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COMMENTARY

The role of adipocyte-specific IL-6-type cytokine signaling in FFA and leptin release

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ABSTRACT

High secretion of interleukin (IL)-6 from white adipose tissue may contribute to metabolic complications in obesity. We have recently shown that IL-6-type cytokine signaling in adipocytes is involved in the development of obesity-associated hepatic insulin resistance and steatosis. In addition, we revealed that adipocyte-specific IL-6 signaling ameliorates glucose metabolism in obesity via enhancing insulin secretion. Mechanistically, IL-6 induces the release of free fatty acid (FFA) and leptin from adipocytes thereby affecting liver metabolism and pancreatic β-cell function, respectively. This commentary further discusses the role of adipocyte-specific IL-6-type cytokine signaling in the regulation of FFA and leptin release. In particular, we outline depot-specific differences in IL-6-induced basal release of the two aforementioned factors. Moreover, we provide evidence that insulin's effect on the release of FFA and leptin is adipose depot-dependent. We conclude that adipose depot-specific targeting of the IL-6 signaling pathway may be a novel approach to blunt obesity-associated metabolic complications.

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The role of adipocyte-specific IL-6-type cytokine signaling in glucose metabolism

The prevalence of obesity and associated diseases such as insulin resistance and type 2 diabetes are increasing worldwide.[1,2] High secretion of interleukin (IL)-6 from adipose tissue may contribute to obesity-induced insulin resistance and, consequently, the development of type 2 diabetes.[3] To induce its intracellular signaling pathways, IL-6 either binds to its soluble or membrane-bound receptor. Subsequently, the assembled IL-6 ligand/receptor complex associates with a homodimer of glycoprotein 130 (gp130), which is a signal transducing protein of all IL-6-type cytokine family members.[4] Using adipocyte-specific gp130 knockout mice (gp130$^{\Delta adipo}$), we recently demonstrated that IL-6-type cytokine signaling in visceral adipocytes contributes to the development of obesity-associated hepatic insulin resistance and steatosis.[5] Mechanistically, obesity-induced IL-6-type cytokine signaling induced basal free fatty acid (FFA) release in mesenteric adipocytes of high fat diet (HFD)-fed mice. Consequently, increased portal FFA flux induced hepatic insulin resistance and lipid accumulation. In humans, omental IL-6 mRNA expression correlated negatively with insulin sensitivity and positively with liver lipid accumulation,[5] supporting a role for visceral IL-6 in the development of obesity-associated hepatic complications. Besides this pathological role of IL-6-type cytokine signaling in adipocytes, we have recently unraveled a physiological role of the latter in improving glucose tolerance in obesity.[6] *In vivo* and *in vitro* experiments revealed that IL-6 stimulates leptin release from adipocytes thereby inducing glucagon-like peptide-1 (GLP-1) release from enteroendocrine cells and subsequent insulin secretion from pancreatic β-cells. In particular, HFD-fed gp130$^{\Delta adipo}$ mice were characterized by impaired glucose tolerance accompanied by reduced circulating leptin, GLP-1 and insulin levels. Importantly, administration of the GLP-1 receptor antagonist exendin 9–39 blunted the observed difference in glucose tolerance between control and knockout mice, indicating a critical involvement of GLP-1 in the observed phenotype. *Ex vivo*, basal leptin release in epididymal adipocytes isolated from HFD-fed gp130$^{\Delta adipo}$ mice was reduced compared to control (gp130$^{F/F}$) mice. Moreover, collected supernatant from gp130-depleted adipocytes reduced GLP-1 secretion from cultured enteroendocrine cells leptin-dependently. Taken together, IL-6-type cytokine signaling induces the release of FFA and leptin from adipocytes in obesity thereby affecting glucose metabolism. While IL-6-induced FFA release induces hepatic insulin resistance and steatosis, IL-6-mediated leptin secretion

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improves glucose tolerance in obesity via inducing insulin secretion. Such opposing effects may suggest that inhibition of IL-6 signaling in adipocytes may not offer an appropriate approach to treat obesity-associated metabolic complications.

Depot-specific differences of adipocyte-specific IL-6-type cytokine signaling

Metabolism of adipocytes may vary depot-dependently in mice and men.[7–9] However, it remains largely unknown whether the stimulatory effect of IL-6 on FFA[10,11] and leptin[12] release differs between adipose depots. Our data indicate that adipocyte-specific IL-6-type cytokine signaling affects FFA and leptin release depot-specifically. In fact, basal FFA release was reduced in portal-drained mesenteric but not in systemically-drained epididymal adipocytes isolated from HFD-fed gp130$^{\Delta adipo}$ mice.[5] In addition, insulin's ability to suppress FFA release was ameliorated in mesenteric but not epididymal adipocytes isolated from HFD-fed knockout compared to control mice.[5] Consequently, portal but not systemic FFA levels were reduced in HFD-fed gp130$^{\Delta adipo}$ mice. In contrast, basal leptin release was reduced in epididymal adipocytes isolated from of HFD-fed gp130$^{\Delta adipo}$ mice, resulting in reduced systemic leptin levels.[6] To elucidate whether insulin's effect on leptin release is dependent on IL-6 cytokine signaling, we assessed leptin release in epididymal adipocytes isolated from HFD-fed gp130$^{F/F}$ and gp130$^{\Delta adipo}$ mice treated with or without insulin. Of note, insulin is an important physiological regulator of leptin release in adipocytes.[13,14] In fact, insulin increases the release of leptin in 3T3-L1 adipocytes and epididymal adipose tissue of lean rodents.[15,16] In epididymal adipocytes isolated from HFD-fed control (gp130$^{F/F}$) mice, insulin had no stimulatory effect on leptin release, indicating evolved insulin resistance (Figure 1). In contrast, insulin stimulated the release of leptin in adipocytes isolated from HFD-fed gp130$^{\Delta adipo}$ mice. Hence, lack of IL-6-type cytokine signaling partly protects adipocytes from HFD-induced impairment in insulin-stimulated leptin release. In summary, IL-6-type cytokine signaling affects FFA release in mesenteric adipocytes while influencing leptin release in epididymal adipocytes (Table 1).

Conclusion and future perspectives

IL-6 is a pleotropic cytokine that exerts diverse and opposing roles in different cells and tissues.[17] In line, our findings indicate that IL-6 affects FFA and leptin release in adipocytes depot-specifically. We cannot exclude that other IL-6-type cytokines may modulate the release of leptin and/or FFA from adipocytes.

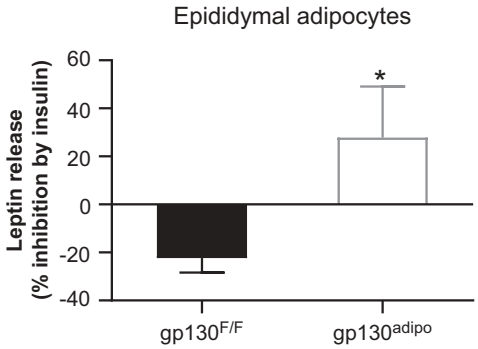

Figure 1. The effect ofDepot-specific differences of adipocyte insulin on leptin release in epididymal adipocytes isolated from HFD-fed gp130$^{F/F}$ and gp130$^{\Delta adipo}$ mice. Isolated adipocytes were incubated with or without 100 nM insulin for 1 hour and leptin release was assessed. Data correspond to the same mice (n = 8) included in a previously published paper.[6] Values are expressed as mean ± SEM. *p < 0.05 (Student's *t* test).

Table 1. Metabolism of adipocyte isolated from HFD-fed gp130$^{\Delta adipo}$ mice.

	Epididymal adipocytes	Mesenteric adipocytes
Basal FFA release	=	↓
Basal leptin release	↓	n.d.
Insulin effect on FFA release	=	↑
Insulin effect on leptin release	↑	n.d.

n.d. not determined

However, among six tested IL-6-type cytokines, only IL-6 significantly induced leptin release from isolated adipocytes.[6] In support for a role of IL-6-induced FFA release in hepatic dys-function, IL-6 infusion induced liver insulin resistance via adipose tissue lipolysis in rats.[18] Importantly, IL-6-mediated FFA release may be restrained to visceral adipose tissue.[5] Accordingly, targeting IL-6 signaling specifically in visceral adipocytes may be a promising strategy to protect the liver from obesity-associated hepatic insulin resistance and steatosis without reducing circulating leptin levels and, consequently, GLP-1 mediated insulin release.[6] Although we did not provide evidence that inhibition of IL-6 signaling in mesenteric adipocytes reduces leptin release, we postulate that such reduction may not affect leptin levels in systemic circulation since mesenteric fat-secreted factors may reach systemic circulation only in minor amounts.[19] Moreover, production and secretion of leptin is higher in systemically compared to portally-drained depots.[20,21] In contrast to its action in visceral adipocytes, IL-6 may have beneficial effects in systemically-drained adipose tissue and, consequently, reduces obesity-induced metabolic complications. In particular, IL-6 activation in subcutaneous

adipose tissue may induce leptin-mediated GLP-1 release in obesity. As GLP-1 is an important inducer of glucose-stimulated insulin release *in vivo*, this may be a useful strategy to prevent the development of type 2 diabetes in insulin resistant patients.[22,23] In conclusion, adipose depot-specific targeting of the IL-6 signaling pathway may be a novel approach to blunt obesity-associated metabolic complications.

Disclosure statement

No potential conflict of interest was reported by the authors.

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