Understanding functional consequences of hepatic macrophage heterogeneity in NAFLD

Obesity is a complex metabolic disorder causing, amongst others, liver diseases ranging from steatosis to cirrhosis, together termed non-alcoholic fatty liver disease (NAFLD). Despite the high incidence rate of NAFLD, there is currently no treatment available and as such the mechanisms involved require further investigation. Hepatic Macrophages (MFs) are suggested to play important roles in NAFLD through their activation, however in recent years it has become clear that there are many distinct subsets of MFs in the inflamed liver and thus it remains unclear which subsets play which roles in NAFLD.

Having recently demonstrated that KCs can be distinguished from other non-resident recruited hepatic MFs by Clec4F and Tim4 expression, we aimed to investigated the different contributions of KCs and other hepatic MFs during different stages of NALFD progression. To this end, male mice were fed a western diet (WD) to mimic the different stages of the human disease and the MF populations were assessed over time.

Using multi-parameter flow cytometry and single cell RNA sequencing, mice fed the WD for 24 weeks were found to harbor a significantly reduced population of Clec4F+ KCs compared with controls. In addition, we also observed the recruitment of a significant number of monocytes and Clec4F- MFs. Tim4 expression coupled with shielded BM chimeras revealed that the monocytes were contributing to both the Clec4F- and Clec4F+ MFs. Intriguingly, contrary to the current hypothesis, KCs were not found to be activated in the WD-fed mice. However, fitting with their transcriptome, which is enriched for lipid metabolism genes, lipidomics analysis of the MF populations found KCs to be enriched for many lipid species compared with the Clec4F- MFs. Thus, we are currently investigating how this contributes to NAFLD pathogenesis.

Keywords : NAFLD,macrophages
Authors :
References : , , ,

Authors

Anneleen Remmerie 1, Liesbet Martens 1, Sofie De Prijck 1, Bavo Vanneste 1, Angela Castoldi 2, Edward Pearce 2, Charlotte Scott 1,

1. IRC, VIB-UGent, Gent, BELGIUM
2. Max Planck Institute of Immunobiology and Epigenetics, Freiburg, GERMANY