Press Release

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To all members of the press

Tohoku University

Epigenomic alterations facilitate the utilization of fat for energy and Mitigating obesity

-Expected to shed light on the development of obesity and diabetes.

【Key Points of the Presentation】

- In mice, proper regulation by the epigenome (#1) has been shown to result in proper energy expenditure and prevent obesity and diabetes.
- When the epigenome was deregulated, the energy-consuming mitochondria (#2) could not be increased and the energy consumption of the individual decreased.
- Even In human adipose tissue, we also found that obesity and blood cholesterol levels were higher when the enzyme responsible for epigenomic changes was low.

【Overview】

There are several types of adipose tissue. White adipose tissue (WAT) stores and supplies energy, whereas brown adipose tissue (BAT) is known as a heat-producing tissue with many mitochondria, which are important for energy burning. When an individual is exposed to cold, beige adipocytes (#3), similar to brown adipocytes, appear in the WAT, allowing adaptation to cold. Since brown and beige adipocytes burn fat, they are attracting attention as a therapeutic target for obesity and diabetes.

A research group led by Professor Juro Sakai of Tohoku University Graduate School of Medicine has shown that when the activity of an enzyme (#4) that rewrites the epigenome is deleted in mice, mitochondrial proliferation (#5) does not occur in WAT and beige adipocytes are not produced. Furthermore, these mice gained weight as they aged and developed metabolic abnormalities. We also found that the expression of epigenetic rewritable enzymes in subcutaneous fat in humans is negatively correlated with obesity and blood cholesterol levels. These results may lead to the application of new treatment and prevention methods for obesity and lifestyle-related diseases.

[Detailed description]

Research Background

The main adipose tissues known are white adipose tissue (WAT), which stores energy in the form of fat, and brown adipose tissue (BAT), which burns fat. When an individual is exposed to cold, brown adipocytes are activated in BAT. In WAT, on the other hand, heat-producing mitochondria-rich beige adipocytes are induced to adapt to cold. It has been previously reported that the histone demethylase JMJD1A (#6) contributes to heat-producing gene expression in these two cell types through two independent mechanisms. In a short time after cold stimulation, JMJD1A is phosphorylated in BAT and rapidly induces heat production by altering the chromatin higher-order structure (#7) of heat-producing genes in a demethylation activity-independent manner (Nat Commun 2015 6:7052, Nat Rev Mol Cell Biol 2016 17(8): 480-95). On the other hand, prolonged cold stimulation causes phosphorylated JMJD1A in WAT to rewrite the epigenome of heat-producing genes via histone demethylation, changing cell quality to heat-producing cells (beige induction) (Nat Commun 2018 9(1):1566, Nat Commun 2022 13(1): 5715). However, it is unclear whether JMJD1A phosphorylation (step 1) and histone demethylation (step 2) contribute to beigefication at the individual level, and furthermore, whether WAT or BAT energy expenditure is involved in balancing individual nutrition and maintaining healthy weight It was not clear whether WAT or BAT energy expenditure is involved in balancing individual nutrition and maintaining a healthy body weight.

Initiatives this time

A research group led by Professor Juro Sakai, Part-time Lecturer Yoshihiro Matsumura (currently Professor at Akita University School of Medicine), Assistant Professor Ryo Ito, Assistant Professor Shiyu Xie, Graduate Student Myagmar Tumenjargal of Molecular Metabolic Physiology at Tohoku University Graduate School of Medicine The graduate students and their research group generated point mutant mice (Jmjd1a-HY mice) lacking JMJD1A enzyme activity and analyzed the effects on systemic metabolism. Long-term cold stimulation caused mitochondrial hyperplasia, increased expression of heat-producing genes, and beige tissue changes in wild-type (WT) WAT mice, whereas these effects were markedly suppressed in HY mice. Similarly, HY mice showed severe obesity and metabolic abnormalities due to reduced mitochondrial density, heat-producing gene expression, and oxygen consumption in WAT even when reared at room temperature (23°C), a mildly low temperature (Figure 1). On the other hand, there were no differences between the two groups in the heat-producing capacity of BAT, individual temperature changes, histological findings of BAT, and heat-producing gene expression when subjected to short-term cold stimulation, and no involvement of JMJD1A histone demethylation capacity in BAT activation was observed (Figure 1). We also performed an epigenome-integration multiplex analysis and identified the enhancer region (#9) *of Pgc1a/b* (#8) , a key gene for mitochondrial hyperplasia, and further elucidated that

JMJD1A regulates *Pgc1a/b* expression in a cold-dependent manner via histone demethylation activity. Furthermore, we found that JMJD1A expression in human adipose tissue is inversely correlated with body mass index, blood triglyceride and cholesterol levels, indicating the contribution of JMJD1A in humans.

These results indicate that mitochondrial hyperplasia and beigefication in WAT are regulated by the JMJD1A-PGC1 axis and that energy expenditure in WAT prevents the onset of obesity and metabolic disorders.

Future Development

Beige adipocytes are prolific energy consumers and have attracted attention as a therapeutic target for obesity and lifestyle-related diseases. In this study, we found that the inability to produce beige adipocytes causes obesity and metabolic abnormalities in individuals, and that histone demethylation is involved in their regulation. The results of this research are expected to be applied to treatment and prevention methods for lifestyle-related diseases including obesity and diabetes.

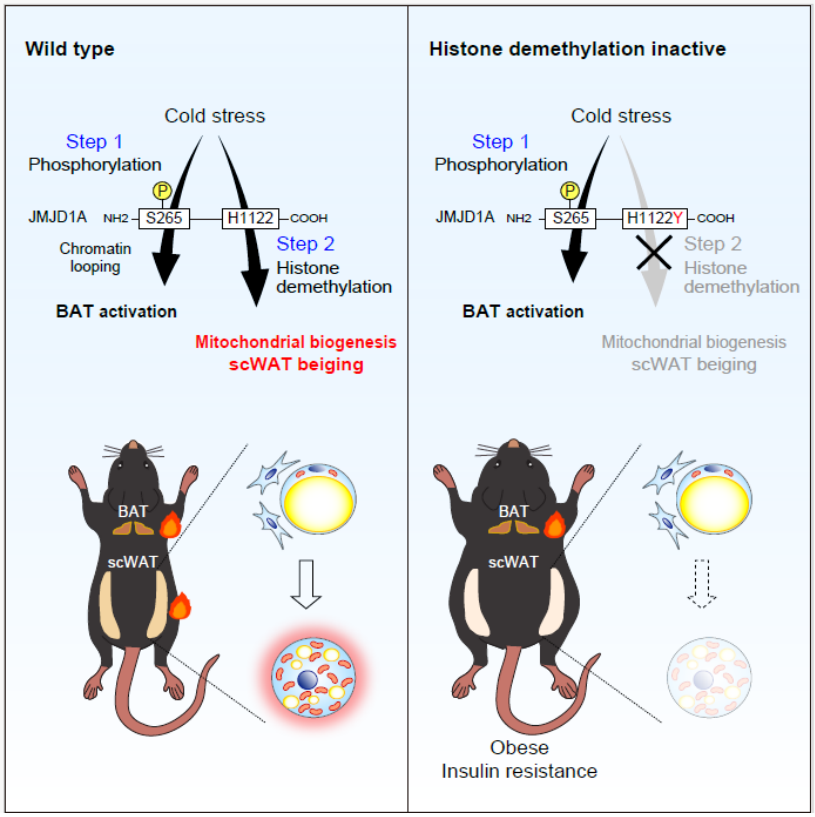

Figure.1: In wild-type mice, JMJD1A is phosphorylated by cold stimuli and promotes heat production via chromatin looping in BAT and beiging and mitochondrial proliferation via histone demethylation in WAT. Jmjd1a-HY mice that have lost demethylation activity activate BAT, but fail to undergo histone demethylation-mediated

WAT beiging and mitochondrial proliferation, resulting in reduced energy expenditure, obesity and insulin resistance.

【Acknowledgments】

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【Terminology Explanation】

＃ 1. Epigenome: Genetic information that can be modified postnatally, beyond the DNA sequence. This includes DNA methylation modifications, as well as post-translational modifications of histones such as methylation and acetylation.

＃ 2. Mitochondria: Organelles within cells responsible for oxidative phosphorylation, producing energy and synthesizing ATP. They also generate heat through uncoupling reactions.

＃ 3. Beige Adipocytes: Fat cells capable of consuming fat and generating heat. They appear in subcutaneous white adipose tissue after prolonged exposure to cold stimuli.

＃ 4. Enzymes involved in epigenome modification: Enzymes known to add or remove post-translational modifications on histones.

＃ 5. Mitochondrial Biogenesis: The process of increasing the number of mitochondria. In beige adipocytes induced by cold stimuli, an increase in mitochondrial numbers promotes heat production.

＃ 6. Histone demethylase enzyme JMJD1A: An epigenetic enzyme that demethylates histones. It removes the 9th lysine residue on histone H3 protein, which suppresses gene expression, thus promoting gene expression.

＃ 7. Chromatin higher-order structure: DNA is wrapped around histone proteins to form nucleosomes, and these nucleosomes are further organized into chromatin. The three-dimensional structure of chromatin regulates gene expression.

＃ 8. Pgc1a/b: Genes encoding PGC1α/β, which control mitochondrial biogenesis. They act as transcriptional coactivators, promoting the expression of genes involved in mitochondrial biogenesis.

＃ 9. Enhancer region: DNA regions that activate gene expression.

[paper info].
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