Proteomic Profiling to Identify Key Players in Fatty Liver Disease

Natalie Krahmer

Institute of Diabetes and Obesity, Helmholtz Center Munich, Germany

Introduction:
Despite the increase in the worldwide prevalence of non-alcoholic fatty liver disease (NAFLD), the cellular processes underlying disease development and progression to non-alcoholic steatohepatitis (NASH) remain poorly characterized. Understanding how hepatocytes change their organelle organization during the development of diet-induced hepatic steatosis and how this is controlled by signaling pathways is prerequisite for the identification of novel pharmacological targets.

Methods:
We have developed a mass spectrometric workflow for protein and phosphopeptide correlation profiling (PCP) to monitor levels, cellular distributions and phosphorylation states of proteins during the development of metabolic diseases in a systematic manner. To investigate the cellular processes during extensive lipid accumulation in diet-induced steatosis and to gain insights into the cellular processes during NASH progression, we used this workflow to map the organelle proteomes and phosphoproteomes in the liver of different murine models for diet-induced fatty liver disease.

Results:
PCP in the liver of mice fed a high-fat-high-sucrose diet revealed insights into the lipid induced organellar reorganization including the rearrangement of the secretory apparatus and changes of contacts between organelles orchestrating lipid metabolism. Organelle mapping in the liver of mice fed a Gubra Amylin NASH diet gave a time-resolved picture of the activation of inflammation pathways, autophagy, cell death and extracellular matrix remodeling steps during NASH progression.

Conclusion:
In summary, our systematic in vivo analyses uncover unknown cellular processes and pathways that remodel during disease progression.