Tuesday August 28th, 2012

2.30pm

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“Bile acids and liver regeneration : the impact of TGR5?”

Hosts: Kristina Schoonjans and Johan Auwerx

Conference Room: AI 1153
EPFL - Lausanne

Abstract
Liver regeneration is a vital process orchestrated by multiple pathways providing the different liver cell types with signals initiating both proliferation and protection. This process involves a complex array of agonists and cellular interactions, not only between hepatocytes and other liver cells (autocrine, paracrine interactions), but also between the liver and the whole organism (endocrine, neuroendocrine, nerves...). Apart from main growth factors, cytokines and other agonists extensively studied so far, we have identified calcium-mobilizing agonists which also contribute to the regeneration process (Gonzales et al., 2010; Lagoudakis et al., 2010; Doignon et al., 2011). In particular, we identified the hormone arginine vasopressin as a neuroendocrine agonist involved in liver regeneration after partial heptectomy (PH), in part in a bile acids and TGR5-dependent manner (Doignon et al., 2011). Bile acids (BA) recently emerged as important players during liver regeneration, although a complete view of their involvement is lacking at the molecular, cellular, and physiological levels. In both experimental models of liver regeneration in rodents, namely PH and CCI4 intoxication, it has been well established (by us and by others), that BA flux to the remnant regenerating liver, and to the whole organism, is rapidly enhanced, with potentially wide signaling consequences. FXR mediated BA effects have received much attention with respect to their roles during liver regeneration; FXR activation by BA indeed provides hepatocyte adaptive (protective) response to liver resection or injury, through regulation of BA entry, synthesis and export in hepatocytes, while FXR mediated activation of the transcription factor Fox M1b contributes to hepatocyte progression in the cell cycle. Beside this body of information, the involvement of the BA membrane receptor TGR5 has not received any published interest. We have began to study liver regeneration in TGR5-KO mice and found that the lack of this BA receptor results in excessive hepatic BA overload culminating in extensive hepatocyte necrosis after PH. The mechanisms involved are currently under investigation.