【Grant-in-Aid for Scientific Research (S)】

A Study on Elucidating Obesity and Lifestyle Diseases through the Epigenome-RNA Modification Axis.

Principal Investigator	Tohoku University, Graduate School of Medicine, Professor SAKAI Juro　　Researcher Number : 80323020
Project Information	Project Number : 24H12345　　Project Period (FY) : 2024-2028 Keywords : Obesity, adipocytes, epigenome, RNA modifications, inter-organ networks

Purpose and Background of the Research

●Outline of the Research

In recent years, post-transcriptional RNA modifications (**epitranscriptome**) and acquired genome modifications (**epigenome**) have been linked to lifestyle diseases like type 2 diabetes associated with obesity. The epigenome regulates gene expression, forming cellular memory and contributing to disease onset. RNA modifications also play a role, affecting gene expression through stability, localization, translation efficiency, and splicing. Yet, it's unclear if these systems coordinate gene expression.

This study aims to uncover the epigenome-RNA modification axis and apply findings to innovative therapies for lifestyle diseases.

● How this study was conceived:

Adipose tissue, crucial for metabolic control, comprises white adipose cells for nutrient storage and brown/beige adipose cells for heat generation. These thermogenic cells are key targets for obesity and lifestyle disease treatment. Brown adipose cells, naturally thermogenic, rapidly activate in cold, expressing genes for adaptation. Prolonged cold exposure induces beige cells in subcutaneous fat, termed “beiging,” yet mysteries remain (Fig. 1). Our prior research revealed one beiging mechanism involving histone demethylase (HDM) enzyme activity, an epigenetic modifier (Fig. 2).

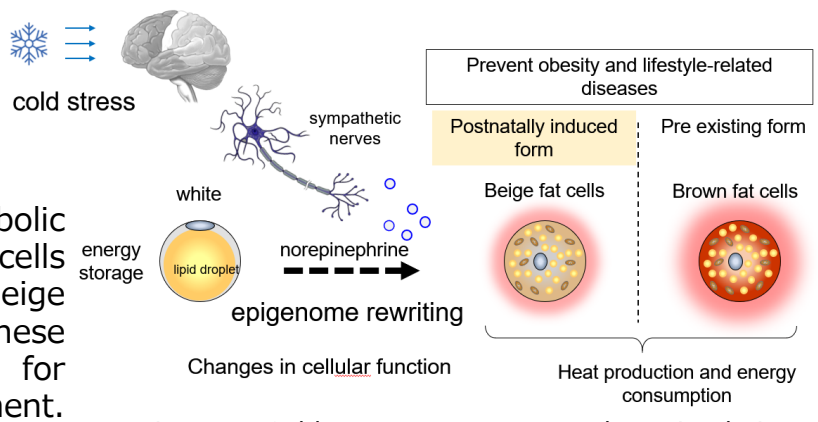

Figure 1. Cold exposure promotes clustering beige adipose cells in subcutaneous white adipose tissue

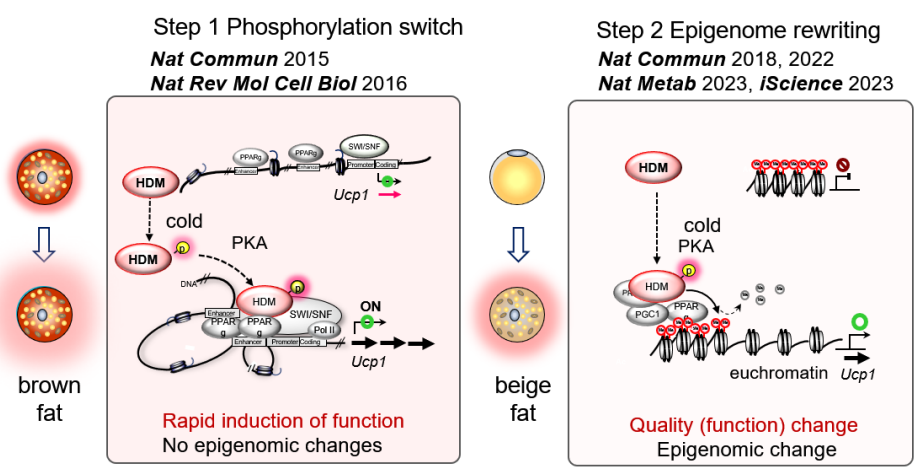

Figure 2. Regulation of adipocyte activity and function by phosphorylation switch and epigenomic rewriting

In conventional HDM studies, analysis focused on methylation changes, neglecting other mechanisms and timeframes. However, specific HDMs act differently: not through demethylation initially, but via protein interactions and chromatin changes (in brown adipose). In chronic cold, they switch to demethylation-based transcriptional control, "beiging" white adipose tissue.

● **Epigenome-Epitranscriptome Axis:**

In recent years, it has been reported that methylation of RNA during transcription is recognized by reader proteins, recruiting epigenome modification enzymes to chromatin. This represents a new concept where RNA modification controls the epigenome. However, the impact of the Epigenome-RNA modification axis on the onset of lifestyle diseases remains entirely unknown. Therefore, this study aims to elucidate the mechanism by which post-transcriptional RNA modifications control gene expression through the epigenome and to clarify the relationship between health and disease (Figs. 3 and 4).

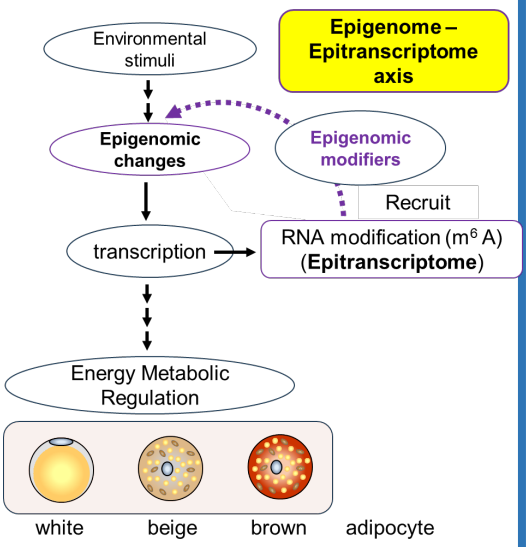

Figure 3. Epigenome-epitranscriptome axis and adipocyte differentiation

Expected Research Achievements

RNA Modifications in Adipocyte Differentiation: Nanopore sequencing and deep learning analyze Post-transcriptional RNA modifications, identifying m^{6}A positions crucial for beiging. It also identifies key modifications, their relation to splicing, and RNA-binding proteins for functional analysis. Modomics analysis conducts mass spectrometry-based analysis of RNA modifications to explore stimuli-induced modifications beyond m6A and their association with m^{6}A (Fig. 3).

<u>Epigenome-RNA Modification Axis</u>

in Adipocyte Metabolic Function: Proteomics analyzes interactions between epigenome modification enzymes and RNA modification reader proteins to understand their relationship. It reveals how RNA modification forms complexes with epigenome enzymes, controlling nearby epigenomes and its link to obesity.

in the Onset of Obesity: Analyzing RNA localization in obese mice due to epigenetic abnormalities (Fig 5), elucidating intercellular communication via co-localization analysis, and identifying RNA modification-related candidate molecules through single-cell analysis(Figs. 4 and 5).

● **Social Relevance of the Progress**: The study aims to understand how environmental stimuli affect cellular quality and adipocyte quality at the molecular level, contributing to new treatments for obesity and lifestyle diseases.

Step3 **Epitranscriptome**

RNA modification regulates epigenome?

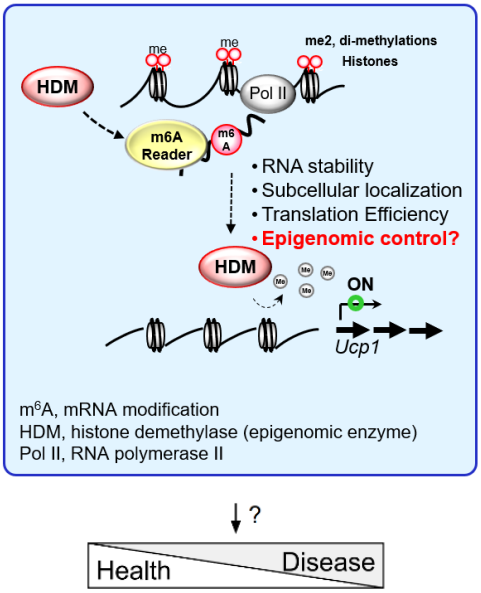

Figure 4. the regulation of cell states and properties via epigenomic-RNA modifications axis (Hypothesis model)

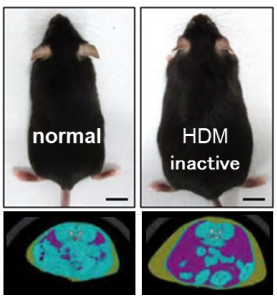

Figure 5. Obese mice caused by inactivation of HDM

Homepage Address, etc.	・http://www.metab.med.tohoku.ac.jp/ (Tohoku University Graduate School of Medicine, Molecular Physiology and Metabolism division) ・http://www.mm.rcast.u-tokyo.ac.jp/ (Metabolic Medicine division, Research Center for Advanced Science and Technology, The University of Tokyo)