p53 Represses GMPS in Liver Cancer

De novo purine biosynthesis is one of the few essential metabolic pathways for which regulation by p53 is largely unknown. Using a large scale proteomics approach, Holzer et al (Am J Pathol 2017, 187:228–235) studied the control of purine biosynthesis by p53. Guanine monophosphate synthetase (GMPS), a key enzyme of de novo purine biosynthesis, was identified as a target of p53 repression in liver cell lines. Down-regulation of GMPS by p21 resulted in cell senescence. Direct knockdown of GMPS by RNA interference reduced cell viability and triggered cellular senescence. These findings were further validated for their in vivo significance. Repression of GMPS by p53 through p21 is a functionally relevant part of the p53-mediated senescence program that might limit tumor cell growth in liver cancer.

Modeling Vascular Graft Infections

Our understanding of the mechanisms behind graft-associated biofilm formation is limited by the lack of relevant animal models. Van de Vyver et al (Am J Pathol 2017, 187:268–279) therefore developed a mouse model to closely mimic the human condition. A polytetrafluoroethylene catheter was implanted within the right carotid artery and eight different strains of Staphylococcus aureus were systemically administered through tail vein injection. Infection with all strains resulted in the formation of biofilm on the grafts, which was monitored by magnetic resonance imaging (MRI) and F-18-fluorodeoxyglucose positron emission tomography (FDG-PET). Following infection, MRI and FDG-PET revealed decreased blood flow in the arteries and high inflammation levels at the site of the catheter, respectively. This novel model will allow studying the development and pathogenesis of biofilms, as well as testing new prevention/treatment options.

Imaging Glomerular Neutrophil Extracellular Traps

Little is known about the formation of neutrophil extracellular traps (NETs) in the glomerulus and their impact on promoting acute glomerular injury. Westhorpe et al (Am J Pathol 2017, 187:318–331) used in vivo two-photon microscopy to image NET formation and retention in real time in the kidneys of mice during an acute inflammatory response. Their model suggests that NETs are transiently generated in the glomerular capillaries and contribute modestly to glomerular injury.

Targeting Colon Cancer

cGMP signaling has therapeutic potential in colitis and colon cancer. Using colon cancer cell lines, mouse colon explants, and human mucosal biopsy specimens, Wang et al (Am J Pathol 2017, 187:377–389) studied the role of the central cGMP effector—type-2 cGMP-dependent protein kinase (PKG2)—in the colon epithelium. Activation of PKG2 inhibited cell proliferation and AKT signaling, activated FOXO3a gene targets, and reduced epithelial redox stress. Enhancement of cGMP signaling in mice with a phosphodiesterase-5 (PDE5) inhibitor mobilized FoxO3a to the nucleus of lumenal epithelial cells, increased FoxO target gene expression, and reduced redox stress. Experiments using human colonic biopsies suggest conservation of these mechanisms across species. The cGMP/PKG2 pathway may be targeted by PDE5 inhibitors for the treatment of intestinal disease.

Managing Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) remains a poorly understood disease. Using in vitro and in vivo models, as well as tissues from NEC patients, Blackwood et al (Am J Pathol 2017, 187:401–417) examined the underlying mechanisms. Increased levels of intestinal cAMP and protein kinase A (PKA) phosphorylation were observed in these models and correlated with increased cellular apoptosis. Depletion or inhibition of PKA potently ameliorated these effects and decreased the severity of bacteria-induced intestinal injury and improved survival in a rat model of NEC. CREB, an important downstream target of cAMP and activated PKA, was activated in rat and human NEC. Pharmacological inhibition of the cAMP-PKA-CREB pathway, particularly via PKA blockade, may aid in managing NEC.