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研究成果報告書

研究課題名
「エピゲノム記憶」の概念の確立～生活習慣病の先制医療の実現に向けて～

Establishment of the concept of “epigenome memory”
Towards the realization of preemptive medicine for lifestyle-related diseases

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Abstract

Epidemiological and experimental evidence has suggested that nutritional environment in early life is associated with metabolic diseases in later life, giving rise to the concept of Developmental Origins of Health and Disease (DOHaD) hypothesis (**Science** 305: 1733-1736, 2004). We previously demonstrated that expression of GPAT1 (*Gpam*), a rate-limiting enzyme of *de novo* lipogenesis, is enhanced in the mouse liver during weaning in association with DNA demethylation-dependent recruitment of the lipogenic transcription factor SREBP-1c and ligand-activated PPARα-dependent DNA demethylation regulates the fatty acid β-oxidation enzymes in the postnatal mouse liver (**Diabetes** 61: 2442-2450, 2012; **Diabetes** 64: 775-784, 2015). Epigenetic modifications such as DNA methylation may be involved in many biological processes, however, the causative effect is unclear.

In this study, we have demonstrated that the fibroblast growth factor-21 gene (*Fgf21*) is subject to PPARα-dependent DNA demethylation in the liver during the postnatal period. Reduction in DNA methylation of *Fgf21* can be enhanced via pharmacologic activation of PPARα during the suckling period. We have also revealed that the DNA methylation status of *Fgf21*, once established in early life, is relatively stable and persists into adulthood. Reduced DNA methylation is associated with enhanced induction of hepatic FGF21 expression after PPARα activation, which may partly explain the attenuation of diet-induced obesity in adulthood. We propose that DNA methylation of *Fgf21* represents a form of epigenetic memory that persists into adulthood, and it may have a role in the developmental programming of obesity (**Nat. Commun.** 9: e636, 2018). However, there is no direct evidence for the effect of site-specific DNA methylation on gene expression. In this study, we employ the dCas9-SunTag and single-chain variable fragment (scFv)-TET1 catalytic domain (TET1CD) system to induce targeted DNA demethylation of the *Fgf21* promoter both *in vitro* and *in vivo*. We have succeeded in targeted DNA demethylation of the *Fgf 21* promoter both in Hepa1-6 cells and in the liver from PPARα-deficient mice, with increased gene expression response to synthetic PPARα ligand administration and fasting, respectively. This study provides direct evidence that the DNA methylation status of a particular gene may determine the magnitude of the gene expression response to environmental cues (**Sci. Rep.** 10: e5181, 2020).

We have also examined the epigenetic memory in other organs outside the liver. We have focused upon DNA methylation of brain-derived neurotrophic factor gene (*Bdnf*) exon IV and its expression and their effect on learning capacity in the offspring derived from dams with thiamazole (MMI)-induced mild maternal hypothyroxinemia (M offspring) and control offspring (C offspring). We have found that M offspring show an impaired learning capacity in the behavior test. Hippocampal *Bdnf* exon IV expression at the basal level is comparable between M and C offspring. However, it is significantly weaker in M offspring than in C offspring after the behavior tests. Persistent DNA hypermethylation is also found in the *Bdnf* exon IV promoter in the hippocampus of M offspring relative to C offspring, which may cause the attenuation of *Bdnf* exon IV expression in M offspring. This study provides evidence that mild maternal hypothyroxinemia induces persistent DNA hypermethylation in *Bdnf* exon IV in offspring as epigenetic memory, which may result in long-term cognitive disorders (**Thyroid** 28: 395-406, 2018).

Collectively, this study has established DNA methylation as a mediator of epigenetic memory, thereby providing the evidence to formulate the guidelines for the nutritional management of women expected to be pregnant and those who are during pregnancy or lactation.