DDC
Texas Medical Center Digestive Diseases Center

14TH ANNUAL
Frontiers in Digestive Diseases Symposium

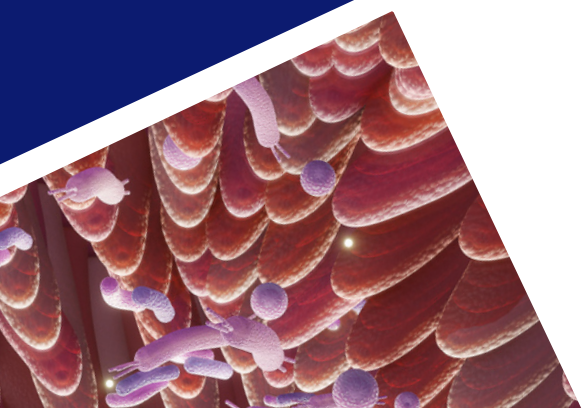
"Metabolic" Communication in Digestive Diseases

March 4, 2023

8 a.m. - 3 p.m.

Baylor St. Luke's
7200 Cambridge
Houston, Texas

Texas Children's Hospital®



CME Accreditation Jointly Provided by
Texas Children's Hospital and Texas Medical Center Digestive Disease Center

TARGET AUDIENCE: Physicians, fellows, residents, medical students, advanced practice providers, nurses, and other healthcare providers. **EDUCATIONAL OBJECTIVES:** At the conclusion of this live activity, participants should be better able to define metabolic communication in digestive diseases, its history and future applications; apply best practices and treatments for digestive diseases through metabolic communication; identify opportunities to apply this knowledge to the detection and treatment of digestive diseases; and Interpret the current metabolic research concerning GI infection and injury. **ACCREDITATION/CREDIT DESIGNATION:** Texas Children's Hospital is accredited by the Texas Medical Association to provide continuing medical education for physicians. Texas Children's Hospital designates this live activity for a maximum of ***3.75 AMA PRA Category 1 Credit(s)TM***. Physicians should claim only the credit commensurate with the extent of their participation in the activity. **DISCLOSURE:** Please visit DDC website for full list of disclosures. These relevant financial relationships have been appropriately mitigated. Persons involved in the planning of this activity have reported no relevant financial relationships with any commercial interest. The members of the Planning Committee and others involved in the planning of this activity have reported no relevant financial relationships with any ineligible companies. **CONFERENCE SUPPORT:** This CME activity is supported by Silvio O Conte Digestive Diseases Research Core Center (NIH P30DK056338).

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 117 members, with 79 full members and 38 associate members. DDC members have approximately $48 million in digestive diseases-related research funding as of 2023. 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-

Contents

"Metabolic Communication in Digestive Diseases"

AGENDA

DDC Texas Medical Center Digestive Diseases Center | 14TH ANNUAL Frontiers in Digestive Diseases Symposium

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

8:10 AM - 8:25 AM **WELCOME REMARKS**

Hashem B. El-Serag, M.D., M.P.H., DDC Co-Director
Jason C. Mills, M.D., Ph.D., DDC Co-Director

SESSION I *(Gut and microbial metabolites that influence metabolism)*

8:25 AM - 9:05 AM **"Gut microbial drivers of host metabolism: Implications for Health and Disease"**

Eugene B. Chang, M.D.
Martin Boyer Professor of Medicine
University of Chicago, Chicago, IL, USA

9:05 AM - 9:25 AM **"Intestinal fructose metabolism and metabolic disease"**

Mark A. Herman, M.D.
Section Chief, Endocrinology, Diabetes, and Metabolism
Baylor College of Medicine, Houston, TX, USA

9:25 AM - 9:45 AM **"Lipid dysregulation of immune responses to intestinal injury"**

Andrea McAlester, Ph.D.
Instructor, Pathology and Immunology, 2021 DDC Pilot Feasibility Awardee
Baylor College of Medicine, Houston, TX, USA

9:45 AM - 10:25 AM **"Regulation of the host-microbiota relationship"**

Theresa Alenghat, VMD, Ph.D.
Associate Professor, Pediatrics
Cincinnati Children's Hospital, Cincinnati, OH, USA

10:25 AM - 10:50 AM **COFFEE BREAK**

SESSION II *(Liver pathophysiology and metabolic disorders)*

10:50 AM - 11:30 AM **"Gut microbiome based personalized medicine in NAFLD"**

Rohit Loomba, M.D., MHSc
Vice Chair, Gastroenterology, Director, Hepatology, & Professor of Medicine
University of California San Diego, San Diego, CA, USA

11:30 AM - 11:50 PM **"Circadian nuclear contenders in NASH and hepatocellular carcinoma"**

Kristin Eckel-Mahan, Ph.D.
Associate Professor, Center for Metabolic and Degenerative Diseases
The University of Texas Health Science Center, Houston, TX, USA

11:50 PM - 12:30 PM **"Bariatric surgery as an integrative physiology approach to obesity treatment"**

Darleen Sandoval, Ph.D.
Professor of Pediatrics and Medicine
University of Colorado, Anschutz Medical Campus, Aurora, CO, USA

12:30 PM - 1:30 PM **LUNCH / BREAKOUT Q&A SESSIONS WITH SELECT SPEAKERS**

#1 Eugene B. Chang, M.D.
#2 Rohit Loomba, M.D., MHSc
#3 Theresa Alenghat, VMD, Ph.D.
#4 Darleen Sandoval, Ph.D.

1:30 PM - 2:45 PM **POSTER SESSION**

2:45 PM - 3:00 PM **POSTER AWARDS / CLOSING REMARKS**

Doug Burrin, Ph.D.
Pilot Feasibility Program Director

Jointly Provided by
Texas Children's Hospital and Texas Medical Center Digestive Disease Center

Frontiers in Digestive Diseases Symposium
"Metabolic Communication in Digestive Diseases"

Saturday, March 4, 2023 | 8:00 am – 3:00pm | Baylor St. Luke's Medical Center | 7200 Cambridge

Join us as we discuss new developments in metabolic research and metabolic communication in digestive diseases. During this conference, the expert speakers will talk on gut and microbial metabolites that influence metabolism, liver pathophysiology and metabolic disorders.

TARGET AUDIENCE: Physicians, fellows, residents, medical students, advanced practice providers, nurses, and other healthcare providers.

EDUCATIONAL OBJECTIVES: At the conclusion of this live activity, participants should be better able to:

- Define metabolic communication in digestive diseases, its history and future applications
- Apply best practices and treatments for digestive diseases through metabolic communication.
- Identify opportunities to apply this knowledge to the detection and treatment of digestive diseases.
- Interpret the current metabolic research concerning GI infection and injury.

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DISCLOSURE: The speakers for this activity have reported no relevant financial relationships with any ineligible companies unless otherwise stated here: Mark A. Herman, MD – Receives Research Support from Eli Lily and Company; Darleen Sandoval, PhD – Serves as a Consultant with Metis Therapeutics; Rohit Loomba, M.D., MHSc - Serves as a consultant to Aardvark Therapeutics, Altimmune, Amgen, Anylam/Regeneron, Arrowhead Pharmaceuticals, AstraZeneca, Bristol Myers Squibb, CohBar, Eli Lilly, Galmed Pharmaceuticals, Gilead, Glympse Bio, Hightide, Inipharma, Intercept, Inventiva, Ionis, Janssen, Madrigal Pharmaceuticals, Merck, Metacrine Inc., NGM Biopharmaceuticals, Novartis, Novo Nordisk, Pfizer, Sagimet, Terns Pharmaceuticals, Theratechnologies, and Viking Therapeutics and receives Research grants were received from Arrowhead Pharmaceuticals, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Galectin Therapeutics, Galmed Pharmaceuticals, Gilead, Hanmi Pharmaceutical, Intercept, Inventiva, Ionis, Janssen, Madrigal Pharmaceuticals, Merck, NGM Biopharmaceuticals, Novo Nordisk, Pfizer, Sonic Incytes and Terns Pharmaceuticals and co-funder of LIpoNexus.*(pending CME Committee member review)*. These relevant financial relationships have been appropriately mitigated. Persons involved in the planning of this activity have reported no relevant financial relationships with any commercial interest.

PLANNING COMMITTEE DISCLOSURE: The members of the Planning Committee and others involved in the planning of this activity have reported no relevant financial relationships with any ineligible companies.

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Gyongyi Szabo, M.D., Ph.D.
Harvard Medical School

Robert Schwartz, M.D., Ph.D.
Weill Cornell Medicine

Gary D. Wu, M.D.
University of Pennsylvania

Keynote Speaker

Eugene B. Chang, M.D.
Professor of Medicine
University of Chicago
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Dr. Eugene B. Chang received his MD from the University of Chicago. A nationally-recognized physician-scientist, he currently serves as the Martin Boyer Distinguished Professor of Medicine and Director of the Microbiome Medicine Program at the University of Chicago where he leads a large, multi-disciplinary group of basic and clinical investigators in studies of host-microbe interactions and disease mechanisms of the gut in states of health and disease (primarily complex immune disorders like inflammatory bowel diseases and metabolic disorders like obesity and metabolic syndrome).

Dr. Chang's lab employs innovative approaches that include cultivation-dependent and –independent technologies for microbial analysis, genetically modified and gnotobiotic mouse models, metabolic and functional measurements, and advanced bioinformatic tools to investigate both the host and the microbiome.

Symposium Speakers

Mark A. Herman, M.D.
Chief of Endocrinology,
Diabetes, and Metabolism
Baylor College of Medicine
Houston, TX

Dr. Herman obtained his MD at UT Southwestern Medical Center. He completed his fellowship in endocrinology at the Joslin Diabetes Clinic at Beth Israel Deaconess Medical Center. Dr. Herman is Chief of endocrinology, diabetes, and metabolism at Baylor College of Medicine where he focuses on the role of nutrient sensing mechanisms and transcriptional control of metabolic programs contributing to the development of diabetes and cardiometabolic disease.

Andrea McAlester, Ph.D.
Instructor
Pathology and Immunology
Baylor College of Medicine
Houston, TX

Dr. McAlester received her PhD from Vanderbilt University. After completing her postdoc at Baylor College of Medicine in molecular virology and microbiology, she become an Instructor in pathology and immunology. Dr. McAlester is a 2021 DDC pilot feasibility awardee and her current research seeks to use human enteroid-derived epithelial monolayers and epithelialmacrophage culture systems to study the impact of diet on human intestinal disease.

Theresa Alenghat, VMD, Ph.D.
Associate Professor
Pediatrics
Cincinnati Children's Hospital
Cincinnati, OH

Dr. Alenghat completed her VMD and PhD at the University of Pennsylvania. She is an Associate Professor of Pediatrics at the University of Cincinnati. The Alenghat Lab investigates epithelial and immune cell homeostasis in the context of intestinal health and disease to provide insight into molecular mechanisms that mediate the host-microbiota relationship and to examine how this level of regulation affects innate immunity and chronic conditions.

Rohit Loomba, M.D., MHSc
Vice Chair, Gastroenterology
Director, Hepatology
Professor of Medicine
University of California
San Diego, CA

Dr. Loomba is an expert in the clinical management of chronic liver diseases and holds a joint appointment in the Division of Gastroenterology in the Department of Medicine and the Division of Epidemiology in the Department of Family and Preventive Medicine, University of California at San Diego School of Medicine. His research focuses on all aspects of nonalcoholic fatty liver disease including aging, epidemiology, genetic and environmental predisposition, natural history, and treatment of nonalcoholic steatohepatitis.

Kristin Eckel-Mahan, Ph.D.
Associate Professor
Center for Metabolic and
Degenerative Diseases
The UT Health Science Center
Houston, TX

Dr. Eckel-Mahan received her PhD from the University of Washington, Seattle, and continued her scientific training at the University of California, Irvine, where she studied the mechanisms by which nutrients and metabolites control the circadian properties of the liver. In 2015, she joined the Institute of Molecular Medicine at The UT Health Science Center as an Assistant Professor in the Center for Metabolic and Degenerative Diseases. The Eckel-Mahan lab studies the roles of the circadian clock in health and disease states.

Darleen Sandoval, Ph.D.
Professor of Medicine
Pediatrics - Nutrition
University of Colorado,
Anschutz Medical Campus
Aurora, CO

Dr. Sandoval is Professor of Medicine in Pediatrics, Section of Nutrition, at University of Colorado, Anschutz Medical Campus. She received her PhD in exercise science at Arizona State University and completed a postdoctoral fellowship at Vanderbilt University. Her work focuses on the role of the gut-brain axis in regulation of metabolism, including mechanisms and consequences of bariatric surgery and understanding the gut peptide, glucagon-like-peptide-1 (GLP-1).

Symposium Organizers

Geoffrey Preidis, M.D., Ph.D.
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Baylor College of Medicine
Texas Children's Hospital

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Associate Professor
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McGovern Medical School
The University of Texas
Health Science Center

Doug G. Burrin, Ph.D.
Professor, Pediatrics
Baylor College of Medicine
Research Physiologist
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Poster Session

"Estrogen-related receptor gamma (ERRγ) as a transcriptional regulator of parietal cell lineage maintenance"

Maple Adkins-Threats, B.S.
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Poster #1
See abstract on page 13

"Development of Small Intestinal Cell Engraftment in Mice"

Sumimasa Arimura, Ph.D.
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Abstract Only
See abstract on page 14

"A study of dietary patterns derived by cluster analysis and their association with nonalcoholic fatty liver disease severity among Hispanic patients"

Maya Balakrishnan, M.D.
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See abstract on page 15

"Impact of IBD and IBD associated dysplastic tissue derived microbiome on colon epithelium"

Nobel Bhasin, Ph.D.
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Abstract Only
See abstract on page 16

"Transplanted human intestinal organoid epithelial barrier function is enhanced by enteric nervous system but not epithelial developmental maturity"

Partha Chakraborty, M.D.
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Poster #2
See abstract on page 17

"Clinical and prognostic biomarker value of blood circulating inflammatory cytokines in hepatocellular carcinoma"

Shadi Chamseddine, M.D.
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Poster #3
See abstract on page 18

"Differential effects of bile acids on smooth muscle contractility in everted mouse ileum"

Diana Chang, DVM
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See abstract on page 19

"Stabilizing histamine release in mast cells signaling from the gut migates neuroinflammation in the brain post-stroke"

Claudia Di Gesu, Ph.D.
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See abstract on page 20

"Microbial stimulation of oxytocin release from the intestinal epithelium via secretin signaling"

Sara Di Rienzi, Ph.D.
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Poster #5
See abstract on page 21

"Rotavirus infection elicits host responses via P2Y1 purinergic signaling"

Kristen Engevik, Ph.D.
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Poster #6
See abstract on page 22

Poster Session

"NARDILYSIN-regulated scission mechanism activates polo-like kinase 3 to suppress the development of pancreatic cancer"

Jie Fu, Ph.D.
MD Anderson Cancer Center
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Poster #7
See abstract on page 23

"Chemotherapy-induced Tumor Immune Remodeling in Pancreatic Cancer"

Zachary Gao, M.D.
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Poster #8
See abstract on page 24

"Rotavirus non-structural protein 4 (NSP4) causes intercellular calcium waves that drive pathogenesis"

Thomas Gebert, B.S.
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Poster #9
See abstract on page 25

"Procedural optimizatons for GI tract tissues collected from non-human primates for targeted metabolomics-based bioanalysis"

Thomas Horvath, Ph.D.
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Poster #10
See abstract on page 26

"An abnormal extracellular environment may contribute to bowel dysfunction in Hirschsprung disease"

Britney Hsu, B.A. (Candidate)
Texas Children's Hospital
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Poster #11
See abstract on page 27

"The Role of SOX2 in Barrett's Esophagus Development"

Ramon Jin, M.D., Ph.D.
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Poster #12
See abstract on page 28

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

Gurpreet Kaur, MS
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Poster #13
See abstract on page 29

"The impact of race on pancreatic cancer treatment and survival in the nationwide veterans affairs healthcare system"

Natalia Khalaf, M.D., M.P.H.
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See abstract on page 30

"Diabetes status and pancreatic cancer survival in the nationwide veterans affairs healthcare system"

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See abstract on page 31

"Histone demethylase KDM5D upregulation drives sex differences in colon cancer"

Jiexi Li, MS
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Poster #14
See abstract on page 32

Poster Session

"Microbial deconjugation of bile acids regulates intestinal permeability in malnutrition"

Lauren Lynch, B.A.
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See abstract on page 33

"Interplay between diet and the gut microbiome in necrotizing enterocolitis (NEC)"

Valeria Melendez Hebib, M.S.
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See abstract on page 34

"Limosilactobacillus reuteri DSM 17938 modulates FOXP3 Deficiency-induced Dyslipidemia in Autoimmune Scurfy Mice"

Erini Nessim Kostandy, M.D.
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See abstract on page 35

"Malnutrition induced fatty liver is influenced by the gut microbiome and sex in young adult mice"

Larissa Neves, B.S.
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Poster #17
See abstract on page 36

"Defining the role of endoplasmic reticulum in the initiation of paligenosis"

Thanh Nguyen, B.S.
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See abstract on page 37

"The Constitutive Androstane Receptor (CAR) drives NAFLD-related Hepatocarcinogenesis"

Noha Osman, Ph.D.
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See abstract on page 38

"Gastric cancer risk in patients with long-term use of proton pump inhibitors: a systematic review and meta-analysis of observational and interventional studies"

Sharon Pan, MS
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See abstract on page 39

"Impact of an electronic medical record QI intervention on Helicobacter pylori treatment and eradication rates within a U.S. hospital system"

Ankur Patel, M.D.
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See abstract on page 40

"Performance of ulcer features in predicting malignancy among gastric ulcers diagnosed on endoscopy"

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See abstract on page 41

"The role of MBNL in smooth muscle function and DM1 GI pathologies"

Janel Peterson, B.S.
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See abstract on page 42

Poster Session

"Patterns of steroid use among a real-world national cohort veterans with inflamatory bowel disues on maintenance infliximab"

Codey Pham, M.D.
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See abstract on page 43

"A systematic review of the behavioral change determinants among patients with NAFLD using the theoretical domains framework"

Megan Pham, B.S.
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See abstract on page 44

"Histamine from limosilactobacillus reuteri 6475 induces proliferation in human small intestinal organoids"

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See abstract on page 45

"Generation of human intestinal organoids from Cronkhite Canada Syndrome patients reveals serotonin as a link to intestinal proliferation"

Victoria Poplaski, B.S.
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See abstract on page 46

"Chronic alcohol intake plays time-dependent role in cerulein-induced chronic pancreatitis in mice"

Amy Qin
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See abstract on page 47

"Infant and adult human intestinal enteroids are morphologically and functionally distinct"

Sasirekha Ramani, Ph.D.
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Poster #26
See abstract on page 48

"Methylome-wide profiling of early-onset colorectal cancer in underrepresented populations"

Karen Riggins, M.D., Ph.D.
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See abstract on page 49

"Generation of human intestinal organoid disease model from very early onset inflammatory bowel disease patients"

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Poster Only

"Rotavirus degrades of DGAT1 and causes increased viroplasm formation and viral"

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See abstract on page 50

"Bile acids differentially regulate smooth muscle contractility in mouse ileum"

Krishnakant Soni, Ph.D.
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See abstract on page 51

Poster Session

"Targeting cancer stem cell plasticity to overcome colorectal cancer resistance and relapse"

Shraddha Subramanian, Ph.D.
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Poster #30
See abstract on page 52

"Gut UGT Activity Loss Precedes the Development of Irinotecan-Induced Severe Diarrhea: Mechanisms, Biomarker, and Prevention"

Rongjin Sun, Ph.D.
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"Optimizing an Artificial Intelligence Algorithm for Microendoscopic Imaging by Integrating Patient-Level Risk Factors for Esophageal Squamous Cell Neoplasia Detection"

Mimi Tan, M.D., M.P.H.
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See abstract on page 54

"Aberrant Gremlin1 Expression Promotes a Fibrogenic Stromal Microenvironment in Pancreatic Ductal Adenocarcinoma"

Rachel Tindall, M.D.
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See abstract on page 55

"Healing of radiofrequency ablation for Barrett's esophagus involves novel patterns of cell plasticity in a longitudinal study of human tissue"

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See abstract on page 56

"PLIN1 is required for rotavirus replication"

Antonio Valentin, B.S.
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Poster Only

"Preterm cesarean versus vaginal birth blunts bile acid - fibroblast growth factor-19 signaling in neonatal pigs"

Caitlin Vonderohe, DVM, Ph.D.
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Poster #35
See abstract on page 57

"Srebp1 activation in early-life malnutrition suppresses Cyp7b1 transcription and bile acid synthesis"

Xiaoyang Wan, Ph.D.
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See abstract on page 58

"Interleukin-33 facilitates liver regeneration through serotonin-involved gut-liver axis"

Yankai Wen, Ph.D.
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Poster #36
See abstract on page 59

Poster Session

"Therapeutic Co-targeting YAP1 and TAZ using Antisense Oligos (ASOs) Suppress Gastric Cancer Progression and Peritoneal Metastases"

Jingjing Wu, Ph.D.
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See abstract on page 60

"Eosinophil orchestrates tissue repair after hepatic ischemia reperfusion injury"

Yang Yang, Ph.D.
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"The role and regulation of YAP1 in paligenosis, the cellular program for conversion of mature cells to precancerous metaplasia"

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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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Abstracts

Estrogen-related receptor gamma (ERRγ) as a transcriptional regulator of parietal cell lineage maintenance

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The most common gastrointestinal ailments worldwide, including indigestion, acid reflux, and gastric cancer arise from aberrant activity of highly specialized, acid-secreting parietal cells (PCs) in the gastric epithelium. While much is known about the structure and function of PCs from morphological and cell physiological studies, little is known about the signalling pathways and transcriptional events that regulate 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. Based on the proliferation status within the gastric glands, the lack of mature PCs, and the abundance of juvenile PCs, we have identified the 36–72-hour timeframe of recovery as the optimal time to study PC regeneration (termed the “Phoenix Stage”).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. Transcriptional analysis reveals that prePCs are a transcriptionally distinct population, co-expressing moderate levels of proliferation, progenitor, and PC-specific markers. Next, we 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 metabolic switch AMPK and directly interacts with mitochondria biogenesis master regulator PCG1α to regulate cellular metabolism. While ERRγ has been shown to regulate functional and metabolic maturation in other highly oxidative cell types (β cells and cardiomyocytes, its role in gastric lineages is relatively unknown. Histological analysis of various PC markers reveals that ERRγ is one of the first PC specific markers to turn on in PC progenitors and prePCs. Furthermore, we demonstrate 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.

Abstracts

Development of Small Intestinal Cell Engraftment in Mice

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Background & Aims: The replacement of diseased epithelial cells with healthy cells in the small intestine (SI) can be a radical treatment for several untreatable patients with epithelial dysfunction. Additionally, this replacement method may make it possible to establish new models of SI diseases with or without known etiology for understanding its pathophysiology and finding new therapeutic targets. However, there is no report regarding the functional/therapeutic replacement of SI epithelium with healthy or diseased SI cells in animals or humans. Here we aimed to create an innovative replacement method for engrafting SI organoids (SIOs) into the mouse SI mucosa.

Methods: The SI lumen of wild-type mice was treated with EDTA and physically brushed with an electric toothbrush to remove the epithelium. After the treatment, GFP-expressing normal SIOs were injected into the lumen of SI in wild-type mice, and their engraftment was verified histologically.

Results: The epithelial cells, but not stromal cells, in SI mucosa were peeled off by EDTA/Brushing method. In addition, the injected GFP-expressing normal SIOs were engrafted into SI mucosa 3 months after injection, covering the area that lacked epithelium as a result of the introduced damage in recipient mice. Furthermore, we succeeded in reflecting the severe invasive phenotype of $Apc^{-/-}$; $p53^{-/-}$; $Pik3ca^{H1047R}$ tumor model mouse using our engraftment technique.

Conclusions: In preliminary studies, we established an orthotopic functional engraftment method for SIOs. Our results suggest that cultured SIOs might be a source of cells for replacing SI epithelial cells or developing mouse models of its diseases.

Future Plans: We will inject healthy or diseased SIOs into the SI mucosa of diseased or healthy mice and investigate whether our engraftment can be a new therapeutic and valuable method for developing novel mouse models for SI diseases. In addition, we will expand our technology to develop gastric cell replacement technology.

Abstracts

A study of dietary patterns derived by cluster analysis and their association with nonalcoholic fatty liver disease severity among Hispanic patients

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Background: Diet is a modifiable NAFLD risk factor, but few studies/investigations have been conducted among Hispanic patients, despite the fact that NAFLD prevalence and severity are highest among this ethnic subgroup. We aimed to identify prevalent dietary patterns among Mexican/Central American patients (M/CA) using cluster analysis and to examine/investigate associations with NAFLD severity.

Methods: This cross-sectional analysis included 421 Harris County NAFLD Cohort Hispanic participants who completed baseline food frequency questionnaires. K means analysis was used to identify clusters of patients sharing similar dietary habits. Multivariable adjusted logistic regression was used to estimate associations of dietary cluster with aminotransferases among the overall sample and with histologic steatosis and fibrosis among a liver biopsy sub-sample (n=186).

Results: We identified two clusters: a plant food/prudent and fast food/meats pattern. The fast food/meats pattern was associated with 2.47 increased odds (95% CI 1.31-4.65) of more severe steatosis than the plant foods/prudent pattern after adjusting for demographics, metabolic score, physical activity, and alcohol(q=0.0159). No significant association was observed between diet and aminotransferases or fibrosis.

Conclusions: Given the importance of sociocultural influences on diet, it is important to understand dietary patterns prevalent among ethnic minority patients with NAFLD. Using cluster analysis, we identified one distinct plant-based versus a distinct fast food/meat-based pattern associated with detrimental effects among our target population. This information is an important starting point for targeted interventions among Hispanic populations.

Impact of IBD and IBD associated dysplastic tissue derived microbiome on colon epithelium

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The risk of developing colon cancer increases significantly in patients with inflammatory bowel disease (IBD). Disruption of the microbial ecosystem is observed in IBD and associated pathologies. The reduction of butyrate-producing bacteria and increase in pathogenic species has been reported to alter the colon microenvironment making it more tumor permissive. The functional impact of an altered microbiome that enables the progression to dysplasia is unclear. Our study examined the composition and impact of mucosa adherent microbiome derived from IBD patients with dysplasia on colon epithelium. Biopsies from patients with IBD were included in the study for culture in "*in vitro"* mini-bioreactor arrays. Paired biopsies from dysplastic and non-dysplastic tissue were included from the same patient. HCT116 colon cancer cells were exposed to metabolites of the biopsy culture. After 48 hours of exposure, the cell lysate and secretome were collected and analyzed by Mass spectrometry. Differentially expressed proteins were determined using Limma. GSEA-based enrichment analysis was performed to determine the functional impact of exposure. The cellular secretome showed an upregulation of Extracellular Matrix proteins associated with epithelial-to-mesenchymal transition (EMT) and tumorigenesis in an inflammatory microenvironment. A similar GSEA analysis of differentially expressed proteins in the cell lysate showed an upregulation of pathways associated with cellular proliferation, EMT, and downregulation of DNA damage response. We verified the proliferative phenotype induced by exposure to microbial metabolites using the BRDU incorporation assay. DNA damage was assessed by examining YH2AX staining in cells. Metabolites derived from the dysplastic tissue induced a significantly higher proliferation(p<0.01) and DNA damage(p<0.05) compared to the paired non-dysplastic tissue. 16S sequencing of the biopsy swabs and the bacterial pellets of cultured biopsies revealed an altered microbial profile in the dysplastic tissue. It was observed that dysplastic tissue-derived biopsies were depleted in the genus Faecalibacterium. This may be indicative of a lower concentration of butyrate-producing Faecalibacterium prausnitzii species. Butyrate-producing bacteria play an important role in maintaining intestinal barrier and epithelial integrity and are preventative against microbial invasion. Together our findings suggest that gut microbial composition and its metabolites in dysplastic tissue enable a tumor-permissive state marked by cellular proliferation and DNA damage.

Abstracts

Transplanted human intestinal organoid epithelial barrier function is enhanced by enteric nervous system but not epithelial developmental maturity

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Introduction: Short bowel syndrome is a devastating disease, incurring over $500,000 in costs per patient in the first year. Mortality has been reduced by multidisciplinary management with parenteral nutrition, teduglutide, bowel lengthening procedures, or intestinal transplantation but morbidity remains significant. Human intestinal organoid (HIO)-derived tissue-engineered intestine (TESI) is a potential cure. Confirmation of proper function is imperative before TESI can be utilized as a human therapy. HIOs contain epithelium and mesenchyme with development analogous to fetal intestine. HIOs mature after transplantation (tHIOs) *in vivo* to better recapitulate adult intestine. However, HIOs lack an enteric nervous system (ENS) which is critical for intestinal functions like nutrient absorption, motility, and barrier maintenance. Prior studies have demonstrated that incorporation of the ENS into HIOs increased epithelial cell proliferation and mediated peristaltic-like contractions. We aimed to improve epithelial barrier function in tHIOs by co-culturing HIOs with enteric neural crest cells (ENCCs) prior to transplantation *in vivo*. Furthermore, we hypothesized that epithelial barrier function in tHIOs would depend on both enteric nervous system and epithelial developmental maturity.

Methods: HIOs and ENCCs were generated from human embryonic stem cells (hESCs). HIOs were co-cultured with ENCCs grown in vitro for 28-40 days. HIOs were transplanted under the kidney capsule of adult NSG mice for up to 18 weeks. Transepithelial electrical resistance (TER) was recorded in an Ussing chamber as a measure of barrier function. H&E staining was performed to evaluate epithelial development per our lab's previously described grading scale (G1 = absence of crypts/villi to G4 = elongated crypt-villus axis). Immunofluorescence (IF) staining was performed for epithelial marker (ECAD), smooth muscle actin marker (SMA), and neuronal marker (TUJ1), to evaluate ENS development. We established an ENS grading scale from 0 to 3 with G0 = no TUJ1 present, G1 = paucity of TUJ1, G2 = ample TUJ1 but no ganglia, G3 = ample TUJ1 and ganglia present. tHIOs were compared to human small intestine (hSI) as controls.

Results: H&E and IF staining confirmed that tHIOs matured *in vivo* with a robust epithelial development surrounded by smooth muscle. Presence of enteric neurons (TUJ1) was confirmed on IF staining. TER was significantly higher in tHIOs with ENS G3 (41.5±5.4) compared to ENS G0 (28.31±3.0) ($p=0.04$) and no different from hSI (43.8±3.7) ($p=0.71$). However, TER was not significantly different amongst the four epithelial developmental grades.

Conclusion: Epithelial barrier function in tHIOs is improved by ENS but not epithelial developmental maturity. Future studies will aim to improve ENS developmental maturity in the tHIOs and also determine how ENS developmental maturity influences other functions in tHIOs, like motility and nutrient absorption.

Clinical and prognostic biomarker value of blood circulating inflammatory cytokines in hepatocellular carcinoma

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Circulating inflammatory cytokines play critical roles in tumor-associated inflammation and immune responses. Recent data has suggested that several interleukins (ILs) mediate carcinogenesis in hepatocellular carcinoma (HCC). However, the predictive and prognostic value of circulating ILs has yet to be validated. Our study aimed to evaluate the association of the serum ILs with overall survival (OS) and clinicopathologic features in a large cohort of HCC patients. We prospectively collected data, and serum samples from 767 HCC patients treated at The University of Texas MD Anderson Cancer Center between 2001 and 2014, with a median follow-up of 67.4 months (95% CI: 52.5, 83.3). Biomarker association with overall survival (OS) was evaluated by the Log-rank method. The median OS in this cohort was 14.2 months (95% confidence interval [CI]: 12, 16.1 months). Clinicopathologic features were more advanced, and OS was significantly inferior in patients with high circulating levels of IL1-R1, IL-6, IL-8, IL-10, IL-15, IL-16, and IL-18. In conclusion, our study shows that several serum IL levels are valid prognostic biomarker candidates and potential targets for therapy in HCC.

Abstracts

Differential effects of bile acids on smooth muscle contractility in everted mouse ileum

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Bile acids are essential for the digestion and absorption of dietary fats. Bile acids also regulate intestinal motility by mechanisms that are poorly understood. We developed a novel technique to study how bile acids influence contractility of the mouse intestine. We gently everted whole segments of ileum from male and female C57BL/6 mice to expose the apical surface containing bile acid receptors. We then mounted the everted tissue in an organ bath, added increasing doses of bile acids, and recorded the force of the contractile response relative to baseline (delta-force) with a force-transducer. Each dose of ursodeoxycholic acid (UDCA) induced a robust contractile response that peaked at 0.089 ± 0.058 grams at a dose of 100 μM. However, deoxycholic acid (DCA) generated a distinct ($P < 0.0001$ by two-way ANOVA) biphasic contractile response, with low doses (10 μM) inducing a moderate delta-force of 0.038 ± 0.022 grams and high doses (100 μM) inducing a negative delta-force of -0.020 ± 0.023 grams. Both male and female mice responded to UDCA and DCA similarly. Contractile responses were not altered by an inhibitor to the apical sodium-bile acid transporter (ASBT), indicating that active transport into ileocytes is not necessary for UDCA and DCA to influence intestinal smooth muscle contractility. Ongoing studies seek to determine whether the gut microbiome and ileocyte cell surface receptors are necessary for the differential effects of these two bile acids on intestinal smooth muscle contractility.

Stabilizing histamine release in mast cells signaling from the gut mitigates neuroinflammation in the brain post stroke

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Clinically, ~65% of stroke patients are left with functional impairments after stroke and 15% die shortly after their stroke. Increasing evidence suggests that peripheral inflammatory responses after stroke play an important role in determining neurological outcome. Mast cells (MCs) are one of the most rapid responders to injury. MCs release histamine (HA), a pro-inflammatory transmitter that enhances inflammation. Gut MCs are a major source of HA. We hypothesize that stroke in aged animals will lead to robust gut mucosal MC-activation and HA release, with subsequent gut disruption and inflammation. Stabilizing peripheral MCs will decrease peripheral/central inflammation, MC trafficking, and improve stroke outcomes.
We used a reversible middle cerebral artery occlusion (MCAO) model of ischemic stroke in aged (18mo) wild-type male mice to investigate the MC role in neuroinflammation post-stroke (PS). We stroke the aged animals and treated the animals with 25 mg/kg BW of cromolyn (MC stabilizer), oral gavage. Cromolyn was administered at 3-h, 10-h, 24-h and every other day PS. Positive control group that were stroked but treated only with saline. In total, four groups, stroke and sham (surgery control), out of these animals one set received cromolyn and one set received saline. We sacrificed animals at 3-h, 24 –h and 3-days after cromolyn treatment post-stroke.

We found that cromolyn administration significantly reduced MC numbers in the brain at 24-hours ($P<0.0051$) and 3 days ($P<0.0005$) PS. In association with that we found behavioral changes with improved motor activity at 3-days post-stroke animals after cromolyn treatment. We also found that gut mast cells are significantly reduced after cromolyn treatment in the 24 hours and 3-days PS groups ($P<0.01$). Additionally, we found significant decrease in neurological deficit score at the 3-days PS animals which was not very prominent at 24-hours ($P<0.0125$). GFP+MC introduction via adoptive transfer to c-kit-/- MC knock-out animals showed elevated MC recruitment to the injury site PS. In addition to the reduction in peripheral inflammation, we found rescue effect on the microbiome composition after cromolyn administration that prevented stroke induced dysbiosis.

Our results show that preventing MC-HA release post-stroke possess clinical value in preventing neuroinflammation PS.

Microbial stimulation of oxytocin release from the intestinal epithelium via secretin signaling

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Intestinal microbes impact host health by affecting the function of the intestine as well as other organs distal to the gut. The small intestinal microbe *Limosilactobacillus reuteri* has been demonstrated to promote normal gut transit, the anti-inflammatory immune system, wound healing, normal social behavior in mice, and prevent bone loss. *L. reuteri*-mediated promotion of wound healing and normal social behavior require oxytocin signaling; however, the initiating events in the gut that lead to *L. reuteri*'s stimulation of oxytocin signaling and beneficial functions throughout the body are not known. Through single cell (scRNA-Seq) data analysis and imaging of human intestinal tissues, we find that oxytocin is made in the intestinal epithelium and is most abundant in the small intestine. By applying *L. reuteri*-conditioned media to segments of the human small intestine, we observe secretion of oxytocin. In human intestinal organoids, oxytocin secretion by *L. reuteri* can be promoted, but only with the use of organoids with a greater number of hormone-producing enteroendocrine cells. These observations suggest that either oxytocin is produced in an enteroendocrine cell or *L. reuteri*'s stimulation of oxytocin secretion depends on the production of a signal from an enteroendocrine cell. Additional imaging and scRNA-Seq analyses indicate that oxytocin is produced in enterocytes. Through a series of experiments utilizing organoids and human intestinal tissue, we determine that the enteroendocrine cell product required for *L. reuteri* mediated oxytocin secretion is the hormone secretin. Altogether, we have determined that the hormone oxytocin is produced in the intestinal epithelium and that the hormone secretin is a central player in the interplay between *L. reuteri* and oxytocin secretion.

Rotavirus infection elicits host responses via P2Y1 purinergic signaling

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Rotavirus causes life-threatening diarrhea in children, resulting in ~200,000 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 (rD6/2) to investigate the effects of purinergic signaling in the context of homologous murine rotavirus infection *in vivo*. C57Black6 mouse pups were orally gavaged rD6/2 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 P2Y1-selective, competitive 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 heterologous rotavirus infection, treatment of rD6/2-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 show that P2Y1 signaling is involved in the pathogenesis of a homologous murine rotavirus infection, which are more severe than infections with non-murine rotaviruses. 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 establish a 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.

Abstracts

NARDILYSIN-regulated scission mechanism activates polo-like kinase 3 to suppress the development of pancreatic cancer

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Pancreatic ductal adenocarcinoma (PDAC) develops through stepwise genetic and molecular alterations. As one of the early steps in metastasis, PDAC cells gain the ability to resist anoikis, detachment-induced apoptosis, which is associated with the acquisition of an aggressive tumorigenic and metastatic phenotype *in vivo.* However, little is known about PDAC anoikis induction and metastasis.

Plk3 plays a pivotal function in regulating cell-cycle progression and apoptosis. Here, we find that development of anoikis resistance and metastasis of *Kras*^{G12D}-driven PDAC in mice is accelerated by deleting *Plk3*, explaining the often reduced Plk3 expression in human PDAC. Importantly, a 41 kDa Plk3 (p41Plk3) that contained the entire kinase domain at the N-terminus (1-353 aa) is activated by scission of the precursor p72Plk3 at Arg354 by metalloendopeptidase Nardilysin (NRDC). Cleavage of p72Plk3 by NRDC also generated p32Plk3, which encodes Plk3 C-terminus harboring signature Polo-box domain (PBD). The cleaved PBD C-terminus was quickly removed by proteasome degradation preventing the p41Plk3 inhibition by PBD. We found that p41Plk3 is the activated form of Plk3 that regulates a feedforward mechanism to promote anoikis and suppress PDAC and metastasis. p41Plk3 phosphorylates c-Fos on Thr164, which in turn, induces expression of Plk3 and pro-apoptotic genes. These findings uncovered an NRDC-regulated post-translational mechanism (PTM) that activates Plk3, establishing a prototypic regulation by scission mechanism. Nardilysin-dependent cleavage of PLK3 induce anoikis of PDAC tumor, playing essential roles in inhibiting PDAC metastasis.

Chemotherapy-induced Tumor Immune Remodeling in Pancreatic Cancer

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Background: Pancreatic adenocarcinoma (PDAC) has limited response to current therapies. Conventional chemotherapy also modifies the patient's immune system, although detailed understanding is lacking. We hypothesize that oxaliplatin (Oxa)-based therapy can favorably alter the tumor immune microenvironment (TiME) to become more immunogenic.

Methods: Treatment with Oxa/5FU was compared to vehicle control treatment in a murine orthotopic syngeneic PDAC model using the Panc02 cell line. Tumors were then processed for immune population analysis using cytometry by time-of-flight (CyTOF) (Fig.1A). FFPE tissue samples of surgical PDAC tumor specimens were evaluated by imaging mass cytometry (IMC). IMC-based immune contextures were compared between histopathologic responders and non-responders.

Results: In the in vivo PDAC model, combination Oxa/5-FU revealed higher populations of CD4 T-cells, activated CD8 T-cells, and M1-like tumor-associated macrophages (TAMs) compared to control ($p < 0.05$, Fig.1B). An increased expression of PD-L1 on cancer cells and TAMs and PD-1 on CD8 T-cells was observed with Oxa/5FU compared to control ($p < 0.05$, Fig.1C).
Of the human PDAC samples processed for IMC (n=22), 9 received upfront surgery, 6 had moderate treatment response to FOLFIRINOX, 7 had minimal or no treatment response. Compared the non-responder group, there was an increase in lymphocyte infiltration in the responder group (Fig.1D) represented by an increased density of tertiary lymphoid structures (TLS) in the responder group ($p < 0.05$, Fig.1E). Patients who underwent neoadjuvant FOLFIRNOX with high TLS density had significant survival benefit (Fig.1F).

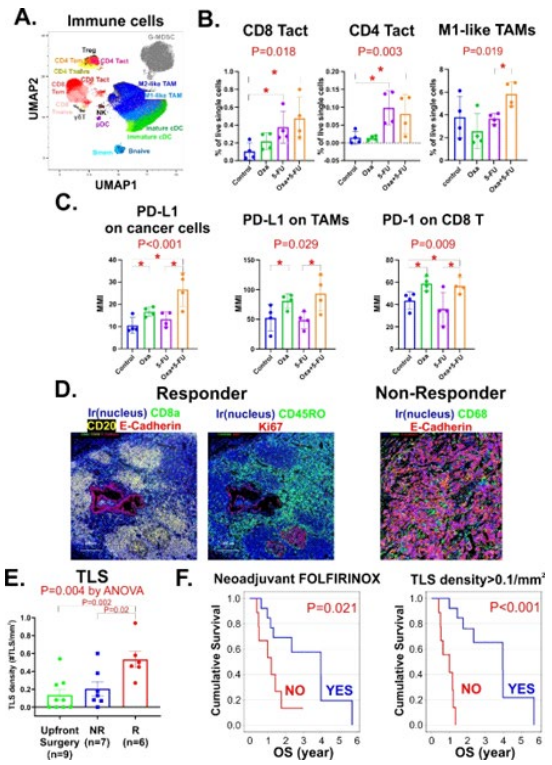

Figure 1: Chemotherapy-induced Tumor Immune Remodeling in Pancreatic Cancer. **A**. Immune atlas of PDAC by CyTOF. **B.** Alteration of the TiME after Oxa-based chemotherapy. **C**. Alteration of immunoregulatory PD-1 and PD-L1 on the TiME. **D**. IMC of PDAC tumor sections from responders and non-responders to FOLFIRINOX therapy. Responders show immune infiltration, as well as tertiary lymphoid structures. Non-responders have abundant tumor-associated macrophages with less lymphocyte infiltration. Functional marker expressions are highlighted, with CD8a as a cytotoxic T-cell marker, CD20 as a B-cell marker, CD45RO as a memory T-cell marker, CD68 as a macrophage marker, Ki67 as a proliferative marker, and e-cadherin an epithelial cell marker. **E**. TLS density is significantly increased in responders (n=6) (total n=22). **F**. Survival benefit of neoadjuvant chemotherapy and high TLS density in resected pancreatic cancer.

Discussion: Our evidence shows that Oxa/5FU can alter PDAC to become more immunogenic, with the observed increase in TLS pointing to favorable immune reactions. The increase in PD-L1/PD1 implies the potential use of combination chemo-immunotherapy to overcome chemoresistance, strongly supporting our ongoing PDAC chemo-immunotherapy clinical trial.

Abstracts

Rotavirus non-structural protein 4 (NSP4) causes intercellular calcium waves that drive pathogenesis

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Acute gastroenteritis (AGE) remains a 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, hypovolemic shock, and multi-system failure. While enteric viruses remain the most common cause of fatal AGE in kids, the drivers of their virulence remain incompletely understood. We recently found that cells infected with rotavirus, the most prevalent enteric virus in kids, release adenosine diphosphate (ADP) to induce coordinated signals known as "**intercellular calcium waves,**" which spread through uninfected neighboring cells. This dysregulates calcium signaling pathways, enhancing fluid secretion from uninfected cells thereby contributing to volume depletion. Understanding how rotavirus triggers intercellular calcium 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 that recombinant expression of a single rotavirus protein, non-structural protein 4 (NSP4), is sufficient to activate intercellular calcium waves. Using the rotavirus reverse genetics system, we show that the diminished calcium wave phenotype associated with an attenuated strain of rotavirus segregates with the NSP4 gene upon reassortment. Furthermore, we show that this attenuation is attributable to a single amino acid polymorphism in the C-terminal cytoplasmic tail of NSP4, implicating this domain as a key upstream mediator of intercellular calcium waves. Finally, we show that the calcium-conducting activity of the NSP4 "viroporin" domain is essential for its ability to induce ADP release. These findings characterize a new role for rotavirus NSP4, offer novel targets for anti-secretory therapeutics, and expand foundational knowledge to support the development of improved live-attenuated vaccines.

Procedural optimizatons for GI tract tissues collected from non-human primates for targeted metabolomics-based bioanalysis

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Introduction: The gut microbiome modulates the mammalian gut-brain-axis through numerous mechanisms including the production of neurotransmitters and neuroactive compounds such as gamma-aminobutyric acid (GABA), tyramine, and dopamine. Enzymatic conversions of glutamate to GABA within the intestinal lumen are performed by gut bacteria that express glutamic acid decarboxylase (GAD; EC 4.1.1.15). Our team studies the physiological development of the gut-brain-axis in non-human primate offspring, and we are particularly interested in GABA production by the mucosal microbiome across the different regions of the offspring gastrointestinal (GI) tract. We aimed to measure GABA pathway metabolites across the GI tract and determine the effect of starting tissue mass on end metabolite quantification.

Methods: Japanese macaque offspring, fed a tightly-controlled diet, underwent necropsy at 36 months old. GI tissues were collected from the stomach, small intestine, and large intestine (n=21 total) and were flash frozen. Samples were prepared at tissue densities of 150 mg/mL and 300 mg/mL in methanol:water (8:2, *v:v*) in MP FastPrep® tubes with ceramic lysing beads. Tissue homogenization was performed using 5 cycles (20 seconds/cycle; speed 6.5m/s) using a MP FastPrep bead mill, incubated for 4 hours at -80oC, and tissue debris was pelleted and the supernatant was collected; tissue homogenization was performed a second time on all samples. A volume of the homogenized tissue samples was diluted in an IS solution, and were subjected to targeted LC-MS/MS-based metabolomics.

Preliminary data: During tissue homogenization, it was noted that samples prepared at a 300 mg/mL tissue density were extremely turbid with large "globules" of non-homogenized tissue present in suspension. The lower density samples (150 mg/mL) tended to be clear with tissues completely homogenized. Quantitative analysis of glutamate, glutamine, and GABA were performed on all tissue homogenates (n=21 per condition; n=42 overall) using a previously published targeted metabolomics method. Briefly, HILIC chromatography was performed using a Supelco 2.7-micron Ascentis Express HILIC (150 x 2.1 mm) analytical column installed on an LC-MS/MS system consisting of a Shimadzu Nexera UHPLC system coupled to a SCIEX QTRAP 6500 using a Selected-Reaction Monitoring (SRM) scan mode and positive polarity. Absolute metabolite concentrations measured for each sample were normalized by tissue density (ng/mg tissue) and tissue-level metabolite comparisons were made using box plots. Statistical analysis performed using an ANOVA linear model showed no significant difference in glutamate, glutamine, and GABA concentrations between the tissue density-based preparations for each tissue type. Interestingly, we did measure significant differences in the normalized metabolite concentrations between tissue regions (i.e., stomach, small intestine, and large intestine) independent of starting mass. These data indicate that that our method can be executed with lower density of precious tissue samples without sacrificing data quality and method performance while boosting method and analytical column robustness.

Abstracts

An abnormal extracellular environment may contribute to bowel dysfunction in Hirschsprung disease

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Introduction: Hirschsprung disease (HSCR) is characterized by a deficit of enteric neurons in the distal bowel. Although the proximal ganglionic bowel is considered normal, many patients continue to experience constipation, enterocolitis, and bowel dysfunction after pullthrough surgery. Recent studies suggest that abnormalities may also exist in the proximal ganglionic bowel in HSCR. We aim to characterize the differences in extracellular matrix (ECM) composition and mechanoreceptor expression in ganglionic HSCR colon compared to wild-type (WT) colon.

Methods: Proximal ganglionic and distal aganglionic colon segments were collected from 2-3 week-old *Ednrb*$^{-/-}$ mice (HSCR; n=3), a model of HSCR, and equivalent colon segments were collected from healthy, wild-type littermates (WT; n=3). Gross architecture, neuronal distribution, and mechanoreceptor expression were characterized qualitatively using hematoxylin-eosin staining, trichrome staining, and immunofluorescence. Collagen content was calculated from trichrome staining and compared statistically using a paired t-test. Expression of ECM-related genes and the mechanoreceptor, Piezo1, were characterized by RT-qPCR and compared statistically using ANOVA.

Results: The expression of mechanoreceptor Piezo1 co-localized with enteric neurons (Tuj1+) and was qualitatively diminished in the ganglionic HSCR colon compared to WT. The interstitial collagen content of proximal ganglionic HSCR colon was significantly greater than that of proximal WT colon ($p<0.05$). Finally, the expression of 12 ECM-related genes were notably different in ganglionic HSCR bowel compared to WT; 11 of these ECM-related genes were similarly dysregulated in aganglionic HSCR bowel, including several genes regulating collagen turnover (collagen, matrix metalloproteinases) and fibrosis (Gremlin1, angiotensinogen). As an internal control, expression of neural cell adhesion molecule was expectedly diminished in aganglionic HSCR bowel.

Conclusions: Ganglionic proximal HSCR colon had increased collagen content, dysregulated ECM-related gene expression, and decreased mechanoreceptor expression when compared to the equivalent segment of WT colon. These alterations may contribute to abnormal function of the ganglionic bowel in HSCR.

The Role of SOX2 in Barrett's Esophagus Development

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Background: Barrett's esophagus (BE) is a precancerous condition defined as replacement of the normal esophageal squamous epithelium with metaplastic columnar intestinal epithelium caused by chronic gastroesophageal reflux disease. Importantly, Barrett's esophagus confers the strongest predisposition to developing esophageal adenocarcinoma. There is a deficiency of knowledge regarding the molecular pathogenesis of Barrett's metaplasia development. To this end, a thorough elucidation of the development context by which BE develops will uncover novel avenues to detect Barrett's metaplasia and revert it back to normal esophagus to ultimately halt the development of cancer. Spatial specification of the developing digestive tract occurs through a series of regulated transcriptional cascades. At embryonic day 9, the dorsal foregut is marked by expression of SOX2, a transcription factor of the Sry-like HMG box family, which is required for esophageal development. SOX2 continues to be expressed in the esophageal epithelium throughout adulthood as an important homeostatic maintenance factor. I hypothesize that SOX2 functions to maintain foregut squamous epithelial identity, and its loss is a critical step during Barrett's esophagus development and the progression to esophageal adenocarcinoma.

Methods/Results: Here, we show using human Barrett's esophagus tissue microarrays that SOX2 is expressed in the normal squamous epithelium and its expression is significantly decreased during the development of intestinal metaplasia. To assay the molecular effects of SOX2 expression changes on Barrett's esophagus, we have conducted a series of experiments involving a wholly novel biobank of human Barrett's esophagus derived organoids. We have been able to expand, cryopreserve, and genetically manipulate these primary cells, and here we characterize these organoids and show that they recapitulate key pathohistologic and molecular features of BE. Using the human BE organoid biobank, we have established and are now characterizing BE organoids that have forced expression of SOX2, and we are developing a high-throughput screening system using a *SOX2* luciferase promoter reporter assay to identify novel compounds and drugs that induce *SOX2* expression. Immediate future avenues will involve defining the direct transcriptional targets of *SOX2*, and interactions with the intestinal transcription factor CDX2 (Caudal Type Homeobox 2).

Conclusions: In summary, it is possible that in BE there is a stepwise transcriptional progression towards a more posterior phenotype with loss of SOX2 expression being an important initial step. Together, these experiments will elucidate novel molecular pathways involved in BE maintenance and may reveal novel therapeutic avenues to treat BE and prevent esophageal cancer.

Abstracts

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

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Background: Unexpected strain-specific innate immune response differences are detected between pandemic-causing GII.4 and non-pandemic GII.3 human noroviruses (HuNoVs) in human intestinal enteroids (HIEs). GII.3 HuNoV is more sensitive to the endogenous interferon (IFN) response. Specifically, knocking out key host immune restriction factors (STAT-1, IFNλ receptor, IFNα receptor) enhances GII.3 replication accompanied by viral spreading while no change is observed in GII.4 replication (Lin et al., PNAS 2020). However, we have yet to achieve continuous passaging of either virus, indicating alternate viral or host factors still restrict the replication. We aim to understand the cellular innate immune responses against HuNoVs and identify host restriction factors.

Methods: We used comparative transcriptomics of wild-type and genetically modified HIEs inoculated with GII.3 HuNoV and inactivated (gamma irradiated) virus to identify host restriction factors. We compared the GII.3 transcriptional response to our previously published RNA-Seq on GII.4 HuNoV followed by validation experiments using multiple approaches with both GII.3 and GII.4 HuNoVs.

Results: One key interferon-stimulating gene (ISG) upregulated in the RNA-seq datasets of HuNoV-infected parental and STAT-1 knockout HIEs is IP-10 (IFN-Gamma induced protein 10). RT-qPCR confirmed transcriptional upregulation of IP-10 following both GII.3 and GII.4 infection. Unexpectedly, secreted IP-10 was detected by ELISA after GII.3, but not GII.4, infection indicating novel mechanism(s) may be utilized by GII.4 to antagonize the innate immune response. Neutralization of IP-10, treatment of HIEs with an IP-10 receptor antagonist, and exogenous treatment of HIEs with purified IP-10 protein did not lead to any change in virus replication.
Conclusions. Although IP-10 is upregulated in HuNoV-infected HIEs, our results suggests that this ISG does not play a direct role in HuNoV replication in HIE epithelial only cultures. Since IP-10 is known to recruit immune cells, ongoing studies are evaluating a possible role of IP-10 in HuNoV replication and pathogenesis using an epithelial/immune cell co-culture system. Continued studies on other identified restriction factors and their modification may enhance viral replication, and allow virus passaging to facilitate functional, mechanistic, and translational studies to help reduce the public health burden of HuNoV infections.

The impact of race on pancreatic cancer treatment and survival in the nationwide veterans affairs healthcare system

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Objectives: Among patients with pancreatic cancer, studies show racial disparities at multiple steps of the cancer care pathway. Access to healthcare is a frequently cited cause of these disparities. The national Veterans Affairs (VA) healthcare system is the largest integrated public health system in the U.S., offering equal access to healthcare for all VA enrollees. Using data from the VA, we examined whether there were significant racial disparities in the continuum of pancreatic cancer care in VA system. We hypothesized that among Veterans with pancreatic cancer, there would be no racial disparities in the receipt of steps in the pancreatic cancer care continuum among Black and White patients.

Methods: We identified all patients diagnosed with pancreatic adenocarcinoma in the national VA Central Cancer Registry from January 2010 to December 2018. We examined the independent association between race and three endpoints: stage at diagnosis, receipt of treatment, and survival. We used logistic regression models to examine the association of race and cancer stage and treatment. We used Cox proportional hazards models to examine the association between race and survival. We adjusted the models for age, sex, body mass index, tobacco, and alcohol use, diabetes status, Deyo-Charlson comorbidity score, year of cancer diagnosis, and cancer stage and treatment.

Results: We identified 8,529 patients with pancreatic adenocarcinoma, of whom 79.5% were White and 20.5% were Black. Black patients were 19% more likely to have late-stage disease and 23% less likely to undergo surgical resection. Black patients had 7% higher mortality risk compared to White patients after adjusting for sociodemographic characteristics and medical comorbidities. This difference in mortality was no longer statistically significant after additionally adjusting for cancer stage and receipt of potentially curative treatment.

Conclusions: Our results show that compared to White patients, Black patients were 19% more likely to be diagnosed with later stage disease and 23% less likely to undergo potentially curative treatment (which includes surgical resection). These disparities translated into a 7% higher risk of death among Black patients. We also found that difference in mortality risk attenuated in models that accounted for cancer stage and receipt of potentially curative treatment, showing that mortality difference is partially but not fully explained by the disparities in the more proximal steps in the pancreatic cancer care continuum.

Contrary to our hypothesis, our data also show that even in a system with equal access to healthcare, racial inequalities exist in the timing of pancreatic cancer diagnosis and receipt of potentially curative cancer treatment. Equal access to healthcare might have reduced but failed to eliminate racial disparities in pancreatic cancer care. Dedicated efforts are needed to understand reasons underlying these disparities in an attempt to close these persistent gaps.

Diabetes status and pancreatic cancer survival in the nationwide veterans affairs healthcare system

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Objectives: Long-standing type 2 diabetes is a known risk factor for developing pancreatic cancer, however its influence on cancer-associated outcomes is understudied. We examined the associations between diabetes status and pancreatic cancer outcomes.

Methods: We identified patients diagnosed with pancreatic adenocarcinoma in the national Veterans Administration System from 2010 to 2018. We classified each patient by pre-cancer diagnosis diabetes status: no diabetes, new-onset diabetes (NOD) of ≤3 years duration, or long-standing diabetes of >3 years duration. Diabetes was defined by ICD codes, HgA1c value ≥6.5, or prescription for anti-diabetic medication. Our two outcomes of interest were receipt of: (1) "potentially curative treatment" and (2) survival. We defined potentially curative treatment as surgical resection only or in combination with chemotherapy and/or radiation therapy

We used logistic regression models to examine the association of diabetes status and cancer treatment types. We used Cox proportional hazards models to examine the association between diabetes status and pancreatic cancer outcome. We adjusted the models for age, race, sex, body mass index, tobacco, and alcohol use, Deyo-Charlson comorbidity score, year of cancer diagnosis, and cancer stage and treatment.

Results: We identified 6,342 patients diagnosed with pancreatic adenocarcinoma, of whom 97.2% were men and 53.6% were non-Hispanic whites. Most had long-standing diabetes (45.7%) prior to their cancer diagnosis,14.5% had NOD, and 39.8% had no diabetes. The average 5-year survival rate was 8.6%, with a median survival time of 4.97 months (IQR 1.87-11.67).

When comparing cancer-specific characteristics, there were no significant differences in AJCC stage at diagnosis by diabetes status. In multivariate logistic regression analysis (adjusted for age, sex, race, BMI, tobacco, and alcohol use, Deyo-Charlson comorbidity score, year of cancer diagnosis, and AJCC stage), there was no association between diabetes status and receipt of potentially curative treatment (no diabetes as reference group; NOD: OR 0.96; 95% CI, 0.75-1.22; long-standing diabetes: OR 0.85; 95% CI, 0.70-1.02).

Patients with long-standing diabetes had 10% higher mortality risk compared to patients without diabetes after adjusting for sociodemographic factors and medical comorbidities (adjusted HR 1.10; 95% CI 1.04-1.17). This difference in mortality remained statistically significant after additionally adjusting for cancer stage and receipt of potentially curative treatment (adjusted HR 1.08; 95% CI 1.02-1.15). There was no significant difference in mortality between patients with NOD compared to those without diabetes.

Conclusions: We examined the association between pre-cancer diagnosis diabetes status and survival among pancreatic cancer patients. We found an increased mortality risk among pancreatic cancer patients with long-standing diabetes that was not seen in those with NOD, highlighting that long-standing diabetes could serve as a potential risk stratifying factor. In line with prior studies, our findings support that long-standing diabetes is an independent prognostic indicator of poorer outcomes among pancreatic cancer patients.

Histone demethylase KDM5D upregulation drives sex differences in colon cancer

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Sex exerts a profound impact on cancer incidence, spectrum and outcomes, yet the molecular genetic bases of such sex differences are ill-defined and presumptively ascribed to X-chromosome genes and sex hormones. Such sex differences are particularly prominent in colorectal cancer (CRC) where men experience higher metastases and mortality. A murine CRC model, engineered with an inducible transgene encoding oncogenic mutant $KRAS^{G12D}$ and conditional null alleles of *Apc* and *Trp53* tumor suppressors (designated iKAP), revealed higher metastases and worse outcomes specifically in males with oncogenic mutant KRAS (KRAS*) CRC. Integrated cross-species molecular and transcriptomic analyses identified Y-chromosome gene histone demethylase *KDM5D* as a transcriptionally up-regulated gene driven by KRAS*-mediated activation of the STAT4 transcription factor. KDM5D-dependent chromatin mark and transcriptome changes showed repression of regulators of the epithelial cell tight junction and MHC class I complex components. Deletion of *Kdm5d* in iKAP cancer cells increased tight junction integrity, decreased cell invasiveness, and enhanced cancer cell killing by CD8+ T cells. Conversely, iAP mice engineered with a *Kdm5d* transgene to provide constitutive *Kdm5d* expression specifically in iAP cancer cells exhibited an increased propensity for more invasive tumors *in vivo*. Thus, KRAS*-STAT4-mediated upregulation of Y chromosome *KDM5D* contributes significantly to the sex differences in KRAS* CRC via its disruption of cancer cell adhesion properties and tumor immunity, providing an actionable therapeutic strategy for metastasis risk reduction for men afflicted with KRAS* CRC.

Abstracts

Microbial deconjugation of bile acids regulates intestinal permeability in malnutrition

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Background: Malnutrition alters the gut microbiome and impairs intestinal functions, including regulation of the gut barrier. Gut microbial alterations have been linked to increased intestinal permeability, resulting in increased bacterial translocation from the intestine and sepsis, a leading cause of mortality in malnourished children. Gut bacteria transform liver-derived primary bile acids into secondary bile acids, each with different biological effects, and a gain or loss of this function through altered microbiomes can impact gut permeability. Some commensal microbes possess bile salt hydrolase (BSH) enzymes, which perform the first step in bile acid transformation by hydrolyzing the amino acid moiety to form unconjugated bile acids. How individual bile acids, especially products of BSH transformation, regulate the gut barrier is poorly understood. We hypothesize that gut microbial transformations of bile acids, specifically BSH-mediated bile acid deconjugation, improves intestinal barrier function.

Methods: Specific pathogen free (SPF) and germ free (GF) C57BL/6J male and female mice were weaned to a low-protein low-fat diet to induce malnutrition, or to an isocaloric control chow. Stool from 8 week old mice was analyzed by metagenomic shotgun sequencing to assess microbial gene content and community structure and mass spectrometry to measure bile acids. Intestinal permeability was assessed *ex vivo* in Ussing chambers by quantifying apical to basal fluorescein isothiocyanate-dextran (4 kDa) translocation over 120 minutes. To determine how different bile acids regulate the gut barrier, bile acids were applied at doses spanning the physiologic range (1 μM – 100 μM) to intestines from healthy control mice in Ussing chambers. To measure bacterial translocation, livers were sterilely harvested and processed, then incubated for bacterial growth on Brain Heart Infusion agar plates aerobically and anaerobically at 37°C.

Results: Malnutrition induced a 79.2% increase in intestinal permeability in SPF male mice. Strikingly, GF malnourished males, which lack gut bacteria, and both GF and SPF malnourished females were protected from increased intestinal permeability. Malnourished SPF male mice exhibited increased translocation of aerobic and anerobic bacteria into the liver. SPF malnourished females but not males had a 1.7-fold increased abundance of microbial BSH genes compared to SPF control females ($P < 0.01$), and were protected from the dramatic loss of the BSH product chenodeoxycholic acid (CDCA) that we observed in malnourished males. When applied *ex vivo* to intestine from healthy control male mice, the primary conjugated bile acid and BSH substrate tauro-chenodeoxycholic acid (T-CDCA) minimally improved barrier function at only the highest dose, whereas the microbial BSH transformation product CDCA dramatically decreased permeability by 48% ($P < 0.0001$), suggesting that BSH deconjugation by gut microbes is a key step in this pathway that makes the intestinal barrier less permeable to translocation.

Conclusion: The gut microbiome plays a causal role in malnutrition-induced gut barrier dysfunction and bacterial translocation, which can lead to sepsis. Microbial BSH activity results in the formation of unconjugated bile acids that decrease intestinal permeability. Increased BSH activity may protect female malnourished mice from gut barrier dysfunction. This knowledge may facilitate novel microbiota-targeting therapies to treat malnutrition and its comorbidities, potentially reducing the risk of bacterial sepsis and child mortality.

Abstracts

Interplay between diet and the gut microbiome in necrotizing enterocolitis (NEC)

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Background: Necrotizing enterocolitis **(NEC)** is the leading cause of death from gastrointestinal disease in premature infants, affecting 5-12% of neonates born at very-low birth weight (<1.5 kg) with a mortality of 20-30%. Although the pathogenesis of this disease is not completely understood, diet composition and dysbiosis of the gut microbiome have both been identified as risk factors for this disease. Human breast milk (HBM) feeding significantly decreases susceptibility to NEC compared to an infant formula diet. However, the mechanisms through which specific diets affect the risk of developing NEC are incompletely understood. The objective of this study was to evaluate the effect of diet composition on the gut microbiome and the pathogenesis of disease using the preterm piglet model of NEC.

Methods: A total of 16 piglets were delivered at 90% gestation. During the 10-day study, piglets were assigned to one of two treatments: (1) Commercially available preterm infant formula (2) human donor milk (HDM). NEC incidence and severity were assessed by evaluation and collection of tissue sections from all segments of the GI tract. The gut microbiome composition was assessed both daily and terminally by 16S and whole genome sequencing (WGS) of stool samples and intestinal contents, respectively.

Results: Piglets fed HDM were significantly protected against NEC compared to formula-fed piglets. Analysis of intestinal contents revealed differences in the gut microbiome composition by diet and diagnosis mostly characterized by a higher abundance of *Clostridium perfringens (C. perfringens)* in formula-fed piglets and in those that developed NEC. The abundance of *C. perfringens* positively correlated with disease severity. Analysis of the daily stool microbiome showed higher levels of *Clostridium sensu stricto* in the stool of DHM-fed and healthy piglets.

Conclusion: Our results suggest that diet impacts the gut microbiome and plays an important role in the pathogenesis of NEC. The high positive correlation of *C. perfringens* abundance and disease severity suggests that this bacterium may play a role in disease pathogenesis. Further studies will aim to further elucidate the role of diet in the abundance of *C. perfringens* and characterizing the relationship between this bacterium and NEC.

Limosilactobacillus reuteri DSM 17938 Modulates FOXP3 Deficiency-Induced Dyslipidemia In Autoimmune Scurfy Mice

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Background: Probiotic *Limosilactobacillus reuteri* DSM 17938 (DSM 17938) has anti-inflammatory effects in scurfy (SF) mice, a mouse model of immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome caused by regulatory T cell (Treg) deficiency due to a Foxp3 mutation. SF mice suffer severe multi-organ inflammation and early death. DSM 17938 prolongs survival of SF mice from <1 month to >4 months of life by reducing Th1 and Th2-associated inflammation. DSM 17938 resets gut microbial dysbiosis and microbiota-associated amino acid- and nucleoside-related metabolites in SF. Lipid metabolites play pivotal roles in the inflammatory process. For example, acylcarnitine has a significant impact on insulin sensitivity and inflammation. How DSM 17938 affects lipid profile in SF mice has not been explored.

Objectives: To analyze whether Foxp3$^+$Treg deficiency changes plasma lipid profile and to analyze the effect of DSM 17938 on serum lipids in SF mice.

Methods: SF mice (B6.Cg-Foxp3sf/Y), generated by breeding heterozygous B6.Cg-Foxp3sf/J female to C57BL/6J (WT) male mice, were fed with DSM 17938 (10^7 CFU/day), daily, starting at day of life 8 in fresh MRS media (SFL) or compared with SF mice (SFC) and WT male littermate controls (WTC) that were fed with MRS fresh media by gavage. Plasma was collected on d21 and lipid profiles were measured using chromatography with tandem mass spectrometry systems. Two-way ANOVA was used for statistical analysis to compare SFC vs WTC, and SFL vs SFC groups.

Results: SF mice demonstrated dyslipidemia compared to normal control mice, with 114 lipid metabolites upregulated and 9 lipids downregulated significantly. There was pronounced upregulation of 12 acylcarnitines, 11 mono- or di-acylglycerols, 14 phospholipids, 11 polyunsaturated fatty acids (FAs), 12 medium chain FAs (MCFAs), 11 long chain FAs (LCFAs), 9 lysolipids, 6 sphingolipids, and 4 FAs involved in branched-chain amino acid metabolism. No changes were observed in primary bile acids (BAs), but two secondary BAs (deoxycholate and taurodeoxycholate) were reduced. Gavage feeding of DSM 17938 to the SF mice resulted in downregulation of lipids compared to the SF mice, with a total of 37 lipids reduced including acylcarnitine, polyunsaturated FAs, phospholipids, MCFAs and LCFAs. Four of the 12 acylcarnitines (33%) and 8 of the 14 phospholipids (57%) that were upregulated in SF mice were downregulated by DSM 17938. Livers of SF mice had marked fat deposition and inflammation, with mild fibrosis.

Conclusions: Significant changes in the lipid profile of SF mice suggest aberrant lipid degradation in IPEX patients. DSM 17938 in Treg-deficiency may modulate lipid metabolism. Further research in targeted lipidomics, including genes related to FA oxidation pathways, may reveal unique benefits of probiotics in systemic inflammatory conditions.

Malnutrition induced fatty liver is influenced by the gut microbiome and sex in young adult mice

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Malnutrition is responsible for 45% of childhood deaths each year and affects boys more severely than girls. Chronic malnutrition increases gut barrier permeability and risk of sepsis, causes dyslipidemia and other metabolic impairments, and dramatically alters the gut microbiome. In severely malnourished children, accumulation of triglycerides in hepatocytes results in non-alcoholic fatty liver disease (NAFLD). Gut microbes influence host metabolism through their production of metabolites and have been implicated in the progression of liver disease. Our laboratory previously reported dramatic alterations of both the microbiome and microbial metabolites including short-chain fatty acids in malnourished mice that develop macrovesicular steatosis. Therefore, we hypothesize that in malnutrition, the altered gut microbiome contributes to the development of NAFLD. To test this hypothesis, we modeled early postnatal malnutrition by feeding mice a low-protein, low-fat diet (LPLFD) that is isocaloric to a control chow diet; both diets were triply-irradiated to facilitate germ-free (GF) studies. At 8 weeks of life, we examined hepatic lipid accumulation with oil red O staining and hepatic protein expression with western blot. SPF malnourished males had profound macrovesicular steatosis that was significantly attenuated in GF malnourished males. However, oil red O staining was similar in livers from SPF and GF malnourished female mice. These results suggest for the first time a potentially causal role of the gut microbiome in malnutrition-induced NAFLD in a sexually dimorphic manner. Preliminary explorations of key proteins implicated in hepatic lipid storage revealed that the nutrient sensing nuclear receptor, peroxisome proliferator-activated receptor-alpha (PPARα), and the autophagy-related protein 9A (ATG9A) both are dramatically decreased in malnutrition and remain decreased in GF conditions. Ongoing studies will seek to determine why GF male mice are protected from malnutrition-induced NAFLD and the molecular mechanisms by which gut bacteria contribute to steatosis in early postnatal malnutrition. These studies may facilitate therapeutic opportunities including fecal microbiota transplant or administration of microbial metabolites to treat or prevent malnutrition-induced NAFLD.

Abstracts

Defining the role of endoplasmic reticulum in the initiation of paligenosis

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Reprogramming is crucial for cellular renewal in adult organs that lack dedicated stem cells for replacement of cell loss after injury. Because such cell plasticity is likely to be executed by a conserved cellular program, we have begun to identify the conserved cellular-molecular features of the process in which differentiated cells are recruited as progenitors. We have characterized three successive stages by which this occurs with differentiated cells: 1) the cells downscale their organelle contents, 2) cells activate a progenitor-like gene network, and 3) cells reenter the cell cycle. We have given this conserved process the name *paligenosis*. Here, we investigate upstream triggers of paligenosis. Using a high-dose tamoxifen (HD-TAM) injury model to induce paligenosis in zymogenic chief cells of the murine stomach corpus, we observed ultrastructural changes in the endoplasmic reticulum (ER) during paligenosis initiation (e.g., swelling of ER lamellae, liberation of ribosomes from rough ER, and overall loss of ER). This led us to hypothesize that dynamic changes in ER were an upstream event in paligenosis. ER functioning is in part monitored by the Integrated Stress Response (ISR) with the paramount ER stress sensor being PERK, a kinase that triggers translation of mRNA on the ribosome by phosphorylating the eukaryotic initiation factor 2 (eIF2α). Phospho-eIF2α halts global translation while upregulating a specific set of genes to restore homeostasis. Here, we go on to show that HD-TAM activates the ISR in paligenotic gastric chief cells, triggering global attenuation of protein synthesis. However, this “ER stress” ISR pathway must occur in a critical, temporally limited window early in paligenosis, as pharmaceutically-induced prolonged ER stress caused paligenosis to halt in early stages with cells failing to proliferate. Blocking the ISR also halted paligenosis in early stages. Ongoing experiments include the use of the glycosylation-inhibiting drug tunicamycin to determine if inducing the ISR via ER stress is sufficient to initiate paligenosis; and deleting PERK in chief cells during paligenosis using *Perk*$^{flox/flox}$; *Mist1*^{CreERT2} mice. Our results provide initial insights on the dynamic functionality of the ER and its role and necessity during cellular regeneration.

This work was supported by funding from the NIH through the National Institute of Diabetes and Digestive and Kidney Diseases and the National Cancer Institute.

The Constitutive Androstane Receptor (CAR) drives NAFLD-related Hepatocarcinogenesis

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Obesity-related non-alcoholic fatty liver disease (NAFLD) is predicted to be the leading cause of HCC by 2030 in Western countries. No approved medical interventions are available for treating NAFLD or surveillance of NAFLD-induced hepatocarcinogenesis.

We previously reported that a human 8-hour shiftwork schedule induces NAFLD-related hepatocarcinogenesis in wild-type (WT) mice via a pathophysiologic pathway very similar to that observed in obese humans. Ablation of *NR1I3, which* encodes the constitutive androstane receptor CAR, prevented NAFLD-induced HCC. CAR was previously known as a master regulator of xenobiotic metabolism in the liver. Our findings suggest that the current understanding on the hepatic function of CAR is incomplete.

Circadian transcriptome analyses revealed that in addition to control xenobiotic metabolism, CAR also promotes metabolic reprograming, hepatic fibrogenesis, inflammatory responses, and hepatocyte trans-differentiation, which drive spontaneous hepatocarcinogenesis. In addition, the CAR controlled hepatic xenobiotic metabolism is constitutively active over a 24-hour period, while Car's HCC promoting functions is gated by the circadian clock under normal physiological conditions. A three-week treatment of androstanol (ANR), an inverse agonist of mouse CAR, not only prevented the progression from NAFLD to NASH but also reversed circadian dysfunction induced NAFLD. RNAseq analysis demonstrates that ANR efficiently suppressed genes promoting hepatic cholestasis, fat storage, fibrogenesis, inflammatory response, and hepatocyte trans-differentiation.

Our studies identify CAR as a liver-specific oncogene that promotes the pathophysiological progression from NAFLD to hepatocarcinogenesis. These studies also suggest that inverse agonists of CAR are potential new drugs for treating NAFLD and preventing spontaneous hepatocarcinogenesis.

Abstracts

Gastric cancer risk in patients with long-term use of proton pump inhibitors: a systematic review and meta-analysis of observational and interventional studies.

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Introduction: There are a number of reports that raise safety concerns on the association between proton pump inhibitors (PPIs) and the risk of gastric cancer both overall as well as isolated gastric cardia.

Methods: We performed an updated systematic review and meta-analysis of observational studies and interventional studies published PubMed through January 2023 that examined the association between greater than 6 months PPI use, and the risk of gastric cancer overall and gastric cardia cancer specifically. Inclusion criteria for observational studies were classification as either a case-control or cohort study, participants 18 years or older, long-term (> 6 months) PPI use, and gastric cancer as a specified outcome. We excluded studies that were conducted in the pediatric population and case reports. Study quality was evaluated using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool. Pooled adjusted risk estimates were calculated using random effects model, and study heterogeneity was examined as I^2 statistic.

Results: We identified 15 publications with 16 studies that fulfilled our inclusion and exclusion criteria: 6 reported nested case-control studies, 1 case-control, 1 prospective cohort, 6 retrospective cohort, and 1 paper with both case-control and prospective cohort studies. Most studies were conducted in Asia (n=6) or Europe (n=6) and only 3 studies in North America. Only 8 studies accounted for *H. pylori*. Most studies (5 of 8) that examined gastric cardia site specific risks reported no significant association. The pooled unadjusted odds ratios from case control studies were 1.51 (95% CI: 1.24, 1.85) from the 5 overall gastric studies, and 1.17 (95% CI: 0.77-1.77) from the 6 gastric cardia studies. Most (12 of 15) reported a statistically significant adjusted risk estimate of the association of PPI usage and overall gastric cancer risk, and 3 studies reported no association. Pooled adjusted risk ratios from cohort studies were 1.95 (95% CI: 1.37-2.77) from the 6 overall gastric cancer studies, and 0.90 (95% CI: 0.48-1.66) from the 2 gastric cardia studies. I^2 ranged between 23 and 88%. Most (15 of 16) had at least moderate risk of bias on the ROBINS-I tool with 1 study having serious risk of bias. We identified only 6 interventional studies that fulfilled our search criteria, of which 1 examined GC as an outcome, and none reporting association between PPI use and increased GC or general cancer risks.

Conclusion: Observational studies show inconsistent and mostly non-significant (individual or pooled) association between PPI and gastric cardia. For the overall gastric cardia, the pooled results show a modest statistical association, but the considerable heterogeneity among studies, limitations of study design and at least moderate risk of bias do not support an etiological relationship between PPI and gastric cancer.

Impact of an electronic medical record QI intervention on *Helicobacter pylori* treatment and eradication rates within a U.S. hospital system

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Background: Despite the benefits of *Helicobacter pylori* treatment, there is variation in treatment regimens and eradication rates. In this quality improvement (QI) study, we determined whether the implementation of an electronic medical record (EMR) order set for *H. pylori* treatment changed rates of optimal treatment regimen usage and of eradication testing and success.

Methods: We determined rates of optimal *H. pylori* treatment, eradication testing, and successful eradication among consecutive patients in the Harris Health System (Houston, Texas) with newly diagnosed *H. pylori* infection identified through the Epic EMR software. The pre-intervention cohort consisted of patients with positive *H. pylori* test from January-February 2022. Then, an EMR order set for *H. pylori* treatment using local antibiotic resistance patterns went live in May 2022 and included optimal treatment regimens (i.e., bismuth-quadruple therapy for 14 days with proton pump inhibitor [PPI]) along with testing for eradication post-treatment within 6 weeks. Rates of treatment and eradication were evaluated in the post-intervention group with positive *H. pylori* test from June-July 2022 and follow up through October 21, 2022. Comparisons of overall as well as optimal *H. pylori* treatment and eradication rates, and time delays between pre- and post-intervention groups were evaluated using chi-2 and t-tests.

Results: We identified 295 patients in the pre-intervention and 153 patients in the post-intervention cohort. The mean age of patients was 48.7 years (standard deviation [SD] 13.6 years), 37% were men, and 74% were Hispanic race/ethnicity (Table 1). Although there was no difference in the pre- and post-intervention cohorts in the overall rates of treatment prescribed (92.5% vs. 91.5%), rates of *optimal* treatment increased from 5.8% to 23.5% ($p<0.01$) after the intervention. Duration between *H. pylori* treatment to eradication testing decreased from 69.5 days to 49.5 days ($p=0.01$). Although rates of eradication testing decreased (56.0% vs. 35.7%, $p<0.01$), rates of patients with successful *H. pylori* eradication increased from 80.6% to 93.8% ($p=0.03$) among those tested.

Conclusions: The implementation of an EMR order set for *H. pylori* treatment and eradication testing significantly increased rates of patients that received optimal, evidence-based treatment and successful eradication of *H. pylori* infection. Future interventions will combine bioinformatic interventions with provider education to increase utilization of post treatment testing.

Performance of ulcer features in predicting malignancy among gastric ulcers diagnosed on endoscopy

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Background: Surveillance endoscopy is recommended after diagnosis of gastric ulcer to evaluate for malignancy and ulcer healing, but the overall prevalence of malignancy among gastric ulcers is low. Our aim was to evaluate the predictive ability of ulcer appearance on initial endoscopy with the risk of having or developing malignant gastric ulcers, and thus the utility of risk stratification, to decrease the need for routine surveillance endoscopy in all patients with gastric ulcers.

Methods: Patients with a diagnosis of gastric ulcer on upper endoscopy were identified using keyword search for ulcer on endoscopic reporting software from two hospitals in Houston, TX from February 2019 to July 2021. Gastric ulcer diagnosis was confirmed on electronic medical record review. Malignant ulcers were defined using histopathologic diagnosis of malignancy (i.e., adenocarcinoma, lymphoma, or other), and benign ulcers were defined by absence of malignancy on histopathology or ulcers that had healed on surveillance endoscopy. Potential predictors of malignant ulcers included: ulcer size >2 cm, elevated ulcer border, irregular ulcer border, location (corpus, antrum), and background atrophic gastritis either by endoscopic appearance or gastric biopsy histopathology. Associations of ulcer features with presence of malignancy were examined using logistic regression analyses, and predictive ability of ulcer features for malignancy were reported as area under the receiver operating characteristic (AUROC) and 95% confidence intervals (CI).

Results: We identified 198 patients with gastric ulcers of whom 87 (44%) had at least one surveillance endoscopy. The mean time to surveillance endoscopy was 130 days (standard deviation [SD] 102 days). The mean age was 61.1 years (standard deviation [SD] 13.9 years), and 147 (74%) were men. Malignant ulcers were found in 16 patients (8%), of which 15 patients were diagnosed on initial endoscopy. The mean ulcer size was 25.6mm for malignant ulcers and 13.5mm for benign ulcers. Corpus location, size >2cm, background gastric atrophy on histopathology, elevated border, and irregular border were significantly associated with malignant ulcers. The strongest predictors of malignant ulcers were irregular border (AUROC 0.89, 95% CI 0.80-0.97), background gastric atrophy on histopathology (AUROC 0.87, 95% CI 0.78-0.96), and elevated border (AUROC 0.84, 95% CI 0.73-0.95). A multivariate model that included irregular border, elevated border, and atrophy on histopathology had the best discrimination for predicting malignant ulcers (AUROC 0.96, 95% CI 0.94-0.99).

Conclusion: Gastric ulcer size >2cm, elevated or irregular ulcer border, and background gastric atrophy were excellent predictors of malignant ulcers. Combining irregular border, elevated border, and atrophy on histopathology had the best performance for predicting malignant ulcers and may be used to risk stratify those with most potential benefit from surveillance endoscopy.

The role of MBNL in smooth muscle function and DM1 GI pathologies

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Introduction: Myotonic dystrophy type 1 (DM1) is the most common adult-onset muscular dystrophy, causing highly variable multisystemic symptoms that predominantly affect the brain, heart, and skeletal muscle. Recent DM1 patient surveys have identified gastrointestinal (GI) disturbances as a highly prevalent patient complaint that affects daily life and well-being. The cause of DM1 GI dysfunction is currently unknown and evidence supports a role for visceral smooth muscle dysfunction. The goal of this project is to elucidate the role of muscleblind-like (MBNL) loss of activity, a primary mechanism of DM1 pathology, in visceral smooth muscle function.

Methods: Using mice expressing a smooth muscle specific, tamoxifen inducible *Myh11-Cre*ER^{T2} driver, floxed *Mbnl1* alleles, and one floxed and one null *Mbnl2* allele (denoted as smoCRE;dKO), we induced MBNL loss and assessed upper and lower GI motility. To quantify small bowel transit, we utilized a cell impermeable FITC dye conjugated to a large dextran molecule that allowed for the quantification of bolus movement after 25 minutes. Colonic motility was measured by bead expulsion assay and fecal water content was quantified. In addition to gross anatomical measurements and histological evaluation of muscularis and mucosal thickness, ex vivo force transduction assays were performed to measure jejunal contractility. RT-PCR was performed using RNA isolated from GI smooth muscle to identify DM1-associated splicing changes.

Results: SmoCRE;dKO mice share homologous misregulated splicing events that previously have been identified in mouse MBNL KO skeletal and cardiac muscle as well as human DM1 tissues. Progression of the mean geometric center of gavaged FITC-dextran is significantly delayed in smoCRE;dKO small bowel compared to smoWT;dKO controls by -1.74 segments ($p=0.0001$). Bead latency was significantly increased in smoCRE;dKO mice by 397 seconds compared to smoWT;dKO controls, indicating impaired large bowel motility ($p=0.0008$). A 16% increase in fecal water content also was found in smoCRE;dKO animals compared to smoWT;dKO controls ($p=0.002$), suggesting potential alterations in gut barrier permeability. While no change in body length or jejunal, ileal, or colonic muscularis thickness was detected between groups, small intestine length was significantly reduced (-5.8±1.2cm, $p=0.0006$) and the thickness of the duodenal muscularis was significantly increased (34±13μm, $p=0.03$) in experimental animals. Preliminary *ex vivo* force transduction experiments of jejunal longitudinal muscle segments showed significantly decreased contraction amplitude and activity at baseline and in response to increasing concentrations of cholinergic stimulus (Corrected $p \leq 0.04$).

Conclusions: These results demonstrate that smooth muscle specific double knockout of MBNL affects upper and lower GI motility via intrinsic myogenic mechanisms that impede longitudinal muscle function. RNA sequencing will be performed in both mouse and DM1 affected human GI samples available in the lab to identify conserved, MBNL-dependent alternative splicing changes. Validated alternative splicing events will then be evaluated *in vitro* for rescue of cellular defects. Findings support a key role for MBNL in gut function. Future work will elucidate the myogenic basis for DM1 GI pathogenesis and provide potential therapeutic avenues for GI dysmotility by identifying key alternative splicing events that regulate visceral smooth muscle cell function.

Patterns of steroid use among a real-world national cohort veterans with inflammatory bowel disease on maintenance infliximab

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Background: Corticosteroids are effective in the acute improvement of symptoms in inflammatory bowel disease (IBD). Still, they are not recommended as maintenance therapy due to a lack of long-term efficacy and adverse effects. Long-term goals for medical management in IBD include achieving steroid-free remission. Biologics such as the anti-tumor necrosis factor alpha Infliximab (IFX) are used to achieve clinical remission. However, patterns of continued steroid use among patients on maintenance IFX have yet to be thoroughly studied. This study aims to evaluate patterns of concomitant steroid use in individuals with IBD on maintenance IFX.

Methods: We performed a retrospective cohort study using the national Veteran's Health Administration dataset. Patients with IBD were identified using a previously validated algorithm of ICD9/10 codes and confirmed by manual chart review. Dispensed medications and demographic data were obtained from VA Corporate Data Warehouse. Patients were eligible for inclusion if they had a confirmed diagnosis of IBD and were on maintenance IFX. Maintenance IFX- index date was defined as the first dose of IFX after January 1, 2017, with receipt of IFX 7 to 9 weeks before and after IFX-index date. The study period for steroid use was nine weeks following the IFX-index date and included steroids dispensed in the inpatient and outpatient setting. Steroids dispensed on the day of IFX infusion were excluded. Categorical variables were compared using the chi-square test.

Results: There were 642 individuals included. The majority (594, 92.5%) were male. The racial breakdown was as follows: 516 (80.3%) White, 85 (13.3%) Black, 18 (2.8%) other races, and 23 (3.6%) with unknown race. 402 individuals (62.6%) had Crohn's disease, and 240 individuals (37.4%) had ulcerative colitis. 44 (7.9%) individuals met the criteria for steroid use. 69 individual steroid prescriptions were dispensed during the 9-week period with the following breakdown: 34 (49.3%) Prednisone, 19 (27.5%) Methylprednisolone, 14 (20.3%) Budesonide, and 2 (2.9%) Dexamethasone. Steroid use appeared to be associated with gender, with 39/594 (6.6%) males and 7/48 (14.6%) females receiving steroids ($p = 0.04$). Steroid use was not associated with IBD type ($p=0.86$), age at IFX index date ($p=0.16$), nor race ($p=0.39$). Steroid type was not associated with IBD type ($p=0.70$), race ($p=0.06$), or gender ($p=0.35$).

Conclusion: We observe relatively low rates of steroid use amongst individuals on maintenance IFX. There appeared to be an association between steroid use and gender, with females receiving more steroids than males. Still, it is difficult to conclude based on the small number of females in the cohort. There appeared to be no association with steroid use when comparing IBD type, age, or race.

Abstracts

A systematic review of the behavioral change determinants among patients with NAFLD using the theoretical domains framework

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Introduction: Behavioral change, with the goal of clinically significant weight loss, is first line treatment for non-alcoholic fatty liver disease (NAFLD). The first step to develop suitable interventions is to identify the determinants of behavioral changes in physical activity (PA) and diet, which would serve as targets for change techniques. With that objective, we undertook a systematic review to map behavioral determinants in patients with NAFLD using the Theoretical Domains Framework (TDF).

Methods: We searched Medline, EMBASE, Cochrane, PsycINFO, and Web of Science from inception to May 6, 2021 to identify publications that reported the psychosocial determinants of PA and diet among adults with NAFLD. Two independent reviewers screened titles/abstracts, reviewed, and extracted data from included papers. Using thematic content analysis, we summarized and analyzed the data to identify behavioral determinants in patients with NAFLD.

Results: We identified 8 papers evaluating the determinants of behavioral change in adults with NAFLD: 7 We identified 8 papers evaluating the determinants of behavioral change in adults with NAFLD: 7 addressed PA, 4 addressed diet, and 1 addressed weight loss in general. Findings were mapped to 9 out of 11 relevant TDF domains. Poor knowledge of NAFLD emerged as an important theme: most patients believed their diagnosis of NAFLD had little to no long-term health consequences; moreover, many did not recognize a causal link between their PA and dietary behaviors and NAFLD. Conversely, patients with a family history of liver disease, obesity, diabetes, and elevated transaminases were more likely to perceive NAFLD as a dangerous condition; these patients were also more likely to place greater value on NAFLD treatment. Low PA self-efficacy emerged as a second important theme: although patients perceived PA as beneficial, most were not sufficiently active at baseline, did not know how to increase their PA, and perceived many barriers to increasing PA including a lack of will power, time, energy, and support from clinicians.

Discussion: Through a systematic review of the literature, we found that there are limited data characterizing behavioral determinants in adults with NAFLD, especially regarding diet. More research is needed, particularly addressing outcome expectations, self-efficacy, and social influences of dietary behaviors. The research so far suggests that interventions should target the following in patients: (1) their understanding of NAFLD and its relation to PA and diet, (2) teach them how to exercise, and (3) help them overcome perceived barriers to PA.

Abstracts

Histamine from limosilactobacillus reuteri 6475 induces proliferation in human small intestinal organoids

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Healthy small intestinal epithelium renews itself every 3-5 days making it the fasting proliferating tissue in the human body. The trillions of bacteria that live within our intestine make up our microbiome which resides in close contact to the intestinal epithelium. However, whether the microbiome can influence human intestinal epithelial renewal is unknown. To determine if commensal organisms from the microbiome can influence intestinal epithelial proliferation, we treated human intestinal organoids (HIOs) with secreted factors produced by *Limosilactobacillus reuteri 6475. L. reuteri 6475* is a commensal bacterium that is generally regarded as safe, and is used as a probiotic supplement in many commercial products. HIOs treated with secreted products made by *L. reuteri 6475* exhibited a specific proliferative response in 3 independent HIOs. Size fractionation of the secreted products revealed the proliferative properties are localized to a specific size fraction. Metabolomics of this size fraction revealed the presence of histamine. Further testing in HIOs confirmed histamine to be responsible for the induction of proliferation. *These findings are the first to demonstrate the potential for microbial-derived factors to modulate proliferation of the human intestinal epithelium, and as such, have the potential to be used as innovative therapies for repair of the intestinal epithelium.*

Abstracts

Generation of human intestinal organoids from Cronkhite Canada Syndrome patients reveals serotonin as a link to intestinal proliferation

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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. Dermatological features of the disease include hair loss, nail changes, and hyperpigmentation. Endoscopically, patients show polyposis, inflammation, and edema (in the upper and lower GI tract). 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 biopsies from two CCS patients. We noted that CCS HIOs are more proliferative and have unique morphologies compared to non-CCS HIOs. RNAseq cell type analysis revealed an increased number of serotonin positive enteroendocrine cells (EECs) in CCS HIOs. Further investigation revealed that serotonin can induce proliferation in non-CCS HIOs suggesting that dysregulation of EEC serotonin production may explain the polyposis syndrome observed in CCS. This work illustrates the important role HIO 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 HIOs can provide a gateway to the development of personalized medicine.

NIH Intestinal Stem Cell Consortium - 1U01DK103168

Chronic alcohol intake plays time-dependent role in cerulein-induced chronic pancreatitis in mice

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Purpose: Alcohol consumption is the most common cause of chronic pancreatitis (CP), a highly debilitating and fibrotic disease of the pancreas. However, underlying mechanisms of the alcohol effect on CP development are not clear. Animals fed with alcohol-supplemented liquid diets are commonly used to study alcohol's effects and mechanisms on CP. In this study, we used alcohol diet feeding combined with cerulein (CAE)-induced CP in mice to examine alcohol effects on CP severity and regulation of the key profibrogenic transforming growth factor (TGF)-β superfamily.

Methods: Adult male C57BL/6 mice were used. Lieber-DeCarli '82 Rodent Liquid Diets was used for control feeds (CON) or supplemented with 4% alcohol for alcohol feeds (EtOH). CP was induced by CAE injections (50 μg/kg, ip, 5 hourly/day, 3 days/week, for up to 4 weeks). The mice were randomized into 4 groups: CON, EtOH, CON+CAE, and EtOH+CAE (n=4-7/group). The mice were acclimated from normal chow to CON diet over one week, then fed either with EtOH or CON diet for up to 6 weeks. CAE was injected during the last 4 weeks. The mice were euthanized at 2 or 4 weeks after CAE injections. The pancreata were harvested for analysis of pancreatic acinar injury via histopathological evaluation and fibrosis via Sirius red staining. RNA was collected and cDNA was prepared. qPCR was used to determine mRNA expression of Col1a2, TGF-β1, Grem1, BMP2, and BMPR2.

Data and Results: At 2 and 4 weeks, no CP injury or fibrosis was observed in CON or EtOH groups. At 2 weeks, CP injury was observed in CON+CAE and EtOH+CAE groups, with histopathological evaluation showing higher CP scores (10±1.18 vs 4.5±0.76, $p<0.05$) and Sirus red staining showing more extensive fibrosis (0.11±0.01 vs 0.06±0.01, $p<0.05$) in CON+CAE compared to EtOH+CAE. qPCR data showed a contrasting mRNA expression trend: EtOH+CAE had increased levels of Col1a2, TGF-β1, Grem1, and BMPR2 compared to other groups ($p<0.05$). At 4 weeks, CP injury was observed in the CON+CAE and EtOH+CAE groups, with similar CP scores (18.7±4.15 vs 17±4.93, $p>0.05$) but more extensive fibrosis in EtOH+CAE compared to CON+CAE (0.03±0.004 vs 0.05±0.005, $p<0.05$), indicating that alcohol feeding strengthened the CAE effects on the pancreatic fibrosis of CP in the 4-week group.

Conclusions: The alcohol feeding in mice opposes CAE-induced CP injury and pancreatic fibrosis at 2-weeks but enhances CAE-induced pancreatic fibrosis at 4-weeks. mRNA expression of the fibrotic factors in EtOH+CAE at 2 weeks foreshadowed this increased fibrosis at 4 weeks indicating a dynamic and time-dependent effect of alcohol consumption on CP severity in the mouse model. Prolonged CP induction in the mouse model may be required for recapitulating human alcohol-associated CP and investigating the mechanisms.

Infant and adult human intestinal enteroids are morphologically and functionally distinct

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Human intestinal enteroids (HIEs) are gaining recognition as physiologically relevant models of the intestinal epithelium. While HIEs from adults are used extensively in biomedical research, there are fewer reports on HIEs from infants. Considering the dramatic changes in body composition and physiology that occur during infancy, it is important to establish models that represent infant intestinal features, development, and diseases. We characterized infant jejunal HIEs to determine if these cultures recapitulate known features of the infant intestinal epithelium and performed comparisons to jejunal HIEs from adults using RNA sequencing (RNA- Seq), morphologic studies and validation of key functional pathways.

RNA-Seq analysis showed significant differences in the baseline transcriptome of infant and adult HIEs, including differences in genes and pathways associated with cell differentiation and proliferation, tissue development, lipid metabolism, innate immunity, and biological adhesion. Validating RNA-Seq results, we observed higher expression of enterocytes, goblet cells and enteroendocrine cells in differentiated infant HIEs while proliferative cells were expressed at higher levels in undifferentiated cultures. Compared to adult HIEs, infant HIEs portray characteristics of an immature gastrointestinal epithelium including significantly shorter cell heights, lower epithelial barrier integrity and function, and innate immune responses to an oral poliovirus vaccine. Infant HIEs also showed marked differences in genes involved in metabolizing nutrients in breast milk.

HIEs established from infant intestinal tissues reflect important characteristics of the infant gut and are distinct from adult cultures. Our data support the use of infant HIEs as an ex-vivo model to advance studies of infant-specific diseases and drug discovery for this population.

Abstracts

Methylome-wide profiling of early-onset colorectal cancer in underrepresented populations

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Early onset colorectal cancer (EOCRC) is the second most common cancer and the third leading cause of cancer mortality in people under the age of 50 in the USA. The incidence of EOCRC has been on the rise over the past four decades and is expected to increase by >140% by 2030. Notably, Blacks and Hispanics are disproportionately affected with the EOCRC diagnosis. It has been proposed that environmental exposures including westernized diet, metabolic factors, and the microbiome might be responsible for the rise in incidence of EOCRC. Epigenetic modifications are well-known mechanisms by which the environment can modulate gene expression without changing the DNA sequence. One such modification is DNA methylation, which controls DNA accessibility, chromatin formation, and gene transcriptional activity. Unfortunately, however, little is known about the role of DNA methylation in EOCRC and much less is understood of EOCRC in minority populations. Therefore, we identified a unique cohort of EOCRC patients within the Baylor College of Medicine/Harris Health System which is comprised of majority minority population with uniquely diverse patient population including, Hispanic 57.6%, African American 24.3%, Caucasian 10.3%, and Asian and Other 7.3%. Using whole-genome bisulfite sequencing, we comprehensively characterized the DNA methylome at single-base resolution in 11 paired tumor-adjacent normal samples. Our analyses revealed distinct EOCRC methylation patterns including both global hypomethylation and promoter-specific hypermethylation, which were not previously captured in The Cancer Genome Atlas (TCGA) Analyses. Among the differentially methylated regions (DMRs), we discovered that DNA and RNA transcription pathways were enriched in EOCRCs at advanced stage. We found that hypomethylated DMRs were associated with genes involved in epithelial-mesenchymal transition signaling, including COL1A1, SMAD3, ZNF703, and TGFBR2. Furthermore, using a trained linear regression model, we observed an accelerated process of epigenetic aging in our EOCRC cohort compared to late onset CRC (LOCRC, CRC diagnosed in patients age 50 and above). Taken together, our work supports a pathogenic role for DNA methylation in EOCRC. We are the first group to take this comprehensive unbiased approach to analyze the methylome in an underrepresented EOCRC cohort of patients.

Rotavirus degrades of DGAT1 and causes increased viroplasm formation and viral yield

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Gastroenteritis is among the leading causes of mortality globally with RV causing ~258 million episodes of diarrhea and ~128,000 deaths annually in infants and children. RV-induced mechanisms that result in diarrhea are not completely understood, but malabsorption is a contributing factor. RV alters cellular lipid metabolism by inducing lipid droplet (LD) formation as a platform for replication factories named viroplasms. Lipid droplets (LDs) play emerging roles in diabetes, obesity, and heart disease. Although LDs are implicated in the replication of several enteric viral pathogens, like rotavirus (RV) that causes severe diarrhea, a role for LDs in gastroenteritis pathogenesis has not been identified. We discovered that diacylglycerol acyltransferase (DGAT1), the terminal step in triacylglycerol synthesis required for LD biogenesis, is degraded in RV-infected cells by a proteasome-mediated mechanism. RV-infected, DGAT1-silenced cells show earlier and increased numbers of LD-associated viroplasms per cell that translate into a 4-5-fold increase in viral yield ($P > 0.05$). Interestingly, DGAT1 deficiency in children is associated with diarrhea due to altered trafficking of key ion transporters to the apical brush border of enterocytes (Haas et al., 2012; Schlegel et al., 2018). Confocal microscopy and immunoblot analysis of RV-infected cells and DGAT1-/- human intestinal enteroids (HIEs) showed a decrease in expression of nutrient transporters, ion transporters, tight junctional proteins, and cytoskeletal proteins. Increased phospho-eIF2α (eukaryotic initiation factor 2 alpha) in DGAT1-/- HIEs and RV-infected cells indicates a mechanism for malabsorptive diarrhea - inhibition of translation of cellular proteins critical for nutrient digestion and intestinal absorption. Our study elucidates a pathophysiological mechanism of RV-induced DGAT1 deficiency by protein degradation that mediates malabsorptive diarrhea as well as a role for lipid metabolism in the pathogenesis of gastroenteritis.

Abstracts

Bile acids differentially regulate smooth muscle contractility in mouse ileum

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Background: Bile acids stimulate propulsive gastrointestinal (GI) transit and regulate motility through multiple receptor-mediated signaling pathways. Bile acid receptors, including the transmembrane G-protein-coupled receptor (TGR5) and the nuclear farnesoid-X-receptor (FXR), are prominently expressed in the GI tract. Mechanisms by which different bile acid receptors mediate intestinal motor functions are not well understood. In this study, we aimed to determine whether different bile acids differentially influence longitudinal smooth muscle contractions in the mouse ileum.

Methods: Distal ileum was isolated from healthy adult C57BL/6 female mice. Intestinal segments were everted over a metal rod to expose the mucosal surface containing bile acid transporters and receptors. The everted segments were suspended in organ baths for isometric force measurements. Ileal segments were treated with 0.1, 1, 10 and 100 μM of ursodeoxycholic acid (UDCA), chenodeoxycholic acid (CDCA), deoxycholic acid (DCA), lithocholic acid (LCA), or glycocholic acid (GCA). To understand potential roles of the cell surface bile acid receptors, ileal segments were treated with 0.1, 1, 10 and 100 μM of agonists to TGR5 (INT-777), muscarinic M1/M3 receptors (cevimeline), or epidermal growth factor receptor (EGF). To understand potential roles of the nuclear bile acid receptors, ileal segments were treated with 0.1, 1, 10 and 100 μM of agonists to FXR (fexaramine), pregnane X receptor (rifampicin), vitamin D receptor (calcitriol), or glucocorticoid receptor (methylprednisolone). Delta-force responses to each stimulus were recorded with a force-transducer.

Results: Intestinal smooth muscle contractility was increased in a dose-dependent manner by UDCA and by agonists to both TGR5 and muscarinic receptors. Conversely, 100 μM of DCA inhibited contractility. CDCA, LCA, GCA, and agonists the nuclear bile acid receptors had no net effect on ileal contractility. The stimulatory effect of UDCA was dependent on tissue eversion; UDCA had no effect when applied to non-everted ileum.

Conclusions: Individual bile acids differentially influence intestinal smooth muscle contractility in a dose-dependent manner. The stimulatory effect of UDCA is dependent upon direct access to the mucosal surface. Understanding how specific bile acids influence intestinal motor functions may facilitate the development of targeted therapies for GI disorders characterized by intestinal dysmotility or altered bile acid homeostasis.

Targeting cancer stem cell plasticity to overcome colorectal cancer resistance and relapse

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Introduction: Despite therapeutic advancements, colorectal cancer (CRC) remains the second deadliest malignancy in the United States. CRC relapse can be attributed to cancer stem cells (CSC), an immortal cell population thought to potentiate metastatic progression by exploiting its self-renewability and differentiation capacity. CSCs exhibit plasticity, whereby they alter their phenotype in response to environmental cues, which bolsters inherent drug resistance. Owing to these mystifying properties, CSCs are an attractive drug target. In the past, our group and others have attempted targeting CSCs using antibody-drug conjugates (ADCs) against the Leucine-rich repeat-containing G protein-coupled Receptor 5 (LGR5), a well-recognized CSC marker that is frequently upregulated in CRC tumors. Our previous attempts at eradicating CRC by targeting $LGR5^+$ CSCs with an LGR5-directed ADC have resulted in incomplete tumor regression or relapse. Followup studies suggest that colorectal cancer cells evade this therapeutic insult by converting it into a quiescent $LGR5^-$ state. Further, the $LGR5^-$, drug-resistant cells use the MET-STAT3 signaling cascade to bolster their invasive and metastatic potential. The long-term goals of this project include elucidating the intercellular players fueling $LGR5^+$ CSC plasticity and developing a dual-targeting therapeutic strategy to overcome CSC-driven tumor heterogeneity.

Hypothesis: Plasticity and drug intolerance in $LGR5^+$ CSCs is regulated by the MET-STAT3 pathway and can be overcome through concurrent MET and LGR5 inhibition.

Methods: The mechanistic relationship between MET-STAT3 and LGR5 on CRC plasticity will be assessed through MET ablation and its effect on downstream signaling via immunoprecipitation and pulldown assays. Anti- MET monoclonal antibodies (mAbs) binding different MET structural domains will be cloned, evaluated *in vitro* for internalization and binding affinity, and conjugated to cytotoxic drug payloads. Efficacy of MET-and LGR5-ADCs alone or in combination will be evaluated *ex vivo* and *in vivo*.

Results: So far, we have successfully cloned two anti-MET mAbs. Both have revealed to be promising candidates following evaluations for specificity, internalization, and ability to inhibit MET phosphorylation using fluorescence-based binding assays, immuno-cytochemistry and immunoblotting. Our preliminary data also suggests that both candidates demonstrate high cell-killing efficacy using a secondary ADC conjugated with Pyrrolobenzodiazepine (PBD).

Conclusions: My proposed dual-targeted therapeutic modality will act as a guided missile that delivers cytotoxic agents to the heterogenous CRC tumors. I believe the elimination of $LGR5^+$ CSCs and their $LGR5^-$ counterparts to be the linchpin of tumor eradication in CRC patients. Ultimately, the proposed study aims to develop a highly translational therapy to improve treatment efficacy and survival of patients bearing drug-resistant gastrointestinal tumors.

Gut UGT Activity Loss Precedes the Development of Irinotecan-Induced Severe Diarrhea: Mechanisms, Biomarker, and Prevention

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Irinotecan has been used widely for various cancer therapy, especially metastatic colorectal cancer. However, 15~40% of treated patients suffer from severe late diarrhea, which limits its application. The irinotecan induced severe diarrhea (IISD) have been attributed to local exposure of its active metabolite SN-38, and intestinal expression of the UGT proteins is critical toward the detoxification of SN-38. Time course study of IISD in mouse and rat after consecutive administration of irinotecan, we now report that the agonist activity of SN-38 at the constitutive androstane receptor (CAR) and pregnane X receptor (PXR) could selectively impaired functions of Ugts in intestine, which accelerated the IISD with increased local accumulation of SN-38. Surprisingly, herbal formula Xiao-Chai-Hu-Tang (XCHT) and it bioactive components wogonin and zingerine can stop the vicious circle, and improved impaired intestinal Ugts functional caused by SN38 through PXR/CAR-UGTs signaling. We also show that loss of UGT activities that precede IISD with human plasma Raloxifene-4'-Glucuronide levels can be used as biomarker to predict the development of IISD. Based on these data we suggest that XCHT and probe drug raloxifene could be used to protect against IISD.

Optimizing An Artificial Intelligence Algorithm for Microendoscopic Imaging by Integrating Patient-Level Risk Factors for Esophageal Squamous Cell Neoplasia Detection

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Background: Artificial intelligence (AI) algorithms assist with interpretation of endoscopically delivered imaging technologies using microscopic or nuclear features. These algorithms could be optimized by integrating patient-level risk factors. Our aim was to compare predictive ability of a high-resolution microendoscopy (HRME) deep learning algorithm to comprehensive risk models that combined the algorithm with demographic risk factors for detection of esophageal squamous cell neoplasia (ESCN).

Methods: We used data from a multicenter clinical trial from 3 hospitals in Houston, Texas and China of patients undergoing ESCN screening and surveillance endoscopy and HRME imaging. HRME images were interpreted using a multi-task convolutional neural network using nuclear segmentation and classification based on Y-Net architecture. Discrimination of the deep learning algorithm in detecting ESCN was compared to comprehensive logistic regression risk models that combined the algorithm with demographic and clinical risk factors.

Results: A total of 233 patients generated 266 esophageal sites (176 with neoplasia) imaged with HRME. Our deep learning algorithm had good discrimination for detecting ESCN (area under the receiver operator characteristics [AUROC] 0.864, 95% CI 0.818-0.911 per-site; AUROC 0.851, 95% CI 0.796-0.907 per-patient). Without the deep learning algorithm, the patient-level risk factors alone (race, age, personal history of esophageal neoplasia, family history of esophageal cancer, smoking, alcohol use) had AUROC 0.848 (95% CI 0.796-0.920). When we combined the deep learning algorithm with select patient-level risk factors (personal history of esophageal neoplasia, family history, smoking, alcohol use), the model improved further (AUROC 0.921, 95% CI 0.879-0.963). The deep learning algorithm performed better in ESCN screening (AUROC 0.956) than surveillance (AUROC 0.741).

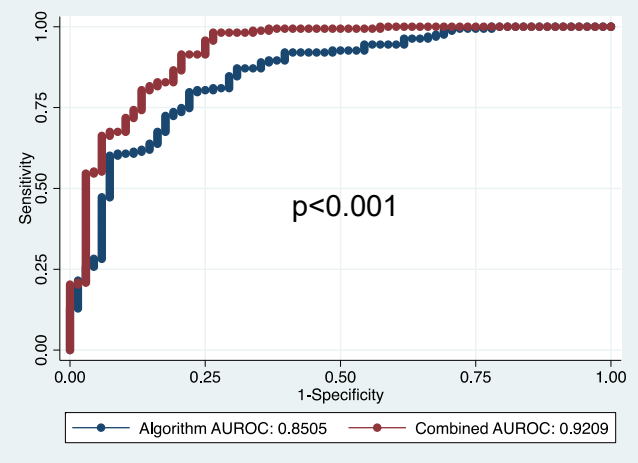

Figure 1: Comparison of discriminatory ability of the deep learning algorithm alone and of the deep learning algorithm combined with patient-level risk factors in detecting esophageal squamous cell neoplasia in the entire study cohort (266 images in 233 patients of whom 166 had esophageal

Conclusion: We found that predictive ability of a deep learning algorithm in detecting ESCN on HRME images improved further with addition of patient-level demographic and clinical risk factors. These risk factors could be incorporated into AI algorithms to optimize cancer detection.

Abstracts

Aberrant Gremlin1 expression promotes a fibrogenic stromal microenvironment in pancreatic ductal adenocarcinoma

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Background: Pancreatic ductal adenocarcinoma (PDAC) is characterized by a unique tumor microenvironment composed of fibroblasts and immune cells. To investigate the molecular mechanisms of the microenvironment, we have identified Gremlin1 (Grem1) as a key profibrogenic factor in chronic pancreatitis and shown high levels of Grem1 mRNA expression in stromal fibroblasts in PDAC. In this study, we investigated the role of Grem1 in the PDAC microenvironment.

Methods: The Cancer Genome Atlas (TCGA) RNA-sequencing data of human PDAC was downloaded and stratified as $Grem1^{High}$ (n=50) and $Grem1^{Low}$ (n=90). Stromal score, immune score, macrophage fractions, and immune cell fractions were compared; Grem1 mRNA level was analyzed by Spearman's t test for correlation between Grem1 and activated or normal stroma related genes (n=150). Custom Grem1 antibodies were generated and used for detecting human Grem1 protein expression in PDAC (n=4) by immunohistochemistry (IHC) staining and in pancreatic cancer and fibroblast cell lines by Western blotting. Grem1 was knocked down by siRNA in pancreatic cancer associated fibroblasts (CAFs), which were then treated with transforming growth factor (TGF)-β (1 ng/ml). Cell lysates and conditioned medium were collected and fibronectin (FN) and collagen1 (Col1) levels were evaluated by Western blotting. Macrophages derived from mouse bone marrow and naïve $CD4^+$T cells derived from mouse spleen were treated with Grem1 (500 ng/ml) or vehicle control for 48 hours and 5 days, respectively. Flow cytometry was performed and analyzed.

Results: Stromal score revealed a higher stromal gene activation in $Grem1^{High}$ than in $Grem1^{Low}$ cases ($p<0.0001$). Grem1 expression positively correlated with >20 activated stromal genes ($r\sim0.41$-0.82, $p<0.001$) and poorly correlated with normal stromal genes ($r\sim0.09$-0.63, $p\sim0.72$-<0.001). Grem1 protein expression was >20-fold higher in CAFs than in cancer cell lines. IHC staining demonstrated Grem1 protein was strongly expressed in stroma and moderately expressed in invasive tumor cells. Grem1 siRNA transfection decreased Grem1 protein expression by 90% ($p<0.05$). When treated with TGF-β, siGrem1 group had reduced levels of secreted FN and Col1 ($p<0.05$). $Grem1^{High}$ and $Grem1^{Low}$ cases had no difference in immune score, but $Grem1^{High}$ showed increased M1 and M2 macrophages and increased regulatory T cells. Macrophages treated with Grem1 showed increased expression of CD80, iNOS, and CD206 ($p<0.05$). Naïve $CD4^+$ T cells treated with Grem1 did not show increased $Foxp3^+$ Tregs.

Conclusion: This study indicates that CAFs overexpress Grem1 in PDAC, and Grem1 acts as a profibrogenic factor and promotes a fibrogenic tumor microenvironment in PDAC via modulating the function of fibroblasts and macrophages.

Healing of radiofrequency ablation for Barrett's esophagus involves novel patterns of cell plasticity in a longitudinal study of human tissue

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Barrett's esophagus (BE) is a precursor of esophageal adenocarcinoma (EAC) that results from chronic epithelial damage by gastrointestinal reflux. BE is characterized by the replacement of normal squamous epithelium with columnar intestinal metaplasia in the distal esophagus. To reduce chances of progression of BE to esophageal cancer, Radiofrequency Ablation (RFA) is performed in higher risk patients.

RFA of the BE mucosa creates a wound that spans three epithelial cell types (stratified squamous, Barrett's metaplasia, and gastric epithelium) yet the wound typically heals completely with squamous epithelium. The repair mechanisms following RFA and the origin of the neosquamous epithelium during wound healing remain poorly understood. Recent endoscopic and histological studies in human BE patients by us and others suggest that RFA wounds are re-epithelialized by squamous cells at the proximal ablated wound edge and by patches of squamous cells emerging as islands derived from ducts of the underlying esophageal submucosal glands throughout the wound. Intestinal metaplasia foci buried beneath the neosquamous mucosa were also present during the healing process that may be a potential source of BE recurrence.

To better understand the neo-epithelialization process and the origin of the neosquamous epithelium, we aimed to characterize the histological features of RFA wound healing in human esophagus endoscopy biopsies from nondysplastic BE patients 1, 2, and 4 weeks after RFA. Using immunohistochemistry, we show the emergence of glands that consists of cells expressing both intestinal (CDX2) and squamous (p63) markers 1 week after RFA. Two weeks after RFA, we show a ductal structure consisting of cells expressing a mixture of p63, intestinal progenitor (SOX9), and metaplastic duct (CK7) markers but negative for CDX2. Four weeks after RFA, we show an area of Barrett's glands with the gland base expressing CK7 and CDX2 and gastric (SOX2) cell lineages but negative for p63. Together, these data uncovered and unexpected previously unidentified highly plastic and transitional cells that may serve as progenitors for the neosquamous mucosa during the healing of the ablation wound after RFA in human BE patients.

We also define the tissue architecture of a human esophagus biopsy obtained at the squamo-columnar junction from a BE patient for the first time using spatial transcriptomic technology. We identified six subpopulations within the biopsy and reveal the spatial landscape of the various subsets within the tissue and potential cross-talk among the various subpopulations. In ongoing work, we hope to identify, for the first time, specific molecular markers of this unique cell plasticity event that involves transdifferentiation of glandular and ductal into normal squamous epithelium.

Preterm cesarean versus vaginal birth blunts bile acid- fibroblast growth factor-19 signaling in neonatal pigs

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Background: Birth by scheduled cesarean section has been shown to affect the development of the small intestine, brain, and microbiome. However, the impact of cesarean versus vaginal birth on the development of bile acid and fibroblast growth factor-19 (FGF19) signaling is unknown. In the fetus FGF19 is a potent growth factor, but postnatally, functions as a negative feedback mechanism for hepatic bile acid synthesis. The objective of this study was to determine the effect of birth modality (cesarean vs. vaginal) and gestational age (preterm vs. term) on plasma hormone levels, bile acid pool distribution, expression of genes in the bile acid-FXR-FGF19 pathway and plasma levels of FGF19 at birth and on day 3 of life in neonatal piglets.

Methods: Four sows underwent a cesarean section on gestation day 105 (n=2) and 114 (n=2; term=115d), and two additional sows were allowed to farrow at term. Half of the piglets were euthanized at birth for tissue and blood collection, and the remaining pigs were nutritionally supported on total parenteral nutrition (TPN) then fed a bolus meal on day 3 of life, at which time tissue and blood were collected. Ex-vivo tissue explants were used to test tissue responsiveness to bile acids and endocrine hormone stimulation. Human ileal enteroids, grown in monolayer, were obtained from the Texas Medical Center Digestive Disease Center, Gastrointestinal Experimental Model Systems Core Laboratory and exposed to bile acids and endocrine hormones.

Results: Piglets born vaginally had a markedly (30x) higher plasma FGF19 at birth than term pigs born via cesarean section, and 70x higher than preterm pigs ($p<0.001$). However, FGF19 gene expression in the distal ileum was similar in all groups ($p>0.05$). Ileal explants from cesarean and vaginally-derived pigs showed similar responsiveness to bile acid stimulation. Plasma FGF19 positively correlated with plasma cortisol ($R=0.579$; $p<0.05$). Porcine tissue explants, as well as human enteroids had increased FGF19 expression and secretion in response to cortisol exposure.

Conclusions: Exposure to maternal or endogenous glucocorticoids in the perinatal period, which occurs during parturition, may have a profound effect on the development of the bile-acid-FGF19 pathway. Future work is focused on identifying the mechanism underpinning glucorticoid-FGF19 signaling in the perinatal period. (Support: USDA-ARS, NIH-NIDDK-RO1-DK094616-04A1)

Srebp1 activation in early-life malnutrition suppresses Cyp7b1 transcription and bile acid synthesis

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Background: Children with severe acute malnutrition have impaired bile acid synthesis, which leads to decreased absorption of fat and fat-soluble vitamins and chronic malnutrition. Bile acid synthesis is tightly regulated by the rate-limiting enzyme Cyp7a1 of the classic pathway and by Cyp27a1 and Cyp7b1 of the alternative pathway. We previously reported that malnutrition induces a selective loss of bile acids generated by the alternative pathway and a loss of Cyp7b1 expression in male but not female mice. Cyp7b1 is regulated at the mRNA level by multiple potential transcriptional regulators, including the sterol regulatory element-binding protein-1 (Srebp1), which represses transcription of Cyp7b1. In this study we sought to determine the nature of the sex differences in hepatic Cyp7b1 expression and the role of Srebp1 in the decreased bile acid synthesis that occurs in early postnatal malnutrition.

Methods: Livers from healthy male and female C57BL/6 mice were harvested from 1 to 12 weeks of age to determine how the relative expression of Cyp7b1 changes over time and by sex in early development. Early postnatal malnutrition was modeled by randomizing dams with 8-day-old pups to receive a low-protein, low-fat diet (LPLFD; 5% fat, 7% protein, and 88% carbohydrate) or an isocaloric control diet (15% fat, 20% protein, and 65% carbohydrate). On day of life 21, pups were weaned to their respective dam's diet until 8 weeks of life, at which time livers were harvested to quantify the expression of Cyp7b1 and Srebp1 mRNA by qPCR and protein by western blot.

Results: Hepatic expression of Cyp7b1 is similar between males and females at birth but becomes sexually dimorphic in the second week of life. Cyp7b1 protein expression peaks for both sexes in the third week of life, with a 4-fold increase in females and a 2-fold increase in males, before returning to levels observed at birth in postnatal weeks 6 through 12. In 8 week old mice, malnutrition dramatically decreases Cyp7b1 expression at both the protein and transcript levels in males but not females. In accord with this finding, hepatic expression of the active Srebp1 protein was increased 4-fold in malnourished males but was unchanged in malnourished females.

Conclusion: Malnutrition leads to induction of the potent transcriptional inhibitor Srebp1, transcriptional repression of Cyp7b1, and decreased bile acid synthesis in male but not female mice. Ongoing experiments seek to determine whether Srebp1 antagonism can rescue Cyp7b1 expression, restore bile acid synthesis, and prevent growth failure in early postnatal malnutrition.

Interleukin-33 facilitates liver regeneration through serotonin-involved gut-liver axis

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Insufficient liver regeneration causes post-hepatectomy liver failure and small-for-size syndrome. Identifying novel therapeutic targets to enhance hepatic regenerative capacity remains urgent. Recently, increased interleukin (IL)-33 was observed in patients undergoing liver resection and in mice after partial hepatectomy (PHx). The present study aims to investigate the role of IL-33 in liver regeneration after PHx and to elucidate its underlying mechanisms. We performed PHx in IL-33$^{-/-}$, ST2$^{-/-}$, and wild-type (WT) control mice, and found deficiency of IL-33 or its receptor ST2 delayed liver regeneration. The insufficient liver regeneration could be normalized in IL-33$^{-/-}$ but not ST2$^{-/-}$ mice by recombinant murine IL-33 administration. Furthermore, we observed an increased level of serotonin in portal blood from WT mice, but not IL-33$^{-/-}$ or ST2$^{-/-}$ mice, after PHx. ST2 deficiency specifically in enterochromaffin cells recapitulated the phenotype of delayed liver regeneration observed in ST2$^{-/-}$ mice. Moreover, the impeded liver regeneration in IL-33$^{-/-}$ and ST2$^{-/-}$ mice was restored to normal levels by the treatment with (±)-2,5-dimethoxy-4-iodoamphetamine (DOI), which is an agonist of the 5-hydroxytrytamine receptor (HTR)2A. Notably, *in vitro* experiments demonstrated that serotonin/HTR2A-induced hepatocyte proliferation is dependent on p70S6K activation**.** Our study identified IL-33 is pro-regenerative in a non-injurious model of liver resection. The underlying mechanism involved IL-33/ST2-induced increase of serotonin release from enterochromaffin cells to portal blood and subsequent HTR2A/p70S6K activation in hepatocytes by serotonin. The findings implicate the potential of targeting IL-33/ST2/serotonin pathway to reduce the risk of post-hepatectomy liver failure and small-for-size syndrome.

Therapeutic Co-targeting YAP1 and TAZ using Antisense Oligos (ASOs) Suppress Gastric Cancer Progression and Peritoneal Metastases

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Gastric adenocarcinoma (GAC) is one of the most common malignancies worldwide and it is the fourth leading cause of cancer-related death. Peritoneal carcinomatosis (PC; malignant ascites or implants) in GAC patients is common and poses a challenge with short survival and lack of effective therapeutics. We and others have demonstrated that deregulation of the Hippo signaling pathway particularly with upregulation of its coactivators-YAP1 or TAZ drive cancer progression and metastases in gastroesophageal cancers suggesting YAP1 and TAZ are potential drug targets in solid tumors. However, discovery of effective drugs to target YAP1 or TAZ remains challenging due to the nuclear localization and lack of inhibitory pocket for YAP1 or TAZ. In this study, using scRNAseq and immunofluorescent staining, we observed that both YAP1, TAZ and their transcriptional factors-Tead1, Tead2, Tead3 and Tead4 are highly expressed in PC tumor cells and high expression of these proteins were associated with poorer prognosis. Further, we note that recently developed YAP or TAZ antisense oligonucleotides (ASO) can effectively and specifically suppress YAP or TAZ expression and transcription accompanied by decreased tumor cell invasion and tumor sphere formation. Further, we observed that YAP1 can interact with TAZ and both bind TEAD1,2,3 ,4 transcriptional factors. Interestingly, inhibition of YAP1 or TAZ alone using the ASOs can complementarily increase the other at the protein and mRNA levels. Besides, treatment with YAP1 ASO alone can increase the interactions between TAZ with TEAD1 and TEAD4 in GAC cells. Furthermore, we revealed that YAP1 KO patient derived tumor cells (GA0518) are more sensitive to TAZ ASO than control cells and simultaneously inhibition of YAP1 and TAZ by ASOs reduces both YAP1and TAZ proteins and mRNA levels with significant decrease in cell proliferation and invasive capacity of YAP1 high tumor cells. Most importantly, co-targeting YAP and TAZ by the ASOs significantly attenuated progression and PC in the PDX model and sensitized to anti-PD1 immunotherapy in the KP-Luc syngeneic model. Taken together, our studies open a new avenue for developing novel therapeutic strategy by co-targeting both YAP1 and TAZ using the ASOs against GAC with PC.

Eosinophil orchestrates tissue repair after hepatic ischemia reperfusion injury

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Hepatic ischemia reperfusion (IR) injury is an inevitable process during liver transplantation surgery, hemorrhagic shock and trauma. Liver injury from IR is a major risk factor not only for early organ dysfunction and failure after liver transplantation but also for acute and chronic rejection and exacerbates the worldwide shortage of transplantable organs. Therefore, research aimed at discovering effective preventive and therapeutic strategies are needed. We have previously shown that eosinophils are rapidly recruited to liver after IR surgery in mice and exert a profound hepato-protective function. Interestingly, our examination of the kinetics of eosinophil recruitment revealed that the peak of eosinophil accumulation in the liver was on day 3 after IR injury, coinciding with the critical time point of liver repair and regeneration after injury. We used an inducible eosinophil-deficient mouse model to deplete eosinophils after the occurrence of hepatic IR injury and observed a marked delay in liver repair compared to eosinophil-intact mice. In contrast, adoptive transfer of bone marrow-derived eosinophils to eosinophil-deficient mice normalized liver repair to a similar extent as in the wild-type mice. Mechanistic studies making use of eosinophil-specific IL-4/IL-13-deleted mice and neutralizing antibodies demonstrated that eosinophil-derived IL4, but not IL-13, is critically involved in liver repair after IR injury. Experiments using hepatocyte-specific and macrophage-specific IL-4Rα knockout mice demonstrated that IL-4 signaling through liver macrophages, but not hepatocytes, plays an essential role in tissue repair after hepatic IR injury. Furthermore, we found that heparin-binding epidermal growth factor-like growth factor (HBEGF) was produced by hepatic macrophages in response to IL-4 release from eosinophils. Moreover, mice lacking liver macrophages-derived HB-EGF exhibited impaired tissue repair after IR injury. Together, these data reinterpreted the role of eosinophils in tissue repair and indicated a crosstalk between eosinophils and macrophages in mediating the effects of liver repair through the IL-4-HB-EGF axis. These findings support further exploration of eosinophils and IL-4/HB-EGF signaling as potential therapeutic targets to improve the outcomes of liver transplantation surgery.

Abstracts

The role and regulation of YAP1 in paligenosis, the cellular program for conversion of mature cells to precancerous metaplasia

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To advance gastric cancer prevention, diagnosis, and treatment, and understand its origins, we aim to understand why precursor metaplasias form and how they progress to cancer. Paligenosis is a recently characterized conserved molecular process which cells use to convert from normal, differentiated, mature cells into proliferative, progenitor-type cells; in the stomach, paligenosis converts digestive-enzyme-secreting chief cells into Spasmolytic Polypeptide Expressing Metaplasia cells (SPEM). Paligenosis occurs by stepwise series of cellular-molecular events characterized by dynamic regulation of mTORC1: Stage 1, mTORC1 decreases, chief cells scale down their secretory apparatus. Stage 2, SPEM genes are induced. Stage 3, mTORc1 increases and the previously mitotically quiescent cells re-enter the cell cycle. Unregulated or "unlicensed" paligenosis imparts nondividing mature differentiated cells the ability to re-enter the cell cycle despite mutations and other genomic abnormalities, making paligenosis a likely initiating process for gastric cancer. The Hippo pathway regulates cell proliferation and differentiation by phosphorylating the transcriptional co-activator YAP1. YAP1 can also act as an oncogene during tumorigenesis, but the regulation of the Hippo pathway and YAP1 in metaplasia and in paligenosis are still unclear. Here we show that YAP1 accumulates in Stage 2 leading to increased expression of many canonical transcriptional targets including cell cycle genes. Overexpression of YAP-S127A in low-dose-tamoxifen-treated *Mist1*$^{CreERT2/+}$*; ROSA26*$^{LSL\text{-}rtTA.IRES.EGFP/+}$*; tetO*^{Yap1S127A} mice induced by doxycycline is sufficient to induce chief cells to enter mitosis while the deletion of YAP1 in *Mist1*$^{CreERT2/+}$*; ROSA26*$^{LSL\text{-}Ai9/+}$*; YAP1*$^{flox/flox}$; *TAZ*$^{flox/flox}$ mice leads to the failure of chief cells to go through paligenosis. *Yap1* mRNA was changed by single-cell RNA sequencing, whereas proteomics with western blot validation showed unchanged total YAP1 protein, suggesting YAP1 may be regulated by subcellular localization. Multi-omic data with western blot and immunohistochemistry validation indicated YAP1 localization is regulated in a Hippo pathway kinase-dependent way and SMAD2/3, key effectors of TGF-β signaling, being potential downstream targets. In summary, our study indicates that YAP1 activity is required for paligenosis, working independently of Hippo and interacting with TGF-β signaling.

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