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

Biological Sciences (Medicine, dentistry, and pharmacy Ⅱ)

Title of Project : The Epigenomic Analysis of Obesity and Insulin Resistance

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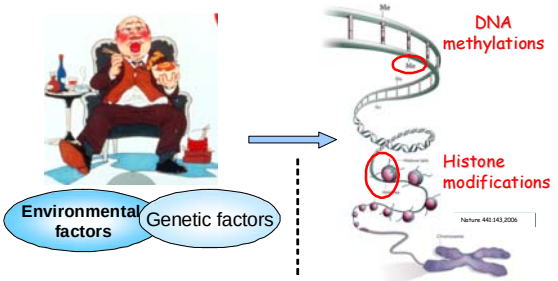
Research Area : Medicine, Dentistry, and Pharmacology

Keyword : Metabolic syndrome

【Purpose and Background of the Research】

Obesity, type 2 diabetes, atherosclerosis, which is often clustered and called metabolic syndrome, is a multifactorial disease in which inherited allelic variation, together with environmental variation, determines the predisposition of an individual to developing the disease. Epigenetics is caused by chromatin modifications such as DNA methylations and histone modifications not by changes in the underlying DNA sequences. Stimuli from cell surfaces are transmitted to the nucleus thereby induces chromatin modifications. Recent study has suggested that environmental stimuli are closely related to obesity and insulin resistance. We have recently demonstrated that H3K9 methylation is related to obesity. In this project we further investigate the epigenetic role in the development of obesity and glyco-lipid metabolism.

Gene-environmental interactions unique to each individual will determine the obese phenotype.



Alterations of environment leads to the epigenomic modifications

【Research Methods】

In 3T3-L1 adipocyte, using next generation giga sequencer and chromatin immuoprecipitaion technique (ChIP-seq), we determine the histone modifications, using mass spectrometer we determine proteome that interacts with histone modification enzymes. By combining these data together with transcriptome and three dimensional chromosome conformation capture technique, we analyze dynamic changes of histone modifications in adipogenesis. For JHDM2A and SETDB1, we generate adipocyte specific knock out mice and examine consequence of H3K9 modifications in the development of obesity and insulin resistance.

【Expected Research Achievements and Scientific Significance】

In this project we will reveal the followings: (1) the mechanism by which the H3K9 methylations regulate obesity and metabolic syndrome, as shown in JHDM2A-/- mice (Inagaki T et al 2009). We also reveal the target genes of JHDM2A in adipocyte. (2) histone methyltransferases and demethylases as well as histone code involved in adiposity and adipogenesis and their pathophysiological roles including their enzymatic activity, protein complexes to exert their effects, and their targets. These analyses will lead us to find out the histone code responsible for the obese phenotype. These findings will also provide us the new therapy and treatment for obesity and metabolic syndrome. Epigenetic analyses may take over the waist circumference for the diagnosis of predisposition to atherosclerosis and type 2 diabetes.

【Publications Relevant to the Project】

1. Wakabayashi K, Okamura M, Tsutsumi S, et al. (2009) The peroxisome proliferator-activated receptor γ /retinoid X receptor α heterodimer targets the histone modification enzyme PR-Set7/Setd8 gene and regulates adipogenesis through a positive feedback loop. **Mol Cell Biol**, 29, 3544-3555.
2. Inagaki T, Tachibana M, Magoori K, et al (2009) Obesity and Metabolic Syndrome in Histone Demethylase JHDM2a Deficient Mice. **Genes to Cells**, 14, 991-1001.
3. Okamura M, Kudo H, Wakabayashi K, et al (2009) COUP-TFII acts downstream of Wnt/β-catenin signal to silence PPARγ gene expression and repress adipogenesis. **Proc Natl Acad Sci U S A**. 10, 5819-5824.

【Term of Project】 FY2010-2014

【Budget Allocation】 159,900 Thousand Yen

【 Homepage Address and Other Contact Information】

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http://www.lsbm.org/staff/sakai.html