

Plasticity of histone modification around Cidea and Cidec genes with secondary bile in the amelioration of developmentally-programmed hepatic steatosis

著者	Ferdous Urmi Jeenat, Kohmura-Kobayashi Yukiko, Muramatsu-Kato Keiko, Hariya Natsuyo, Jain Divyanu, Tamura Naoaki, Uchida Toshiyuki, Suzuki Kazunao, Ogawa Yoshihiro, Shiraki Nobuaki, Mochizuki Kazuki, Kubota Takeo, Kanayama Naohiro, Itoh Hiroaki
journal or publication title	DOHaD研究
volume	8
number	3
page range	15-16
year	2019
URL	http://hdl.handle.net/10271/00003607

優秀演題候補セッション

Plasticity of histone modification around Cidea and Cidec genes with secondary bile in the amelioration of developmentally-programmed hepatic steatosis

Urmi Jeenat Ferdous¹, Yukiko Kohmura-Kobayashi¹, Keiko Muramatsu-Kato¹, Natsuyo Hariya², Divyanu Jain¹, Naoaki Tamura¹, Toshiyuki Uchida¹, Kazunao Suzuki¹, Yoshihiro Ogawa^{3,4}, Nobuaki Shiraki⁵, Kazuki Mochizuki⁶, Takeo Kubota⁷, Naohiro Kanayama¹, Hiroaki Itoh¹.

¹Department of Obstetrics and Gynecology, Hamamatsu University School of Medicine, Hamamatsu, Japan; ²Department of Nutrition, Faculty of Health and Nutrition, Sciences, Yamanashi Gakuin University, Yamanashi, Japan; ³Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; ⁴Department of Molecular and Cellular Metabolism, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan; ⁵Department of Life Science and Technology, School of Life Science and Technology, Tokyo Institute of Technology, Yokohama, Japan; ⁶Laboratory of Food and Nutritional Sciences, Department of Local Produce and Food Sciences, Faculty of Life and Environmental Sciences, University of Yamanashi, Yamanashi, Japan; ⁷Faculty of Child Studies, Seitoku University, Matsudo, Japan.

Background: Evidence is increasing to support the relationship between nutritional imbalances in the early developmental period and a predisposition for Non-alcoholic fatty liver disease (NAFLD) in later life. We recently reported that a treatment with tauroursodeoxycholic acid (TUDCA), a secondary bile acid, improved developmentally-deteriorated hepatic steatosis in an undernourishment (UN, 40% caloric restriction) *in utero* mouse model after a postnatal high-fat diet (HFD; containing 60% lipids; formula number D12492, Research Diets Inc.).

Aim: To investigate epigenetic mechanism underlies developmental programming as well as marked recovery by TUDCA treatment in hepatic steatosis in a mice model.

Methods and Results: We focused on two genes, Cell Death-Inducing DNA Fragmentation Factor-Like Effectors A (Cidea) and C (Cidec). We performed a microarray analysis and selected 9 genes of interest (GOI), because longitudinal comparison (before and after HFD) showed UN changed their gene expression specifically in UN offspring and cross-sectional comparison after HFD revealed that TUDCA treatment completely recovered the changes of their gene expression. Gene enrichment analysis using DAVID Bioinformatics Resources 6.8 showed that Cidea and Cidec are most involved in function of lipid droplet and lipid particle pathway among 9 GOI. Indeed, they are enhancers of lipid droplet (LD) sizes in hepatocytes and showed the greatest up-regulation in expression by UN among 9 GOI that were completely recovered by TUDCA, concomitant with parallel changes in LD sizes. Then, we investigated significant differentially methylated sites using overlapping peaks by DNA MBD sequencing by next-generation sequencer. Neither maternal caloric restriction (UN) nor the TUDCA treatment had any effect on DNA methylation around entire 24kb Cidea genes and entire 11kb Cidec genes. We further investigated histone modifications around Cidea and Cidec genes by ChIP assay, concerning mono- and di- methylation of H3K9, H3K27, and H3K36, di-methylation of H3K4, tri-methylation of H3K9, H3K27 and H4K20, and acetylation of H3K9 and H4. TUDCA remodeled developmentally-induced histone modifications (di-methylation of H3K4, H3K27, or H3K36) around the Cidea and Cidec genes in UN pups only. Changes of these histone modifications may contribute to the markedly down-regulated expression of Cidea and Cidec genes in UN pups, which was observed in alleviation of hepatic fat deposition even under HFD.

Conclusion: Using the present experimental animal model, we demonstrated the plasticity in the

developmentally programmed histone modifications around the specific genes of Cidea and Cidec, in the process of the amelioration of hepatic steatosis by TUDCA treatment. The present study has provided the unexplored therapeutic target of the histone modification for the future of precision medicine for developmentally-programmed hepatic steatosis.