学位論文内容の要旨
Abstract of the dissertation

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Study on the role of gut microbiota and intestinal environment in adipose tissue development in preweaning mice

(乳子期マウスの脂肪組織発達における腸内細菌および腸内環境の役割に関する研究)

Obesity has become a global health issue that requires urgent attention. While current treatments focus on dietary regulation, physical exercise, and pharmacological interventions, an approach that enhances energy expenditure through thermogenic adipocytes, namely, brown and beige adipocytes, represents a promising strategy. Given that the mass of brown adipose tissue (BAT) declines with age and human BAT mainly consists of beige adipocytes, it is important to identify methods that promote the induction of beige adipocytes. Interestingly, beige adipocytes are transiently induced in white adipose tissue (WAT), known as WAT browning, during the postnatal period in mice. Unlike in adults, this induction appears to occur independently of sympathetic stimulation; however, the regulatory mechanisms remain unknown. Therefore, this study aimed to elucidate the mechanisms underlying beige adipocyte induction during the postnatal period in mice, which could provide novel insights into increasing thermogenic adipocytes to combat obesity.

Chapter I revealed that beige adipocytes were induced before weaning in association with gut microbiota formation in mice. Disruption of gut microbiota by maternal antibiotic (Abx) treatment or alteration of gut microbiota by maternal high-fat diet (HFD) feeding substantially suppressed beige adipocyte induction in the pups. Moreover, cecal microbiota transplantation from pups of HFD-fed dams replicated this suppression, indicating the critical role of gut microbiota. Notably, the abundance of Porphyromonadaceae and Ruminococcaceae was positively and negatively correlated with the expression of the beige marker gene, respectively.

Given that gut microbiota regulates host metabolism through microbial signals and metabolites, including bile acids (BAs) and short-chain fatty acids (SCFAs), Chapter II

aimed to investigate the contribution of these metabolites to postnatal WAT browning by generating BA- or SCFA receptor-deficient mice. Maternal Abx and HFD altered BA profiles and reduced secondary BAs in pups, suggesting a link between microbiota-dependent BA metabolism and beige adipocyte induction. However, knockout of the BA receptor TGR5 demonstrated minimal impact on beige adipocyte markers, indicating that TGR5 signaling is not crucial for postnatal WAT browning. Maternal Abx during late lactation significantly inhibited beige adipocyte induction, suggesting that gut microbiota formed during the late lactation plays a crucial role in WAT browning. RNA sequencing analysis suggested the suppression of FXR signaling, which regulates BA and lipid metabolism, in the intestines of the pups. However, pharmacological inhibition of FXR did not affect beige adipocyte induction. Furthermore, maternal Abx during late lactation reduced cecal SCFA levels, yet knockout of the SCFA receptors GPR43 and GPR41 did not influence WAT browning, implying that SCFA-GPR43/41 signaling is not critical in this mechanism.

Collectively, these findings highlight the pivotal role of gut microbiota in the induction of beige adipocytes during the postnatal period. Although this study could not elucidate the specific mechanisms underlying postnatal WAT browning, it suggests that this induction is independent of the TGR5, GPR43, and GPR41 signaling pathways. Further research is necessary to identify additional regulatory factors to elucidate this mechanism, which may contribute to the establishment of novel obesity countermeasures.