【Grant-in-Aid for Scientific Research(S)】
Biological Sciences (Medicine, dentistry, and pharmacy Ⅱ)

Title of Project : Analysis of the functional interaction among bone, gut and energy metabolism with a special reference to gender difference

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Research Area : Oral Bioscience, Biochemistry, Pharmacology
Keyword : osteocalcin, incretin, insulin, energy metabolism, bone property

【Purpose and Background of the Research】

Globalization of markets has brought Japanese a westernized dietary habits and lifestyle, increasing the rate of obesity and metabolic syndrome. Because obesity and metabolic syndromes are caused by energy flux disruptions, elucidation of the regulatory mechanism of energy metabolism raises the possibility for new targets of therapy for the diseases.

Recently, it has been reported that bone is an active endocrine organ that secretes hormones. Especially, bone derived osteocalcin (OC) is a hormone that promotes insulin production, enhancing glucose utilization and energy expenditure.

On the other hand, incretins are gut-derived hormones secreted in response to the food intake. Incretins have numerous physiological functions including potentiation of glucose-stimulated insulin secretion. Therefore, we assume that OC might be involved in secretion of incretins. We then term this "bone-gut-metabolism flow, BGM Flow".

We found that female, but not male, mice lacking PRIP (phospholipase C-related but catalytically inactive protein), showed increased bone formation with high serum OC level. Therefore, in this study, we are going to challenge to clarify the mechanisms involved in BGM Flow, with a special reference to the roles of PRIP and gender difference.

【Research Methods】

Using wild-type and PRIP-KO mice, and when needed mice generated by mating PRIP-KO mice with metabolism-relating genes deficient mice, *in vivo* experiments are performed to analyze the effect of OC application on body weight, serum levels of incretins and insulin, body temperature, respiratory ratio, GTT and ITT etc. *In vitro* experiments are also performed using the organs and cells isolated from the above-mentioned mice, and cultured cell line regarding incretin and insulin signaling

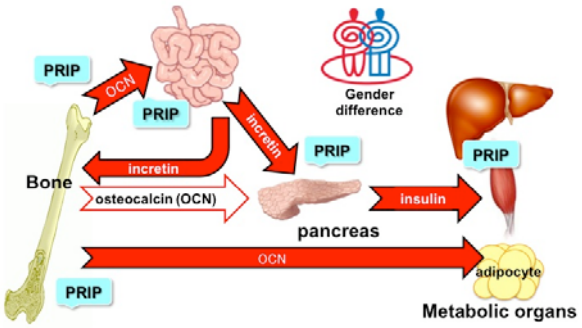

Figure 1 BGM Flow (Bone-Gut-Metabolism)

【Expected Research Achievements and Scientific Significance】

In the machinery of glucose/energy metabolism regulation by bone-derived OC, we would originally confirm the presence of Gprc6a, a putative uncarboxylated-OC receptor, in the epithelial cells of mouse small intestine, and OC induces incretin secretion. In addition to the direct effect of OC on insulin secretion from pancreas, it is for the first time to show that the effect also through the incretin secreted from the gut. Furthermore, the establishment of "BGM Flow" would be a reasonable extension of our PRIP-related works. The outcome would provide a new insight into obesity/energy metabolism studies and their therapies.

【Publications Relevant to the Project】

・ Tsutsumi, K., Matsuda, M., Kotani, M., Mizokami, A., Murakami, A., Takahashi, I., Terada, Y., Kanematsu, T., Fukami, K., Takenawa, T., Jimi, E. and Hirata, M.: Involvement of PRIP, phospholipase C-related but catalytically inactive protein, in bone formation. *J. Biol. Chem.* 286:31032-31042, 2011.

・ Gao, J., Takeuchi, H., Zhang, Z., Fukuda, M. and Hirata, M.: Phospholipase C-related but catalytically inactive protein (PRIP) modulates synaptosomal-associated protein 25 (SNAP-25) phosphorylation and exocytosis. *J. Biol. Chem.* 287:10565-10578, 2012.

【Term of Project】 FY2012-2016
【Budget Allocation】 167,700 Thousand Yen
【Homepage Address and Other Contact Information】

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