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From the Editor's desk...

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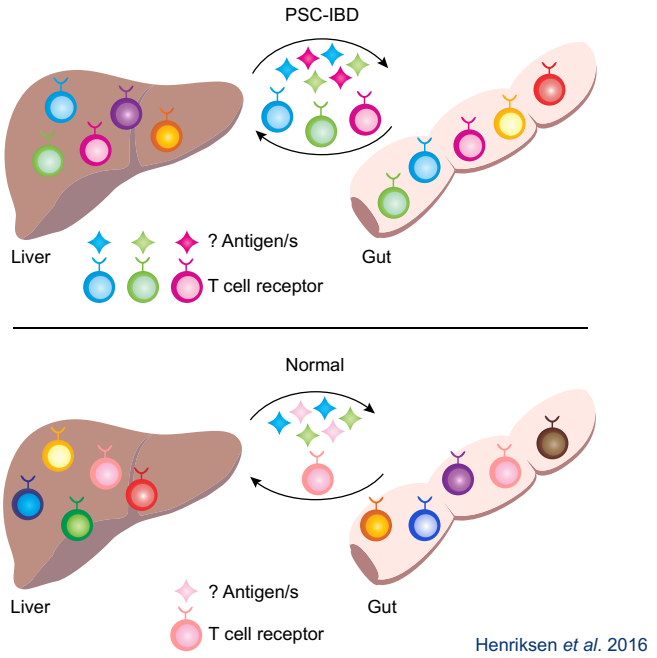
SELECTION OF THE MONTH

Memory T-cells of common clonal origin involved in PSC-IBD pathogenesis:

The immunologic mechanisms involved in the pathogenesis of PSC-IBD are unclear and the current hypotheses suggest that T cells recruited into the liver from the gut may drive hepatic inflammation. Henriksen *et al.* studied liver and colonic biopsies to determine whether the T cells obtained from these organs share common receptors and antigenic specificities. **The authors used high throughput sequencing and made the novel observation that in the PSC-IBD patients, memory T cells of common clonal origin was detected in the paired biopsies suggesting that memory T cells driven by shared antigens may be important in the pathogenesis**. These data allow potentially novel approaches to therapy targeting the memory T cells.



Henriksen *et al.* 2016

ACUTE LIVER INJURY

Kruppel-like factor 2 and autophagy cooperate to protect the endothelium

The transcription factor, kruppel-like factor 2 (encoded by *KLF2*), which is induced by simvastatin (among other inducers), promotes endothelial protection. Guixé-Muntet *et al.* hypothesized a role of autophagy in kruppel-like factor 2-mediated endothelial protection. They now show that stimulation of autophagy results in kruppel-like factor 2 overexpression which accentuates autophagy by a positive feedforward mechanism. Acute liver injury caused by ischemia/reperfusion (I/R) inhibits the autophagy/kruppel-like factor 2 cooperation and results in endothelial cell death. **Interestingly, simvastatin-pretreatment protects mice against I/R-associated endothelial injury because of sustained autophagy and kruppel-like factor 2 expression and subsequent endothelial cell survival**. Because I/R is an important issue following liver transplantation, the findings by Guixé-Muntet and colleagues suggest that simvastatin could be useful in preventing this complication.

CHOLESTATIC LIVER DISEASE

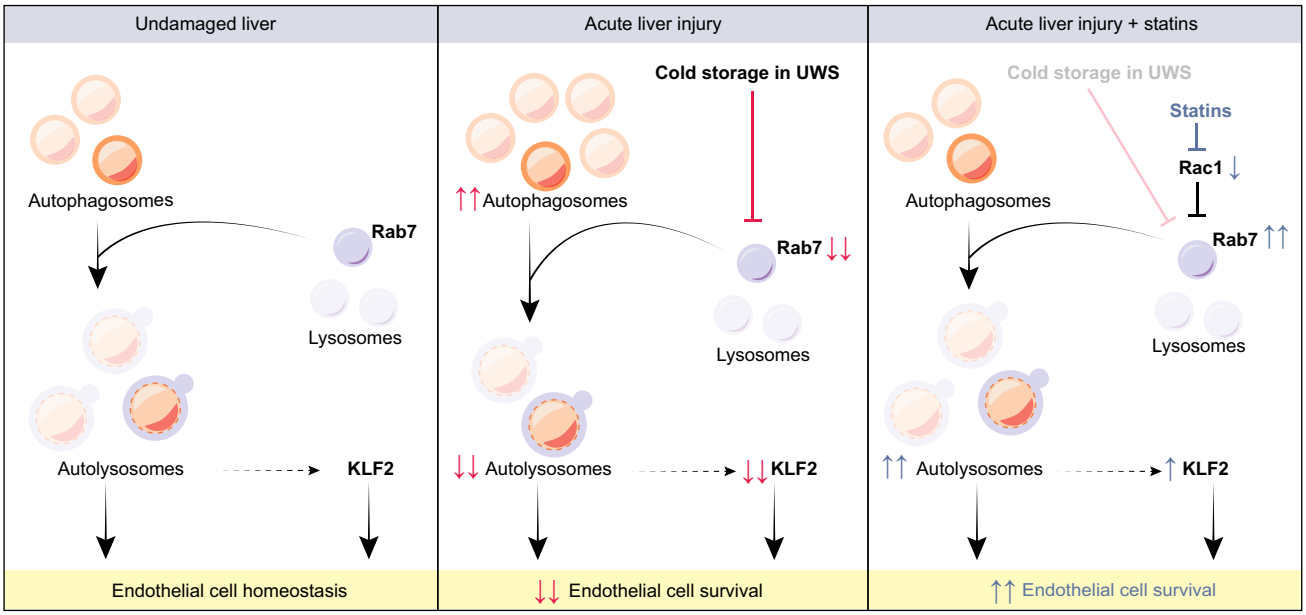
Parsing the phenotype of *ABCB11* deficient mice

Impairment of the canalicular bile acid (BA) transport via the bile salt export pump (encoded by *ABCB11*, also known as *BSEP*, *PFIC2*) causes cholestasis. Absence of bile salt export pump in humans causes progressive familial intrahepatic cholestasis type 2, a severe cholestatic liver disease in children. In contrast to humans, *Abcb11* deficiency in mice is associated with a milder phenotype lacking the development of progressive cholestasis. This finding may at least in part be explained by differences in BA composition, metabolism and transporters between mice and men. In this issue of the *Journal*, Fuchs *et al.* addressed the question by investigating wild-type and *Abcb11*$^{-/-}$ mice that were subjected to common bile duct ligation or 3.5-diethoxycarbonyl-1.4dihydrocollidine (DDC) feeding as models for cholestasis with biliary obstruction and bile duct injury. They show that **mice with inborn *Abcb11* deficiency exhibit an adaptive increase of polyhydroxylated BAs that may precondition and thereby protect against acquired cholestatic liver and bile duct injury**.

CHOLANGIOCARCINOMA

Cancer stem cells (CSCs) shape tumor-associated macrophages (TAM)

CSCs play a crucial role in clinical severity of cholangiocarcinoma. Macrophages are not only involved in tissue homeostasis and immune defense against pathogens, but can also be regulators of cancer, and are called TAM in these cases. Raggi *et al.* hypothesized that CSCs may induce a tumor-promoting TAM phenotype. They reveal that **CSCs shape tumor-initiating niche by educating associated macrophages via signals such as interleukin**



Guixé-Muntet *et al.* 2016

(IL)-13 (known to promote M2 phenotype), IL-34 (known to stimulate monocytes via the M-CSF receptor) and osteoactivin (encoded by *GPNMB*, for transmembrane glycoprotein NMB, whose functions are elusive).

HEPATOCELLULAR CARCINOMA (HCC)

Dissecting anti-tumor immunity, No touch multi-bipolar radiofrequency *vs.* mono-polar techniques for small HCC

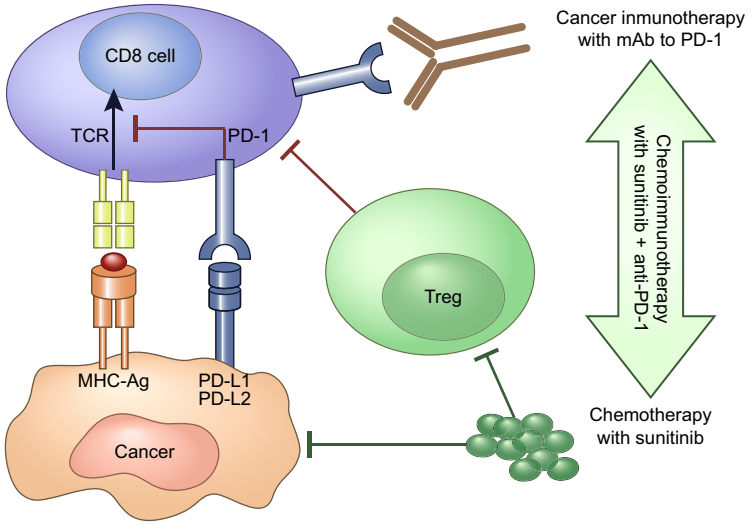
Dissection of anti-tumor immunity during tumor initiation and progression has been a challenge in the absence of clinically relevant animal models. Li *et al.* report very important new findings in the current issue of the *Journal*. First, they show that a combination of intraperitoneal injection of carbon tetrachloride and intra-splenic inoculation of oncogenic hepatocytes is able to induce progressive HCCs in fibrotic livers of immunocompetent mice. This model recapitulates main features of human HCC. Second, using this new animal model, they find that both immunosuppressive regulatory T cell (**Treg**) accumulation and upregulation of programmed cell death protein 1 (i.e., **protein PD-1**, whose engagement at $CD8^+$ T cell surface inhibits the cytotoxic, anti-tumoral action of these cells), are two independent mechanisms inducing profound immune tolerance in HCC. Third, **using this model, they reveal that therapy using a combination of sunitinib (a novel small molecule that blocks multiple receptor tyrosine kinase) with antibodies against protein PD-1 achieves significant tumor control, supporting translation of this approach for the treatment of patients with HCC.**

Although very encouraging results have been reported after treatment of small HCC with multi-bipolar radiofrequency ablation (RFA), the mono-polar technique remains the most frequently used technique worldwide. Hocquelet *et al.* compared the rate of RFA failure between mono-polar RFA and "No Touch" Multipolar RFA for the curative treatment of small HCC (⩽5 cm) in a large multicenter case-matched study. **They show that in the context of HCC ⩽5 cm, "No Touch" Multipolar RFA provides better primary success and sustained local tumor response without increasing severe complications rates.**

NON-ALCOHOLIC STEATOHEPATITIS (NAFLD)

Effect of aerobic *vs.* resistance physical exercise and role of sarcopenia and PARylation

Recent studies suggest that sarcopenia is present in many patients with NAFLD. In this issue, Koo *et al.* studied the appendi-



Chemoimmunotherapy against HCC

Li *et al.* 2016