AFTER SHORT-TERM EXPOSURE OF MICE TO A HIGH FAT DIET, F4/80 POSITIVE MACROPHAGES ARE PREFERENTIALLY FOUND IN THE VICINITY OF LIPID-LOADED HEPATOCYTES

N. Lanthier, N. Van Hul, J. Abarca-Quinones, V. Lebrun, C. Sempoux, Y. Horsmans, I.A. Leclercq

Laboratory of Gastroenterology, Faculty of Medicine, Université Catholique de Louvain (UCL), Brussels, Belgium.

Department of Pathology, Faculty of Medicine, Université Catholique de Louvain (UCL), Brussels, Belgium.

Background: Inflammation and macrophage infiltration of the adipose tissue have been causally associated with the development of insulin resistance.

Hypothesis and aim: Here we formulate the hypothesis that Kupffer cells, the hepatic resident macrophages, are implicated in the pathogenesis of hepatic insulin resistance. The aim of the study is to analyse the Kupffer cell population in a model of hepatic fat accumulation induced by high fat feeding.

Materials and methods: Male C57BL6 mice were fed a high fat diet (containing 60% of fat) or a standard chow for 3 days, a model known to induce moderate hepatic steatosis and hepatic insulin resistance (Samuel VT, J Biol Chem. 2004, 279: 32345). Hepatic steatosis was evaluated on liver histology and by quantification of hepatic lipid content. F4/80, a cell surface glycoprotein expressed on a wide range of mature tissue macrophages including Kupffer cells, was evaluated by immunohistochemistry.

Results: In control mice, hepatocytes appear normal and F4/80 positive cells are scattered in the entire lobule. Short term high fat feeding causes a ~3 fold increase in liver lipid content. Fat accumulates as lipid vacuoles predominantly in the hepatocytes of the intermediate lobular zone (zone 2). Contrasting with the observation in controls, after high fat feeding, the majority of F4/80 positive cells are found in the intermediate zone, where the lipid vacuoles also developed, while the centrilobular zone is almost completely depleted of F4/80 positive cells.

Conclusion: In steatosis induced by a high fat diet, fat-loaded hepatocytes co-localise with F4/80 expressing Kupffer cells. This suggests that macrophages migrate and/or are specifically activated in the area of steatosis. The links between Kupffer cells, steatosis and development of hepatic insulin resistance are under investigation.