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Maintenance of Subcutaneous Fat Homeostasis Improves Systemic Metabolic Dysfunction in Obesity

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COMMENTARY

Obesity and diabetes continue to be major health problems worldwide (1). The fat tissues distributed throughout the body can be classified into two main types—brown and white adipose tissue (2). Evidence has been found to suggest that adipose tissue dysfunction has a causative role in the development of systemic metabolic disorders. Brown adipose tissue (BAT) was initially reported to be involved in heat generation. BAT is predominantly found in infants and rodents and was once thought to disappear with aging. However, BAT has since been identified in adults and is now recognized to be a metabolically active tissue that contributes to the maintenance of systemic metabolism (3,4). BAT has a massive capacity to dissipate energy as heat, and the development of BAT dysfunction due to metabolic stress promotes the progression of systemic metabolic dysfunction (5). Visceral fat is a metabolically active endocrine organ that secretes several humoral mediators known as adipokines. Chronic sterile inflammation occurs in visceral fat as a result of metabolic stress, and an imbalance between production of proinflammatory and anti-inflammatory adipokines leads to systemic metabolic dysfunction (6). Compared with visceral fat, subcutaneous fat has more beneficial effects on systemic metabolism (7). Subcutaneous fat contains beige cells, which are identified as cells positive for the uncoupling protein 1 and negative for the myogenic factor 5. Beige cells that arise from the browning of subcutaneous fat improve systemic metabolic dysfunction in obesity (8,9). Accordingly, many studies have investigated the browning of subcutaneous fat and its potential to combat obesity.

In this issue of *Diabetes*, Liu et al. (10) report that the protein inhibitor of activated STAT 1 (PIAS1, also known as E3 SUMO-protein ligase PIAS1) in subcutaneous fat plays a critical role in the maintenance of metabolic homeostasis in obesity. They found that PIAS1 is a key regulator in the suppression of inguinal fat inflammation and systemic metabolic dysfunction in murine models of obesity. PIAS1 was predominantly expressed by inguinal white adipose tissue (iWAT), which corresponds to subcutaneous fat, and its expression by iWAT showed a marked decrease in various prediabetic mouse models, such as *ob/ob* mice, *db/db* mice, and mice with dietary obesity. Liu et al. suggest that PIAS1 has at least two beneficial roles in systemic metabolism. First, PIAS1 acts as a direct regulator of the insulin sensitivity of mature adipocytes. They show that the depletion of PIAS1 significantly reduced insulin signaling in adipocytes. Treatment of adipocytes with tumor necrosis factor-α (TNF-α) led to a marked reduction of insulin signaling, whereas forced expression of PIAS1 inhibited the suppression of insulin signaling. These results suggest that PIAS1 has a critical role in regulating insulin sensitivity, but further studies are needed to elucidate the mechanisms involved. PIAS1 may also be involved in the modulation of the inflammatory response. Forced expression of PIAS1 in the iWAT of prediabetic mice suppressed the expression of proinflammatory cytokines, reduced the levels of chemoattractants such as *Ccl2* and *Mip2* (*Cxcl2*), and inhibited the infiltration of macrophages into iWAT. PIAS1 inhibited the binding of p65 nuclear factor-κB to the promoter of *Tnf* and *Mip2* and suppressed the expression of these proinflammatory adipokines. PIAS1 also negatively regulated the activation of c-Jun N-terminal kinase (JNK) and p65 in prediabetic iWAT by the modification of phosphorylation. In vitro studies demonstrated that mediators of metabolic stress (such as TNF-α and palmitate) and their downstream effector (JNK) downregulated PIAS1 expression, indicating the existence of a negative feedback loop between PIAS1 and JNK (Fig. 1). Using fat transplantation models, Liu et al. (10) elegantly show that overexpression of PIAS1 could improve WAT-induced systemic metabolic dysfunction in obese animals. Taken together, these results

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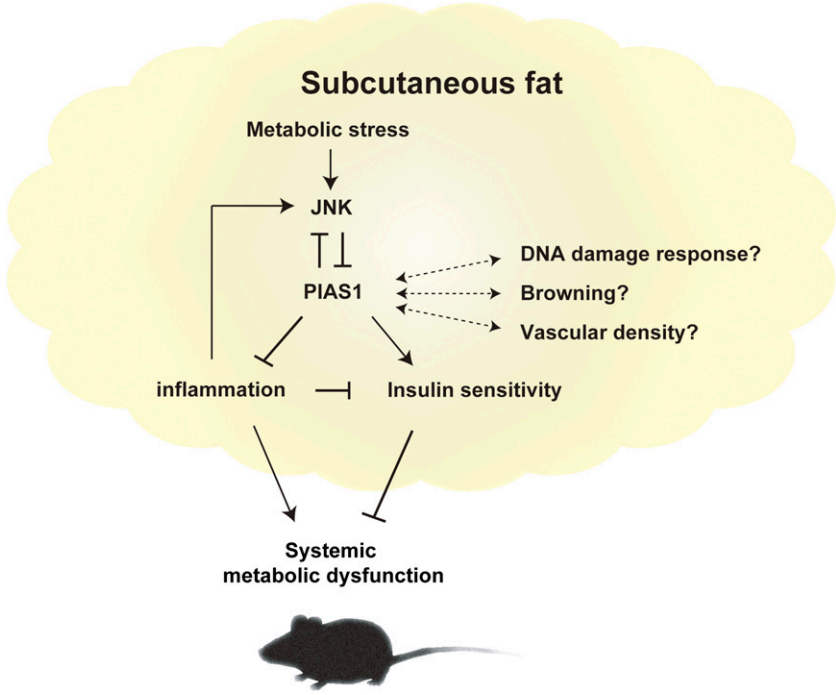

Figure 1—PIAS1 contributes to the maintenance of systemic metabolic homeostasis by inhibiting inflammation and enhancing insulin sensitivity in subcutaneous fat. Metabolic stress activates JNK and suppresses PIAS1 expression in subcutaneous fat, leading to systemic metabolic dysfunction. In turn, PIAS1 is a negative regulator of JNK activity, forming a negative feedback loop.

indicate that PIAS1 is critically involved in the maintenance of systemic homeostasis through the regulation of both insulin sensitivity and inflammation in subcutaneous fat. Although PIAS1 reduced inflammation of iWAT and improved systemic metabolic dysfunction in prediabetic mice, inflammation of visceral fat was not affected by altering PIAS1 expression in iWAT. This is an interesting finding because inflammation of visceral fat is generally thought to have a critical role in the development of systemic metabolic dysfunction in obesity, mainly through increased TNF-α production. Inhibition of the whitening of BAT and maintenance of homeostasis have been recently shown to suppress the onset of systemic metabolic dysfunction in the presence of sustained visceral fat inflammation (5). These results indicate that nonvisceral fat tissues, such as subcutaneous fat and BAT, have the potential to suppress the progression of metabolic dysfunction and suggest a novel therapeutic strategy for combating obesity and diabetes through the maintenance of homeostasis in both nonvisceral and visceral fat.

It is widely accepted that the accumulation of DNA damage has a pathological role in the development of systemic metabolic dysfunction (11). Metabolic stress augments the production of reactive oxygen species that causes DNA damage in visceral fat, thereby promoting adipose tissue inflammation and systemic metabolic dysfunction (12–14). Persistent inflammation per se can induce DNA damage, suggesting that a vicious cycle may exist in which metabolic stress leads to increased DNA damage and exacerbation of adipose tissue inflammation. It has been reported that PIAS1 accumulates at sites of DNA double-strand breaks and promotes DNA repair in a human osteosarcoma cell line (U2OS) (15). Although DNA damage presumably accumulates when subcutaneous fat is subjected to metabolic stress, Liu et al. (10) report that PIAS1 is significantly reduced in iWAT. This difference may be due to cell context-dependent responses, so further studies will be needed to define the contribution of DNA damage in subcutaneous fat to obesity. Another unanswered question is whether PIAS1 modulates the browning of subcutaneous fat. It is generally accepted that capillary rarefaction is correlated with the dysfunction of visceral fat. Forced expression of *Vegfa* promotes angiogenesis in subcutaneous fat, leading to its browning and contributing to the suppression of systemic metabolic dysfunction (16). As the growth of the capillary network in subcutaneous fat is closely connected with its browning, analyzing the contribution of PIAS1 to angiogenesis and the browning processes would also be interesting. Subcutaneous fat is anatomically more accessible than visceral fat and thus has advantages from the viewpoint of drug delivery. Accordingly, maintenance of subcutaneous fat homeostasis through the modulation of key molecules such as PIAS1 has the potential to become a next-generation therapy for obesity and diabetes.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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