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Elucidating the role of lipid metabolism in metabolic diseases and cancer with special emphasis on lipid droplets

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Purpose: Lipids promote the development of diseases such as obesity, diabetes and liver steatosis (NAFLD) as well as cancer by so called lipotoxic effects. Fundamentally, lipid metabolism is highly compartmentalized within the cell and previous data demonstrated that intracellular organelles adapt their compositions and interactions in response to metabolic challenges and pathologic conditions. In this regard, a central position is occupied by lipid droplets (LDs), which are responsible for interception and storage of excessive and potentially toxic lipids. In human cancer, aberrant lipid metabolism and reactivation of lipid biosynthesis with subsequent intracellular accumulation of LDs is frequently observed, while basic interconnections are still unclear. Hence, this project aims to analyze changes in the proteome of lipid metabolism with its global cellular effects in the context of metabolic diseases and colon cancer. Based on the crucial role of the mono-unsaturated fatty acid (MUFA)-synthesizing enzyme stearoyl-CoA desaturase 1 (SCD1) in cancer, we focus on the analysis of alterations in lipid metabolism in SCD1-deficient cells, including its effects on LD formation, synthesis and processing of lipids and the impact of altered lipid composition on cell membrane viscosity.

Methods: To investigate alterations of expression levels and distributions of cellular proteome, a mass spectrometric workflow for protein correlation profiling (PCP) was established on lipid treated rat liver cells. Further, confocal microscopy, GC-MS/MS lipidome analysis and determination of cell membrane viscosity by two-photon fluorescence lifetime imaging (FLIM) were employed on SCD1-deficient colon cancer cells.

Results: Preliminary PCP analysis in liver cells revealed a localization shift of several proteins to LDs, including ER-specific enzymes for lipid metabolism, which was more pronounced after oleate treatment compared to palmitate or cholesterol. Confocal imaging confirmed the formation of LDs in hepatocytes, as well as in colon cancer cells. Lipidome analysis confirmed an overall reduction of phospholipids in SCD1-deficient cancer cells under serum deprivation, with a higher proportion of saturated fatty acids, and reduced membrane viscosity.

Conclusion: Our results indicate that specific lipids seem to diversely impact compartmentalization and organelle arrangement, suggesting particular lipid processing pathways. SCD1-deficient cancer cells that lack the ability to further process and detoxify saturated fatty acids show reduced proliferation, survival, and altered lipid composition. As consequence, membrane viscosity of SCD1-deficient cells seems to be reduced, in accordance with reduced cell migration. Ongoing proteome analysis will provide further insights in subcellular changes to further assemble the puzzle of altered lipid metabolism in cancer cells.