Identification of factors secreted from the fatty liver: impact on metabolic function in other tissues

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Non-alcoholic fatty liver disease (NAFLD) is a common health problem that is associated with obesity. Liver steatosis is an early manifestation in the aetiology of NAFLD, which precedes the development of other obesity-related metabolic complications such as type 2 diabetes. We used an “omics” approach to test the hypothesis that protein or lipid signals originating from the steatotic hepatocyte may induce “cross-talk” with other tissues to modulate metabolic phenotypes.

Male C57Bl/6J mice were fed a low-fat (LFD) or high-fat diet (HFD) for six weeks to induce simple steatosis, without inflammation. Hepatocytes were isolated, cultured for 48 h and the secreted products were collected in the culture medium for analysis. The isolated HFD hepatocytes contained 9-fold more intracellular triacylglycerol than LFD hepatocytes, with no indication of inflammation or damage. Isobaric tags for relative and absolute quantification (iTRAQ)-mass spectrometry analysis of the secreted media detected 140 proteins, with prominent changes between LFD and HFD. Enrichment analysis revealed marked upregulation for inflammation processes and atherosclerosis in the secretome of HFD hepatocytes. Quantitative analysis of the hepatocyte lipid secretome by electrospray ionisation-tandem mass spectrometry detected 16 lipid classes and >300 lipid species. Triglyceride, phosphatidylethanolamine and ceramide were increased in the HFD medium. Incubating GLUT4myc-L6 myotubes with conditioned medium from HFD hepatocytes altered fatty acid metabolism, caused insulin resistance but did not upregulate inflammatory pathways.

In conclusion, this proteomic evaluation revealed that hepatic steatosis, in the absence of inflammation, invoked modest changes in the protein and lipid secretory profile. These changes in the secretion profile were, however, sufficient to cause insulin resistance in skeletal muscle and thereby stimulate further research examining the mechanistic causes of steatosis-induced insulin resistance in muscle.