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Undernourishment *in utero* not only regulates morphology of hepatocyte but also primes dynamic changes in lipid composition

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【目的】 Undernourishment *in utero* primes hepatic steatosis under obesogenic diet and alleviation of Endoplasmic Reticulum (ER) stress improved the condition (ScieReports;16867,2015). How maternal nutrition play role in pathophysiology is still unknown. Therefore, we aimed to study the morphological changes in the hepatocytes and performed Liquid Chromatography Mass Spectrometry (LCMS) to identify defect in metabolic pathways. 【方法】 Sampling of blood and liver of CN57Bl mice (n=16) aged 22 weeks, pups (group A; n=8) obtained from dams fed *ad libitum* (normal nutrition (NN)) and pups (group B; n=8) from dams with 40% caloric restriction (undernutrition (UN)) was done. From 17 weeks onward we have subdivided both group to vehicle (Veh;n=4) and Tauroursodeoxycholic acid (TUDCA, a chemical chaperon of ER stress;n=4) administrated group under High Fat Diet (HFD). Liver weight, liver weight-bodyweight ratio, Triglyceride content, total Triglyceride were measured. Using Oil Red O stain and WinRoof software we have calculated the mean size of the hepatocyte, percentage of the area of lipid deposition. LCMS was done by Q Exactive Benchtop Orbitrap LC-MS/MS System. 【結果】 Liver weight, liver weight-bodyweight ratio, Triglyceride content and total Triglyceride amount (P<0.0001) was significantly elevated in UN compared to NN pups. Moreover UN *in utero* induced enlargement of hepatocyte size (group A [NN] vs group B [UN]; mean size=1745±187 (SD) μm^2 , 2250±147 μm^2 , p<0.01,

respectively) and increase lipid deposition by 63.7% (group A [NN] vs group B [UN] $35.4 \pm 12.8\%$, $46.4 \pm 7.8\%$, $p < 0.01$). Administration of TUDCA improved the condition by reduction of cell size by 19.33% ($P > 0.05$) and lipid deposition by 82.2% ($P < 0.001$) (group B [UN-Veh] vs group B [UN-TUDCA]). LCMS analysis showed that 9 lipid metabolites were increased in UN *in utero*; 7 of them were significantly reduced by TUDCA treatment; however, 2 of them further increased with all the improvement of total triglyceride deposit. UN *in utero* also caused reduction of 14 lipid metabolites all of which were increased by TUDCA administration. We speculate that dynamic changes of lipid composition were induced by UN *in utero* or by alleviation of ER stress.

【結論】 Undernourishment *in utero* significantly enlarged hepatocyte and aggravated intercellular lipid deposition in offspring with dynamic changes of lipid composition.