COMMENT ON BU ET AL.

Insulin Regulates Lipolysis and Fat Mass by Upregulating Growth/Differentiation Factor 3 in Adipose Tissue Macrophages. Diabetes 2018;67:1761–1772

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In a recent article, Bu et al. (1) claim to describe a novel role for growth/differentiation factor 3 (GDF3) and the activin receptor–like kinase 7 (ALK7) in the regulation of adipose tissue lipolysis by insulin. It is an intriguing observation. I find, however, that several of the inconsistencies between the current study and previous studies from other laboratories, including mine (2,3,4), can be due to the authors' comparison of strains of mice that differ in many other genes besides *Alk7*, particularly given the way in which the Tsumura, Suzuki, obese diabetes strain and its derivatives were generated. In this regard, I find the conclusions made in this article about ALK7 function based on direct comparison of C57BL/6 and BALB/c mice particularly troublesome. These two strains of mice are totally different and diverge in dozens of genes, besides *Alk7*. It is invalid to make a claim about the function of a single gene based on phenotype comparisons of these two strains. The only way to be sure of the observations made by Bu et al. is to use gene-targeted approaches that affect the *Alk7* gene specifically and nothing else. Such mouse strains have existed for many years, and it is not clear why the authors have not used them in the study. Moreover, the so-called *Alk7*-deficient mice used here are global mutants affecting all tissues from the time of conception. This severely limits the conclusions of the study, particularly with regard to insulin signaling. My group has previously shown that a global knockout of ALK7 affects many tissues besides fat, such as pituitary (5), hypothalamus (5), and the β-cells of the pancreas (4), which in fact secrete higher levels of insulin in the absence of ALK7 (4). No firm conclusion can be derived about tissue-autonomous roles of ALK7 in adipose tissue from a global mutant. I would strongly encourage Bu et al. to use *Alk7* knockout and conditional mutant mice that specifically target the *Alk7* gene to validate their studies, and we would be happy to provide those mice to them for that specific purpose. Until then, I would argue that the observations made by Bu et al. (1) can only be considered as preliminary. This concern is all the more urgent at this moment, when many observations made in the biomedical sciences are being questioned with all kinds of reproducibility problems, many of them arising from inappropriate animal models.

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