Cell-based strategies against fatty liver

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Introduction: According to the World Population Review (worldpopulationreview.com/), obesity rates increase continuously mounting to one third of the global population. Diseases like diabetes type 2, ischemic stroke and cardiovascular complications are often associated with obesity, thus making it the leading cause of worldwide deaths (who.int/). Non-alcoholic steatohepatitis (NASH) is a prevalent organ manifestation of obesity and the metabolic syndrome, which may progress to fibrosis and cirrhosis, the latter a prominent driver of hepatocellular carcinoma. The only curative option for the treatment of liver cancer is liver transplantation, yet not offered to each patient in need because of donor organ scarcity. Mesenchymal stromal cells (MSC) may represent a way out because of their anti-inflammatory and pro-regenerative features.

Methods: NASH was induced in immunodeficient mice by feeding artificial diets. Human bone marrow-derived MSC were differentiated into the hepatocytic lineage and transplanted into livers via splenic delivery. Biochemical and histological analyses were performed to detect MSC effects on the molecular and tissue levels. The mechanisms of stromal cell action were analyzed in co-cultures of primary mouse hepatocytes and human MSC.

Results: MSC treatment of mouse fatty livers decreased hepatic triglycerides and ameliorated hepatic inflammation and fibrosis. Albeit still deteriorated, liver tissue integrity was improved by the MSC featuring restoration of hepatocyte polarity and zonal organization of the parenchyma. When grown in steatosis inducing cell culture medium, primary mouse hepatocytes accumulated triglycerides, which was blunted in co-culture with human bone marrow-derived MSC. This was not due to paracrine cell-cell communication between hepatocytes and MSC, but rather mediated by the delivery of human mitochondria to the mouse hepatocytes via tunneling nanotubes. Going back to the in vivo situation in fatty mouse livers after MSC treatment, we detected human mitochondria in mouse hepatocytes indicating donation from transplanted MSC.

Conclusion: MSC ameliorate NASH and improve tissue homeostasis in fatty mouse livers by donating human mitochondria to mouse hepatocytes, thereby providing oxidative capacity for lipid breakdown and mitigation of lipid overload and perturbation of tissue homeostasis.