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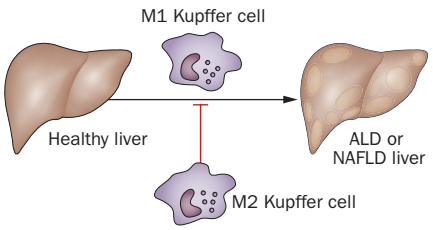
LIVER DISEASE

Kupffer cells regulate the progression of ALD and NAFLD

The balance of classic proinflammatory M1 Kupffer cells and alternatively activated anti-inflammatory M2 Kupffer cells is important for the tight regulation of the development of liver injury in alcoholic liver disease (ALD) and NAFLD, new findings published in *Hepatology* have revealed.

"Activation of Kupffer cells to secrete proinflammatory mediators is a key event in the initiation of ALD and NAFLD, and limiting their polarization into an M1 phenotype is considered to be an attractive strategy in preventing progression of both of these diseases," explains Sophie Lotersztajn, the corresponding author of this study.



The researchers found that patients who are morbidly obese or those who are heavy alcohol drinkers, but who have little hepatic injury and steatosis, have higher expression levels of M2 Kupffer cell genes than patients who have more extensive liver lesions (including hepatocyte steatosis and fibrogenesis).

Data from mouse models of ALD and NAFLD supported these findings from patients. Mice that are resistant to the effects of alcohol or a high-fat diet had a high M2:M1 Kupffer cell ratio. By contrast, mice that developed liver lesions had a high M1:M2 Kupffer cell ratio.

Lotersztajn and colleagues then went on to demonstrate that M2 Kupffer cells isolated from these resistant mice promoted apoptosis of M1 Kupffer cells *in vitro*. Further cell-culture experiments revealed the underlying details of this mechanism: M2 Kupffer cells release IL-10, which promotes selective M1 Kupffer cell death by apoptosis via paracrine activation of arginase. Indeed, anti-IL-10 antibodies blocked the proapoptoic effects of M2 Kupffer cells *in vitro* and neutralization of IL-10 impaired apoptosis of M1 Kupffer cells in alcohol-exposed mice.

"Our main finding is that by combining human data, animal models and cell-culture experiments, we have identified a novel mechanism to neutralize M1 Kupffer cell emergence, which relies on selective induction of their apoptosis by M2 Kupffer cells," says Lotersztajn.

"Our results suggest that pharmacological interventions targeting M2 Kupffer cell polarization during early stages of ALD and NAFLD may represent an attractive strategy for the limitation of inflammation and hepatocyte injury," concludes Lotersztajn.

Katherine Smith

Original article Wan, J. *et al.* M2 Kupffer cells promote M1 Kupffer cell apoptosis: A protective mechanism against alcoholic and non-alcoholic fatty liver disease. *Hepatology* doi:10.1002/hep.26607.