INSIDE LAB INVEST

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STAT3 helps with survival but not liver regeneration in the lean mouse

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The mechanisms by which the mammalian liver is able to substantially regenerate its mass after partial hepatectomy or other damage has been under study for more than 80 years. Growth factors and cytokines have been shown to play a key role in stimulating and regulating the proliferation of liver tissue. These studies have in turn spawned investigation of the intracellular signaling pathways that regulate nuclear transcription in hepatocytes and other liver cell types. Among these, the STAT3 signaling pathway figures prominently. However, it has been difficult to dissect out the specific role of STAT3 in stimulating liver regeneration, as opposed to its role in responding to necroinflammatory injury *per se*. In a previous murine model of conditional knockout of STAT3 using the Cre-lox method, an albumin promoter was fused to the open reading frame of Cre. The resultant conditional knockout of STAT3 in the liver was accompanied by hepatic steatosis and animal obesity, leaving open the question of whether altered hepatic regeneration was due to absence of STAT3 or to the accompanying steatosis.

In this issue, Moh *et al* generated a model of conditional hepatic L-Stat3 knockout without obesity or hepatic

steatosis, by using a transthyretin factor promoter fused to the open-reading frame of Cre. The L-Stat3^{-/-} mice were lean and did not exhibit either obesity or hepatic steatosis. Interestingly, the authors did not obtain substantive evidence that STAT3 expression in the liver was required for adequate liver regeneration after 70% partial hepatectomy or after severe hepatic injury from CCl₄ exposure. Survival was negatively affected by absence of hepatic STAT3. Although this report does not provide evidence for a direct role of STAT3 in liver regeneration (that or other

STAT pathways can compensate), a key benefit is nevertheless obtained by this study. The creation of a lean conditional knockout mouse for hepatic expression of STAT3 is a technological *tour de force*. The fact that these animals tolerate a major surgical procedure less well than wild-type animals suggests that STAT3 is involved in the homeostasis associated with traumatic injury. The recognition that STAT3 deficiency is related to the increased mortality may be of importance for clinical management of patients with severe liver injury and bears further investigation.

Mast cells harness the newest cytokine, IL-33, to enhance their functions

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IL-33, the latest identified interleukin, belongs to the IL-1 family, and as such assumes a dual function as either a proinflammatory transcription factor or a soluble factor inducing the MyD88-dependent induction of Th2 cytokines. It was already known that IL-1 can enhance IgE/Ag-FcεRI activation of mast cells. The IL-33 receptor is preferentially expressed on Th2 T cells and mast cells, suggesting a role for this cytokine in both cell types. In this issue, Iikura *et al* report that IL-33 enhances survival, adhesion, and IL-8 and IL-13 cytokine production by human mast cells. Interestingly, IL-8 and IL-13 secretion can be induced by IL-33 directly, independently from FcεRI or TLR stimulation, which puts this cytokine in a unique position to directly activate

mast cells in an antigen-independent, TLR-independent pathway. The role of IL-13 in the pathology of atopic asthma and allergic dermatitis should be further examined, but this report identifies it as a promising target for intervention.

Is Crohn's disease contagious?

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While a genetic component of Crohn's disease is well recognized and a growing list of susceptibility genes have been identified, the factors that trigger disease onset have been more elusive. Many have hypothesized that enteric bacteria, both commensal and pathogenic, may be involved, based on the observations that broad-spectrum antibiotics can induce temporary clinical remission in some patients, many patients display evidence of defective immune tolerance to intestinal microflora, and germ-free

animals often fail to develop experimental inflammatory bowel disease. In this issue, Sasaki *et al.* addressed this hypothesis by characterizing invasive bacteria isolated from colon biopsies. Remarkably, nearly all invasive strains isolated from Crohn's disease patients and nearly half of those from ulcerative colitis patients were *E. coli*, whereas only 2% of the invasive strains isolated from control subjects were *E. coli*. When studied *in vitro*, invasive *E. coli* isolated from Crohn's disease and ulcerative colitis patients induced high levels of tumor necrosis factor expression in cultured macrophages and disrupted barrier function in cultured epithelial cells. Thus, at least *in vitro*, inflammatory bowel disease-associated invasive *E. coli* strains are able to induce cellular responses that mirror changes reported in human patients.

These intriguing results provide a link between invasive *E. coli* and inflammatory bowel disease, but generate at least as many questions as they answer. For example, even though invasive *E. coli* are present in some patients, it remains to be seen if they are truly able to overcome host defenses *in vivo*. Are invasive *E. coli* the only culprits? Are these bacteria alone sufficient to cause disease in genetically susceptible hosts? Are concurrent environmental cofactors required? Answers to these questions could significantly impact our understanding of inflammatory bowel disease pathogenesis and, optimistically, guide us to new strategies for treatment or even prevention.

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Genome-wide association studies: beyond Mendelian traits Genetic analyses have contributed greatly to our understanding of disease. However, phenotype-driven studies have been most successful with Mendelian traits, leaving a gap in our understanding of complex genetic diseases. Large-scale genome-wide association (GWA) studies, in which single-nucleotide polymorphisms that blanket the genome are used as markers of genetic linkage, are now coming to the fore. In a recent issue of *Nature*, the Wellcome Trust Case Control Consortium (WTCCC) reported a GWA study of seven diseases in a total of 17,000 individuals. The WTCCC study and additional GWA studies, reported in *Nature Genetics*, have led to the identification of genetic markers for bipolar disorder, coronary artery disease, Crohn's disease, hypertension, rheumatoid arthritis, and diabetes. Some of the loci found confirm previous work, but many are newly discovered. This ability to pinpoint novel genetic associations in complex multifactorial diseases is a huge step forward in identifying basic disease mechanisms. The next challenge will be to develop tools to transform these breakthroughs into understanding of pathogenesis and therapeutics.

Nature 2007;447:661–678; doi:10.1038/nature05911

Nature Genetics 2007;39:813–814; doi:10.1038/ng0707-813

Nature Genetics 2007;39:830–832; doi:10.1038/ng2061

Nature Genetics 2007;39:857–864; doi:10.1038/ng2068

Transferring human mutations to mice:

Steinbeck revisited Functional deficiency of flap endonuclease 1 (FEN1), a multifunctional nuclease that mediates DNA replication, repair, and apoptotic DNA degradation, has been implicated in genomic instability and cancer predisposition. After identifying specific mutations that reduced FEN1 nuclease activities in human cancer, researchers created knock-in mice containing one *FEN1* mutation. Both homozygous and heterozygous knock-in mice displayed a mutator phenotype, increased DNA damage-induced apoptosis, and accumulation of apoptotic nuclear debris. The mice were also predisposed to autoimmune disease and lung cancer. This approach represents a means of testing *in vivo* biological relevance of mutations associated with human diseases, including those linked in genome-wide association studies, and may also prove useful in the development of therapies targeted to specific common mutations.

Nature Medicine 2007;13:812–819; doi:10.1038/nm1599

Putting another notch in the mast The transcription factor GATA-3 is one of the earliest genes induced when Notch signaling triggers thymic T-cell differentiation. GATA-3, which is essential for early T-cell differentiation, is thought to direct cells to the T lineage. The authors of a recent paper in *Nature Immunology* transgenically expressed GATA-3 in developing prethymic and intrathymic lymphoid precursors. Overexpressed GATA-3 was antagonistic, not synergistic, with Notch for survival of pro-T cells. More remarkably, GATA-3 did not necessarily confer T lineage but could divert T precursors toward mast-cell differentiation. These results identify an unexpected link between T-cell and mast-cell developmental programs. Because Notch is frequently mutated in human T-cell lymphomas, future studies of GATA-3 mutations may also provide insight into the pathogenesis of leukemia/lymphoma and, perhaps, systemic mastocytosis.

Nature Immunology 2007;8:845–855; doi:10.1038/ni1486