Loss of GNMT impairs liver regeneration

Researchers at the CICbioGUNE-Ciberedh led by José Maria Mato and M-Luz Martínez-Chantar, in collaboration with investigators at the Keck School of Medicine (USA) and at the University of Vanderbilt (USA), have discovered that mice deficient in GNMT, the main enzyme responsible for catabolism of excess hepatic S-adenosylmethionine (SAMe) have impaired liver regeneration. The finding that lack of GNMT enzyme increases mortality after partial hepatectomy has important clinical implications, since GNMT is down-regulated in patients at risk of developing HCC, such as in hepatitis C virus- and alcohol-induced liver cirrhosis, and liver resection is a well established therapeutic measure in severe liver patients. The study, published in the August issue of Hepatology, confirms that down-regulation of intracellular SAMe levels is critical for hepatocyte proliferation and viability during liver regeneration. The study shows a new relationship between AMPK, the main controller of the energetic status of the liver, and NFκB, the controller of the acute phase response after partial hepatectomy, in regulating proliferation and survival.

These findings, together with a previous study from the same lab (Hepatology, 2008), show that chronic supra-physiological levels of hepatic SAMe dysregulate hepatocyte proliferation. On the one hand, this induces uncontrolled hepatocyte proliferation leading to hepatocellular carcinoma development (Hepatology, 2008) and on the other hand, blocks controlled hepatocyte proliferation after partial hepatectomy, leading to impaired liver regeneration (Hepatology, 2009).