

Tauroursodeoxycholic acid (TUDCA)の投与は、肝臓におけるCIDEA ならびにCIDEA遺伝子周囲のクロマチン構造の変容を介して、胎生期低栄養に起因する肝脂肪変性を改善する

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Treatment with Tauroursodeoxycholic Acid Improved Developmentally Programmed Hepatic Steatosis by Altering Chromatin Structures Around CIDEA And CIDEA Genes.

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【背景・目的】

Undernourishment *in utero* primes hepatic steatosis under obesogenic diet and alleviation of Endoplasmic Reticulum (ER) stress by Tauroursodeoxycholic acid (TUDCA) improved the condition. To clarify the cellular and molecular mechanism behind we aimed to profile genetic expression by microarray analysis and association with histone modification regulating gene expression by chromatin immunoprecipitation (ChIP) assay.

【対象・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 on high fat diet (HFD). RNA extracted from their liver tissues to perform Microarray Analysis using Affymetrix Gene Chip® WT PLUS Reagent Kit and Transcriptome analysis software for statistical analysis. Hepatic tissue was also used to extract DNA fragments for Chromatin immune precipitation (ChIP) assay.

【結果】

UN *in utero* led to upregulation of 38 genes (NN vs UN; Fold change ≥ 2 or ≤ -2 , $p < 0.05$) compared to NN. Among them Cell death inducing DFF A/C (CIDEA/C) genes reported to play a key role to develop hepatic steatosis were highly expressed (Fold change 11.5 & 5.6, $p < 0.001$, respectively) in UN *in utero* confirmed by quantitative PCR. ER-stress alleviation, by TUDCA administration reduced expression of CIDEA/C concomitant with improvement of hepatic steatosis. ChIP assay revealed divergent changes of modifications by

methylation at H3K4, H3K27, H3K36-dimethylation and acetylation at H3K9 proportionate with CIDEA/C gene expression. Treatment with TUDCA reversed level of chromatin modifications to improve developmentally programmed hepatic steatosis.

【結論】

We propose ER stress inhibitor TUDCA can cure developmentally programmed hepatic steatosis by remodeling chromatin structure to regulate genetic expression of CIDEA/C responsible for deterioration of UN *in utero* induced hepatic steatosis.