ImmunoTools *special* Award 2015

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Regeneration immune actors in a setting of chronic liver injury

The understanding of mechanisms for liver fibrosis and regeneration, in a context of chronic injury and the comprehension of differences in terms of liver rate of recovery according to gender could be considered the first step in developing new targeted therapeutic strategies for ameliorating life quality during chronic liver diseases. The purpose of the study is to characterize the most critical mediators, both immune and inflammatory, which act as "check points" in the injured liver and determine the fate of the organ, with particular emphasis to the role of gender. After the development of a mouse model of chronic liver injury chemically-induced as first-line of the study, we aim at possibly extend our observations in humans. The main focus of this project will be the study of the role and characterization of serum and liver infiltrating inflammatory populations both in male and female mice, in the presence of a chronic chemically-induced noxa. The characterization of their phenotype, with a particular attention to their immaturity grade, in the context of a fibrotic or regenerative liver will contribute to add another piece of knowledge of biological mechanisms of chronic liver injury. Our findings will be translated to humans in particular by studying the most relevant immune populations and relevant cytokines both in sera and liver biopsies of patients with chronic liver diseases, with a focus on viral hepatitis and NASH.

Recent findings demonstrated unexpected roles for specific immune cell types in promoting a permissive local environment for effective cell replacement and restoration of tissue integrity (*Forbes SJ, 2014*).The remarkable capacity of the liver to adapt to injury through tissue repair relies on an integrated and complex process which includes regeneration and wound healing with the synthesis of extracellular matrix proteins. Regarding this last aspect, deregulation of the sensitive mechanism of balance between the synthesis and degradation of extracellular matrix results in the replacement of parenchyma by connective tissue (*Sziksz E, 2015*). These mechanisms are modulated by a dynamic interplay between hepatocytes and non-

parenchymal cells, as well as the microenvironment. Complex interactions of immune cell subsets are thought to regulate this repair process, such that fibrosis and wound healing can be considered chaperons of the innate immune in the response to tissue damage. Immune cells have been identified as key players in the fibrotic cascade, with the capacity to exert either injury-inducing or repair-promoting effects (*Pellicoro A, 2014*).

As a part of the project, liver infiltrating cells will be characterized, including pro-fibrotic monocytes-derived hepatic macrophages, according to their profile and positivity for F4/80, as well as HPCs and stellate liver cells both in males and females. To verify if a different gender-dependent modulation of T cell-mediated response exists following chemical toxicity, $CD4^+$ and $CD8^+$ subsets and a multi-cytokines panel expression (IL-2, IL-4, IL-6, IL-10, TNF-alpha, Interferon-gamma, among others) will be considered. The specific populations differently modulated during the chronic injury according to gender will be characterized from both a cytofluorimetric and a molecular point of view. These same populations, properly defined by their immune-phenotype, will be then validated in the human setting.