partially supported by USPHS grant CA-134283 from the National Cancer Institute.

Public Link: http://ocrss.louisville.edu/clients/hscro/conspectus/searchview.php?ID=4044

Close Window

Title: Withaferin A in combination with Cisplatin suppresses mucin family proteins in Epithelial Ovarian Cancer Cells [2015]

Authors: Jenna Chong[1] Sham Kakar[1] Physiology[1] 2015

Keywords: Epithelial Ovarian Cancer, Withaferin A, Mucin, Cisplatin

Abstract:

MUC 16 (CA-125), a transmember glycoprotein is used as a serum biomarker for diagnosis of ovarian cancer. Initially, ovarian cancer is treated with a combination of cytoreductive surgery and platinum/taxane chemotherapy which is effective in 70-80% of the cases. After first round of treatment, serum MUC 16 level is a good indicator of survival; however, an increase of MUC 16 indicates recurrent of epithelial ovarian cancer in which platinum/taxane based chemotherapy is only 30% effective. Investigators have reported that MUC 1, 4 and 16 in ovarian cancer and their role in not just cancer cell proliferation but also in metastasis. We hypothesize that combining Withaferin A (WFA) with cisplatin (CIS) sensitizes EOC to cisplatin which will down regulate the expression of MUC1, MUC 4 and MUC 16. In the present study, the effects of WFA, CIS both alone and in combination were determined in epithelial ovarian cancer cell line A2780 and orthotropic ovarian tumors generated in mice by injecting A2780 cell line directly into ovaries. Immunohistochemical and western blot analysis revealed that CIS alone increases the expression of MUC 1, MUC 4 and MUC 16 in A2780 cells as well as in ovarian tumors. In contrast, WFA alone or in combination with CIS suppressed the expression of MUC 1, MUC 4 and MUC 16 in A2780 cells as well as in tumors. Combination of WFA with CIS was found to be highly effective in suppression of MUC 1, MUC 4 and MUC 16, suggesting that the WFA and CIS combination therapy may be a potential therapy for ovarian cancer. Partially supported by NCI grant R25-CA134283

Public Link: http://ocrss.louisville.edu/clients/hscro/conspectus/searchview.php?ID=4121

Close Window

Title: A CRISPR/Cas9 System to Edit Rat Mcs1b Candidate Causal Variants [2015]

Authors: Thomas Gordon[1] Alissa Doll Saasha Kareparembil David Samuelson[3] Pan-African Studies[1] Medicine[2] and Biochemistry & Molecular Genetics[3] 2015

Keywords: Msc1b, Cancer, CRISPR/Cas9

Abstract:

Studies have been conducted testing the cancer suppressing effect of a rat quantitative trait locus (QTL) named Mammary Carcinoma susceptibility 1 (Mcs1). While mapping the Msc1 locus, three subloci were found: Mcs1a, Mcs1b, Mcs1c. Mammary carcinoma susceptibility 1b (Mcs1b) is also a quantitative trait locus, located in rats-on chromosome RNO2, that confers decreased susceptibility when introgressed into a Wistar Furth mammary cancer susceptible genome. A74-SNV-18 is a candidate single nucleotide variant located at Mcs1b. We developed a CRISPR/Cas9 system, an RNA-guided nuclease-mediated gene editing system, to delete A74-SNV-18 in order to determine if this candidate causal variant has an effect on Mcs1b associated phenotypes. This work was supported by National Institute grant R25-CA134283.

Public Link: http://ocrss.louisville.edu/clients/hscro/conspectus/searchview.php?ID=4309

Close Window

Title: The Effects of Ligand Treatment on the Dimerization of EGFR-GFP and ErbB3-dsRED in Chinese Hamster Ovary Cells [2015]

Authors: Hailey Griffey Jamie Rush[2] Brian Ceresa[2] Arts & Sciences[1] and Pharmacology and Toxicology[2] 2015

Keywords: EGFR, ErbB3, Chinese Hamster Ovary Cells, CHO cells

Abstract:

Purpose. To better understand the effects of homo- and heterodimerization between two ErbB receptor kinase family members, epidermal growth factor receptor (EGFR) and ErbB3, on the biological function of the cell.

Methods. Chinese hamster ovary (CHO) cells stably and transiently express EGFR fused with a green fluorescent protein (GFP), and Erb3 fused with a red fluorescent protein (dsRED). CHO cells were serum starved and underwent dose-response using three separate ligands – EGF, BTC, and NRG1. Immunoblotting and widefield fluorescent imaging observed the presence and activity of EGFR-GFP and ErbB3-dsRED in CHO cells.

Results. Immunoblotting and widefield fluorescent imaging of transfected CHO cells demonstrate that EGFR-GFP and ErbB3-dsRED are stably present in separate clone CHO cells after transfection. Immunoblotting of phosphorylated EGFR suggests that concentrations of 4.8nM and 16nM of ligand result in significantly increased activity of the receptor kinase. Furthermore, widefield fluorescent imaging of CHO EGFR-GFP cells shows EGFR-GFP colocalized into endosomes after EGF and BTC treatments.

Conclusions. EGFR-GFP and ErbB3-dsRED are stably present in CHO cells. EGF and BTC treatment at concentrations of 4.8nM and higher promotes an increase in phosphorylation activity of EGFR-GFP. ErbB3-dsRED demonstrates little to no phosphorylation activity under ligand treatment when no other ErbB family dimer partner is present in the cell.

Supported in part by NCI grant R25-CA134283.

Public Link: http://ocrss.louisville.edu/clients/hscro/conspectus/searchview.php?ID=4149

Close Window

Title: Design and Synthesis of Polymer Blend Electrospun Fibers for Sustained Release of siRNA to the Female Reproductive Tract [2015]

Authors: Justin Heidel[1] Jill Steinbach[1] Bioengineering[1] 2015

Keywords: Engineering, Cancer, Nanotechnology, siRNA, Electrospun, Fiber, Gene, Therapy

Abstract:

Human Papilloma Virus (HPV) is the leading cause of cervical cancer in women worldwide, with HPV types 16 and 18 comprising 70% of cases. Although vaccines provide preventative protection, efficacious, non-invasive treatment of established HPV infection remains elusive. Due to the harsh microenvironment of the FRT, preventative and therapeutic agent delivery is challenging, often causing rapid degradation – especially of biological agents including genes and proteins. To overcome these challenges, nanotechnologies, such as electrospun fibers (EFs), can be customized to protect and encapsulate active agents; provide specific targeting; and sustainably deliver biologics and chemotherapeutics. Factors including surface morphology and fiber diameter can be altered, enabling high encapsulation, prolonged release, and subsequently efficacious biodistribution. The immediate goal of this study was to engineer versatile poly(lactic-co-glycolic acid)-poly(ethylene oxide) (PLGA-PEO) and poly(DL-lactone-co-e-caprolactone)-poly(ethylene oxide) (PLCL-PEO) blended fibers to achieve high encapsulation efficiency and sustained release of siRNA. Here we evaluated morphology, size, loading, and controlled-release to obtain a better understanding of the factors that modulate EF properties and siRNA delivery to the FRT. The long-term goal of this study is to evaluate the most promising formulation to deliver siRNA that targets the HPV18 E6 oncogene in HeLa cells *in vitro*. We hypothesize that these siRNA EFs will provide an efficacious delivery platform to protect and sustainably deliver siRNA in the microenvironment of the FRT. These preliminary results will allow us to rationally design formulations to effectively delivery to our desired target. This research supported by Cancer Education Program NIH/NCI R25-CA134283

Public Link: http://ocrss.louisville.edu/clients/hscro/conspectus/searchview.php?ID=4122

Close Window

Title: Perceived survivorship needs in patients with human papillomavirus (HPV)-positive and (HPV)-negative head and neck cancer [2015]

Authors: Erica Holland Rebecca Redman[2] Nursing[1] and medical-oncology [2] 2015

Keywords: survivorship

Abstract:

Introduction

As survivorship rates for cancer patients increase, the need for survivorship resources is also increasing. Because of this, the identification of survivorship needs within certain cancer populations is actively being studied. We hypothesize that patients' perception of their survivorship needs will change throughout treatment and survivorship. In addition, we hypothesize that survivorship needs will vary among different demographics.

Methods

For this study, patients were asked to partake in a survey. Data was collected on the different patient demographics, and their planned or completed treatment plans. Patients were asked about which phase of treatment they are in, and then to rank their concerns after treatment in order of importance to them. They were also asked about various resources, and how useful they felt those resources would be.

Results

A total of 20 surveys have been distributed and returned thus far. Of those completed, 40% were patients with HPV+ head and neck cancer. Of both HPV+ and HPV- patients, their top concerns were with physical side effects followed by cancer recurrence, and cosmetic and emotional side effects. Overall, patients were most interested in utilizing a pain clinic followed by support groups, complementary medicine, and nutritional counseling as various forms of resources.

Conclusion

In this preliminary analysis, physical side effects of treatment and risk of cancer recurrence dominate survivorship concerns of patients with head and neck cancer, regardless of tumor HPV status. Data collection and survey administration are still ongoing

The authors are grateful for the support of National Cancer Institute grant R25-CA134283.

Public Link: http:///ocrss.louisville.edu/clients/hscro/conspectus/searchview.php?ID=4335

Close Window

Title: Mechanistic Insight Into Vinyl Chloride-Induced Liver Injury: Role of Dietary Fatty Acids. [2015]

Authors: Brenna Kaelin[1] Adrienne Bushau[1] Lisanne Anders[1] Heegook Yeo[1] Gavin Arteel[1] Matt Cave[2] Craig McClain[2] Juliane Beier[1] Pharmacology and Toxicology[1] and Medicine[2] 2015

Keywords: Vinyl chloride , Polyunsaturated fatty acids, Liver disease , NAFLD

Abstract:

Vinyl chloride (VC) is a relevant chemical toxicant and an important occupational/environmental pollutant. Most studies on the risk of VC exposure to human health have focused on the effect of VC alone (high doses) and not taken into consideration VC interactions (low doses) with risk-modifying factors. It has been shown that certain dietary fats such as polyunsaturated fatty acids (PUFA), linoleic acid (LA) in particular, exacerbate fatty liver diseases. The purpose of the current study was to determine the role of LA metabolites in sensitizing the liver to VC via molecular, organelle, and cellular effects.

Mice were administered a bolus dose of chloroethanol (or vehicle) 10 wks after being fed a linoleic acid rich high fat diet (HPUFA; 42% corn oil)-fed or low fat control diet (LPUFA; 13% corn oil). Animals were sacrificed 0-24 hours after ClEtOH exposure. Samples were harvested for determination of liver damage, inflammation, oxidative and ER stress.

In LFD-fed control mice, chloroethanol caused no detectable liver damage or inflammation. In HPUFA-fed mice, chloroethanol increased HPUFA-induced liver damage, steatosis, infiltrating inflammatory cells and hepatic expression of proinflammatory cytokines and genes affected in ER stress. Furthermore, chloroethanol altered protein expression of genes involved in ER stress.

Together, VC and HPUFA cause liver damage, inflammation and ER stress markers. This serves as proof-of-concept that VC hepatotoxicity may be modified by a linoleic acid rich diet. These data implicate exposure to VC as a risk factor in development of liver disease in susceptible populations.

Partially supported by NCI grant R25-CA134283

Public Link: http://ocrss.louisville.edu/clients/hscro/conspectus/searchview.php?ID=4054

Close Window

Title: I3C Decreases Cyclin E Expression and Represses Cancer Cell Growth [2015]

Authors: Nicholas Kemper[1] Xiao-Mei Rao[2] Stephen Wechman[2] H. Sam Zhou[3] Kelly McMasters[2] Biology[1] Pharmacology & Toxicology, Surgery[2] and Pharmacology & Toxicology, Microbiology & Immunology, Surgery[3] 2015

Keywords: Indole-3-Carbinol, Adenovirus, Cyclin E, CDK2

Abstract:

Introduction: A product of glucobrassicin breakdown; Indole-3-Carbinol (I3C) is one compound among several derived from cruciferous vegetables that have been identified for their anticancer effects. Previous studies have shown that I3C induces G_1 phase arrest, and works synergistically with Adenovirus to slow cancer cell replication, upregulate apoptosis, and may play a role in prevention and combination therapy for tumor treatment. Overexpression of cyclin E has been linked to tumorigenesis as it aids cell cycle transition into S phase where DNA replication can occurs. ED1 cells have been transgenically induced to overexpress cyclin E causing tumorigeneses. Thus, ED1 mice should serve as a novel murine intermediate of cellular and human models, and serve as an effective in vivo model for Ad and I3C combination therapy.

Methods: In order to investigate the preventative and therapeutic potential of I3C, the current study utilizes MTT assay, crystal violet staining, and immunoblot analyses to understand the effect of I3C on cancer replication.

Results: I3C inhibits cell proliferation and metabolic activity in a dose-dependent manner. I3C downregulates the expression of cell cycle proteins cyclin E, CDK2, and p-pRb.

Conclusion: I3C downregulates the expression of cell cycle proteins, which inhibits the proliferation of cancer cells. ED-1 cells are particularly susceptible to I3C treatment and should serve as a good model for the effects of I3C on human-type cyclin E in a murine model.

This research was supported by the National Cancer Institute grant R25-CA134283.

Public Link: http://ocrss.louisville.edu/clients/hscro/conspectus/searchview.php?ID=4232

Close Window

Title: CANNABIGEROL MODULATES THE EFFICACY OF ANANDAMIDE ON THE CB2 CANNABINOID RECEPTOR [2015]

Authors: Alyssa Laun[1] Pritesh Kumar[1] Zhao-Hui Song[1] Pharmacology and Toxicology[1]
2015

Keywords: cannabinoid, cannabigerol, cb2

Abstract:

Cannabigerol (CBG) is a non-psychoactive phytocannabinoid isolated from cannabis. It has been shown to have pro- apoptotic and anti-proliferative effects in numerous cancer cell lines, as well as possessing antibacterial properties. The aim of this study was to determine the binding character and functional effect of CBG on the cannabinoid receptor type 2 (CB2) stably expressed in HEK293 cells. A homogeneous time-resolved fluorescence method was used to quantify cannabinoid-induced, CB2-mediated inhibition of cyclic adenosine monophosphate (cAMP) levels. At concentrations up to 1 µM, CBG by itself had no effect on forskolin-stimulated cAMP accumulation. Furthermore, CBG did not significantly modify cAMP inhibition induced by synthetic cannabinoids CP-55,940, HU-210, or endocannabinoid 2-arachidonoylglycerol (2-AG). However, CBG was found to increase the efficacy of endocannabinoid anandamide (AEA). Orthosteric binding was assessed using a competition binding assay, and a dissociation kinetic assay was used to determine allostery. When membranes collected from the cells were treated with µM CBG, it was determined that CBG binds with low CB2 affinity and does not bind allosterically. Finally, the action of CBG on anandamide degradation was measured using thin layer chromatography. It was observed that CBG decreased degradation in membranes. Taken together, these results demonstrate that CBG is neither an orthosteric or allosteric agonist nor an antagonist at the CB2 receptor. In addition, these data suggest that CBG possibly changes the efficacy of AEA on CB2 receptor via metabolic modulation.

Acknowledgements: This work is partially supported by NCI training grant R25 CA134283

Public Link: http://ocrss.louisville.edu/clients/hscro/conspectus/searchview.php?ID=4279

Close Window

Title: Nucleoside diphosphate kinase-dependent suppression of apoptosis in esophageal cancer cells by the oral pathogen Porphyromonas gingivalis. [2015]

Authors: Maya McFrazier[1] Xiaoxian Duan Diane Renaud Richard Lamont David Scott Huizhi Wang Department of Oral Immunology and Infectious Diseases, University of Louisville School of Dentistry[1] and Dental[2] 2015

Keywords: Esophageal cancer, Porphyromonas gingivalis, apoptosis, ndk

Abstract:

Esophageal cancer is the eighth most frequent tumor and sixth leading cause of cancer death globally. Recent evidence suggests that a Gram negative, anaerobic bacterium that is a causative agent of periodontitis, *Porphyromonas gingivalis*, is strongly associated with esophageal cancer. Indeed, *P. gingivalis* infection strongly correlates with disease stage and survival time. However, the potential mechanisms by which this important oral pathogen may predispose to the development of esophageal cancer are entirely unknown. It has previously been established that *P. gingivalis* produces a nucleoside diphosphate kinase (NDK) that can promote epithelial cell survival by hydrolyzing extracellular ATP and preventing apoptosis initiated by the purinergenic receptor, $P2X_7$. Therefore, we set out to determine if *P. gingivalis* was able to inhibit drug-induced apoptosis in esophageal cancer (KYSE-30) cells, hypothesizing that this phenomenon may be dependent upon a functional *ndk* gene. Campothecin, derivatives of which are being tested for treatment of esophageal cancer, induced apoptosis in KYSE-30 cells. Infection with wild type *P. gingivalis* inhibited CAMP-induced esophageal cancer cell death, whereas *ndk*-deficient *P. gingivalis* mutants were less efficient in blocking apoptosis**.** Therefore, the epidemiological association noted between *P. gingivalis* and esophageal cancer may be partly explained by NDK-dependent inhibition of apoptosis.

This study was supported by a NCI R25 grant, University of Louisville Cancer Education Program (CA134283); and by grants DE023633 (HW) and DE017680 (DAS) from the National Institute of Dental and Craniofacial Research, NIH.

Public Link: http://ocrss.louisville.edu/clients/hscro/conspectus/searchview.php?ID=4165

Close Window

Title: A Multi-Organ Study Using Microwave: A Comparison of the Solero system to the Sulis V pMTA and the NeuWave Certus 140 systems [2015]

Authors: Rachel O'Connor[1] Robert Martin[2] Bioengineering[1] and Surgical Oncology[2] 2015

Keywords: Microwave, Ablation

Abstract:

Microwave ablation is designed to deliver a controlled transmission of electromagnetic energy into a targeted tissue during a medical procedure. The microwave energy causes water molecules in the cells to rotate millions of times per second, which causes frictional heating. The frictional heating causes the targeted cells to die (ablation). The system includes a probe that is image guided (ultrasound, fluoroscopy) through either a percutaneous, laparoscopic or an open approach to the site of interest (lung, liver, kidney). The targeted tissue will be coagulated and will lack blood flow. Typically the procedure is performed percutaneously or laparoscopically which provides rapid recovery, shorter hospital stays and immediate improvements without an open incision.

This study is designed to evaluate and verify the Solero microwave ablation system as compared to the Sulis V pMTA and to the NeuWave Certus 140 microwave ablation systems. The goal of this GLP study is to evaluate and establish equivalence of the Solero system to the Sulis V and NeuWave systems with respect to safety and effectiveness. This will be established by tracking the safety and morbidity profile after 28 day survival of the 15 animals in the study. Six animals were ablated using the Solero and Sulis, and three animals used the Neuwave.

Results concluded the efficacy of the Solero system appears to match that of the Sulis V and NeuWave systems. Thus far, a total of 8 female pigs have been ablated with 7 in current stable condition

Supported in part by National Cancer Institute grant R25-CA134283

Public Link: http://ocrss.louisville.edu/clients/hscro/conspectus/searchview.php?ID=4305

Close Window

Title: Distress, Anxiety, Depressive Symptoms and Malnutrition Biomarkers on Head and Neck Cancer Progression and Overall Survival [2015]

Authors: Abbigail Pace[1] Adam Seibert[2] Whitney Rebholz[3] Liz Wilson[4] Jeffrey Bumpous[5] Elizabeth Cash[6] Western Kentucky University, Hospitality Management: Dietetics [1] University of Louisville School of Medicine[2] Department of Psychological and Brain Sciences[3] Department of Otolaryngology- HNS and Communicative Disorders[4] Department of Otolaryngology- HNS and Communicative Disorders, University of Louisville School of Medicine[5] and Department of Otolarynoglogy-HNS and Communicative Disorders, University of Louisville School of Medicine[6] 2015

Keywords: Distress, Anxiety, Depressive Symptoms, Cancer Cachexia, Head and Neck Cancer

Abstract:

Abstract

Our data show that depressive symptoms predict greater likelihood of interruption and incomplete response to treatment in head and neck cancer (HNC). Given relationships between depression and appetite, these patients are at high risk for cachexia. We hypothesized that greater psychological symptoms and malnutrition biomarkers would be associated with increased weight loss, and poorer two-year disease-free (DFS) and overall survival (OS).

Patients with primary HNC (N=98) completed distress, anxiety and depression measures. Pretreatment albumin and hemoglobin, weight lost during treatment, and two-year follow-up data were collected. Hierarchical and Cox regressions adjusted for age, stage, site, and treatment tested hypotheses.

Oropharyngeal (33.7%), laryngeal (17.3%), and oral (10.2%) cancers were included. Many patients reported clinically significant anxiety (42%) and/or depressive symptoms (33%). The vast majority demonstrated biomarker levels WNL, and N=65 demonstrated weight loss averaging 3.6kg. Anxiety, depressive symptoms, and malnutrition biomarkers did not relate to weight loss over the course of treatment. Anxiety was associated with poorer DFS (HR=1.124, 95% CI=1.005-1.258, p=.041), depressive symptoms were associated with poorer OS (HR=1.109, 95% CI=1.012-1.216, p=.027). Lower pretreatment hemoglobin was associated with poorer OS (HR=.740, 95%CI=.561-.977, p=.033).

Depressive symptoms are associated with a greater likelihood of poorer short-term (treatment interruption and incomplete response) and long-term (OS) outcomes in HNC. Malnutrition biomarkers should be further examined to determine their predictive value. Future studies should also examine biological (e.g., inflammatory, immunologic) factors with the potential to mediate psychosocial symptoms and their relationship to tumor progression and survival. (Support: NCI R25-CA134283)

Public Link: http://ocrss.louisville.edu/clients/hscro/conspectus/searchview.php?ID=4467

Close Window

Title: Impact of Quercetin on miR-21, Cell Proliferation and Migration of Metastatic and Non-Metastatic Prostate Cancer Cell lines [2015]

Authors: Thomas Packer[1] Dominique Jones[1] LaCreis Kidd[1] Pharmacology & Toxicology[1] 2015

Keywords: quercetin, miRNA-21, prostate cancer, cell proliferation, cell migration, in vitro

Abstract:

Overexpression of oncogenic microRNAs (miRs) may be counteracted by chemopreventive agents such as quercetin. Reports suggest quercetin reduces cell behavior associated with aggressive prostate cancer (PCA) *in vitro* and modulates the expression of selected miRs *in vivo*. However, it is not clear whether quercetin modulates expression of a known oncomiR (miR-21) and cancer behavior in an African-American derived PCA cell line (E006AA). We hypothesized quercetin will reduce cell proliferation, migration and miR-21 levels in metastatic (PC-3) and non-metastatic (E006AA) PCA cells. To test this hypothesis, cells were treated with various concentrations of quercetin to determine an effective concentration (EC_{50}) for each cell line. Cellular proliferation was assessed after 24 and 48hrs using Trypan Blue Exclusion and BrdU assays. Cellular migration of cells treated with their calculated EC_{50} was assessed after 12 and 24hrs compared with vehicle control using a wound healing assay. miR-21 levels were measured using qRT-PCR. There was a 29-69% decrease in cell proliferation for PC3 and E006AA cells treated with quercetin (12.5-75µM) compared with vehicle control. Quercetin treatment (23-39.475µM) revealed a 43-69% reduction in migration of PCA cells after 24 hrs. Our data suggests quercetin modulates cellular proliferation and migration through a non-miR-21 mediated pathway. These findings may serve as a foundation for future studies on the identification and validation of new therapeutic strategies for pre- and metastatic PCA. Research was supported by NCI grant R25-CA134283.

Public Link: http://ocrss.louisville.edu/clients/hscro/conspectus/searchview.php?ID=4501

Close Window

Title: Temozolomide Enhances Breast Cancer Virotherapy Regardless of Estrogen Receptor Status [2015]

Authors: Rigoberto Perez-Hernandez[1] Heshan Sam Zhou[1] Rajesh Sharma[2] Kelly M. McMasters[1] Jorge G. Gomez-Gutierrez[1] The Hiram C. Polk MD Department of Surgery[1] and James Graham Brown Cancer Center[2] 2015

Keywords: Oncolytic Adenovirus, Autophagy, Temozolomide, Breast Cancer, Tamoxifen

Abstract:

Tamoxifen (TAM) resistance is a major clinical challenge in the treatment of breast cancer (BC). The resistance mechanism of TAM-treated BC cells is pro-survival autophagy. Autophagy is the basic mechanism involving cell degradation of dysfunctional cellular components. Nevertheless, oncolytic adenoviruses (OAds) selectively kill cancer cells by viral oncolysis leaving intact normal cells. The purpose of this study was to evaluate the capacity of TAM-induced autophagy to enhance OAd-mediated oncolysis in human and murine BC cells.

Estrogen receptor positive (ER+) BC (human MCF-7 and murine 4T1) and estrogen receptor negative (ER-) BC (MDA-MB-231) cell lines were infected with an OAd (E1B-deleted Adhz60) alone or in combination with TAM or Temozolomide (TMZ). Previously, our group showed that TMZ increased virotherapy potency in other cancer cells. Crystal violet staining assay revealed that the combination therapy of Adhz60 with TAM or TMZ resulted in greater cell killing (<30% cell viability) compared to single therapy and controls ($p<0.05$). The Adhz60-mediated oncolysis increased in the presence of TAM only in MCF-7 cells. Interestingly, TMZ enhanced virotherapy potency in all three cell lines. The enhanced oncolysis was associated with an increase of adenoviral E1A expression. To the best of our knowledge, this is the first time that TAM is used to increase ER+ BC cell virotherapy. More importantly, we also discovered that TMZ enhanced Adhz60-mediated oncolysis independently of ER status. Our results provide evidence of a novel combinatorial regimen as an alternative to treat BC.

Research supported by the National Cancer Institute-Grant R25-CA134283

Public Link: http://ocrss.louisville.edu/clients/hscro/conspectus/searchview.php?ID=4056

Close Window

Title: Determining Whether SUMO Interacts with Ubiquilin [2015]

Authors: Cody Sheffield Levi Beverly [2] Other[1] and Pharmacology/Toxicology[2] 2015

Keywords: SUMO, Ubiquilin

Abstract:

SUMO proteins are a type of post-translational modification that have a vast array of functions including: nuclear transport, assisting with apoptosis, and protein stability, among others. This project was an attempt to look at the role that SUMO plays, if any, in the protein Ubiquilin. Ubiquilin was chosen for a variety of reasons. For example: Our lab has shown that loss of Ubiquilin results in cell proliferation, as well as epithelial-mesenchymal transition (EMT), which is a process observed in cancer. Our lab has previously shown that Ubiquilin function has been lost in a large percentage of certain cancer cell types. This suggests an important role for Ubiquilin in cancer biology Interestingly, SUMO proteins also play a role in the inhibition of EMT, possibly suggesting that loss of Ubiquilin function is due to SUMOylation, or a problem with the SUMOylation pathway for Ubiquilin. Our hypothesis was that Ubiquilin was either directly or indirectly associated with one or more of the three isoforms of SUMO. To test this, we cotransfected 293T cells with FLAG-Ubiquilin and HA-SUMO. We then immunoprecipitated the cell lysates using FLAG agarose beads, and finally used western blotting to test for HA expression. Unfortunately in the given time we failed to establish the link and our results were inconclusive. Further studies would repeat this process, changing different aspects of the IP process to establish better conditions for the experiment. This research was supported by the National Cancer Institute grant R25-CA134283.

Public Link: http://ocrss.louisville.edu/clients/hscro/conspectus/searchview.php?ID=4407

Close Window

Title: Wide versus Narrow Margins after Partial Hepatectomy for Hepatocellular Carcinoma [2015]

Authors: John Simmons Jack Rostas[2] Robert Martin[3] Arts & Sciences[1] Surgical Oncology [2] and Surgical Oncology[3] 2015

Keywords: Hepatocellular Carcinoma, margins, recurrence

Abstract:

Background/ Purpose:

The optimal balance between oncological results and preserving parenchyma after resection of hepatocellular carcinoma (HCC) has not been clearly elucidated. The goal of this study was to compare the outcome after partial hepatectomy for HCC in which a margin less than or equal to 5 mm or greater than 5mm was achieved.

Methods:

A review of our prospective 2455 patient Hepato-Pancreatico-Biliary database was performed on all patients undergoing primary resection of HCC at a single center from December 2002 to April 2015. Patients were stratified into resection margins 5mm or less (“narrow”) and those greater than 5mm (“wide”). Primary outcome was patterns of recurrence and disease free survival (DFS).

Results:

One-hundred thirty patients were included in the analysis (margin ≤5 mm, n =41 and margin >5 mm, n =89). Baseline and operative characteristics were similar between both groups. At the time of analysis 54 patients had developed a total of 56 recurrences, 15 (37%) in the narrow margin group and 41 (46%) in the wide margin group, p = 0.45 (Table). The pattern of recurrence was similar in the two groups (narrow versus wide): intra-hepatic 11 (79%) versus 30 (75%), p = 1, and extra-hepatic 6 (43%) versus 17 (43%), p =1. Median DFS was similar in both groups, 18.1 versus 19.5 months, p = 0.85.

Conclusions:

A narrow resection margin does not detract from the oncologic outcomes after partial hepatectomy for HCC. Tailoring resection margins may lead to greater preservation of hepatic parenchyma.

Grant Support: National Cancer Institute Grant R25-CA134283

Public Link: http://ocrss.louisville.edu/clients/hscro/conspectus/searchview.php?ID=4138

Close Window

Title: Effect of Hybrid Surface-Modified Nanoparticles on Knockdown of HPV 18 E6 in vitro [2015]

Authors: Lee Sims[1] Jill Steinbach[1] Bioengineering[1] 2015

Keywords: Gene knockdown, PLGA nanoparticles, HPV 18 E6, surface modification

Abstract:

Background: Cancers of the female reproductive tract have a very high incidence rate, being the third leading cause of cancer-related death in women worldwide. Specifically, cervical cancer is the leading cause of death of more than 4,000 women per year in the US alone and is associated with a very high rate of late-stage diagnosis. This is attributed to the minimal symptoms associated with human papillomavirus (HPV) 16 and 18 related cervical cancer. There are few non-invasive treatments for late-stage diagnosis. To overcome this, drug delivery vehicles, such as polymer nanoparticles (NPs), can be utilized to transport non-invasive treatments by protecting agents during delivery, prolonging delivery, and safely localizing drugs and biologics to the tumor microenvironment.

Objective: The long-term goals of this study were to develop poly(lactic-co-glycolic acid) (PLGA) siRNA NPs with a variety of surface modifications to: 1) therapeutically treat HPV 18 related cervical cancer and 2) evaluate how each surface modification contributes to oncogene E6 expression *in vitro*.

Methods: NPs were synthesized using a double emulsion, oil-in-water, technique. *In vitro*, monolayer assays were conducted using reverse transfection of siRNA NPs to evaluate HPV 18 E6 gene expression. Real-time PCR (RT-PCR) was used to determine the gene expression of the E6 oncogene.

Results: Experiments showed that NPs modified with MPG resulted in the most significant gene knockdown.

Conclusions: This coincides with our hypothesis for 2D monolayer experiments due to MPG modified NPs having shown the highest cellular internalization in previous experiments.

Supported by NCI grant R25-CA134283

Public Link: http://ocrss.louisville.edu/clients/hscro/conspectus/searchview.php?

ID=4069

Close Window

Title: pH Specific Dual Targeting of Colloidal Mesoporous Silica Nanoparticles for Pancreatic Adenocarcinomas [2015]

Authors: Alexander Sobolev Lacey McNally Benjamin Fouts Philip Chuong Matthew Neal Molly McNally Medicine[1] 2015

Keywords: nanoparticle, pancreatic cancer, mesoporous silica, contrast agent

Abstract:

Despite continued efforts to increase the survivability rate, the outlook for patients with pancreatic cancer has not substantially improved. In order to combat the difficulty of detection and treatment of the disease, we present a nanoparticle to act as a contrast agent in order to target pancreatic adenocarcinomas. We created colloidal mesoporous silica nanoparticles (CMSN's) using a standard procedure and obtained particles with diameters of a 32±10 nm. The particles were then loaded with IR-780 fluorescent dye and conjugated with a dual pH targeting system of a chitosan coating and V7 peptide. This creates an ideal setup for the particle to detect the acidic environment of an adenocarcinoma. After characterization of the particle, *in vitro* testing identified pH specificity in both S2VP10 and Panc 1 cell lines at pH 6.6 that is 8X and 5X times higher than pH 7.4. In agarose and intralipid tissue phantoms, imaged using Multispectral Optoacoustic Tomography (MSOT), 20X and 4X increased signal was detected at pH 6.6 in S2VP10 and Panc1, respectively. In vivo testing utilizing an athymic mouse model with advanced pancreatic adenocarcinomas followed. After tail vein injection, MSOT images after 8 hours showed tumor specific targeting and little off-target accumulation. Particles were also seen in the aorta indicating that some still remained in circulation.

Public Link: http://ocrss.louisville.edu/clients/hscro/conspectus/searchview.php?ID=4168

Close Window

Title: Inhibiting the Anaphase-Promoting Complex/Cyclosome: An Innovative Approach for Cancer Chemotherapy [2015]

Authors: Karen Udoh[1] J. Mason Hoffman [1] John O. Trent[2] J. Christopher States[1]
Pharmacology and Toxicology[1] and Medicine[2] 2015

Keywords: Anaphase Promoting Complex, inhibitors, mitosis, chemotherapy, drug development, cyclin b, securin

Abstract:

The anaphase promoting complex/cyclosome (APC/C) is a large, E3 ubiquitin ligase that regulates the cell cycle, in particular the metaphase to anaphase transition in mitosis and the re-entry into G1 phase. Inhibition of the APC/C results in mitotic arrest and apoptosis in cancer cells. ANAPC2 and ANAPC11 are shown to be two vital subunits for APC/C function. *in silico* screening of ANAPC2 identified compounds that are predicted to prevent the association of ANAPC2 and ANAPC11. Thus, we hypothesize that the relative levels of the APC/C molecular targets, securin and cyclin B, will increase in cells treated with lead compounds. To gain better insight on the inhibition of the APC/C in cancer cells, HeLa cells were treated with lead compounds 3, 8, 10, and 11 at their respective IC50s for 24 h and then harvested to make lysates. The Bradford Protein Assay was used to determine the protein concentrations in each of the samples. To examine the relative levels of securin and cyclin B, a western blot analysis was performed. Results showed that cells treated with compounds 3, 8, 10, 11 do not have increased levels of securin and cyclin B. However, future analysis may reveal that treatment with the lead compounds causes a decrease in the levels of ubiquitinylated cyclin B and securin. This research was supported in part by University of Louisville Cancer Education Program NIH/NCI grant R25-CA134283 and a Kentucky Lung Cancer Research Program grant to JCS.

Public Link: http://ocrss.louisville.edu/clients/hscro/conspectus/searchview.php?ID=4039

Close Window

Title: Targeting ATP-binding cassette transporter (ABCB5) in BRAF inhibitor resistant melanoma [2015]

Authors: Jingjing Xiao Hongying Hao[2] Kelly McMasters[2] Other[1] and Surgery[2] 2015

Keywords: ABCB5, BRAF inhibitor, melanoma

Abstract:

More than 50% of metastatic melanoma patients have a specific mutation in the serine/threonine kinase BRAF. This results in constitutive activation of the RAS-RAF-MEK-ERK-MAP kinase pathway, which causes uncontrolled cell growth. Vemurafenib (also known as PLX4032) is an oral chemotherapy agent that targets the specific mutation V600E in the BRAF protein. It has shown very promising results, but melanoma cells rapidly develop resistance to the BRAF inhibitor PLX and disease progression ensues. The mechanisms by which melanomas develop BRAF inhibition resistance remain unknown, but the overexpressed ABCB5 oncoprotein, an ATP-binding cassette (ABC) transporter, has been shown to efflux anti-cancer drugs from melanoma. We hypothesize that ABCB5 contributes to the PLX resistance of melanomas by effluxing anti-cancer drugs. Our goal is to determine whether ABCB5 is highly expressed in BRAF inhibitor resistant melanoma cells and to demonstrate that inhibition of ABCB5 may overcome BRAF inhibition resistance. We first established three PLX resistant melanoma cell lines, SK-28PLX, A2058PLX, and A375PLX. We showed that ABCB5 was overexpressed in SK-28PLX and A2058PLX cells, but not A375PLX cells, and that ABCB5 overexpression is associated with activation of p-ERK status. Knockdown of ABCB5 by siRNA resulted in the re-sensitizing of PLX in A2058PLX resistant cells. These results confirm that overexpression of ABCB5 may be one of the causes for resistance to the BRAF inhibitor in melanoma cells. It provides a starting point for personalized treatment strategy in targeting ABCB5 in BRAF inhibitor resistance melanomas.

Public Link: http://ocrss.louisville.edu/clients/hscro/conspectus/searchview.php?ID=4062

Close Window

Title: Exploring Energy Metabolism Changes In Vinyl Chloride Induced Non-Alcoholic Fatty Liver Disease (NAFLD) [2015]

Authors: Heegook Yeo[1] Heegook Yeo[1] Lisanne Anders[1] Adrienne Bushau[1] Brenna Kaelin[1] Gavin Arteel[1] Matt Cave[1] Craig McClain[1] Juliane Beier[1] Pharmacology and Toxicology[1] 2015

Keywords: Vinyl chloride, NAFLD, metabolism, liver

Abstract:

Vinyl chloride (VC) is a ubiquitous environmental contaminant ranking 4th on the ATSDR Hazardous Substances Priority List. We have previously reported increased hepatocellular necrosis in a highly exposed occupational cohort and in vitro models. A major paradigm shift in environmental research is to assess the impact of underlying disorders that may modify risk. Arguably, the most ubiquitous underlying disorder in world is obesity. The impact of obesity-induced liver damage (i.e., NAFLD) on hepatic injury caused by VC is unknown. The purpose of this study was to investigate hepatic injury caused by chloroethanol (ClEtOH; VC metabolite) and the changes in energy metabolism in a high-fat diet (HFD) induced obesity model.

Mice were administered a bolus dose of chloroethanol (or vehicle) after 10 weeks of HFD (42% milk fat) or low fat control diet (LFD; 13% milk fat). Animals were sacrificed 0-24 hours after ClEtOH exposure. Samples were harvested for determination of changes in hepatic carbohydrate and lipid metabolism.

In LFD control group, chloroethanol did not cause significant changes to the liver. In HFD-fed mice, chloroethanol altered the expression of key genes and proteins involved in carbohydrate and lipid metabolism in animals on a HFD.

Chloroethanol (as a surrogate VC exposure) not only exacerbated liver injury in a '2-hit' paradigm but also caused direct metabolic changes. This serves as proof-of-concept that VC hepatotoxicity may be modified by diet-induced obesity and NAFLD. These data implicate exposure to VC in the development of liver disease in susceptible population.

Funding: National Cancer Institute grant R25-CA134283

Public Link: http://ocrss.louisville.edu/clients/hscro/conspectus/searchview.php?

ID=4277