ImmunoTools *special* Award 2014

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Gender influences in liver acute injury

Hepatic inflammation is a complex process that modulates the outcome of acute liver injury (ALI) exerting hepatoprotective or detrimental effects [Kubes et al., 2012]. Controlled at cellular level, the inflammatory process involves distinct liver-resident cells, immune cells and bioactive molecules, such as cytokines and chemokines [Kubes et al., 2012]. Experimental evidences demonstrate that the liver response to damage is characterized by a gender dimorphic pattern [Choudhry et al., 2005].

Direct and indirect effects of sex hormones have shown to control the inflammation process [Smirnova et al., 1992; Smirnova et al., 1993]. Using animal models of tissue damage, androgens resulted to be immunosuppressive while estrogens contributed to wound repair exerting immunoprotective activity [Knoferl et al., 2001; Knoferl et al., 2002]. As liver regeneration shows to be slower and more difficult in males than in females, in this project a liver acute damage model will be obtained by injection of CCl4 in Balb/c mice (males and females). By cytometrical multiparametric method, the endogenous and exogenous populations of monocyte and lymphocyte lineages will be explored using antibodies specific for CD14, CD11b, F4/80, CCR2 (monocyte markers) and CD3, CD4, CD8a, CD19, CD20, CD25, CD45 (lymphocyte markers). The expression level of target antigens on cells isolated from CCl_4-untreated animals will be assumed as reference to discriminate the immunoreactivity of test groups.

It has been shown that, after acute damage, inflammatory Gr1 ^{high} monocyte-derived macrophage subpopulation (Karlmark et al., 2009) are recruited to liver.

Macrophages play pivotal role in initiation, propagation, and resolution of ALI. Their involvement is essential during the initial inflammatory phase by secreting cytokines and growth factors, and recruiting inflammatory cells (Duffield, 2003). Moreover, macrophages control the reparative process leading to hepatic remodeling and the restoration of liver functionality (Duffield et al., 2005).

As the homing of immunosuppressive myeloid cells in male and female mice is not yet well characterized in ALI model, the populations expressing Gr1 ^{high} and Gr1 ^{low} will be detected at different time points from CCl_4 injection using flow cytometry analysis. In order to define the regulatory role of sex hormones in the inflammatory phase of liver acute injury, some animals will be treated with antagonists of androgens and estrogens and than, after animal sacrifice, the liver subpopulations will be submitted to the detection of Gr1 ^{high} cells.

As experimental evidences suggest that the higher susceptibility to complications of ALI in males could depend on immunosuppression [Angele et al., 1997; Wichmann et al., 1997], the present study will explore in Balb/c mice, at different time points from CCl_4 intraperitoneal administration, T-cell mediated response by identifying $CD4^+$ and $CD8^+$ subsets and cytokine panel expression (IL-2, IL-4, IL-6, IL-10, TNF-alpha, interferon-gamma) to verify if a different modulation of Th1 and Th2 cell-mediated response is involved in male and female mice following chemical toxicity.