ImmunoTools *special* Award 2015

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Inflammation in human hepatic cirrhosis

Liver cirrhosis is an end stage hepatic derangement characterized by a progressive replacement of the hepatic architecture by non-functional fibrotic tissue. The implication of the innate immune system in the pathogenesis of liver cirrhosis has been largely described. In this respect, chronic hepatic inflammation and fibrosis are key features associated with macrophage accumulation in the liver (*Ramachandran and Iredale, J.Hepatol. 2012; Zimmermann et al., Front Physiol 2012*). Also, increased hepatic and systemic damage is associated with the elevated production of pro-inflammatory cytokines such as IL-1β, TNF-α, IL-6, as well as anti-inflammatory cytokines, IL-10 and TGF-β (*Dasarathy, JPEN J.Parenter.Enteral Nutr. 2008*). Since macrophages are involved in many of the pathophysiological events associated with liver cirrhosis (*Heymann et al., Inflamm.Allergy Drug Targets. 2009*) these cells are good candidates to be current targets for anti-inflammatory therapy intended to avoid progression of liver injury. Our group previously reported the primed status of peritoneal monocyte-derived macrophages (M-DM) from cirrhotic patients, which is related to ERK phosphorylation and IL-6 secretion (*Ruiz-Alcaraz et al., Eur.J.Clin.Invest. 2011*), and more recently, that the release of the pro-inflammatory cytokines TNF-α and IL-6 by peritoneal M-DM from this clinical setting strongly depends on the MAPK signaling pathways, while the PI3K-Akt pathway plays a prominent role in the modulation of the anti-inflammatory IL-10 mediated function (*Tapia-Abellan et al., Liver Int. 2013*). IL-1β is an important pleiotropic cytokine with immune and pro-inflammatory activities. Its potent pro-inflammatory role is mediated by induction of additional mediators, including IL-1β itself, IL-1α, TNF-α, IL-6, IL-8, COX-2 and PGE2. Its autocrine properties allow that even small localized IL-1β concentrations are able to induce potent biological functions. Hence, processing and secretion of biological active IL-1β is tightly regulated at several levels. Infectious and inflammatory mediators induce NF-κB-dependent transcription of the *IL1B* gene. IL-1β is further regulated at the level of RNA stability and translational

control, and requires post-translational proteolytic cleavage to acquire its active properties. Activation of caspase-1 by inflammasome assembling plays a critical role in this process, although it also exists a caspase-1 non-dependent mechanism for IL-1β processing (*Dinarello, Annu.Rev.Immunol. 2009).* Assembly of this multi-protein complex is triggered by a wide range of structurally diverse DAMPs (Damage Associated Molecular Patterns) or Pathogen Associated Molecular Patterns (PAMPs) stimuli.

In this project we study the relative importance of ERK1/2, JNK and p38 MAPK and PI3K-Akt pathways on the expression and release of inflammatory cytokine as IL-1β in M-DM obtained from the ascites of cirrhotic patients, trying to gain further insights into the pathogenesis of liver cirrhosis that could lead to identify novel targets for pharmaceutical intervention to prevent or reduce hepatic damage. We will purify M-DM from ascites and analyze them by flow cytometry with ImmunoTools´ antibodies, examine the effects of several PAMPs and signaling inhibitors on secretion of cytokines by ImmunoTools´ ELISAs in M-DM from the ascites of cirrhotic patients.