DDC
Texas Medical Center Digestive Diseases Center

13TH ANNUAL
Frontiers in Digestive Diseases Symposium

Single Cell Biology

Refining concepts of lineage and identity

MARCH • 26 • 2022
NRI BUILDING • 8AM - 3PM

PROVIDED BY TEXAS CHILDREN'S HOSPITAL

Target Audience: Physicians, specialists, fellows, residents, researchers, medical students, and other health care providers who are interested in digestive diseases research.

Educational Objectives: At the conclusion of this live activity, participants should be better able to define the use of single cell biology, its history and future applications in GI infection and injury, apply best practices and treatments for digestive diseases through single cell biology, identify opportunities to apply this knowledge to the detection and treatment of digestive diseases, and interpret the current single cell research concerning GI infection and injury.

Accreditation / Credit Designation: Texas Children's Hospital (TCH) is accredited by the Texas Medical Association to provide continuing medical education for physicians. Texas Children's Hospital designates this live educational activity for a maximum of *4.5 AMA PRA Category 1 Credit(s)™*. Physicians should claim only the credit commensurate with their participation.

Texas Children's Hospital®

DDC
Texas Medical Center Digestive Diseases Center

About the Texas Medical Center Digestive Disease Center (DDC)

The Texas Medical Center Digestive Diseases Center facilitates cutting-edge digestive diseases research, promotes translational collaborative research between basic and clinical areas, develops new projects, nurtures new investigators, and provides GI educational activities.

The DDC is a federally funded center (NIH P30DK056338) designed to serve basic and clinical scientists at institutions within the Texas Medical Center, including Baylor College of Medicine, The University of Texas Health Science Center at Houston, and the MD Anderson Cancer Center.

The DDC supports three basic science cores: Tissue Analysis and Molecular Imaging, Functional Genomics and Microbiome, Gastrointestinal Experimental Module Systems; and one clinical core: Study Design and Clinical Research.

Current DDC membership includes 103 members, with 62 full members and 41 associate members. DDC members have approximately $38 million in digestive diseases-related research funding as of 2022. The overall theme of the DDC is “Molecular mechanisms and outcomes of injury, infection, or metabolic dysfunction of the digestive system.”

Visit the DDC website to learn more about upcoming enrichment activities, funding opportunities, and other valuable resources.

Visit the DDC online!

https://www.bcm.edu/research/research-centers/texas-medical-center-digestive-

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AGENDA

IN PERSON
VIRTUAL / LIVE
PRE-RECORDED VIDEO

7:30 AM - 8:10 AM **BREAKFAST**

8:10 AM - 8:25 AM **WELCOME REMARKS**
Hashem B. El-Serag, M.D., M.P.H.
Center Co-Director

SESSION I *(moderated by Jason Mills, M.D., Ph.D., Center Co-Director*

8:25 AM - 9:20 AM **"Deconstructing the liver and pancreas lineages: Paths & plasticity"**
Francesca Spagnoli, M.D., Ph.D.
Professor of Regenerative Medicine
King's College London, United Kingdom

9:20 AM - 10:00 AM **"Mapping the human intestine and colon by single cell transcriptomics"**
Scott Magness, Ph.D.
Associate Professor of Medicine, Gastroenterology & Hepatology
University of North Carolina, Chapel Hill, North Carolina

10:00 AM - 10:40 AM **"Single cell transcriptomics reveals a concerted epithelial plasticity program in pancreatic injury and tumorigenesis"**
Kathy DelGiorno, Ph.D.
Assistant Professor, Cell & Developmental Biology
Vanderbilt University Medical School, Nashville, Tennessee

10:40 AM - 11:00 AM **COFFEE BREAK**

SESSION II *(moderated by James Versalovic, M.D., Ph.D. Center Associate Director)*

11:00 AM - 11:25 AM **"Fortifying the Fence one Cell at a Time: Intestinal response to viral infection"**
Sarah Blutt, Ph.D. (2016 DDC PF Awardee)
Associate Professor, Virology & Microbiology
Baylor College of Medicine, Houston, Texas

11:25 AM - 12:05 PM **"Single Cell Transcriptomics of the Stomach Reveals New Insights into Gastric Metaplasia"**
Richard DiPaolo, Ph.D.
Professor and Interim Chair, Molecular Microbiology & Immunology
Saint Louis University School of Medicine, St. Louis, Missouri

12:05 PM - 12:35 PM **"Cellular Origin of Gastric Cancer: Focusing on PPARD and Signaling Circuit"**
Xiangsheng Zuo, Ph.D. (2021 DDC PF Awardee)
Assistant Professor, Gastrointestinal Medical Oncology
The University of Texas MD Anderson Cancer Center, Houston, Texas

12:35 PM - 1:35 PM **LUNCH / BREAKOUT SESSIONS**
Francesca Spagnoli, M.D., Ph.D.
Scott Magness, Ph.D.
Kathy DelGiorno, Ph.D.
Richard DiPaolo, Ph.D.

1:35 PM - 2:45 PM **POSTER SESSION**

2:45 PM - 3:00 PM **POSTER AWARDS / CLOSING REMARKS**
Doug Burrin, Ph.D.
Pilot Feasibility Program Director

Directly provided by Texas Children's Hospital
Hosted by the Texas Medical Center Digestive Diseases Center
Saturday, March 26, 2022 | 8:00 am – 3:00pm | NRI Building, 7th Floor

"Deconstructing the liver and pancreas lineages: Paths and plasticity"
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Gastroenterology & Hepatology, University of North Carolina, Chapel Hill, North Carolina

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DISCLOSURE: Kathleen DelGiorno, Ph.D., provides contracted research support to Cumberland Pharmaceuticals. Other speakers listed above have reported no relationships with proprietary entities related to the content of this activity. Persons involved in the planning of this activity have reported no relevant financial relationships with any commercial interest.

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Dr. Spagnoli received her Ph.D. in Genetics from the Pasteur Institute in Paris, France. She then did her postdoc at The Rockefeller University, New York, USA, in the Brivanlou lab. In 2008, she established her own research group at the Max Delbrück Center in Berlin, Germany, where she initiated new lines of investigation on the control of pancreatic cell identity and lineage reprogramming strategies. She subsequently moved to King's College London, where she is Full Professor in Regenerative Medicine and Group Leader in the Centre for Stem Cells and Regenerative Medicine. She has been the recipient of prestigious grants, including the ERC Starting grant, ERC Proof-of-Concept grant, and Wellcome Trust Investigator award. More recently, she became the coordinator of a FET Open European Consortium on bioengineering pancreatic tissue. She is also the Director of Wellcome Trust PhD Programme called "Advanced Therapies for Regenerative Medicine."

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Dr. Magness is an Associate Professor in the University of North Carolina/NC State University joint Departments of Biomedical Engineering. He is the founder and director of the UNC Center for GI Biology and Disease Advanced Analytics core for single cell genomics and EpCultures. Dr. Magness' group pioneered new 3D organoid technologies and has developed a number of next-generation 2D platforms that leverage stem cells derived from organ transplant donors or patient biopsies for basic, translational science and commercial applications. Dr. Magness is the recipient of a Transformative Research Award from the National Institutes of Health for this work. He is the founder of Altis Biosystems Inc., which is a hybrid biological tools/CRO company focused on providing the pharmaceutical industry with better preclinical cell culture models of the human gut.

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Kathleen (Kathy) DelGiorno, Ph.D. graduated with a B.S. in Biology from the United States Air Force Academy in 2005. She went on to serve as a Biological Research Officer in the U.S. Air Force for two years before working as a Research Associate studying pancreatic and adrenal cancers at the Translational Genomics Research Institute; simultaneously earning an M.S. from the University of Florida in Pharmacy. She earned her Ph.D. in Molecular Genetics and Microbiology from the State University of New York at Stony Brook and then completed three years of Postdoctoral research at Fred Hutchinson Cancer Research Center. Dr. DelGiorno continued her research in pancreatic cancer in the Wahl laboratory at the Salk Institute for Biological Studies. She now serves as Assistant Professor in the Department of Cell and Developmental Biology at Vanderbilt University.

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Dr. Blutt's research focuses on the biology of the intestinal epithelium, emphasizing the intestinal stem cell (ISC) and its role in maintaining intestinal function. Her work contributes to the understanding of how ISCs and the surrounding niche repair damaged epithelium and maintain its many important functions.

Organoids recapitulate many epithelial functions and provide a new preclinical platform to study human disease. Dr. Blutt has expanded and developed this technology at Baylor College of Medicine to include other epithelial models, including the airway, nasal cavity, liver, bladder, and vagina. Dr. Blutt is an Associate Professor of Virology & Microbiology at Baylor and leads the TMC Digestive Disease Center Gastrointestinal Experimental Model Systems Core, which provides services, training, and gastrointestinal organoid reagents to investigators within the medial center, nationally, and internationally.

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Dr. DiPaolo is Professor and Interim Chair in the Department of Molecular Microbiology & Immunology at Saint Louis University. He received his PhD in pathology and immunology at Washington University, St. Louis in 2002 and completed a fellowship in cellular immunology at the National Institute of Allergy and Infectious Diseases in 2007.

Dr. DiPaolo is interested in how inflammation induces cancer. His early research focused on a mouse model of inflammation induced gastric cancer, and studying the roles cytokines, regulatory T cells, and the gastric microbiome play in regulating gastric carcinogenesis. Today, his research program includes studies of immune cells, cytokines, and receptors as a means to understand and regulate a number of inflammatory diseases.

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Dr. Zuo currently serves as an Assistant Professor in Department of Gastrointestinal (GI) Medical Oncology at The University of Texas M.D. Anderson Cancer Center. As a senior cancer research scientist by training, she has an extensive laboratory and animal research experience in studying GI inflammation and tumorigenesis especially in the organs of the stomach, colon and pancreas.

Dr. Zuo's research has utilized human patient tissues, cancer cell lines, and mouse models to understand the role and molecular mechanisms of determining factors in GI inflammation and tumorigenesis through in vitro and in vivo studies. She is a 2021 DDC Pilot Feasibility Awardee.

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"Causes of death after intrahepatic cholangiocarcinoma diagnosis: A population-based study"

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"Constructing a molecular profile for regenerating parietal cells"

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"Cell autonomous adenosine signaling through Adora2b promotes pancreatic ductal adenocarcinoma"

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Poster #5
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"Circadian dysfunction promotes NAFLD-related carcinogenesis in human hepatocytes"

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"Modeling and dissecting poorly differentiated gastric cancer initiation"

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"The TMC Digestive Diseases Center (DDC) Tissue Analysis & Molecular Imaging (TAMI) Core"

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"The TMC Digestive Diseases Center (DDC) Functional Genomics & Microbiome (FGM) Core"

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"The TMC Digestive Diseases Center (DDC) Gastrointestinal Experimental Model Systems (GEMS) Core - Organoid Subcore"

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"The TMC Digestive Diseases Center (DDC) Gastrointestinal Experimental Model Systems (GEMS) Core - Gnotobiotic Subcore"

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"The TMC Digestive Diseases Center (DDC) Study Design & Clinical Research Core"

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Poster #36

Causes of death after intrahepatic cholangiocarcinoma diagnosis: A population-based study

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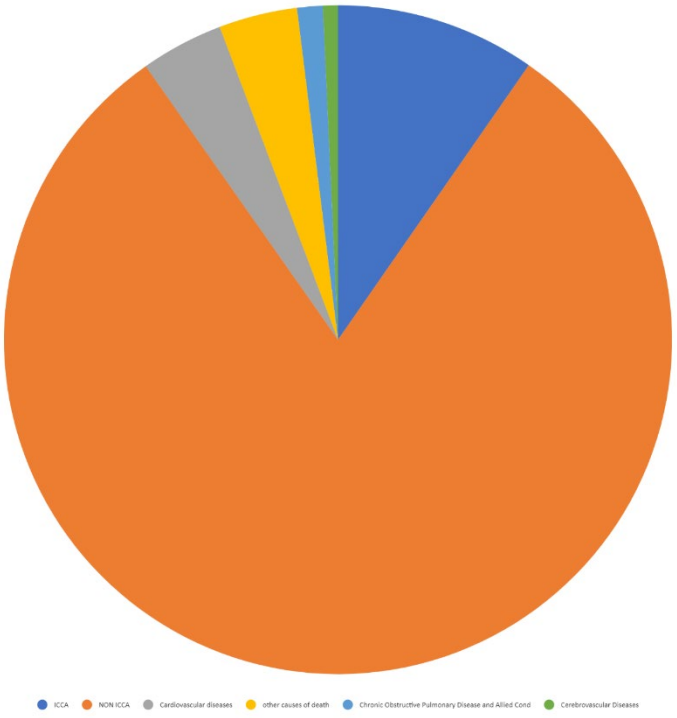
Abstract: Background: Intrahepatic cholangiocarcinoma (ICCA) has shown a substantial increase in mortality globally. On the contrary, perihilar cholangiocarcinoma (pCCA) and distal cholangiocarcinoma (dCCA) have been decreasing; however, studies on causes of death in ICCA patients remain limited. We aim to focus on and evaluate the causes of death after ICCA diagnosis.

Methods: In this retrospective cohort, we studied 276,712 ICCA patients diagnosed between 2004 and 2016 in the United States. The standardized mortality ratio (SMRs) with 95% confidence intervals (CIs) for each cause of death using the SEER*Stat software version 8.3.9.2.

Results: Out of the 276,712 patients diagnosed with ICCA, 203,914 (73.7%) were between 50 and 79 years (The mean age at diagnosis was 63.51 years); 220,648 (79.7%) were white, and 144,942 (52.4%) were females. 35,814 patients (12.9%) died during the follow-up period with a mean age of 70.83 years. The highest number of deaths (34,444; 96.2%) occurred within the first year following the diagnosis. During all latency periods, 3,339 (9.3%) deaths were from ICCA, and 27,790 (77.6%) were from other cancers. The most common cancer causes were lung and bronchus cancer (9862; 27.5%) followed by pancreatic cancer (3475; 9.7%), and 4,685 (13.1%) from non-cancer causes. Cardiovascular diseases were the leading non-cancer causes (SMR 1.95; 95% CI (1.85-2.06)), followed by Chronic Obstructive Pulmonary Disease and related Conditions (SMR 2.52; 95% CI (2.29-2.78)).

Conclusion: Following ICCA diagnosis, the most common cause of death was lung and bronchus cancer followed by pancreatic cancer and ICCA, and cardiovascular disease represents a substantial percentage of non-cancer deaths (4.97%).Our findings provide critical insights into how ICCA survivors should be followed-up and monitored regarding future health risks.



Abstracts

Constructing a molecular profile for regenerating parietal cells

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Highly specialized, acid secreting parietal cells are essential for maintaining homeostasis in the stomach; however, gastric injury, such *as Helicobacter pylori* infection, can lead to loss of parietal cells, which by mechanisms that are not completely understood, can cause progression to gastric cancer. While much is known about the structure and function of parietal cells from morphological and cell physiological studies, little is known about the signaling pathways and transcriptional events that guide parietal cell fate specification and maturation during homeostasis and recovery from injury. To better resolve the morphological and molecular mechanisms that guide parietal cell fate decisions and maturation, we have developed an acute, reversible injury model that allows targeted ablation of parietal cells with a short recovery period as they regenerate. Because the 36–72-hour timeframe of recovery features rare mature PCs and numerous proliferating and juvenile PCs, we termed this the “Phoenix Stage”, the optimal time to study parietal cell regeneration. To characterize, for the first time, the morphological and molecular sequence of events that occur during PC development from the stem cell, we used electron microscopy, immunostaining, bulk and single-cell RNA-seq at multiple Phoenix Stage timepoints. We previously determined that regeneration of PCs requires metabolic regulation by the energetic sensor AMPK and a transcriptional co-activator PCG1α. We confirm these roles and further identify the first transcriptional regulator of PC differentiation, maturation, and maintenance: Estrogen-related receptor gamma (ESSRG or ERRγ), a nuclear hormone receptor that is regulated by AMPK and directly interacts with PCG1α to regulate cellular metabolism. ERRγ has not been previously shown to govern differentiation in any tissue. But we show it is required for PC census, as even haploinsufficiency for the gene causes significantly decreased PCs, and complete ablation results in gastric units completely lacking PCs. Extensive dimension-reduction and pseudotime analyses of single-cell RNA-Seq data of PC precursors also reveals many additional, novel genes involved in PC differentiation. By identifying the molecular regulators governing PC regeneration following injury, we can develop methods to reverse or prevent ailments characterized by loss of parietal cell, like gastric cancer and autoimmune gastritis.

Obstructive sleep apnea induced gut dysbiosis stimulates a proinflammatory response that promotes neuroinflammation and hypertension

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Background and Hypothesis: Obstructive sleep apnea (OSA) is an independent risk factor for the development of hypertension (HT). We have previously demonstrated that OSA induces gut dysbiosis, and a dysbiotic microbiota is causal in the development of HT. However, the mechanisms linking gut dysbiosis to blood pressure (BP) regulation are unclear. Recent studies have demonstrated that gut dysbiosis can induce a pro-inflammatory response of the host resulting in peripheral- and neuro-inflammation, key factors in the development of HT. **We therefore hypothesized that OSA induced gut dysbiosis elicits a pro-inflammatory response that promotes neuroinflammation and hypertension.**

Methods: OSA was induced in 8-week-old male rats (60 apneas/hour for 8 hours during the sleep phase) by repeatedly inflating a surgically implanted tracheal balloon. Sham rats underwent balloon implantation without inflations. After two weeks of apneas, lymphocytes were isolated from aorta, brain, cecum, ileum, mesenteric lymph node, and spleen for assessment by flow cytometry. In studies examining the role of IL-17, a monoclonal antibody to IL-17 was injected every 48 hours during the 2 weeks of apneas to neutralize circulating IL-17. To track the distribution of lymphocytes originating from the gut, cells in the Peyer's patches of the small intestine were labelled by microinjection of carboxyfluorescein succinimidyl ester (CFSE) dye.

Summary of results: Following 2 weeks of OSA we found a significant decrease in anti-inflammatory regulatory T (Treg) cells along with an increase in T_H17 (IL-17+) in the brain, cecum, and ileum and T_H1 (IFN-γ+) in cecum and ileum (n=7, $p<0.05$ for each). A significant increase in the Th17/Treg ratio, a sign of inflammation associated with hypertension, was observed in brain, cecum and ileum of OSA, versus sham, rats (n=7, $p<0.05$ for each). To examine the role of T_H17 cells, we injected an IL-17 neutralizing antibody or control IgG antibody during the 2 weeks of OSA. Compared to OSA rats receiving IgG control, neutralization of IL-17 significantly reduced BP of OSA rats after 1 and 2 weeks (n=6, $p<0.05$ for each). Additionally, neutralization of IL-17 resulted in a significant increase of Tregs and decreased Th1 cells and TNFα expressing cells in brain, cecum and ileum of OSA rats (n=6, $p<0.01$ for each). To examine the distribution of lymphocytes originating from the gut, cells in the Peyer's patches of sham and OSA rats were labelled with CFSE. We observed significant increases in CFSE+ Th1, Th2, and Th17 cells in the brain, MLN and spleen of OSA as compared to sham rats (n=6, $p<0.05$).

Conclusion: Overall, we found that OSA induced gut dysbiosis is associated with a pro-inflammatory response in the gut and brain that involves IL-17 signaling. Our findings suggest that gut dysbiosis may serve as the trigger for widespread inflammation, and treatment strategies to prevent or reverse gut dysbiosis may prove useful in reducing neuroinflammation and HT.

Abstracts

Cell autonomous adenosine signaling through Adora2b promotes pancreatic ductal adenocarcinoma

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Significance: The main goal of this study is to evaluate the mechanisms by which elevated extracellular adenosine generation and signaling through the Adenosine 2B receptor (Adora2b) promotes pancreatic intraepithelial neoplasia (PanIN) and pancreatic ductal adenocarcinoma (PDAC). PDAC is one of the most lethal malignancies and therapeutic resistance remains a major roadblock to improving survival. *KRAS* mutations are prevalent in human PanIN and PDAC; yet mechanisms directly targeting K-RAS for treating PDAC remain unsuccessful. To *make progress toward defining new therapeutic strategies*, we have developed cell of origin genetically engineered mouse (GEM) models of PDAC which rely on expression of mutations in *Kras* and/or *Trp53*. We recently described RNA-seq analysis of ductal versus acinar derived tumors from our murine models. These new analyses revealed *NT5E*/CD73 is highly expressed in tumors arising in pancreatic ducts and in human Squamous and Basal subtypes. CD73 is the ectoenzyme that converts extracellular precursor nucleotides (5'AMP) to adenosine and functions as a pacemaker for adenosine generation and signaling through 4 adenosine receptors (Adora2a, Adora2b, Adora1 and Adora3), which are expressed on epithelial and stromal cells.

Methods: We elevated Adora2b in Kras mutant murine pancreatic ducts and used immunohistochemistry to evaluate cellularity of Adora2b in human chronic pancreatitis, PanIN and PDAC. In addition, we used cBioPortal to analyze correlative gene expression and overall survival in human PDAC. We studied the functional consequences of elevated Adora2b using pharmacologic inhibitor and genetic approaches.

Results: We show high levels of adenosine in human and murine cancer cell line supernatants compared to normal human pancreatic cells. Our analysis of human sequencing data shows Adora2b is significantly elevated in PDAC compared to normal pancreas. Notably, in reviewing TCGA data from human pancreatic tumors, we observed high expression of Adora2b is significantly correlated with worse prognosis in PDAC patients and with high CD73 and KRAS expression. Using immunohistochemistry, we show expression of Adora2b in 88% of PanIN and PDAC and we present new data that inhibiting Adora2b reduces PDAC cell line growth and reduces PDAC development in spontaneous murine PDAC GEM models. In addition, we show genetic loss of Adora2b significantly reduces the abundance of PDAC.

Conclusions: Adenosine signaling is an important cell autonomous driver of PDAC initiation and progression. In future studies, we will evaluate the use of Adora2b inhibitors in spontaneous GEM models and well as confirm the protective effect of genetic deletion of Adora2b in PDAC. In addition, we are evaluating the mechanistic consequences of Adora2b signaling in PDAC using in vitro and in vivo methods.

Pro-Inflammatory role of bone morphogenetic protein 2 in acute pancreatitis in aged mice

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Background: Susceptibility of acute pancreatitis (AP) increases with aging in human. However, the underlying mechanisms are not well defined. We previously reported that in young mice, bone morphogenetic protein (BMP) signaling is upregulated in cerulein-induced AP; AP injury can be attenuated by a BMP antagonist, noggin, suggesting a pro-inflammatory role of BMP signaling. In this study, we explored role of BMP signaling in aging-related AP-induced inflammation.

Methods: AP was induced in young (4m) and aged (24m) male C57BL/6 mice by cerulein (50μg/kg, 9 hourly ip injections); control mice received PBS (n=2 mice/group). The mice were euthanized 1h after the last injection, the blood was harvested for analysis of serum cytokines, and the pancreas was harvested for cyclooxygenase (COX) 2-protein expression. Primary pancreatic acini were isolated and treated with BMP2 (1.6nM for 24h); the cell lysates were prepared for COX2 protein expression.

Results: *In vivo*, basal and cerulein-induced serum IL-6 levels in aged mice were dramatically increased compared to young mice (30- and 17-fold respectively, $p<0.05$); basal and cerulein-induced serum TGF-β1 levels revealed a similar pattern, with 1.2- and 2.2-fold increases respectively ($p<0.05$). Basal and cerulein-induced serum BMP2 levels in aged mice increased 1.8- and 5.5-fold respectively compared to young mice ($p=0.093$); a similar pattern was observed in basal and cerulein-induced pancreatic COX2 protein levels. *In vitro,* aged acinar cells had remarkably higher basal and BMP2-induced COX2 protein expression compared to young acinar cells.

Conclusion: We demonstrate increased basal and AP-induced inflammation in aged mice compared to young mice. Increased BMP2 levels *in vivo* in aged mice and enhanced BMP2-induced inflammatory response *in vitro* in aged acinar cells suggest that BMP2 may play a pro-inflammatory role in aging-related AP-induced inflammation.

Abstracts

Serotonin receptor 4 (5-HT4R) mediates contractility in transplanted human intestinal organoids (tHIOs) with an enteric nervous system (ENS)

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Introduction: Short bowel syndrome (SBS) is a devastating condition. Tissue-engineered small intestine (TESI) may be a solution. Human Intestinal Organoids (HIOs) are a TESI model derived from human pluripotent stem cells (hPSCs). A successful TESI model recapitulates the three main functions of intestine: propulsive peristalsis, nutrient absorption, and barrier maintenance. HIOs mature considerably in vivo as transplanted HIOs (tHIOs). Research to date has demonstrated the successful integration of a rudimentary enteric nervous system (ENS) and preliminary functions, such as muscle contractility. However, the mechanisms responsible for complex HIO function remain unknown. Serotonin (5-hydroxytryptamine) receptor 4 (5-HT4R) is expressed by the intestinal epithelium, mesenchyme, and enteric neurons. 5-HT4R agonists have been shown to stimulate motility as well as enteric neurogenesis and survival, whereas 5-HT4R antagonists abrogate agonist effects. Thus, understanding the role of 5-HT4R in HIOs may help to optimize the generation of a functional HIO- derived TESI for therapeutic application in children suffering from SBS. Our hypothesis is that 5-HT4R mediates contractility in HIOs with an ENS.

Methods: HIOs and ENS precursors were generated in vitro from hPSCs. HIOs were co-cultured with ENS precursors and grown in vitro for 28 days. HIOs were transplanted into immunocompromised mice. tHIOs were harvested for analysis after 6-16 weeks in vivo. Immunohistochemistry was performed on tHIOs+ENS to confirm the presence and location of 5-HT4R. tHIOs were cut into strips and mounted in a contractility apparatus. After equilibration, ex vivo contractile activity data was recorded at baseline and with 10nM of GR113808, a 5-HT4R antagonist. Total contractile activity was calculated as the area under curve and amplitude as the average cycle height. Both were normalized to tissue cross sectional area.
Frequency was calculated as the average contractions per minute.

Results: Immunohistochemistry revealed that tHIOs+ENS expressed 5-HT4R primarily in the epithelium, rather than enteric neurons, similar to human ileum. The total contractile activity and amplitude in tHIOs+ENS decreased significantly after the addition of GR113808. There was no significant difference in the frequency of contractions in tHIOs+ENS after the addition of GR113808.

Conclusion: We demonstrated that 5-HT4R regulates *ex vivo* contractility in tHIOs+ENS. The 5-HT4R antagonist may be primarily working through epithelial 5-HT4R, but this remains to be confirmed in future studies utilizing a genetic knockout HIO model. Future studies will focus on 5-HT4R agonist ability to stimulate ENS development and function in tHIOs.

Abstracts

Rotavirus infection elicits host responses via P2Y1 purinergic signaling

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Rotavirus causes life-threatening diarrhea in children, resulting in ~130,000 deaths each year. Rotavirus infects a limited number of cells at the tips of the villi in the small intestine. Yet, rotavirus dysregulates cells far away from the site of infection. We recently identified, using simian (SA11) and rhesus rotavirus (RRV) that infected cells release the purinergic signaling molecule ADP, which binds to the P2Y1 receptor on nearby uninfected cells. Furthermore, using the *in vivo* mouse model, mild rotavirus diarrhea in mouse pups was alleviated by daily treatment with a P2Y1 inhibitor. To elucidate the role of purinergic signaling via P2Y1 receptors during rotavirus infection, we used the mouse-like rotavirus (D6/2) to investigate the effects of purinergic signaling in the context of severe rotavirus infection *in vivo*. C57Black6 mouse pups were orally gavaged D6/2 rotavirus at day 4-6 of age and assessed over the course of 5 days. Beginning at day 1 post infection, infected pups were treated daily by oral gavage with saline or 4mg/kg MRS2500, a selective P2Y1 antagonist. Stool was collected and scored for diarrhea daily prior to each treatment. Pups were euthanized and small intestine tissue was collected at 3 and 5 days post infection for immunostaining, qRT-PCR and luminal contents. Similar to mild rotavirus infection, treatment of D6/2-infected mouse pups with MRS2500 results in decreased severity and incidence of diarrhea. MRS2500 treated pups also exhibit decreased luminal serotonin and chloride content compared to control infected pups. Together, these results confirm that P2Y1 signaling is also involved in the pathogenesis of a homologous murine rotavirus strain. Viral stool shedding, assessed by qRT-PCR for rotavirus gene 11 levels, revealed that MRS2500 treated pups had significantly lower viral shedding starting at day 4 post infection compared to saline treated pups, which suggests P2Y1 signaling may amplify rotavirus replication. Collectively these findings point to the conserved role of purinergic signaling in the pathophysiology of rotavirus infection, and indicate P2Y1 is a new candidate for host-targeted therapeutics that could have both antiviral and antidiarrheal effects against rotavirus pathophysiology.

Circadian dysfunction promotes NAFLD-related carcinogenesis in human hepatocytes

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The increased risk of obesity and NAFLD-related hepatocellular carcinoma (HCC) is coupled with the prevalence of chronic circadian disruption. We previously reported that chronic circadian disruption (jet lag) induces obesity, metabolic syndrome, and NAFLD-related HCCs in wild-type (WT) mice. We predicted that circadian dysfunction is also an independent risk factor of hepatocarcinogenesis in humans.

To test this hypothesis, we generated humanized mice by repopulating normal human hepatocytes in the livers of immune deficient *Fah*$^{-/-}$;*Rag2*$^{-/-}$;*Il2rg*$^{-/-}$ (FRG) mice and studied the role of chronic circadian dysfunction in spontaneous carcinogenesis in human hepatocytes. We found that circadian dysfunction significantly decreased the survival of humanized *FRG* mice and increased carcinogenesis in human hepatocytes. Immunohistochemical studies and PCR genotyping found about 50% all tumors identified as humanized HCCs in which tumor microenvironment was composed of murine non-hepatocytes while tumors were derived from human hepatocytes. Pathological analysis revealed that carcinogenesis of humanized HCCs followed a pathway closely resembling to that described for NAFLD-related HCCs in humans, with the HCC incidence independent of gender or age of human hepatocyte donors. Our large-scale transcriptome analyses defined dynamic changes in circadian profiles of hepatocyte- and microenvironment-specific transcriptomes during pathophysiological progression of hepatocarcinogenesis in human hepatocytes, which bore striking resemblances to those found in human NASH, cirrhosis, and HCCs.

Our studies demonstrate that chronic circadian dysfunction is an independent risk factor of NAFLD-induced carcinogenesis in human hepatocytes and suggest that circadian homeostasis should be considered an important clinical feature in the future diagnosis and treatment of NASH, cirrhosis and HCC in humans. The striking resemblance in the molecular mechanism of NAFLD-related hepatocarcinogenesis in humanized FRG mice with that described for obese-related hepatocarcinogenesis in humans establishes humanized FGR mice as a novel and clinically relevant model for developing therapeutic options for HCC prevention and treatment.

Stromal HIF2 regulates cellular crosstalk in the pancreatic cancer microenvironment

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Pancreatic ductal adenocarcinomas (PDAC) have a dense, hypoxic, and immunosuppressive stroma that contributes to treatment resistance, particularly immunotherapy resistance. Cancer-associated fibroblasts (CAFs), particularly those expressing alpha-smooth muscle actin (αSMA+), are the most abundant stromal component, as well as mediators of stromal deposition in PDAC. The hypoxia-inducible factors (HIFs) mediate the cellular response to hypoxia, yet, despite their known association to poor PDAC outcomes, their role within the PDAC microenvironment remains unclear. In this study, we aimed to elucidate the function of the HIFs within the pancreatic tumor microenvironment. We used a dual recombinase mouse model that developed spontaneous PDAC tumors driven by *FSF-KrasG12D/+*, *Trp53 frt/frt*, and *Pdx1-Flp* and restricted the deletion of HIFs to αSMA+ CAFs using *αSMACreERT2/+* and either *Hif1α lox/lox* or *Hif2α lox/lox* alleles. Survival, gross, and histopathological analyses were performed on mice and tumor samples, coupled to bulk and single-cell RNA Seq. Interestingly, CAF-specific loss of *Hif2α*, but not *Hif1α*, suppressed primary tumor growth and improved survival by 50% (P = 0.0003 by log-rank test, n = 21-23 mice/group). Moreover, deletion of *Hif2α* in CAFs only had a modest impact on tumor fibrosis, yet it significantly decreased the intratumoral recruitment of immunosuppressive macrophages and regulatory T cells. CAF-macrophage crosstalk was then modeled *ex vivo* using conditioned media from CAFs cultured in hypoxia and treated with PT2399, a class of FDA-approved HIF2 inhibitor. CAFs treated with PT2399 failed to induce murine macrophage migration, as compared to that of CAFs treated with vehicle. Moreover, pharmacological and genetic inhibition of HIF2 in CAFs impaired their ability to induce macrophage M2 polarization. Lastly, pharmacological HIF2 inhibition enhanced response to checkpoint immunotherapy in syngeneic flank and orthotopic PDAC models. Taken together, our results suggest that loss of HIF2 signaling in CAFs slows PDAC growth and decreases tumor immunosuppression by regulating the recruitment of M2 macrophages and possibly regulatory T cells. Further understanding of HIF2's role in mediating CAF–immune cell crosstalk could lead to the quick repurposing of HIF2 inhibitors to improve PDAC's response to immunotherapy.

Abstracts

Investigating calcium dysregulation and enteric virus virulence using forward and reverse genetics

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Acute gastroenteritis (AGE) remains the second leading cause of death among children under the age of 5 worldwide. AGE becomes fatal when pathogen-associated upregulation of secretory activity in the intestine causes severe volume depletion and multi-system failure. While enteric viruses remain the most common cause of fatal AGE in kids, the drivers of their virulence (i.e. secretory activity) remain incompletely understood. We recently found that cells infected with rotavirus, the most prevalent enteric virus in kids, release adenosine diphosphate (ADP) to coordinate signals known as “intercellular Ca^{2+} waves,” which spread through uninfected neighboring cells. This dysregulates Ca^{2+}signaling pathways, enhancing fluid secretion and thereby contributing to volume depletion. Pharmacological blockade of Ca^{2+}waves in rotavirus-infected mouse pups decreases disease severity, suggesting they are integral to rotavirus virulence. Understanding how rotavirus triggers intercellular Ca^{2+} waves may allow us to design safer, more effective vaccines and therapeutics, but we still lack a mechanistic understanding of this process. Here, we report data showing that recombinant expression of a single rotavirus protein, non-structural protein 4 (NSP4), is sufficient to induce Ca^{2+} waves. Using the rotavirus reverse genetics system and human intestinal organoids, we show that both the diminished Ca^{2+} wave phenotype and the diminished secretory stimulation associated with an attenuated strain of rotavirus segregate with NSP4. Furthermore, we show that this attenuation is attributable to a single amino acid polymorphism at the c-terminal end of NSP4. This implicates the c-terminal end of the cytosolic domain and a putative PDZ-binding motif therein as key upstream mediators of intercellular Ca^{2+} waves. These findings deepen our understanding of pathogenesis, offer novel targets for anti-secretory therapeutics, and expand foundational knowledge to support the development of improved live-attenuated vaccines.

Increased expression of β-Catenin in canonical pathway of colon cancer cells with exposure to low-dose arsenic

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Introduction: Arsenic is an identified carcinogen for various malignancies and there is supportive epidemiological evidence for colorectal cancer (CRC). The potential importance is underscored by the observation that in Texas there is both a higher incidence of CRC and there is greater exposure to arsenic in drinking water. Dysregulation of β-Catenin pathway via loss of GSK-3β inactivation is a key ubiquitous early event in colorectal carcinogenesis enabling transcription of critical genes. We, therefore, wanted to assess impact of arsenic on β-Catenin.

Methods: We developed a system with long term, low dosage of arsenic to better mimic human exposure using inorganic Arsenic in human CRC cell line (HT-29 cells). We used standard techniques (qPCR with GAPDH, Western blot with β-actin standardization) for measuring molecular dysregulation.

Results: Low dose arsenic increased cell number by 17.2% ($p<0.01$). β-Catenin protein was dramatically increased by 55.8±23.9%. However, there was no increase in β-Catenin mRNA suggesting post translational modification in the expression of the protein. In this regard, the inactivated GSK-3β (Serine-9 phosphorylated) was increased by 32.5±0.5% ($p<0.05$) with low dose arsenic treatment. We evaluated the β-Catenin mRNA expression by 50% ($p < 0.05$) by Week 11 and beyond.

Conclusion: We demonstrate, for the first time, that low dose arsenic augmented the β-Catenin pathway in CRC along with reduction in expression of mRNA at translational level. Future studies will explore the precise mechanisms of action.

The role of the microbiome in immune dysregulation in common variable immunodeficiency

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We seek to identify the role of the microbiome in immune dysregulation in Common Variable Immunodeficiency (CVID). CVID patients have two distinct phenotypes: patients who develop infections-only (INF), and patients who develop autoimmune and inflammatory complications (noninfectious complications (NIC)). Compared to INF-CVID, NIC-CVID patients have higher morbidity and mortality rates. Studies showed associations between NIC-CVID and gut microbiome aberrations, including imbalanced microbial composition, leaky gut, and systemic inflammation. To investigate the role of dysbiosis in the immune responses in CVID, we performed fecal microbiota transplant (FMT) from CVID patients to C57Bl/6J Germ-Free (GF) mice. GF-mice received FMT from NIC-CVID, INF-CVID, or a healthy control (CTL). Thirty days later, gut microbial alpha and beta diversity were significantly different between NIC, INF, and CTL-FMT recipients. Furthermore, FMT recipients from all CVID donors (NIC and INF) had significantly higher serum IgG2b and IgG2c, indicating inflammation. We next treated 50% of the mice in each group with normal saline (NS) and 50% with a single dose of intraperitoneal human IgG (h-IgG). Compared to NS, h-IgG resulted in a significant change in gut microbiome beta diversity in NIC-FMT but not in INF or CTL-FMT recipients. In addition, IgG-treated NIC-FMT recipients had a decrease in the relative abundance of *Eggerthella*, *Bifidobacterium,* and *Ruminococcaceae* genera. Dysregulation of the same genera has been described in CVID patients.

Thus, we provide a proof of concept that FMT from CVID patients to GF-mice recapitulates the microbiome alteration seen in CVID patients. Our data are from a single donor per group; however, confirmatory experiments using additional donor samples are underway. Our work will help provide new insight into immune dysregulation in CVID. It will also help identify the anti-commensal effects of IgG therapy. Our ultimate goal is to develop therapeutics to modulate the gut microbiome, treat, and prevent NIC development in CVID.

Abstracts

Single cell atlas of stomach in parietal specific injury

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Background: Stem cells constantly react to stimuli to maintain tissue homeostasis. Acid-secreting parietal cells (PC) play an especially pivotal role in maintaining an acidic environment in the stomach. While the function and morphological profiles of parietal cells are well established, little is known about the transcriptional changes parietal cells undergo between homeostasis and recovery from injury. To define the transcriptional changes of parietal cells at the single cell level in response to acute parietal cell specific injury, we have developed an acute, reversible injury model that allows targeted ablation of parietal cells.

Design: To profile the molecular changes associated with parietal cells during injury repair, cells were isolated from the corpus at 36, 48, and 72 hours after injury, as well as vehicle-treated control for single cell RNA sequencing (scRNA-seq).

Results: The combined libraries from control, 36 h, 48 h, and 72 h were processed using CellRanger (10x Genomics, version 3.0) and aligned to the mouse genome. After quality control using mitochondrial percentage (<25%), feature RNA (>700/cell), and removal of doublets, 38,040 cells with 18,549 genes were identified. The combined data were subjected to principal component analysis and unbiased UMAP dimensionality reduction, resulting in transcriptional profiles from 28,278 epithelial and 9,762 non-epithelial cells, including immune (macrophage, dendritic cells, mast cells, endothelial cells), and mesenchymal/stromal cells. Our analysis shows transcriptomic changes in the various epithelial and non-epithelial cell types responding to PC injury. Previously, we had showed that generation and maintenance of PCs require AMPK and PGC1a. Our trajectory analysis now identifies a specific PC progenitor cell population characterized by decreased cyclin-dependent kinase inhibitors and induction of the AMPK signaling target and PGC1a-interacting orphan nuclear receptor *Esrrg*.

Conclusion: A single-cell resolution atlas of mouse stomach in homeostasis and after PC-specific injury maps out distinct cellular/molecular paths for parietal cell regeneration, accompanied by differential immune microenvironment features.

Abstracts

The role of UBE2C in Barrett's esophagus development and progression to esophageal adenocarcinoma

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Barrett's esophagus (BE) is a precancerous condition that confers the strongest predisposition to developing esophageal adenocarcinoma (EA). Current management for BE involves endoscopic surveillance with unclear effectiveness at preventing cancer progression given the increase in EA incidence over the past several decades in the United States. In addition, it is known that the majority of patients with BE do not "progress" or develop cancer. Clearly, there is deficiency of knowledge regarding the pathogenesis of Barrett's metaplasia development and progression to esophageal adenocarcinoma, and specifically a lack of biomarkers to define those at highest risk for cancer development. Ubiquitin-conjugating enzyme E2 (UBE2C) is a highly conserved protein that regulates ubiquitination and degradation of mitotic cyclins needed for cell-cycle progression. It is often aberrantly expressed in many cancers including esophageal adenocarcinomas with canonical oncogene properties. We have amassed a unique biobank of human biopsy-derived BE organoids that we have extensively characterized histologically, transcriptionally, and genomically at bulk and single cell resolutions. We demonstrate that our BE biobank includes a diverse spectrum of organoids with varying degrees of esophageal, gastric, intestinal, and metaplastic molecular characteristics that also recapitulates the genomic mutational landscape of this precancerous condition (ie *TP53* mutations). Using this resource, we have identified a novel subpopulation of BE cells that is defined by elevated *UBE2C* expression. Immunohistochemical staining of these organoids confirmed expression of UBE2C in this subset of BE cells. Subsequently, we have detailed UBE2C expression in human BE tissue *in vivo* using a curated human BE and gastroesophageal adenocarcinoma tissue microarray. Interestingly, we show that UBE2C is expressed in a subset of Ki-67 positive dividing BE cells. Finally, we demonstrate that the expression of UBE2C increases in a stepwise fashion during BE development and neoplastic progression, specifically from normal cardia/esophagus to nondysplastic BE to dysplastic BE to gastroesophageal adenocarcinoma. In summary, we show for the first time that UBE2C is expressed in a subset of proliferating Barrett's esophagus cells and may play a role in directly promoting esophageal adenocarcinoma tumorigenesis.

Abstracts

Understanding the viral-host interactions that promote and restrict strain-specific human norovirus infection

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Human noroviruses (HuNoVs) are the leading cause of viral gastroenteritis worldwide. With no FDA-approved vaccines or anti-viral drugs, HuNoVs cause a significant health burden. Most infections worldwide are caused by variants of the GII.4 genotype. In studies with pandemic-causing GII.4 and non-pandemic GII.3 HuNoVs, unexpected strain-specific differences were discovered in innate immune responses in human intestinal enteroids (HIEs). GII.3 virus was found to be more sensitive to the endogenous interferon (IFN) response; GII.3, but not GII.4, replication was restricted by the host innate immune responses. Knocking out key host immune restriction factors (STAT-1, IFN lambda receptor, IFN alpha receptor) enhanced GII.3 replication accompanied by viral spreading while no change was seen in GII.4 replication. However, we have yet to achieve continuous passaging of either virus, indicating alternate viral or host factors still restrict replication. A recent RNA-seq dataset of GII.3 infection of parental and knockout HIEs has revealed interferon-stimulated genes (ISGs) that may continue to restrict GII.3 replication. Inhibition or knockouts of these ISGs are being used to dissect their roles in continued restriction of both GII.3 and GII.4 virus replication and passaging. Finally, the lack of restriction for the GII.4 virus provides one explanation for widespread infections by this pandemic HuNoV. Ongoing studies are testing the hypothesis that GII.4 antagonizes innate immune responses and induces distinct innate responses compared to GII.3. Understanding the GII.3 and GII.4 infection-mediated cellular innate immune responses and host restriction factors will provide mechanistic insights into viral-host interactions that may aid in the development of therapeutics to combat HuNoV infection and pathogenesis. Identifying the viral-induced restriction factors and modifying them may enhance viral replication, allow virus passaging, and improve our cultivation system to facilitate functional, mechanistic, and translational studies that will help reduce the public health burden of HuNoV infections.

Evaluating the pancreatic cancer diagnosis pathway in U.S. veterans

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Background: Pancreatic cancer is currently the number three cancer killer in the U.S. and is projected to rise to number two in the next decade. Nearly 85% of patients have incurable (locally advanced or metastatic) disease at diagnosis, suggesting need for early cancer detection efforts. We characterized the timeliness of pancreatic cancer diagnosis and treatment.

Methods: We reviewed electronic health records of 150 consecutive patients diagnosed with pancreatic adenocarcinoma at a large VA medical center from 1/2015 to 12/2020 with at least 3 years of comprehensive medical data prior to cancer diagnosis. We evaluated clinician notes, referral patterns, diagnostic tests, including radiology and pathology files and determined key time intervals related to diagnosis and treatment. In a subset of 50 randomly selected patients, we further evaluated for presence of known pancreatic cancer risk factors and cancer-associated presenting signs and symptoms.

Results: Of 150 patients, 127 patients presented with symptomatic disease at diagnosis (i.e., not incidentally found on imaging). Average time between onset of first cancer-associated symptom as self-reported by patient and physician documentation of symptom was 68 days (range 1-365 days); onset of first symptom to histological diagnosis (diagnostic interval) was 122 days (range 3-586); and histological diagnosis to treatment initiation (treatment interval, n=46) was 36 days (range 7-92 days). Notably, 40% (61 out of 150) of patients had a diagnostic interval of >90 days - a delay known to be associated with lower odds of potentially curative surgical resection. In a subset of 50 records reviewed in detail, most patients (63.3%) had at least 1 known risk factor (e.g., diabetes, current tobacco use, obesity) in combination with a classic warning sign or symptom of pancreatic cancer at the time of diagnosis. Details of initial cancer presentation and setting of care are shown in Table 1.

Conclusion: The average diagnostic delay for pancreatic cancer was >90 days, suggesting the presence of opportunities for earlier diagnosis. Most patients had at least 1 known risk factor and a classic warning sign or symptom of pancreatic cancer. As a next step, we will evaluate types of diagnostic process breakdowns in a large national cohort.

Table: Symptoms and other characteristics of pancreatic cancer patients at one VA facility (2015-2017)

Characteristics	N (%)
No. of participants	50 (100)
***Initial cancer sign or symptom**	
Abdominal or back pain	27 (54)
Anorexia or weight loss	21 (42)
Nausea or vomiting	7 (14)
Change in bowel habits	11 (22)
Jaundice	11 (22)
Other	10 (20)
Incidental finding on imaging	7 (14)
Setting of first complaint	
Ambulatory clinic visit	
General provider	17 (34)
Specialty provider	4 (8)
Emergency department	19 (38)
Upon presentation to outside hospital	3 (6)
Incidental finding on imaging	7 (14)

*A patient could have more than one sign/symptom accounted for in this section

Evaluating gaps in the pancreatic cancer diagnosis pathway: A study of emergency presentations

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Background: The diagnosis of cancer through emergency presentation, or "emergency cancer diagnosis" (ECD) is defined as a cancer diagnosis made following emergent onset of cancer-related symptoms rather than through routine screening or clinical care. ECD is associated with greater mortality and lower likelihood of curative therapy, even when adjusted for stage. Pancreatic cancer is the third leading cause of cancer death in the U.S., yet ECD among pancreatic cancer patients remains understudied. To fill this gap, we studied characteristics of ECDs among pancreatic cancer patients.

Methods: In a retrospective cohort study, we reviewed the electronic health records of 264 consecutive patients diagnosed with pancreatic adenocarcinoma at a large VA medical center from 2015 to 2020. We evaluated clinician notes, referral patterns, and diagnostic tests to determine presence of emergency cancer presentations (i.e., ECDs). Our primary outcome of interest was ECD, which is a cancer diagnosis preceded within 30 days by an emergency event (defined as an unplanned hospitalization or emergency department visit).

Results: Of 264 pancreatic cancer patients, average time between onset of first cancer-associated symptom as self-reported by patient and physician documentation of symptom was 57 days (range 1-365 days); onset of first symptom to histological diagnosis (diagnostic interval) was 104 days (range 4-536); and histological diagnosis to treatment initiation (treatment interval, n=137) was 37 days (range 1-126 days). Sixty-one percent (161/264) of patients had ECD. Among the 161 patients with emergency presentations: 13.6% had more than one ER visit within the 30-day period prior to cancer diagnosis; 79.5% were self-referred to ER (i.e., not sent by primary or specialty provider); 91.9% had cancer-associated signs or symptoms as primary complaint; and 89.4% were admitted for further work up with average length of stay 8.8 days. Most pancreatic cancer patients with emergency presentations (83.2%) had their emergency admission for a presumed cancer-related concern and were diagnosed with cancer within that initial encounter. Compared to the patients without ECDs (n=103), those with ECDs (n=161) were slightly more likely to be Black (37.3% vs 28.2%; *p*-value 0.11) and were significantly more likely to have stage IV disease (55.3% vs 43.7%; *p*-value 0.04).

Conclusion: In an equal access healthcare system, we found that most patients with pancreatic cancer had ECDs (61.0%), which was associated with more advanced stage disease. Enhanced understanding of the process breakdowns that lead to ECDs are needed to inform meaningful interventions. As the largest provider of cancer care in the U.S., the VA provides an ideal setting for developing and implementing pathways to optimize diagnostic processes in cancer care.

The impact of race on pancreatic cancer treatment and survival in the nationwide Veterans Affairs Healthcare System

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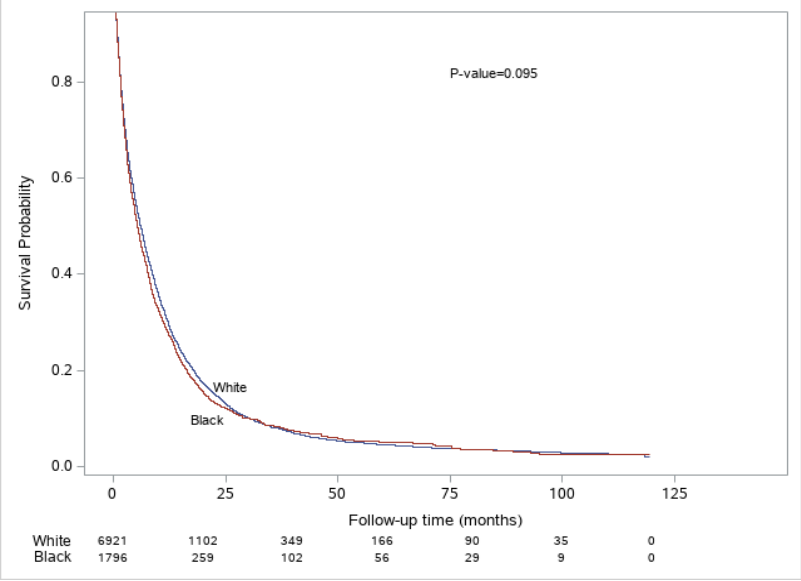
Background and aims: Pancreatic cancer is a highly lethal cancer that is increasing in incidence. Diagnosis at early disease stage treated with curative therapy is the only way to reduce pancreatic cancer-related mortality; however, data consistently show Black patients are diagnosed with later stage disease, are less likely to receive stage-appropriate treatment and have lower overall survival compared to White patients. In this article, we examine the impact of race on quality of pancreatic cancer care in the U.S. Department of Veterans Affairs (VA) healthcare system, a more equitable healthcare system than the private sector.

Methods: We identified all veterans diagnosed with pancreatic adenocarcinoma in the VA Central Cancer Registry from 2010 to 2018. Using multivariable logistic regression analysis, we examined the association between race and cancer outcomes of stage and treatment, adjusting for age and medical comorbidities. We also examined overall survival by race using Cox proportional hazards regression analysis and Kaplan-Meier survival analysis.

Results: We identified 8,529 veterans diagnosed with pancreatic adenocarcinoma during study period, of whom 8,306 (97.4%) were men, 6,778 (79.5%) were White, and 1,751 (20.5%) were Black. At time of diagnosis, Black patients were more likely to be younger, have a lower BMI, be current tobacco and alcohol users, and have a history of diabetes mellitus compared to White patients. In univariate analyses, there were no differences between stage at diagnosis, receipt of any cancer treatment, or median survival by race. However, when treatment type was examined with multivariable logistic regression, Blacks were less likely than Whites to undergo surgical resection (odds ratio (OR) 0.75; 95% confidence interval (CI) 0.63-0.90). When survival was examined by Cox proportional hazards regression analysis, there was no significant difference in survival between Blacks and Whites on unadjusted (hazard ration (HR) 1.04; 95% CI 0.98-1.10) as well as adjusted (HR 1.02; 95% CI 0.96-1.07) analysis (Figure 1, Kaplan-Meier survival curve).

Conclusions: The racial disparities in pancreatic cancer care well-described in prior studies in terms of diagnosis, treatment and survival were not seen in the nationwide VA healthcare system. This is likely a result of equitable access to care irrespective of race and socioeconomic status. Better understanding of underlying factors associated with disparities in pancreatic cancer care in less equitable healthcare systems is essential for improving health outcomes of this morbid disease.



The association between chronic and new-onset diabetes and pancreatic cancer care outcomes in the nationwide Veterans Affairs Healthcare System

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Background and aims: Diabetes onset after age 50 is an important condition associated with pancreatic cancer. While chronic diabetes is a known moderate risk factor for pancreatic cancer, up to 1 in 4-5 pancreatic cancer patients develop diabetes through a paraneoplastic process within the 3 years preceding their cancer diagnosis, coined “new-onset diabetes” (NOD). It remains unknown if NOD is associated with earlier timing of pancreatic cancer diagnosis despite being a clinical marker of early, occult disease. We examined the association between presence and chronicity of diabetes and pancreatic cancer outcomes among patients in the national Veterans Affairs (VA) healthcare system.

Methods: We identified all veterans diagnosed with pancreatic adenocarcinoma in the VA Central Cancer Registry from 2010 to 2018. We classified each patient by pre-cancer diagnosis diabetes status: no diabetes, chronic diabetes >3 years, or NOD ≤3 years. Diabetes was defined by presence of ICD codes or HgA1c value ≥6.5 prior to pancreatic cancer diagnosis. Using multivariable logistic regression analysis, we examined the association between diabetes status and cancer outcomes of stage and treatment. We also examined overall survival by diabetes status using Cox proportional hazards regression analysis and Kaplan-Meier survival analysis.

Results: We identified 8,831 veterans diagnosed with pancreatic adenocarcinoma during 2010-2018. 48.8% had no prediagnosis diabetes, 33.4% had chronic diabetes, and 17.7% had NOD. There was no difference in stage by diabetes status. On multivariable logistic regression analysis (adjusting for age, sex, race, BMI, smoking/alcohol use, CA19-9 levels, and Deyo-Charlson comorbidity index scores), patients with diabetes were more likely than their nondiabetic counterparts to have higher stage (III-IV vs. 0-II) disease: chronic diabetes (OR 1.16, 95% CI 1.01-1.34), NOD (OR 1.23, 95% CI 1.07-1.47). Patients with NOD were the most likely of the 3 groups to receive chemotherapy, an association also seen on multivariable analysis (OR 1.24, 95% CI 1.06-1.4) compared to no diabetes.

On Cox proportional regression, compared to the reference group of patients with no diabetes, patients with chronic diabetes had 20% higher mortality (unadjusted hazard ratio (HR) 1.2, 95% CI (1.10-1.2)), an association not seen with NOD (HR 1.0, 95% CI: 0.9-1.1).

Conclusions: Results from our study do not support that patients with NOD are diagnosed at earlier stages or have improved outcomes compared to those with no or chronic diabetes. Better recognition of clinical clues of early, occult pancreatic cancer such as NOD and understanding factors associated with missed opportunities to diagnose pancreatic cancer earlier among patients with NOD is important for improving health outcomes of this morbid disease.

Dissecting genetic interactions initiating esophageal squamous cell cancer and remodeling immune landscape

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Esophageal squamous cell carcinoma (ESCC) accounts for over 80% of esophageal cancer, with a poor prognosis mainly due to a lack of symptoms at early stages. Although an early diagnosis of ESCC may lead to better outcomes, it is challenging to detect early ESCC as it originates from the basal cell layer and invades into the lamina propria. Therefore, it is imperative to understand the mechanisms of ESCC initiation and establish model systems recapitulating ESCC neoplasia. Several studies have identified the frequent genetic alterations in ESCC patients. However, key genetic interactions initiating ESCC remain elusive. Employing CRISPR-based genetic manipulation of murine esophageal organoids (EOs), 9 candidate genes most frequently deleted in ESCC patients were combinatorically ablated to establish 32 EO lines. Among those, *Trp53; Notch1* double knock-out (PN) or *Trp53; Cdkn2a; Notch1* triple knock-out (PCN) was sufficient to induce ESCC neoplasia in vitro and in vivo. Transcriptomics confirmed that PN and PCN EOs exhibited transcriptional signatures of ESCC patients. Single-cell transcriptomics identified distinct cell lineage, multiple root cells, key regulons of PN and PCN EOs, compared to wild-type EOs displaying normal esophageal differentiation from one cellular origin. Intriguingly, only PCN EOs-derived cells developed tumors in immunocompetent mice. Mechanistically, the PCN-activated Rela-Ccl2 axis induces T cell exhaustion to escape immune surveillance. Our study unveils that loss of *TP53*, *NOTCH1*, and *CDKN2A* is the minimum and pivotal driver to initiate ESCC by not only inducing cell-autonomous esophageal neoplasia but also remodeling immune landscape, which establishes the model system recapitulating human ESCC initiation.

Abstracts

Characterizing stem-cell derived human intestinal organoids for evaluation of antivirals for human norovirus

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Background: Human noroviruses (HuNoVs) are the leading cause of acute gastroenteritis. In immunocompetent hosts, symptoms usually resolve within three days; however, persistent norovirus can be debilitating or life-threatening in immunocompromised persons. There are no licensed therapeutics for HuNoV due to a near half-century delay in its cultivation. Treatment for chronic HuNoV infection in immunosuppressed patients includes off-label nitazoxanide (NTZ), a broad-spectrum antimicrobial agent licensed for treatment of Giardia-induced gastroenteritis. Non-transformed, multicellular human intestinal organoids (HIOs) are a physiologically relevant cell culture system derived from intestinal stem cells and have great potential for antiviral studies including allowing for evaluating the diversity of human responses by generating them from different donors. In spite of these advantages, there have been few studies using HIOs for antiviral research. **Objective**: The aim of this project is to characterize and utilize our HIO model of HuNoV replication to determine the effects of NTZ treatment on replication of several HuNoV strains and identify NTZ metabolites in intestinal cells. **Methods:** A pipeline for antiviral testing was established to use a standard viral dose and a range of 5 drug doses with cytotoxicity testing. The half maximal tissue culture infectious dose ($TCID_{50}$) for 7 HuNoV strains were determined in two HIO lines (called J2 and/or J4 FUT2-*knockin*). Each HIO line was infected with 100 $TCID_{50}$s of virus in conjunction with ascending concentrations of NTZ. Cytotoxicity in four HIO lines (J2, J2 STAT1-*knockout*, J4, J4 FUT2-KI) was evaluated by 4 different Promega commercial assays: LDH, CellTox, MTS, and CellTiter-Glo. Basal mRNA expression of drug metabolizing enzymes was measured by RNAseq of the J2, J2 STAT1-KO, and J4 FUT2-KI HIO lines. **Results:** Evaluation of infectivity of 7 HuNoV strains in J2 and/or J4 FUT2-KI showed differences in permissibility between the two HIO lines. NTZ induces a dose-dependent inhibition of a subset of HuNoVs in HIO cultures. The viability in HIOs after drug treatment was discordant between HIO lines using different cytotoxicity assays, particularly when measured with the LDH assay. Modification of the LDH protocol was necessary to improve accuracy. RNAseq showed differing basal expression of drug-metabolizing enzymes between HIO lines from different donors. Metabolism of NTZ in HIOs is under evaluation. **Conclusions:** HIOs are an innovative cell culture model for evaluating antivirals and drug metabolism and have the capacity for providing an understanding of biologically diverse responses by using cultures from multiple donors. LDH cytotoxicity assays have some limitations with this system, but these limitations can be overcome by adjusting the protocol or using other assays. NTZ can inhibit some HuNoVs and the mechanisms for differential effects between strains are under investigation.

Cholestasis alters the maturation of the preterm neonatal gut microbiome and bile salt deconjugation

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Background: Cholestasis (impaired bile flow from the liver to the intestine) affects ~1:2500 births, causes poor neonatal growth, and may progress to liver failure and death. Underlying causes of most cases are unknown. Ursodeoxycholic acid (UDCA), a secondary bile salt, is used in the treatment of cholestatic liver disease; however, its effects in preterm neonates are poorly understood. Normal bile flow requires an intact liver-gut-microbiome axis that contains bile salts. Liver-derived primary bile salts are transformed into secondary bile salts by microbial bile salt hydrolase (BSH) enzymes. In turn, bile salts shape gut microbiota composition and function. How the liver-gut-microbiome axis develops over time in preterm newborns, and whether cholestasis alters this development, is unknown. We aimed to test the hypotheses that: 1) The gut microbiome of extremely premature neonates without cholestasis contains BSH genes and develops in a predictable manner over time; 2) Cholestasis interrupts this pattern of development; 3) The microbial alterations in cholestatic neonates are reflected in altered composition of the bile salt pool; 4) UDCA treatment quantitatively modifies bile salt profiles.

Methods: In this single-center study, 24 infants < 1500 grams birthweight born at Texas Children's Hospital were enrolled. A subset of infants with cholestasis (n=12) with mean peak conjugated bilirubin 7.0 mg/dL were compared to age matched controls without cholestasis (n=12). Weekly stool samples were collected throughout hospitalization and analyzed by whole metagenomic sequencing, mass spectrometry, and *in vitro* BSH enzymatic activity assays.

Results: Principal coordinate analysis revealed that gut microbiota from extremely preterm neonates without cholestasis develop in a predictable manner with increasing postconceptional age (P<0.0001). Pathway analysis identified increasing secondary bile salt biosynthesis as the most distinctive metagenomic feature of preterm development (P<0.00001). Control neonates also had increasing abundance over time of BSH genes (P<0.0001) and of the BSH carrier *Clostridium perfringens* (P<0.0001). Strikingly, this pattern of development was completely absent in cholestasis. Instead, cholestasis increased microbial community diversity without increasing BSH genes or *C. perfringens*. BSH enzymatic activity and its products – unconjugated bile salts – were reduced in cholestatic neonates compared to gestational age matched controls (P<0.05). Total fecal bile salts were reduced in cholestasis (P=0.0001) but completely restored by UDCA treatment. Samples from cholestatic neonates on UDCA had 522-fold higher quantities of fecal UDCA compared to untreated cholestatic neonates (P<0.0001), indicating that UDCA treatment alters the composition of the bile salt pool. Compared to the controls, cholestatic neonates required more days of parenteral nutrition and antibiotics. Cholestatic infants exhibited poor growth, with lower head circumference and weight velocities.

Conclusion: We identified a pattern of development of the extremely preterm neonatal gut microbiome and bile salt profile that is interrupted by cholestasis. Increased microbiota diversity in cholestasis may reflect a lack of bile salts in the intestine. UDCA dominates the fecal bile salt pool in cholestatic neonates treated with enteral UDCA. Ongoing studies are exploring the liver-gut-microbiome axis as a therapeutic target to enhance neonatal growth.

Abstracts

Altered gut microbes increase gut barrier permeability in malnutrition

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Background: Malnutrition contributes to 45% of deaths among children under 5 years of age. Malnourished children suffer from gastrointestinal pathophysiologies including increased intestinal permeability. A leaky gut causes nutrient malabsorption and bacterial translocation resulting in sepsis, an important cause of mortality. Mechanisms underlying malnutrition-induced gut barrier dysfunction are poorly characterized. Among the numerous factors that regulate gut barrier permeability are metabolites derived from the intestinal microbiota. These include short chain fatty acids (SCFAs) and secondary bile acids (BAs). We modeled early postnatal malnutrition by feeding mice a low-protein, low-fat diet. We recently reported that malnourished male (but not female) mice have a leaky gut and dramatically altered microbiota community composition by 16S rRNA gene sequencing. In the present study, we used germ-free (GF) mouse models, deep metagenomic sequencing, and mass spectrometry to test the hypothesis that increased intestinal permeability in malnourished mice is associated with altered microbial metabolic function.

Methods: Specific pathogen free (SPF) and GF C57BL/6 mice were weaned to a low-protein low-fat diet or isocaloric control chow. Stool from 8-week-old SPF mice was analyzed by whole genome shotgun (WGS) sequencing and mass spectrometry targeting microbial metabolites that regulate gut permeability. Intestinal permeability was assessed with the Ussing chamber system.

Results: Increased jejunal permeability in SPF malnourished male mice was associated with increased bacterial community richness (33.6 vs. 39.1 mean OTUs, $p=0.01$) and Fisher diversity (mean 2.26 vs. 2.76, $p<0.001$). Alpha diversity was unchanged in malnourished females, which do not have a leaky gut. The metagenome of malnourished mice contained significant alterations in the KEGG pathways of secondary bile acid and SCFA biosynthesis. Malnutrition reduced intestinal concentrations of the SCFAs propionate, 2-methylbutyrate, isobutyrate, isovalerate, and valerate (FDR<0.25) and of the secondary bile acids deoxycholic acid and ursodeoxycholic acid in both sexes ($p<0.05$). Only malnourished males had decreased concentrations of butyrate (15%, FDR<0.25) and lithocholic acid (35%, $p=0.03$). Strikingly, the increased jejunal permeability observed in SPF malnourished males is completely abolished in GF malnourished males.

Conclusion: Malnutrition-associated leaky gut is sexually dimorphic and associated with an altered gut microbiome and reductions in SCFAs and secondary BAs, which help regulate gut barrier function. Ongoing studies will examine whether decreased concentrations of the microbial metabolites butyrate and lithocholic acid causes malnutrition-associated leaky gut in male mice.

The enteric nervous system improves intestinal epithelial barrier function in transplanted human intestinal organoids.

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Introduction: Short bowel syndrome is characterized by insufficient nutrient absorption due to congenital defects, surgical resection, or injury. Mortality has been reduced by multidisciplinary management with parenteral nutrition, teduglutide, bowel lengthening procedures, or intestinal transplantation, however, morbidity remains significant. Human intestinal organoids (HIOs) differentiated from pluripotent stem cells may provide an alternative therapy as an autologous source of transplantable intestinal tissue. HIOs contain epithelium and mesenchyme with development analogous to fetal intestine. HIOs mature after transplantation (tHIOs) *in vivo* to better recapitulate adult intestine. HIOs lack an enteric nervous system (ENS) which is critical for intestinal functions like nutrient absorption, motility, and barrier maintenance. We aimed to improve epithelial barrier function in tHIOs by co-culturing HIOs with enteric neural crest cells (ENCCs) prior to transplantation *in vivo* to restore the missing ENS.

Methods: HIOs and ENCCs were differentiated from human embryonic stem cells (hESCs) and GFP-labeled hESCs respectively. RT-qPCR and immunofluorescence (IF) staining for ENCC differentiation markers were used to confirm ENCC differentiation. IF staining for neuronal and glial markers was used to determine if ENCCs could differentiate into diverse ENS tissue *in vitro*. Day 4/5 gut spheroids were suspended in matrigel with or without ENCCs and cultured for up to 40 days. Fluorescence microscopy was used to monitor ENCC survival and migration within HIOs. IF staining was used to identify ENS tissue within HIOs. HIOs±ENS were transplanted under the kidney capsule of adult NSG mice and allowed to develop for up to 18 weeks. Transepithelial electrical resistance, a measure of epithelial barrier function, of tHIOs±ENS was recorded with an Ussing Chamber. Epithelial, mesenchymal, and neuronal development was examined by IF staining.

Results: Upregulation of HOX3B, HOX5B, and PAX3, and positive IF staining for SOX10 confirmed ENCC differentiation. Positive IF staining for neuronal and glial markers TUJ1, 5-HT, AChR, NOS1, GABA, S100β, GFAP, and BLBP confirmed ENCCs could differentiate into a diverse ENS *in vitro*. Fluorescence microscopy showed that ENCCs survive in co-cultures with HIOs and migrate into HIOs. IF staining for TUJ1 confirmed that ENCCs differentiate within HIOs. IF confirmed that the epithelium and mesenchyme of tHIOs±ENS and the ENS of tHIOs+ENS matured *in vivo*. Transepithelial electrical resistance was improved by the ENS in an older cohort of 16-18 week tHIOs±ENS but not in a younger cohort of 8-12 week tHIOs±ENS.

Conclusion: ENCCs co-cultured with HIOs survive, migrate into the HIOs, and differentiate into neurons. The ENS matures further in tHIOs, forming ganglia in the mesenchyme. Epithelial barrier function of tHIO+ENS improved over time as the ENS tissue matured.

Role of BMP signaling during zebrafish enteric neural crest development

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The vertebrate enteric nervous system (ENS) consists of a series of interconnected ganglia within the muscle walls of the gut and is largely responsible for coordinating peristalsis, water balance, and regulation of hormonal secretions. During development, neural crest cells (NCC) that contribute to ENS migrate into the primitive foregut and migrate caudally along its length, during which time they are referred to as enteric neural crest cells (ENCCs). While ENCCs migrate as a group along the gut, they receive various extrinsic signals from the surrounding tissue and neighboring NCCs that promotes their proliferation, migration, differentiation and multipotency. Due to the complex and combinatorial nature of the signaling mechanisms involved in the establishment of the ENS, it has been difficult to tease apart major driving forces of many of the defects involved in aberrant ganglion formation in the gut. Through single cell RNA sequencing analysis of zebrafish NCCs and NCC-derived tissues, we identified differential expression patterns of a number of BMP pathway member encoding transcripts in NCC and ENS progenitor populations during development. Through immunohistochemical and hybridization chain reaction (HCR) analysis we demonstrate active BMP signaling and expression of target genes in NCC and ENS progenitor populations in vivo, across space and time. We also discovered that broad chemical attenuation BMP signaling using the small molecule inhibitor K02288 during specific phase of ENS progenitor development reduces the number of enteric progenitors in the most distal gut, in the zebrafish model. Overall, these results suggest that BMP plays a key role during the very early colonization phases of ENS development. The elucidation of BMPs as important members of the enteric gene regulatory network will help to delineate the effects of BMP signaling, which serves as a driver for proper ENS colonization and formation.

Using natural language processing to accurately identify dysplasia in pathology reports for patients with Barrett's esophagus

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Objectives: We aimed to develop and validate a natural language processing (NLP) algorithm to identify esophageal dysplasia in patients with Barrett's esophagus (BE) on histopathology reports with varying report formats in a large integrated electronic medical records (EMR) system. **Background:** Identifying dysplasia status for the purposes of research on BE and esophageal adenocarcinoma in electronic data repositories often requires manual data abstraction. NLP is a branch of computer science and linguistics that creates structure to unstructured free text. This automated method can reliably analyze large amounts of data and has been successfully employed in identifying key clinical information from EMR; however, not in the context of BE. **Methods:** We randomly selected 600 pathology reports for NLP development and 400 pathology reports for validation from patients with suspected BE in the national VA administrative databases. BE diagnosis was ascertained by the presence of ICD-9-CM code 530.85, combined with at least one EGD test (CPT codes 43200-43259, excluding 43246) within 12 months of the initial BE diagnosis date. The presence of BE (intestinal metaplasia) and presence and grade of dysplasia was verified/classified by manual review of the pathology report coinciding with the EGD code. NLP software (CLAMP) was used to develop an algorithm to identify dysplasia. Using findings from manual review as the reference standard, algorithm performance characteristics were calculated as recall (also known as sensitivity), precision (also known as positive predictive value), accuracy (proportion of tests that are either true positive or true negative), and F-measure (harmonic mean of precision and recall) of identifying dysplasia. **Results:** *Development.* Among the 600 patients, 561 had a pathology report available. On manual review, 104 patients (18.5%) were found to not have BE on pathology. Among the 457 patients with confirmed BE, 397 (86.9%) had no mention of dysplasia or were described as having non-dysplasia Barrett's esophagus (NDBE), 37 (8.1%) had low-grade dysplasia, 16 (3.5%) were indefinite for dysplasia and 7 (1.5%) had high-grade dysplasia (HGD). The NLP algorithm was highly accurate in identifying dysplasia from the 561 pathology reports. Compared with manual review, the NLP algorithm could identify dysplasia with 98.0% accuracy, 91.7% recall (44 of 57) and 93.2% precision, with an F-measure of 92.4%. Among the 7 patients with HGD, all were classified by the algorithm as having dysplasia. Only 6 of 501 patients (0.6%) with no BE or NDBE on the pathology report were incorrectly classified by the algorithm as having dysplasia. *Validation*. Among the 400 patients in the development cohort, 317 had a pathology report available. On manual review, 83 (26.2%) patients were found to not have BE on the selected pathology report. Among the 234 with confirmed BE, 191 (81.6%) had NDBE, 23 (9.8%) had LGD, 7 (3.0%) were indefinite for dysplasia, 9(3.8%) had HGD, and 4 (1.7%) had esophageal adenocarcinoma. Compared with manual review, the NLP algorithm could identify dysplasia with 97.9% accuracy, 88.4% recall, and 100.0% precision, with an F-measure of 93.8%. Among the 13 patients with HGD or esophageal adenocarcinoma, 11 (84.6%) were classified by the NLP algorithm as having dysplasia. Only 3 of 274 patients (1.1%) with no BE or NDBE on the pathology report were incorrectly classified by the NLP algorithm as having dysplasia. **Conclusion:** NLP yielded a high degree of accuracy for identifying dysplasia from diverse types of pathology reports for patients with BE. This algorithm can be applied and would facilitate research and possible clinical care in EMR system with text reports in large data repositories.

Abstracts

Radiofrequency ablation remodels the tumor microenvironment and promotes systemic immunomodulation in pancreatic cancer

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Significance: Pancreatic ductal adenocarcinoma (PDAC) has one of the lowest 5-year survival rates of all cancers and is projected to become the second deadliest cancer by 2025 (1). A major contributing factor to the overall low 5-year survival rate is failure to respond to therapy. PDAC has profound desmoplasia and a well-documented hypoxic tumor microenvironment (TME). In PDAC, several therapeutic approaches, including chemotherapy and radiation alone or combined with immune checkpoint inhibitors, have shown minimal therapeutic success, placing an imperative need for the discovery and application of innovative treatments. Endoscopic ultrasound guided radiofrequency ablation (EUS-RFA) is a promising local ablative and potential immunomodulator therapy for PDAC (2). **Hypothesis:** We *hypothesized* RFA promotes local and systemic immunomodulating effects that can be identified for new combination therapeutic strategies. **Methods:** To test our hypothesis, a syngeneic PDAC mouse model was performed by symmetrically injecting 100k KPC cells in bilateral flanks of C57BL/6 female mice. RFA treatment initiated when tumors reached 200-500 mm^3 and was performed only in the right flank. The left flank tumor (non-RFA side) was used as a paired control for further analysis. **Results and Conclusions:** RFA promoted a significant reduction in tumor growth rate 4 days after treatment in RFA treated and non-RFA side tumors when compared to controls. Histological analysis revealed upregulated expression of Caspase3, suggesting increased induction of apoptosis in RFA side and non-RFA side tumors from RFA-treated mice. We quantified significantly increased neutrophil infiltration, which we hypothesize potentiates the systemic immune response to induce necrosis in non-RFA side tumors. These data indicate RFA promotes local and systemic anti-tumor responses in a syngeneic mouse model of PDAC implicating RFA treatment for local tumors as well as metastatic disease.

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Quality improvement initiative to improve *helicobacter pylori* testing and treatment after diagnosis of gastroduodenal ulcers

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Introduction: *Helicobacter pylori* (*H. pylori*) infection is a common cause of gastroduodenal ulcers (GDU). Current guidelines recommend eradication of *H. pylori* to promote healing of GDU and prevention of associated diseases. We aimed to quantify and improve the rate of *H. pylori* testing, eradication, and increase the use of efficacious regimens after GDU diagnosis in a multi-ethnic population. **Methods:** Patients with GDU on upper endoscopy were identified from Ben Taub, a safety-net hospital in Houston, Texas using keyword search from endoscopic reporting software. Baseline data was obtained from consecutive patients with GDU diagnosis from 8/2020-2/2021 and post-intervention data from 5/2021-8/2021. We extracted *H. pylori* testing (stool antigen, serum antibody, biopsy) and antibiotic treatment regimen. Efficacious *H. pylori* regimen was defined as quadruple therapy (three antibiotics), or bismuth-based quadruple therapy based on recent local antibiotic resistance patterns. Fishbone diagram and process maps were created to explore causes of low treatment and eradication rates. An intervention was created based on these causes and change in rates of *H. pylori* treatment, cure confirmation, and efficacious *H. pylori* regimen were monitored. **Results:** 198 patients with GDU were included (mean 14.2 patients per month) with 40.7% prevalence of *H. pylori* (Figure 1). Most patients were men (58.5%) and non-white (27.3% black, 48.0% Hispanic, 8.6% Asian). Most had gastric ulcers (n=121, 61.1%), 50 (25.3%) had duodenal ulcers and 27 (13.6%) had both. Based on root cause analysis, it was found that lack of awareness by providers/patients and poor patient engagement due to language were barriers to *H. pylori* testing and treatment. Our intervention consisted of 1) education to primary care, gastroenterology, and hospitalist providers about *H. pylori* testing after GDU diagnosis and efficacious treatments, and 2) creation of letter templates in 3 languages (English, Spanish and Vietnamese) to facilitate patient education about treatment. Of 37 patients with H. *pylori* associated GDU in the pre-intervention group, 88.4% had *H. pylori* treated compared to 95.0% of 16 patients in the post-intervention group (p=0.43). In the pre-intervention group, 29.3% had confirmation of *H. pylori* eradication compared to 27.0% in the post-intervention group (p=0.91). Prior to our intervention, 70.4% were prescribed efficacious *H. pylori* treatment compared to 93.8% after our intervention (p=0.04; Figure 2). **Conclusion:** An improvement was observed in *H. pylori* testing and treating with efficacious regimens among patients with GDU. Next interventions will focus on implementation of electronic medical record order sets to facilitate H. pylori cure confirmation testing and efficacious treatment prescriptions.

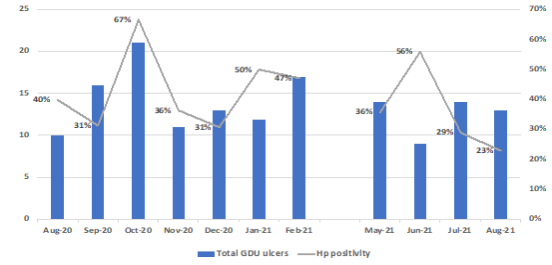

Figure 1. Total patients with gastroduodenal ulcers (GDU) diagnosed on endoscopy and prevalence of H. pylori (Hp) infection in pre- and post-intervention cohorts.

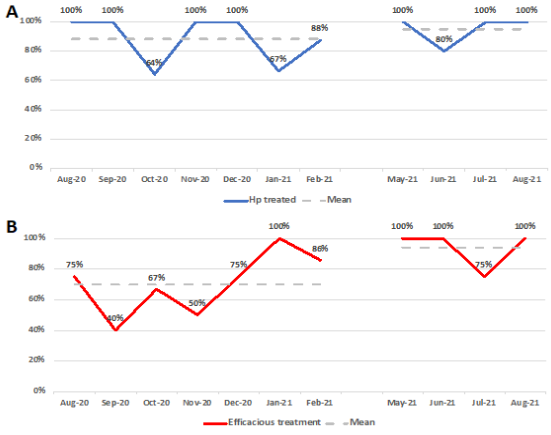

Figure 2. Rates of *H. pylori (Hp)* treatment (A) and rates of efficacious treatment regimens (B) in pre- and post-intervention cohorts with endoscopic diagnosis of

Contemporary prevalence and predictors of *helicobacter pylori* infection in a U.S. population

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Background: *Helicobacter pylori* infection leads to most peptic ulcers and gastric cancer cases. The prevalence of *H. pylori* has been declining overall but there is no current screening strategy in the U.S. to identify and treat patients with *H. pylori* infection. The purpose of our study was to identify the prevalence and predictors of *H. pylori* infection among patients undergoing upper endoscopy with gastric biopsies for any indication in the Harris County Hospital System in Houston, TX.

Methods: We identified all consecutive patients undergoing upper endoscopy with gastric biopsies for any indication from two hospitals in the Harris County Hospital System in Houston, TX during 1/2015-12/2016. We abstracted demographic, lifestyle, laboratory, endoscopic, and histopathologic data from the electronic medical record to evaluate previous as well as active *H. pylori* infection seen on gastric biopsy. We determined the overall as well as sex and race/ethnic specific prevalence of *H. pylori* infection. We evaluated associations between demographic, lifestyle, and endoscopic features with *H. pylori* infection in logistic regression models and reported as odds ratios (OR) and 95% confidence intervals (CI).

Results: Of 943 patients who underwent gastric biopsies, 376 were men (39.9%) with mean age 53.0 years (SD 11.6 years). Most were Hispanics (51.1%) or blacks (26.0%) with a small proportion of whites (11.1%). The overall prevalence of *H. pylori* infection was 52.8% (n=498), which was highest among Hispanics (60.2%), blacks (51.0%), and Asians (52.3%) compared to whites (21.9%). Predictors of *H. pylori* included race (vs. white, black adjOR 3.76, 95% CI 2.19-6.45; Hispanic adjOR 5.31, 95% CI 3.14-9.00; Asian adjOR 3.96, 95% CI 1.93-8.11) and proton pump inhibitor use (adjOR 1.50, 95% CI 1.10-2.05). Female sex was protective for *H. pylori* infection (adjOR 0.65, 95% 0.47-0.91). Gastric polyps identified on endoscopy were associated with the absence of *H. pylori* (OR 0.57, 95% CI 0.37-0.88). There were no significant associations with age, BMI, family history of gastric cancer, tobacco use, or alcohol use.

Conclusion: In this contemporary U.S. cohort of patients undergoing endoscopy with gastric biopsies, the overall prevalence of *H. pylori* infection is very high (52.8%). Black, Hispanic, and Asian race were associated with high *H. pylori* infection, while men were at increased risk of developing this infection. These findings call for developing a *H. pylori*-screening strategy in certain high-risk U.S. populations.

Abstracts

Generation of human intestinal organoids from Cronkhite Canada Syndrome reveals new insights into a rare disease

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Cronkhite Canada Syndrome (CCS) is a rare, non-inherited polyposis syndrome affecting 1 in a million individuals. Despite over 50 years of CCS cases, the etiopathogenesis and optimal treatment for CCS remains unknown. CCS patients present with diarrhea (80%), dysgeusia, abdominal pain/discomfort, dry mouth, anemia, and weight loss. Endoscopically, patients show polyposis, inflammation, and edema (in the upper and lower GI tract). Dermatological features of the disease include hair loss, nail changes, and hyperpigmentation. In order to investigate and better understand the etiology and pathology of CCS, we generated human intestinal organoids (HIOs) from the large and small intestinal stem cells isolated from two CCS patients. We noted that CCS organoids grow faster, larger, and have unique morphologies compared to non-CCS organoids. Cell type analysis revealed an increased number of serotonin positive enteroendocrine cells (EECs). Further investigation revealed that serotonin can induce organoid proliferation suggesting that dysregulation of EEC serotonin production may explain the polyposis syndrome observed in CCS. This work illustrates the important role organoid cultures can play in understanding disease etiology and in the generation of novel and innovative therapies to treat these diseases. Our use of this technology to gain insight into CCS demonstrates how organoids can provide a gateway to the development of personalized medicine.

Malnutrition alters hepatic heme homeostasis to impair bile acid biosynthesis

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Keywords: Bile acids, cholesterol, CYP7A1, hepatocytes, mouse models

Background: Bile acids act as detergents for dietary lipid emulsification and as hormones that regulate numerous metabolic pathways. In malnutrition, bile acid synthesis is impaired, leading to fat malabsorption and metabolic abnormalities that result from altered nuclear receptor signaling. In our mouse model of early postnatal malnutrition, we reported that impaired bile acid synthesis leads to decreased farnesoid-X-receptor (FXR) activation and decreased expression of FXR-dependent coagulation factors, resulting in coagulopathy. It is unknown why bile acid synthesis is impaired in malnutrition. The rate-determining enzyme in the classic pathway of bile acid synthesis is CYP7A1, which converts cholesterol into the bile acid intermediate 7α-hydroxycholesterol. Our malnourished mice have normal expression of CYP7A1 with 2-fold increased cholesterol, suggesting that impaired CYP7A1 *activity* might underlie the buildup of cholesterol and decreased bile acid synthesis. CYP7A1 activity requires a single prosthetic moiety, heme. We hypothesized that malnutrition impairs the classic pathway of bile acid synthesis by inhibiting heme synthesis, thus reducing the availability of the essential cofactor for CYP7A1 activity.

Methods: C57BL/6 mice were malnourished by low-protein low-fat diet or were maintained on control chow. After 8 weeks, mice received intraperitoneal heme or vehicle, and then primary hepatocytes were isolated for heme quantification and for CYP7A1 activity by mass spectrometry. Total fecal bile acids were quantified. In vitro bile acid synthesis was assessed in HepG2 hepatocytes incubated with heme or succinylacetone, a potent inhibitor of heme synthesis.

Results: Malnutrition reduced hepatic CYP7A1 activity by 65% ($p=0.023$) and heme concentrations by 44% ($p=0.002$). Inhibiting heme synthesis in vitro with succinylacetone decreased bile acid production by 61% ($p<0.0001$); bile acid synthesis was restored by adding free heme to succinylacetone-treated cells. Strikingly, treating malnourished mice with heme completely restored intestinal bile acid levels.

Conclusions: We present the first direct evidence that impaired CYP7A1 activity is responsible for decreased bile acid synthesis in malnutrition. Supplementation with heme increases bile acid synthesis both in vitro and in vivo. These results suggest a novel, unexplored link between heme homeostasis and bile acid synthesis that ultimately could be leveraged to combat malnutrition-induced liver dysfunction.

Modeling and dissecting poorly differentiated gastric cancer initiation

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Gastric cancer (GC) is the second most common cause of cancer death in Asia. Poorly differentiated gastric cancer (PDGC) is one of the GCs with poor clinical response to the current regimen. To date, the mechanism of PDGC development remains elusive. Therefore, it is imperative to dissect the biology of PDGC initiation by employing reliable preclinical models. Herein we sought to determine key genetic interactions pathologically associated with PDGC tumorigenesis. We previously identified the *CRACD* (Capping Protein Inhibiting Regulator of Actin Dynamics/*CRAD/KIAA1211*) gene as a tumor suppressor related to colorectal cancer. The *CRACD* gene is frequently inactivated in PDGC. *Cracd* KO mice and gastric organoids (GOs) displayed gastric epithelium hyperplasia with the loss of actin dynamics. Analyses of genetically engineered GOs (*Kras*^{G12D}; *Trp53* KO [KP] and *Cracd* KO; *Kras*^{G12D}; *Trp53* KO [CKP] showed that compared to KP organoids, CKP GOs exhibited neoplastic features with the expression of PDGC markers. Consistently, xenograft and allograft models showed that CKP is sufficient to develop aggressive tumors resembling PDGC, while KP transplants represented low tumorigenicity determined by less tumor incidence, smaller tumor size, and minor invasiveness. Single-cell transcriptomics showed that CKP-driven tumors recapitulate the transcriptional signatures of human PDGC, with distinct cell lineage trajectory, root cell clusters, and regulons, compared to KP. Together, our study defines *CRACD* as a tumor suppressor, of which inactivation disturbs the transcriptional landscape of gastric epithelium and drives PDGC initiation, which may be further translated into the development of a biomarker-guided regimen for *CRACD* mutations-associated PDGC.

Notes

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