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学　位　論　文　要　旨

畜産科学専攻　専攻　博士後期課程
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論文題目：Elucidating Exogenous Stimulation and Molecular Mechanisms for Browning in Pig Adipocytes（ブタ脂肪細胞の褐色化に関する外因性刺激および分子機構の解明）

要旨

White adipocyte transformed to beige adipocyte with adrenal stimulation such as cold environment, thyroid hormones, burn injuries, and catecholamine preparations. The transition from white adipocytes to beige adipocytes (browning) alters their metabolic functions, influencing physiological functions in both mammals and humans. The browning was focused on human health care and it expected to serve as a new therapy for metabolic diseases such as obesity, diabetes mellitus, and dyslipidemia. However, the molecular mechanism of browning is not clearly understood.

The study of browning has been performed mainly in human or mouse fat tissues and on culture cell lines, such as 3T3-L1, derived from mouse embryonic cells. As ethical issues are posed by the use of human samples, it is difficult to use them for experiments on browning. Furthermore, previous study observed that different expressions between in vivo and in vitro conditions, and reported the result in experiments of adipocyte depend on the animal species. On the other hand, primary cultures of fat can be immensely beneficial for the investigation of adipocyte functions. Therefore, other animal models and primary cultures can be applied to study browning to obtain insights on human metabolic diseases.

Pig shares similar features with human in terms of anatomy, genetics and physiology, making it a valuable animal model for human research. Previous studies have been reported to genetic similarity between pig and human with genome-wide sequencing of various tissues. In addition, the pig lacks functional UCP1 which is related to browning similar to adult humans, and so pigs are sensitive cold environment. Then, this study focused on Mangalica Pig which has unique physiology and lard-type pig, it is a traditional breed in Hungary. This study specifically targeted the Mangalica Pig, a traditional breed in Hungary with unique physiology and characteristics as a lard-type pig. Mangalica has cold tolerance and can live in a grazing environment year-round. However, it remains unclear whether white adipocytes undergo browning in response to seasonal changes in Mangalica, and the molecular mechanisms by which Mangalica acquires cold tolerance are yet to be revealed.

In this study, I conducted experiments to understand the molecular mechanisms of fat browning. At the cellular level (*in vitro*), I induced browning in adipocytes using primary cultures from a commercial pig breed's fat tissue. At the in vivo level, experiments with Mangalica were carried out to explore cold stimulation in thermogenic physiology, focusing on muscle and fat tissues. The goal was to achieve a comprehensive understanding of the browning process. In the cellular experiment, the administration of 1 μM isoproterenol to pig fat primary cultures significantly increased the gene expression of PGC-1α and UCP3, which are associated with browning, as well as the COX family genes related to mitochondrial function. Additionally, 1 μM isoproterenol upregulated lipolysis, leading to a significant decrease in the size of lipid droplets and lipid particle content. These results revealed browning in white adipocytes of pigs lacking UCP1. In the in vivo experiment, there was a distinct developmental pattern in fat tissue between Mangalica and a commercial pig breed. In Mangalica, the gene expression of ATP2A1 and SLN in muscle, as well as the gene expression of PGC-1α, UCP1, UCP2, and UCP3 in fat, was significantly higher in winter compared to summer. The genes upregulated in the fat of Mangalica were consistent with the browning observed in pig fat primary culture. These findings suggest that the fat tissue of Mangalica undergoes browning in winter, contributing to its cold tolerance.

This study is the first study that demonstrate fat browning using fat primary culture from pig, shedding light on the potential for browning in the fat tissue of Mangalica. These findings offer valuable insights into the mechanism of browning in white adipocytes and hold promise for contributing to the therapeutic interventions for human obesity.