Raf activation is an important mediator of the MAP kinase cascade to induce cell proliferation or differentiation in several cell types; however, increasing evidence demonstrates that Raf is an important mediator of cell survival. The mechanism by which Raf protects cells from apoptosis appears to be dependent both on cell type and context, and has yet to be described in the gastrointestinal tract.

In a manuscript submitted to Gastroenterology, D. Brent Polk, M.D. and the lead author of the study, Karen Edelblum, Ph.D., show that Raf protects against colitis-induced injury and inflammation by promoting anti-apoptotic signaling in the colon epithelium. Using inducible Raf intestinal epithelium-specific (Raf KOIE) knockout mice, Polk and colleagues found that these mice are more susceptible to dextran sulfate sodium (DSS)-induced colitis than wildtype littermates.

During acute injury, Raf is required for colon epithelial cell survival by promoting anti-apoptotic signaling through activation of NF-κB in a novel MEK-independent manner. While Raf-mediated cell survival appears to be MEK-independent, Raf KOIE mice also lack the hyperproliferative response typically observed during recovery from DSS-induced epithelial injury.

The investigators found that regenerating colon crypts in Raf KOIE mice exhibit decreased ERK phosphorylation compared to wildtype mice.
to wild-type mice, indicating that Raf promotes ERK activation to support epithelial regeneration during recovery from acute colitis.

This study provides the first demonstration that Raf kinase is protective in epithelial tissues in response to injury and inflammation. Furthermore, this is the first study to demonstrate the role of Raf in colon epithelial cell survival and place Raf as a MEK-independent regulator of NF-kB activation in vivo in the context of a disease state. The finding that Raf expression promotes hyperproliferation following injury to regenerate damaged epithelium indicates that Raf may independently regulate two biological processes necessary for maintenance of epithelial tissue responses to damage and inflammation.

This observation may provide a key to understanding the role of Raf in biological processes linking chronic inflammation to carcinogenesis in tissues such as the colon epithelium. The research was supported by the National Institutes of Health.

Fang Yan, M.D., Ph.D.

Dr. Fang Yan joined Dr. Brent Polk’s laboratory in Department of Pediatrics, Division of Gastroenterology, Hepatology, and Nutrition as a postdoctoral fellow in 1998. After she completed three successful years of training, she was appointed to the faculty position as a Research Instructor in 2001, and then in 2003 she was promoted to a Research Assistant Professor.

Dr. Yan’s research focuses on investigating gastrointestinal growth, development and diseases. During her three years of fellowship, she exhibited remarkable talent for research and her studies were highly productive. She finished several studies determining the mechanisms of tumor necrosis factor (TNF) signaling pathways regulating intestinal epithelial cell growth and survival. She found that kinase suppressor of Ras (KSR) is a regulatory kinase determining the fate of intestinal cells exposed to TNF through initiating anti-apoptotic signals. Her results were quite impressive and provided important insights into understanding the role of cytokines in inflammatory bowel disease, with potential implication for tumor development associated with chronic inflammation.

Under the support of the Pilot and Feasibility grant from the Vanderbilt Digestive Disease Research Center (DDRC) and the NIDDK Mentored Research Scientist Development Award (K01, which is mentored by Dr. Brent Polk and co-mentored by Dr. Richard Peek, Dr. Yan has pursued a new line of investigation into the role of intestinal epithelial cell-microbial interactions on gastrointestinal development and inflammation. She has used Lactobacillus rhamnosus GG (LGG) as a model probiotic organism to investigate the mechanism(s) underlying microbial-host interactions. Her publications in this field are the first report to reveal that probiotic bacterium promotes intestinal epithelial cell survival through regulating cell signaling pathways. Furthermore, she has purified and cloned two novel probiotic bacteria-derived proteins (p40 and p75) which promote intestinal epithelial cell survival in the environment of inflammation. Currently, she is focusing on determining the effects and the mechanisms of p40 on intestinal inflammation in two mouse models of colitis. Her research demonstrates
Fang Yan, M.D., Ph.D.

creative and innovative approaches to develop probiotics-derived proteins for potential clinical applications. The results from Dr. Yan’s studies will contribute meaningfully to understand probiotic regulation of gastrointestinal development and diseases.

Dr. Yan was the first Young Investigator Award recipient from the Vanderbilt DDRC in 2002. Other honors she has received include the Crohn’s and Colitis Foundation of America (CCFA) Young Investigator Award, Nestle New Investigator Award from the Children’s Digestive Health and Nutrition Foundation, the Young Investigator Award at the Second World Congress of Pediatric Gastroenterology, Hepatology and Nutrition at Paris, France, in 2004, and scholarships from the American Gastroenterology Association, Federation of Associated Societies of Experimental Biology (FASEB), and CCFA.

Dr. Yan has been highly productive with thirteen research papers published in high-impact peer-reviewed journals and three review papers. She has presented her research at numerous national and international meetings, including the Distinguished Abstract Plenary Session and Poster of Distinction Session at Digestive Disease Week.

As an award recipient, she was invited to present her research regarding probiotic bacterial regulation of intestinal functions at the International Scientific Association for Probiotics and Prebiotics Conference held in London, UK, in June 2007. She will present her probiotic research at the Basic Science Plenary Session during Digestive Disease Week at AGA on May 17-22, 2008.

Dr. Yan’s previous research support included a Pilot and Feasibility grant from the Vanderbilt DDRC, Nestle Nutrition Research Grant, NIH Individual National Research Service Awards for Postdoctoral Fellows (F32), and CCFA Research Fellowship Award. Currently, her research is funded by the NIH K01 award.

Mark Frey, Ph.D.

Mark Frey, Ph.D. is interested in the intestinal epithelial response to injury and inflammation, and in how dysregulation of the restitution and repair processes can contribute to diseases such as inflammatory bowel disease and colon cancer.

Dr. Frey’s undergraduate education was in the History and Philosophy of Science and Medicine program at the University of Chicago, where he was a College Honors Scholar. He subsequently pursued his Ph.D. studies in Molecular Pharmacology and Cancer Therapeutics at Roswell Park Cancer Institute, investigating the role of protein kinase C (PKC) isoforms in cell cycle regulation in the laboratory of Jennifer Black, Ph.D.

In this work he demonstrated that PKCa activation in intestinal epithelial cells triggers a program of cell cycle withdrawal involving up-regulation of the p21 and p27 cyclin-dependent kinase inhibitors, cyclin D degradation, and activation of the retinoblastoma tumor suppressor protein and its family members, p107 and p130. These results delineated isoform-specific functions of individual PKCs in intestinal epithelial cells and identified PKCa as a potential tumor suppressor.

Dr. Frey came to Vanderbilt in 2002 as a postdoctoral fellow in Dr. Brent Polk’s laboratory. As a fellow, he was the recipient of a Crohn’s and Colitis Foundation of America Research Fellowship Award for his studies on the involvement...
Andrew T. Gewirtz, Ph.D., Associate Professor from the Department of Pathology, at Emory University School of Medicine, presented “Toll-like receptor 5-mediated immune responses to enteric microbes” as part of the VDDRC Seminar Series Noon Session on March 25, 2008 at the Medical Center East, South Tower.

Abstract of Dr. Andrew Gewirtz’s presentation:
The intestine is normally colonized by a large and diverse commensal microbiota and is occasionally exposed to a variety of potential pathogens.

In recent years, there has been substantial progress made in identifying molecular mechanisms that normally serve to protect the intestine from such enteric bacteria and which may go awry in chronic idiopathic inflammatory diseases of the gut.

One specific molecular interaction that appears to play a key role in governing bacterial-intestinal interactions is that of the bacterial interactions is that of the bacterial protein flagellin with toll-like receptor 5.

The presentation discussed studies performed in vitro, in mice, and in humans that indicate an important role for the flagellin-TLR5 interaction in regulating both the innate and adaptive immune responses in the intestine.
Michael Rosen, M.D.

Michael Rosen, M.D., of the Division of Pediatric Gastroenterology, Hepatology and Nutrition, was awarded $35,000 from the American College of Gastroenterology. The award was given for Dr. Rosen's project -"The role of 11-13 and NKT Cells in New-Onset Pediatric Ulcerative Colitis."

Dr. Brent Polk, Director of the Vanderbilt Digestive Disease Research Center, stated that this information may be one of the best avenues for prevention and treatment. The ACG’s purpose is to support clinical breakthroughs that improve patient care and the capabilities of practitioners. The ACG has recognized Dr. Rosen for his outstanding work in pediatrics related to ulcerative colitis.

Dr. Rosen graduated from Harvard Medical School in 2007 and is the first recipient of the Thomas A. Hazinski, M.D., Scholarship by the Master of Science in Clinical Investigation Program.

VDDRC Seminar Speakers 2008 - “Women’s Year”

June 10, 2008
Lora Hooper, Ph.D.
Assistant Professor
Department of Immunology
UT Southwestern Medical Center, Dallas, TX
Host: Brent Polk, M.D.

August 26, 2008
JeanMarie Houghton, M.D., Ph.D.,
Associate Professor of Medicine
Department of Cancer Biology
University of Massachusetts Medical School, Worcester, MA
Host: Richard M. Peek, Jr.

October 26, 2008
Deborah L. Gumucio, Ph.D.
Professor
Department of Cell and Developmental Biology
Director, Center for Organogenesis
University of Michigan Medical School, Ann Arbor, Michigan
Host: Michelle Southard Smith, Ph.D.

November 4, 2008
Susan J. Henning, Ph.D.
Professor /Cellular & Molecular Physiology
Associate Director, Office of Medical Research
University of North Carolina Chapel Hill, NC
Host: Brent Polk, M.D.

December 2, 2008
Cathryn Nagler Anderson, Ph.D.
Associate Professor
Center for Immunology & Inflammatory Disease/Division of Rheumatology
Massachusetts General Hospital, Charleston, MA
Host: Brent Polk, M.D.

The greatest mistake in the treatment of diseases is that there are physicians for the body and physicians for the soul, although the two cannot be separated.
~Plato
The VDDRC News Digest is the official quarterly publication of the VDDRC. Each issue features an area of research interest and highlights research activities in one of the core laboratories. The Digest also includes news, a feature publication by a VDDRC member, and upcoming events. If you have suggestions for a future issue of the VDDRC News Digest, please contact us.

New Translational Pilot and Feasibility Award

In direct recognition of the success of the VDDRC Pilot and Feasibility (P/F) Program, Vanderbilt University is now providing additional institutional funding support in the amount of $100,000 per year for the lifetime of our funded center.

A portion of these funds will be matched by VDDRC funds to support a new translational research P/F Project that is partnered with the Vanderbilt Discovery Grant Program to specifically advance the clinical and translational component of the VDDRC.

The Discovery Program provides an institutional source of pilot funds that are designed to foster cross-University collaborative research projects within Vanderbilt. For the new VDDRC partnering award, $25,000 of VDDRC P/F funds are designated to support one-half of a project that is matched by $25,000 from new Vanderbilt institutional support ($50,000 total). This new award is required to be translational, multidisciplinary, and at least one of the two primary investigators must be a physician.

In addition to promoting the clinical component of the VDDRC, this targeted opportunity has given the VDDRC additional institutional visibility for attracting young investigators or established investigators in other disciplines to the study of gastrointestinal disease.

The first recipients of the VDDRC Translational Award are Lee Gorden and Alex Brown for their project entitled “Alterations in Signaling in Steatosis and Steatohepatitis”.

The major goal of this project is to identify abnormalities in signaling lipids in fatty liver as a means to provide a foundation for the development of novel strategies to prevent and/or treat fatty liver disease.

These investigators will study the effect of steatosis and steatohepatitis on the specific glycerophospholipids, diacylglycerols, and lipid signaling species by utilizing state-of-the art lipidomic profiling techniques.

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