ImmunoTools *special* Award 2023

Pedro Melgar Lesmes, PhD

Department of Biomedicine, Faculty of Medicine, University of Barcelona, Casanova 143, 08036 Barcelona, SPAIN

Modulation of macrophages to reduce liver fibrosis and boost hepatic regeneration

Liver diseases are rising throughout the world and increasingly problematic in Western countries. The burden of these diseases in Europe is the largest in the world and continues to grow as rates of obesity, alcohol consumption, and viral hepatitis rise.

Liver fibrosis results from chronic injury of the hepatic parenchyma and is driven by active extracellular matrix remodelling with progressive and abundant deposition of collagen. During the process of hepatic fibrogenesis there is a complex interrelation between the different cell types present in the liver. Following liver injury, damaged hepatocytes release reactive oxygen species and other fibrogenic mediators that induce the recruitment of inflammatory cells and the activation of hepatic stellate cells (HSCs). Macrophages are specialised cells of the innate immune system involved in the detection, phagocytosis and destruction of bacteria and other harmful foreign bodies. Non-resident macrophages originate from circulating monocytes that leave the blood stream to differentiate in distinct tissues in response to injury. Macrophages are abundant during all stages of hepatic injury and repair and have significant influence on the balance of tissue damage progression and resolution. Indeed, macrophage activation is a prognostic parameter for variceal bleeding and overall survival in patients with cirrhosis. After injury, resident hepatic macrophages (Kupffer cells) attract blood monocytes, which then differentiate into macrophages. Recruited macrophages secrete an array of pro-angiogenic and pro-inflammatory cytokines that activate HSC, which produce collagen to confine tissue damage. In this scenario, our project is aimed to understand how chronic inflammation occurring in chronic liver disease defines macrophage phenotypes, and how we can design nanoparticles to target and treat inflammatory macrophages in liver diseases. Among the different cytokines present in chronic liver diseases, we will test the effects of a panel of cytokines on the expression of macrophage regulatory factors and other related factors. The pro or anti-inflammatory cytokines kindly provided by ImmunoTools to test activation or repression of macrophage regulatory factors in primary mouse hepatic macrophages will be the following:

These cytokines and the combination of them will allow better understanding the regulatory pathways activated in macrophages to switch from the pro-inflammatory (M1-like phenotype) to the anti-inflammatory and pro-regenerative (M2-like phenotype). These pathways will be intervened using our therapeutic strategies at the nanoscale to reduce liver fibrosis and to boost hepatic regeneration. According to the findings of molecular regulatory pathways found in these *in vitro* experiments using primary mouse hepatic macrophages, then we will design and test the therapeutic tools in mouse models of liver fibrosis and hepatic regeneration to give insight into the microenvironment modulating the behaviour of macrophages in chronic liver disease.

This project has a profound translational character and is aimed at finding and establishing new therapeutic strategies in liver diseases, one of the most prevalent diseases in Western countries and with a high social and economic cost. The treatment of choice in patients with acute or chronic liver failure is liver transplantation; however, the complications associated with advanced stages of the disease, along with the onset of graft dysfunction after transplantation, are the major processes that contribute to maintaining a high mortality rate in these patients. It is therefore imperative to identify new therapeutic targets and tools to stop or reverse the progression of the fibroproliferative phenomena in liver disease.