

(様式4)

学位論文の内容の要旨

(歩 云) 印

Insulin Regulates Lipolysis and Fat Mass by Upregulating Growth/Differentiation Factor 3 in Adipose Tissue Macrophages

(インスリンと脂肪組織マクロファージを介する新奇・脂肪蓄積機構の解明)

(学位論文の要旨)

We previously clarified that activin receptor-like kinase 7 (ALK7), one of the type I TGF- β receptors, is mainly expressed in mature adipocytes in white adipose tissues, and that ALK7 signaling increases fat mass via suppression of lipolysis. Although growth/differentiation factor 3 (GDF3) has been suggested to function as a ligand of ALK7 under excess nutrient and obese conditions, how GDF3 production is regulated still remains unclear. We found that GDF3 is mainly expressed in CD11c⁺ adipose tissue macrophages (ATMs) in stroma-vascular fraction (SVF), and that depletion of ATMs by clodronate liposome enhances lipolysis and reduces fat accumulation in ALK7-intact obese mice, but not in their ALK7-deficient counterparts. Furthermore, a physiologically low level of insulin converts CD11c⁻ ATMs into GDF3-producing CD11c⁺ ATMs ex vivo and directs ALK7-dependent fat accumulation in vivo. Depletion of ATMs or transplantation of GDF3-deficient bone marrow counteracts the in vivo effects of insulin on both lipolysis and fat accumulation in ALK7-intact obese mice. These results reveal a novel mechanism by which insulin regulates both fat metabolism and mass via GDF3-ALK7 axis between ATMs and adipocytes.