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IGF1 and Adipose Tissue Homeostasis

Jacqueline M. Stephens

A new study by Chang et al. published in this issue of *Obesity* examines the role of regulation and function of insulin-like growth factor-1 (IGF1) in adipose tissue (1). Although the majority of circulating IGF1 comes from liver (2), several studies in the past decade have suggested that IGF1 modulates adipocyte development and function *in vitro* (3-5). Yet the contribution of IGF1 to adipogenesis and fat cell function in the whole animal is poorly understood. Based on their initial observation that IGF1 expression is increased in adipose tissue macrophages (ATM) in obese mice, the Ferrante group followed up on this striking data and examined the role of IGF1 in both fat cells and macrophages in adipose tissue.

The generation of two animal models revealed that the loss of IGF1 in either Lys2 expressing cells or adiponectin expressing cells revealed no prominent changes in adipose tissue development or glucose metabolism. In obese mice, IGF1 levels are decreased in adipocytes but increased in ATMs. In another model of murine obesity, enhanced IGF1 expression in ATMs has also been observed (6). Clearly, IGF1 is differentially regulated in adipocytes and macrophages in white fat. However, the end result is no substantial changes in overall expression of IGF1 in obesity due to the increased recruitment of ATMs. To effectively demonstrate this differential IGF1 regulation, clodronate was used to deplete ATMs. Macrophage depletion in lean adipose tissue showed no decrease in IGF1 since adipocytes are the primary source of adipose tissue IGF1, but a 75% reduction in IGF1 expression was observed in obese adipose tissue.

Collectively, these results clearly demonstrate that a robust regulatory system exists to modulate IGF1 levels in adipose tissue. So what is IGF doing in adipose tissue if it is not regulating adipose tissue development or glucose homeostasis? The animal models used in this study revealed that ATM-derived IGF1 maintains fat mass following a cold challenge, whereas adipocyte-derived IGF1 remodels gonadal but not subcutaneous fat, in the context of high-fat feeding. The studies in this article appear to be carefully conducted and the results are convincing. Previous studies also have revealed depot-specific differences in IGF1 action in subcutaneous and visceral fat (7). Of note, an additional provocative observation from this Ferrante study reveals cold-challenged mice do not have an increase in tyrosine hydroxylase in ATMs, as has recently been shown (8).

Overall, this comprehensive study by the Ferrante group reveals compensatory regulation by macrophages in adipose tissue to maintain IGF1 levels in conditions of obesity and underscores the importance of examining various adipose tissue depots based on differential responses observed in gonadal fat in mice lacking adipocyte IGF1. This study not only highlights the complexity of hormone action, but justifies the importance of examining contributions of individual cell types in adipose tissue as well as location of adipose tissue depots. I suggest that you read this paper with your trainees as there is a lot to discuss.

**References**