INSIDE LI

doi:10.1038/labinvest.2010.114

Novel compound targeting NF- κ B pathway has efficacy in treatment of colitis models

[See page 1004](#)

Inflammatory bowel disease (IBD), a chronic inflammatory disease of the intestinal tract, is thought to arise from a disruption of mucosal immune homeostasis, resulting in altered processing of enteric antigens, pathogenic T-cell activation, and chronic inflammation. Current therapies are not curative, and there are few nontoxic therapies. Activation of nuclear factor kappa B (NF- κ B) increases epithelial tight junction permeability, facilitating the uptake of luminal antigens that promote inflammation, and leads to upregulation of the expression of proinflammatory proteins involved in IBD development. Thus, activation of NF- κ B appears to be central to the pathogenesis of IBD, and targeting NF- κ B represents a valid treatment strategy.

Previously, Kim and colleagues showed that guggulsterone—a compound extracted from the gum resin of the *Commiphora mukul* tree that has been used in the treatment of a variety of diseases for thousands of years in traditional Indian folk medicine—blocks NF- κ B signaling and attenuates colitis in mouse models. In

their present study, the same authors have synthesized four guggulsterone derivatives with more favorable pharmacological properties. One of these derivatives, GG-52, was shown to inhibit I κ B kinase activation of NF- κ B and to downregulate inflammatory cytokine expression. Moreover, GG-52 reduced the severity of colitis in mouse models. Comparison with known treatment modalities such as sulfasalazine and prednisolone demonstrated similar efficacy. Further studies are clearly indicated to establish whether GG-52 might be a better treatment for IBD than currently available therapeutic options.

Spectral cytopathology of cervical cytology specimens

[See page 1068](#)

Cervical cytology screening has been one of the great success stories of cancer prevention, reducing the rate of cervical cancer by 75% between 1955 and 1992. Yet cervical cancer is still a major public health problem. Furthermore, cervical cytology screening requires considerable human effort to screen the millions of pap smears taken each year. Infrared spectroscopy offers an alternative to conventional cytology, whereby infrared microspectroscopy can be performed on conventional cytological

preparations and paired with sophisticated data analysis to determine whether a cytological sample is abnormal.

As previously reported in *Laboratory Investigation*, Diem and co-workers developed spectral cytopathology that exhibited potential utility for the examination of cytopathology specimens from oral mucosa. In their current work, the investigators examine the utility in screening cervical cytology samples. They found that the technique was able to discriminate between normal and abnormal cervical squamous cells. Furthermore, it identified samples that had normal cytology by conventional cytological classification but a history of abnormal cervical cytology. Presumably, spectral changes were present that were insufficient to produce morphological changes. The authors emphasize that the biochemical changes recognized by spectroscopy are much more widespread in the samples than the morphological changes relied on in traditional cytological methods, which can be quite focal. Furthermore, spectral cytopathology

has obvious potential for automation that could eliminate a component of the manpower required to process these specimens. Further studies are required to develop and validate this promising technology.

Mesenchymal stem cell therapy in diabetic mice

[See page 985](#)

Diabetes is responsible for considerable morbidity, mortality, and health-care costs and is on the rise in the United States and elsewhere. Peripheral vascular disease is one of the more common complications of

diabetes, necessitating the amputation of tens of thousands of limbs each year due to inadequate treatment modalities. The cost associated with disabilities consequent to these amputations is enormous. Stem cell therapy holds great promise in the treatment of diabetes, in which restoration of blood flow to peripheral tissues is of considerable potential benefit. To determine the potential benefits of such

therapy, Matrougui and colleagues assessed the ability of mesenchymal stem cells (MSCs) to restore blood flow to ischemic hindlimbs of mice with type 2 diabetes (db⁻/db⁻).

The authors demonstrated that localized injection of purified MSCs into the ischemic hindlimbs of db⁻/db⁻ mice resulted in increased vascular perfusion compared with controls, and that pretreatment of MSCs with epidermal growth factor enhanced the cells' ability to promote blood flow. Mice treated with MSCs also showed increased vascular density, presumably because db⁻/db⁻ mice have defects in neovascularization that can be remedied by treatment with MSCs. Remarkably, the investigators found that the new blood vessels were derived from the MSCs. Further studies are necessary to show a clinical benefit from this procedure, but it is reasonable to suspect that increased blood flow will decrease the need for amputation in diabetes-associated peripheral vascular disease.

Potential for lethal graft-versus-host disease from T-cell-receptor gene therapy

T-cell-receptor (TCR) gene therapy is based on the introduction of tumor- or pathogen-reactive TCR $\alpha\beta$ chains in peripheral T cells. This therapy has the potential to revolutionize the treatment of tumors and pathogens such as HIV. However, several potential safety concerns have been raised, most notably regarding the potential of the introduced TCR chains to yield self-reactive T cells. In a recent article in *Nature Medicine*, Schumacher and colleagues asked whether TCR gene therapy had the potential to generate graft-versus-host disease (GVHD). Using TCR gene therapy in mice, the authors found that the mice developed a GVHD syndrome characterized by pan-destruction of the hematopoietic compartment, autoimmune pancreatitis, and colitis. They also demonstrated strategies whereby they could limit the occurrence of TCR-transfer-induced GVHD.

Nature Medicine 2010;16:565–570; doi:10.1038/nm.2128

Critical role of CSF1R in MOZ-TIF2-induced leukemia

Previously, Kitabayashi and colleagues generated a mouse model of acute myelogenous leukemia (AML) by introducing c-Kit⁺ mouse myeloid stem/progenitor cells infected with a retrovirus encoding monocyte leukemia zing finger (MOZ)-TIF2 into lethally irradiated mice. As reported in a recent letter in *Nature Medicine*, they sought to identify the leukemia-initiating cells (LICs) in this model. Using flow cytometry, they identified a colony-stimulating factor receptor^{high} (CSF1R^{high}) population that had substantially more LICs than CSF1R^{low} cells. Furthermore, by inducing apoptosis in CSF1R^{high} cells with a clever drug-inducible suicide-gene strategy, they demonstrated that they could cure MOZ-TIF2-induced leukemia. Finally, they found that MOZ-TIF2 activates PU.1-mediated transcription of *Csf1r*. Overall, these results suggest that *Csf1r* has the potential to be an effective therapeutic target in MOZ-TIF2-driven AML.

Nature Medicine 2010;16:580–585; doi:10.1038/nm.2122

Mutations in optineurin in familial amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder characterized by degeneration of primary motor neurons of the primary motor cortex, brainstem, and spinal cord. About 10% of ALS cases are familial (FALS), and mutations have been identified in 20–30% of FALS patients. In a recent letter in *Nature*, Kawakami and colleagues describe how they identified additional genes responsible for FALS via homozygosity mapping in ALS patients from consanguineous marriages. They identified mutations within *OPTN*, which encodes optineurin, a protein that is known to negatively regulate activation of nuclear factor kappa B (NF- κ B). The *OPTN* mutations identified in FALS were shown to result in NF- κ B activation, presumably leading to neuron death. The authors thus provide a plausible hypothesis that NF- κ B activation, owing to defects in optineurin function, may lie at the heart of the pathogenesis of at least some cases of FALS.

Nature 2010;465:223–226; doi:10.1038/nature08971

A gene expression signature predicts prognosis in autoimmune disease

Because patients with autoimmune diseases vary significantly in their clinical behavior, it is desirable to be able to predict prognosis in order to prescribe appropriate immunosuppressive therapy. However, this has been difficult using existing biomarkers. To establish better biomarkers for prediction of prognosis in autoimmune diseases, MacAry and colleagues, in a recent letter in *Nature Medicine*, asked whether RNA expression signatures of subsets of inflammatory cells might better serve the purpose. They discovered that the expression signature of CD8⁺ T cells predicted relapse prospectively in antineutrophil cytoplasmic antibody-associated vasculitis and systemic lupus erythematosus. More severe prognosis was associated with enrichment of a human-effector-memory expression signature. Finally, they found that CD8⁺ T-cell expression of as few as three genes could discriminate between good and bad prognostic groups.

Nature Medicine 2010;16:586–591; doi:10.1038/nm.2130