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MALDI-TOF lipidomic imaging of the oviduct after short and long-term exposure to an obesogenic diet in outbred mice.

Kerlijne Moorkens[1], Jo LMR Leroy[1], Jusal Quanico[2], Geert Baggerman[2,3], Waleed FA Marei[1]

[1]University of Antwerp, Belgium; [2]Centre for Proteomics, University of Antwerp, Wilrijk, Belgium; [3]Unit Health, Vito, Mol, Belgium; kerlijne.moorkens@universiteitantwerpen.be

Metabolic disorders associated with the consumption of an obesogenic (high fat/high sugar (HFHS)) diet are strongly linked with reduced fertility in women. Direct detrimental effects of such metabolic alterations on oocyte quality have been documented, however the impact on the oviductal microenvironment where fertilization and early embryo development take place, is less characterised. Furthermore, when such changes appear after the start of a HFHS diet remains unclear. The aim of this study was to test whether the introduction of a HFHS diet in mice can lead to changes in lipid composition in the oviductal epithelial cells (OECs) and when these changes start to appear. Seven week old female outbred Swiss mice were fed with either control (CTRL; 10% fat) or HFHS (60% fat in diet, 20% fructose in drinking water) diet. Mice (n=3 per treatment per time point) were sacrificed and oviducts were collected at 3 days (3d), 1 week (1w), 4w, 8w, 12w and 16w after the start of dietary treatment. MALDI mass spectrometry imaging was performed to image lipids on sections of the oviduct (ampulla) using a Rapiflex MALDI TOF mass spectrometer (Bruker Daltonics, Bremen, Germany) with norharmane as matrix. Spectra at mass range of m/z 400-2000 were obtained in positive and negative reflectron modes (10µm resolution). Data sets were analyzed with SCiLS Lab 3D, version 2016b. Spatial segmentation of ion spectra showed differences in spatial distribution of lipid species between the oviductal epithelium and stroma. For further analysis we focused on the OEC layer, which was identified by co-registering the MS images with the optical scans of the H&E staining of the same section. Spectra from the OEC cluster were subjected to Receiver Operating Characteristic (ROC) analysis to calculate discriminative m/z values and determine differentially regulated lipids (DRLs) in the HFHS versus CTRL mice at each time point. Assignments were done from MS/MS spectra. ROC analysis revealed a different lipid profile in HFHS oviducts compared to the CTRL, which was shown by the detection of 303 and 247 discriminative masses (DMs) between HFHS and CTRL mice in negative and positive mode respectively, when including all time points. The total number of detected DMs in both reflectron modes increased over different time points, in negative mode this is from 10 DMs at 3d, 40 at 1w, 44 at 4 and 8w, to 55 at 12w and finally 110 DMs between CTRL and HFHS mice at 16w. The DRLs (across all time points) were focused in specific mass ranges, namely around 700-900 m/z in both modes which indicates differential abundance in phospholipids (phosphatidyl(P)-choline, P-serine, P-ethanolamine, P-inositol) and sphingomyelin. A few DRLs were detected around 1500 m/z suggesting a differential abundance of the mitochondrial lipid cardiolipin. In conclusion, exposure to an obesogenic diet results in changes in lipid profile in the oviductal epithelium even after a short exposure time of only 3 days. These changes progressively increase after longer exposure. Further analysis is ongoing to functionally annotate the detected DRLs and study their potential pathophysiological impact on the oviductal microenvironment and ultimately on the growing embryo.

Keywords: obesogenic diet, oviduct, MALDI imaging