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Title: Identifying serum exosomal microRNA signatures in melanoma patients [2013]

Authors: Samantha Barry, M.S.,[1] Deyi Xiao, M.D.,[1] Douglas Taylor, Ph.D.,[2] Sabine Waigel, M.S.,[3] Wolfgang Zacharias, Ph.D.,[3] Hongying Hao, M.D., Ph.D.,[1] Kelly M McMasters, M.D., Ph.D.[1] Surgery,[1] Department of Obstetrics, Gynecology and Womens Health[2] and Microarray Facility, University of Louisville.[3]

Keywords: serum, exosome, microRNA, melanoma

Abstract:

Melanoma is the 6th most common cancer in the U.S. with a median survival rate of less than one year. Early diagnosis of melanoma is challenging because the traditional histopathologic methods cannot sufficiently distinguish benign from malignant lesions. Minimal invasive and dependable determinants that can refine the individualized diagnosis are needed. Exosomes are small membrane vesicles (~30-120nm) that are secreted from cells and contain protein and RNAs. They are implicated in cell-cell communication. Previous studies have shown that miRNAs in tumor exosomes contribute to progression of disease via mRNA silencing. Characterizing the differences in expression of exosomal miRNA between melanoma and non-melanoma patients could lead to a method for earlier and more quantitative diagnosis. In the current study, blood exosomes were isolated from non-melanoma subjects and Stage I melanoma patients. miRNA array was applied to compare the miRNA expression profiles between non-melanoma controls and Stage I melanomas. Real time RT-PCR was performed to confirm some of the differentially expressed miRNAs in these two groups. We showed that a panel of exosomal miRNAs (such as has-miR-1228 and has-miR-1825) has significant changes in Stage I melanoma patients vs non-melanoma controls. These results provide a starting point for further characterization of exosomal miRNA signatures in melanoma patients. This research could lead to a minimally invasive method for specific diagnosis of malignant melanoma. Funding was provided by the National Cancer Institute grant R25-CA134283

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Title: Tobacco-Induced Dysregulation of Matrix Metalloproteinases in HL-60 cells [2013]

Authors: Harrison Black, BS,[1] Akhilesh Kumar, Ph.D,[1] David Scott, Ph.D.[1] Oral Health and Systemic Disease Research.[1]

Keywords: Matrix Metalloproteinases, Tobacco, Nicotine, Immune cells

Abstract:

Background: Matrix metalloproteinases (MMPs) are proteins that have a unique role in immunity, tissue remodeling, and tumorigenesis. MMPs can break down extracellular components, release bioactive molecules, and induce epithelial-mesenchymal transitions. Nicotine (3-(1-methyl-2-pyrrolidinyl) pyridine), a key toxic component of tobacco, is thought to dysregulate matrix metalloproteinase secretion in innate immune cells. Our model utilizes HL60 cells, which are derived from an individual with acute promyelotic leukemia and have been commonly employed as model of innate immune cell differentiation and function. **Aim:** We set out to examine the influence of nicotine on MMP secretion and activity by HL60 cells. **Method:** HL60 cells were differentiated into monocytes in the presence of PMA and exposed to different doses of nicotine 100 and 1000 ng/ml for up to 48hrs. Gel zymography, ELISAs, micro-array and matrigels were used to characterize the MMP production. **Conclusion:** Nicotine decreased the MMP9 activity in a dose- and time-related manner, without affecting the activity of MMP2, in monocyte-like HL60 cells.

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Title: Development of a blood test as an innovative screening tool for lung cancer [2013]

Authors: James Bradley, B.S.,[1] Kavitha Yaddanapudi, PhD,[1] John Eaton, PhD. Medicine[1] and Pharmacology & Toxicology.[2]

Keywords: Lung cancer, adenocarcinoma, screening, immunotherapy

Abstract:

Lung cancer is the major cause of cancer-related deaths worldwide, accounting for about 1.3 million deaths annually. Approximately $10.3 billion is spent on lung cancer treatment in the United States each year. Often, clinical symptoms only appear during later stages of cancer development at which point the cancer may have metastasized. Various screening strategies have been tested for detection of early stage lung cancer but only one cumbersome technique (low-dose computed tomography) has shown minor promise. We have developed an inexpensive and fast alternative blood test that will detect antibodies appearing early in the development of lung cancer. The test involves flow cytometric analyses of A549 (human lung adenocarcinoma) cells, as well as other cancer cell lines, incubated with dilute patient serum and a secondary anti-human IgG or IgM antibody (tagged with the fluorescent tag, R-Phycoerythrin). Several groups have examined the serum titer of antibodies against specific lung cancer antigens as a possible screening tool, but the strength of our approach is that it is a broad-spectrum screen that will identify antibodies against a variety of known and unknown cell surface antigens. In addition to detecting lung cancer in its earliest stages, preliminary data also suggest our technique offers the exciting possibility of identifying novel human lung cancer antigens that may serve as targets for future immunotherapy. Supported by grant R25- CA-134283 from the National Cancer Institute.

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Title: High-Risk Population in Idiopathic Pancreatic Adenocarcinoma: Guidelines for Screening [2013]

Authors: Elizabeth Bruenderman,[1] Robert CG Martin, MD.[2] Medicine[1] and Surgery, University of Louisville.[2]

Keywords: Pancreatic cancer, High-risk, Screening

Abstract:

Background: Pancreatic cancer (PC) is one of the deadliest forms of cancer in the US, with an annual incidence to death ratio of 0.92, because of the late stage at diagnosis. Identification of high-risk individuals that would be ideal for screening is needed, in order to identify precursor lesions and small early stage disease. Those with a genetic predisposition have largely been identified, but little is known about those at high-risk for idiopathic PC. This study asserts that a high-risk population does exist in idiopathic pancreatic adenocarcinoma, and proposes simple guidelines for screening.

Methods: A systematic review was conducted of the literature regarding identification and screening of high-risk groups.

Results: Those with the highest genetic risk of developing PC include those with hereditary pancreatitis (87 times more likely at age 55), Peutz-Jehgers syndrome (132 times more likely at age 50), *p16-Leiden* mutations (48 times more likely), and familial pancreatic cancer kindreds (32 times more likely). Those with the highest risk of developing sporadic PC include those with new-onset diabetes over age 50 and smoking history.

Conclusion: Given that idiopathic PC is the single largest patient population effected with this devastating disease, some form of screening should be initiated. Currently, the medical community does nothing to attempt early detection of PC. However, sufficient evidence now exists to begin a screening protocol in a high-risk cohort, which would be patients with new-onset diabetes over age 50 and a smoking history.

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Title: The Role of p38 in AS1411 Activity [2013]

Authors: Matthew Forsthoefel, B.S.,[1] E. Merit Reyes-Reyes, Ph.D.,[1] Paula J. Bates, Ph.D.[1]
Medicine and Biochemistry.[1]

Keywords: AS1411, p38, nucleolin, EGFR, siRNA

Abstract:

The anticancer agent, AS1411, is a G-rich phosphodiester oligodeoxynucleotide, which forms a stable quadruplex structure and binds specifically to nucleolin as an aptamer. It efficiently inhibits proliferation and induces cell death in many types of cancer cells, but has little effect on normal cells. We have also shown that AS1411 is taken up by macropinocytosis and stimulates further macropinocytosis by a nucleolin-dependent mechanism in several cancer cells. AS1411 activity correlates with stimulated macropinocytosis, suggesting this hyperstimulation of macropinocytosis may explain the unusual cancer cell death caused by AS1411. Macropinocytosis is a ligand-independent endocytic pathway that is normally activated by growth factor receptor stimulation. One of the downstream effectors of phosphorylated EGFR, p38, has been shown to become activated when treated with AS1411. Therefore in this study, we investigated the participation of the EGFR signaling pathway, specifically the role of p38, in AS1411-induced macropinocytosis and cell death. Pre-incubation of DU145 cells with a specific p38 siRNA did not significantly alter the survival of cell lines treated with AS1411. Furthermore, pre-incubation with the same p38 siRNA did not significantly inhibit the stimulation of AS1411-mediated macropinocytosis. We also found that following pre-incubation of DU145 cells with a specific EGFR inhibitor, the AS1411-dependent interaction between Nonmuscle myosin IIA and EGFR is inhibited. These results suggest that the activation of p38 is not critically involved in the effect of AS1411 on cancer cells. Supported by grant R25-CA-134283 from the National Cancer Institute.

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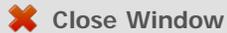
Title: micro-RNA 885-5p and its role in the TGF-β pathway using prostate cancer cell lines derived from European- and African-American men [2013]

Authors: Jonathon Lindner, M.S.E.,[1] Dominique Jones, B.S.,[1] Diana Avila, B.S.,[1] Leila Gobejishvili, Ph.D.,[2] David Barker, Ph.D.,[2] Lee Schmidt, B.S.,[1] Geoffrey Clark, Ph.D.,[1] LaCreis Kidd, Ph.D.[1] Pharmacology and Toxicology[1] and Medicine.[2]

Keywords: TGF-β pathway , Prostate Cancer, PCa, micro-RNA 885-5p

Abstract:

 Limited studies suggest microRNAs (miRNAs) show promise as biomarkers to elucidate gene expression programs that control prostate cancer (PCA) pathogenesis. Previously, we demonstrated that miR-885-5p was under-expressed in serum collected from 15 prostate cancer patients diagnosed with non-metastatic/bone specific-metastatic disease relative to 5 disease-free individuals. miR-885-5p presumably targets TGF-β signaling, which regulates cell cycle signaling and cell death, based on pathway analysis tools/databases. The study evaluated whether re-expression of miR-885-5p within a PC-3 cell line would alter the expression of downstream TGFβ cell cycle signaling targets (p300, p107/RBL1, SP1, E2F4, E2F5). The expression of target genes were measured in PCA (E006AA, LnCaP, DU-145, PC-3), a transiently transfected PC-3, and normal epithelia RWPE-1 cell lines. Re-expression of miR-885-5p in PC-3 cell-lines was performed using a lenti-viral vector (System Biosciences), followed by flow cytometry and qRT-PCR confirmation. Relative to a control cell line (RWPE1), cell cycle signaling targets (p300, p107/RBL1, E2F5) were over-expressed in all the PCA cell lines. Ectopic expression of miR-885-5p in PC-3 cell lines did not significantly alter the selected cell cycle signaling-related genes. Further investigation of other PCA cell lines is needed to assess whether re-expression of miR-885-5p interrogates miRNA targets and associated gene products in the TFG-β signaling pathway. Improved understanding of the characteristics of miRNAs in prostate tumorigenesis and ultimately restoring normal miRNA-mRNA regulation pathways could improve prognostic tools and find new therapeutic targets against advance prostate cancer.

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Title: Developing Computational Tools for Molecular Comparison and Placement of Detectable Uncharacterized Metabolites [2013]

Authors: Joshua Mitchell, B.S.,[1] Hunter Moseley, PhD.[1] Chemistry.[1]

Keywords: Metabolism, metabolomics , CREAM, bioinformatics, biochemistry

Abstract:

Detection and identification of metabolites is key to modeling and understanding complex cellular/extracellular metabolic networks. Advances in metabolomics, especially in ultra-high resolution mass spectrometry enable the rapid analysis of many thousands of peaks (observables), representing a few thousand metabolites. However, a barrier to meaningful interpretation of this mass spectrometry (MS) data is the identification of detectable, but unknown metabolites and their placement within metabolic networks. Recent development of chemoselective (CS) probes that tag metabolite functional groups boosts the speed and accuracy of metabolite detection and provides new computational avenues for metabolite identification. We have developed algorithms that combine this additional functional group information with molecular formulas to improve metabolite identification. With these tools, we can detect all instances of 204 functional groups within the Human Metabolome and KEGG Compound databases. Using both molecular formula and functional group composition of a detected metabolite, determined by techniques such as CS tagging, adduct formation, and the mass-to-charge resolution of Fourier-transform ion-cyclotron-resonance MS (FT-ICR-MS), more compounds can be identified than with molecular formula alone. Using a small subset of possible CS tags, our algorithm identifies 65% of database compounds vs. 45% with molecular formula alone. A historic isomeric and stereoisomeric analysis of both HMDB and KEGG Compound indicate that these improvements in identification should hold as these databases grow. The high isomerism and low stereoisomerism in these databases indicates that our techniques will allow for the identification of a large number of metabolites indistinguishable by molecular formula alone.

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Title: Enhancement of Oncolytic Adenovirus Therapeutic Efficacy by Combination with Temozolomide [2013]

Authors: Jonathan Nitz,[1] Kelly McMasters, MD, PhD,[1] Sam Zhou, PhD,[1] Jorge Gomez-Gutierrez, PhD.[1] Medicine.[1]

Keywords: Oncolytic, Adenovirus, Temozolomide, Lung

Abstract:

Adenoviral therapy is especially promising for lung tumors because adenoviruses have a natural predilection for the lung, making inhalational therapy feasible. Adenoviruses with deletion of the *E1b* gene have been used in clinical trials to treat cancers that are resistant to conventional therapies. The efficacy of viral replication within cancer cells determines the results of oncolytic therapy. Oncolytic adenovrius lacking the *E1b* gene induces autophagy in lung cancer cells. Inhibition of autophagy with 3-methyladenine (3MA) resulted in a decreased synthesis of adenovirus structural proteins, and thereby a poor viral replication; promotion of autophagy with rapamycin increased adenovirus yield. This indicates that adenovirus-induced autophagy correlates positively with virus replication and oncolytic cell death. These results further suggest that the chemotherapeutic agent, temozolomide (TMZ), which increases cancer cell autophagy, may improve the efficacy of oncolytic virotherapy. In this study an oncolytic adenovirus lacking *E1B* gene (Adhz60) was combined with TMZ and the lung cancer killing effect was assessed. It was found that TMZ increased adenovirus early proteins which resulted in increased virus yield, and combination therapy induced synergistic lung cancer killing effect in comparison with cells treated with only Adhz60 or TMZ, there was a close association between increased E1A expression and increased accumulation of autophagy marker LC3-II in cells infected with Adhz60 and treated with TMZ. These results suggest that combination therapy of oncolytic adenovirus and TMZ is a promising approach for lung cancer therapy. Supported by grant R25- CA-134283 from the National Cancer Institute.

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Title: Pancreatic Adenocarcinoma Detected with Targeted Liposomes [2013]

Authors: David D. Picklesimer, MS,[1] Tess V. Dupre, BS,[1] Justin S. Huang, BS,[1] Charles W. Kimbrough, MD,[1] Shanice V. Hudson, BS,[1] Christopher England, MS,[1] Lacey R. McNally, Ph.D.[1] Medicine.[1]

Keywords: Pancreatic adenocarcinoma, IGF-1R, liposome, imaging

Abstract:

Background and Objective:
Therapeutic drugs for pancreatic adenocarcinoma are limited because of off-target toxicity. We hypothesize that preferential targeting by ligand-guided liposomes will allow delivery of therapeutic concentrations while limiting undesirable toxicity. This study evaluates the ability to target S2VP10 and PANC-1 pancreatic adenocarcinoma cells with Syndecan-1 ligand-targeted liposomes binding to the IGF-1R receptor.

Methods:
S2VP10 and PANC-1 cells were evaluated for IGF-1R expression using Western blot. IGF-1R targeted liposomes encapsulating a 750-NIR dye were constructed using Syndecan-1 ligand as the targeting ligand for IGF1-R. Binding of targeted liposomes was compared to non-targeted liposome using flow cytometry. S2VP10 or PANC-1 pancreatic adenocarcinoma cells were orthotopically implanted into SCID mice. When tumors reached 3mm diameter, 200 μL of 5 OD Syndecan-1 liposomes were injected by iv. Fluorescent imaging confirmed targeted liposome binding *in vivo* and of the pancreas and liver *ex vivo*.

Results:
IGF-1R was expressed by S2VP10 cells at higher levels than PANC-1 cells as observed by western blot. Flow cytometry showed 86% and 80% uptake for S2VP10 and PANC-1 cells, respectively. Fluorescence imaging showed peak S2VP10 pancreas tumor liposome uptake at 24 hours and *ex vivo* uptake within the pancreas tumor but not in the liver.

Conclusions:
These experiments suggest that Syndecan-1 ligand-targeted liposomes would improve tumor targeting and delivery of therapeutic concentrations of drugs to pancreatic adenocarcinoma tumors.

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Title: Biochemical consequences of cancer-specific somatic mutations in Ubiquilin-1 [2013]

Authors: Sean Shannon, BS,[1] Levi Beverly, PhD.[2] Medicine[1] and Pharmacology and Toxicology.[2]

Keywords: Ubiquilin, UBQLN1, NSCLC

Abstract:

Ubiquilin-1 (UBQLN1) has been implicated as a key player in the pathogenesis of several neurodegenerative diseases, however thus far its potential role in tumorigenesis has been overlooked. UBQLN1 acts as an adaptor molecule to mediate degradation of ubiquitinated proteins by the proteasome, engage with the aggresome pathway, aid in autophagy, and modulate receptor trafficking. Our previous work has shown that disrupting the function of UBQLN1, via siRNA-mediated loss, causes lung epithelial cells to develop many hallmarks of cancer, including increased proliferation, colony formation, and epithelial-mesenchymal transition. Also, UBQLN1 interacts with several proteins implicated in cancer development, including IGF1R, VCP, and BCLb. Nearly ten percent of human non-small cell lung cancers (NSCLC), especially adenocarcinomas, have been shown to contain non-synonymous, somatic mutations in Ubiquilin-family genes. We hypothesize that many of these mutations impact the stability, function, or interactions of UBQLN1 to contribute to tumorigenesis. Herein, we demonstrate by engineering and expressing somatic mutations specific to NSCLC that these UBQLN1 mutants have significantly altered stability and function. This sheds light not only on our understanding of UBQLN1 function, but also the processes associated with lung adenocarcinoma pathophysiology. This potentially translates to Ubiquilin involvement in tens of thousands of new cases and deaths each year due to NSCLC. Further work is needed to fully unravel the effects of these mutations on UBQLN1 interactions, especially with proteins linked to cancer development, and the influences they ultimately place on tumorigenesis.

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Title: Dysregulated microRNA expression in colon adenoma tissue [2013]

Authors: Benjamin Turner, BS,[1] Henry Roberts, BS,[2] M. Robert Eichenberger, MS,[2] Susan Galandiuk, MD.[1] Medicine[1] and Other.[2]

Keywords: Colon adenoma, microRNA, colorectal cancer, biomarker, laser capture microdissection

Abstract:

 Introduction:

 Early detection of colorectal (CR) adenomas is important in reducing colorectal cancer (CRC) mortality, therefore biomarkers used to detect CR adenomas are in great need. MicroRNAs are small non-protein-coding RNAs responsible for regulation of gene expression and whose expression is altered during the progression of CRC. The purpose of this study was to identify dysregulated expression of miRNAs in CR adenoma tissue for the potential use as biomarkers for the prevention of CRC.

 Methods:

 Adenomatous colon tissue and non-neoplastic colon tissue were isolated from the same patient using laser capture microdissection on prepared slides of formalin fixed paraffin embedded bowel resections. Total RNA from each sample (n=3) was extracted and amplified. The expression of 380 miRNAs was measured using microfluidic array technology.

 Results:

 Two of the 380 miRNAs were dysregulated in colon adenomas compared to non-neoplastic tissue from the same patient (*P < 0.05)*, one upregulated (*miR-29b*) and one downregulated (*miR-361*).

 Conclusion:

 CR adenoma tissue shows dysregulation of at least two miRNAs known to be involved in tumorigenesis. This miRNA expression is unique compared to that of CRC and therefore may be a reliable biomarker for early detection of CR adenomas.

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Title: Restrictive Blood Transfusion Protocol in Liver Resections Patients Reduces Blood Transfusions without Worsening Overall Outcomes [2013]

Authors: John Wehry,[1] Robert Martin, MD.[2] Medicine[1] and Surgical Oncology.[2]

Keywords: transfusion, liver, resection

Abstract:

 Background: Continued reports demonstrate the effects of hospital transfusion related to a longer length of stay, more complications, and possibly worse overall oncologic outcomes. The hypothesis for this study was that a restrictive transfusion protocol would reduce overall blood transfusions with no worsening in overall outcomes.

 Methods: A cohort study was performed using our prospective database from 1/2000 to 6/2013. September of 2011 served as the separation point for the date of operation criteria because this marked the implementation of more restrictive blood transfusion guidelines.

 Results: A total of 186 patients undergoing liver resection were reviewed. The restrictive blood transfusion guidelines reduced the percentage of patients that received blood from 31.0% before 09/01/2011 to 23.3% after this date (0.03). Prior surgery and endoscopic stent were the two preoperative interventions associated with receiving blood. Patients who received blood before and after the restrictive period had similar predictive factors: Major hepatectomies, higher intra-operative blood loss, lower pre-operative hemoglobin, older age, prior systemic chemotherapy, and lower pre-operative nutritional parameters (all P<0.05). Patients who received blood did not have worse overall progression free survival or overall survival.

 Conclusion: A restrictive blood transfusion protocol reduces the incidence of blood transfusions and the number of packed red blood cells transfused. Patients who require blood have similar pre-operative and intra-operative factors that cannot be mitigated in oncology patients. Restrictive use of blood transfusions can reduce cost and does adversely effects patients undergoing liver resection.

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Title: Novel Therapies for BRAF-Inhibitor Resistant Melanoma [2013]

Authors: Matthew Zeiderman, BA,[1] Michael Egger, MD MPH,[1] Charles Kimbrough, MD,[1] Christopher England, MS, Tess Dupre, BS, Kelly McMasters, MD PhD,[1] Lacey McNally, PhD.[3]

Surgery,[1] Pharmacology & Toxicology[2] and Medicine.[3]

Keywords: BRAF, metastatic, melanoma, targeting, therapy, drug, resistant, emmprin

Abstract:

 Most patients develop resistance to Vemurafenib(PLX) treatment after 6 months. We identified a uniquely expressed receptor by PLX-resistant melanoma cells to provide novel target for cancer cells. Extracellular matrix metalloproteinase inducer (EMMPRIN) is highly expressed in metastatic melanoma. Using an S100A9 ligand, we created an EMMPRIN targeted probe and liposome that binds to melanoma cells *in vivo*, thus designing a novel *in vivo* drug delivery vehicle.

Methods

 PLX-sensitive and PLX-resistant melanoma cells highly express EMMPRIN. EMMPRIN targeted liposomes were created using S100A9 ligand and encapsulating CF-750 NIR-dye. Both PLX-sensitive and resistant cells were evaluated utilizing flow cytometry. A2058PLX and A2058 cells were subcutaneously injected into athymic mice. Once tumors were palpable, S100A9 liposomes were IV injected. Probe and liposome accumulation were evaluated using fluorescent imaging and multispectral optoacoustic tomography at 6 hr intervals.

Results

 PLX-sensitive and resistant A2058 expressed high levels of EMMPRIN. Intracellular accumulation of dye was increased with S100A9 liposomes (49.9%) compared to control liposomes.

 We also observed accumulation of S100A9 liposomes within subcutaneous A2058 and A2058PLX tumors *in vivo* using NIR-fluorescent imaging and multispectral optoacoustic tomography at 12h and 18h. While S100A9 probe accumulation peaked at 18h, S100A9-liposomes accumulated within the tumor beginning at 18h through 48h.

Conclusion

In conclusion, the use of EMMPRIN targeted liposomes via an S100A9 ligand is a novel delivery system which could improve concentration of drug within tumors and reduce systemic toxicity. This method may efficaciously treat patients with BRAF-inhibitor resistant metastatic melanoma.

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