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

Biological Sciences (Medicine, Dentistry, and Pharmacy)

Title of Project : Elucidation of lifestyle-related diseases development due to environmental factors and epigenetic memory

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Research Project Number : 16H06390 Researcher Number : 80323020
Research Area : Metabolic Medicine, Molecular biology
Keyword : metabolic syndrome, epigenome, signal transduction

【Purpose and Background of the Research】

Metabolic syndrome associated with obesity and its related metabolic disorders such as type 2 diabetes and hyperlipidemia is a major challenge of the 21st century biomedical. Epigenomic gene regulation is an adaptive mechanism to the environment changes and is deeply involved in the lifestyle-related diseases. However, how the external cues determine the specific epigenomic changes were not clearly understood.

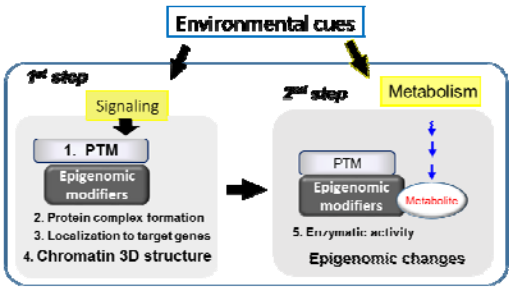
We recently revealed that post-translational modification (PTM) of histone modification enzyme and its consequent protein complex formation (1st step) is the key step to determine specify (Figure). In this study, we elucidate the mechanisms of 1st step further and elucidate mechanisms of consequent histone modification changes (2nd step). This 2nd step rewrites epigenome and ensures sustained and stable gene expressions and may relate to the predisposition to life style diseases under certain environment and nutrition conditions. Through these, we aim to develop innovative and effective treatment of lifestyle-related diseases.

【Research Methods】

Using metabolomics together with epigenomic analyses, we elucidate the mechanisms of "re-writing" of epigenome. We analyze metabolome and how nutrition and metabolites regulates histone modification enzymes and consequently rewrite epigenome. We will reveal further the JMJD1A-Ser265 phosphorylation protein complex to elucidate p-Ser265 mediated thermogenesis and browning of fat cells. We generates S265A knock-in mice and analyze the phenotype, especially the browning of fat cells. We further analyze AMPK mediated phosphorylation of JMJD1A, its phosphorylation sites, and its roles in energy metabolism. We evaluate the role of histone methyltransferase SETDB1 by elucidating the ubiquitination and the protein complex for E3 ubiquitin ligase and deubiquitinating enzymes. Thereby we reveal the role of SETDB1 in previously we identified H3K9/H3K4 bivalent chromatin.

【Expected Research Achievements and Scientific Significance】

To inhibit protein phosphatase complex for phospho-JMJD1A would be effective to maintain P-JMJD1A-PPARγ complex thereby activates thermogenic gene program. In addition, by elucidating 2 sequential model for epigenomic memory (Figure), drug design and discovery for histone modification enzymes would become more specific by aiming to the 1st step that determines the gene targets and protein complex. In addition, by elucidating the 2nd step, we could develop new approach to change predisposition to obesity and metabolic syndrome by reprograming epigenome.



Epigenetic memory

【Publications Relevant to the Project】

・Matsumura Y. et al. (2015) H3K4/H3K9me3 Bivalent Chromatin Domains Targeted by Lineage-specific DNA Methylation Pauses Adipocyte Differentiation. **Molecular Cell**, 60, 584-596,
・Abe Y, et al. (2015) JMJD1A is a signal-sensing scaffold that regulates acute chromatin dynamics via SWI/SNF association for thermogenesis. **Nature Commun**, 6, 7052

【Term of Project】 FY2016-2020

【Budget Allocation】 140,700 Thousand Yen

【Homepage Address and Other Contact Information】

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