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Spotlight

Adipose Progenitor Cells Contribute to Lipid Spillover during Obesity

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A recent study (Girousse *et al.* *Cell Rep.* 2019;27:323–333) shows that CXCR4$^+$ adipose progenitors (APCs) contribute to lipid spillover during high-fat feeding through their release from subcutaneous fat depots (ScATs) and migration to skeletal muscle where they differentiate into adipocytes. Pharmacological antagonism of CXCR4, which prevents the CXCL12-dependent retention of APCs in ScAT, mimics the effects of overfeeding.

Obesity is the consequence of an imbalance between energy intake and energy expenditure. During the initial stages of obesity, subcutaneous adipose depots (ScATs) expand to accommodate the storage of excess dietary fat. Progressively, the expansion limit is reached and the nonstored lipids start spilling over into other tissues [1]. The resulting deposition of fat in visceral adipose depots, skeletal muscle, liver, pancreas, and myocardium has been positively correlated with insulin resistance and an increased risk of developing metabolic disorders including type 2 diabetes (T2D) and cardiovascular disease [2]. It is widely accepted that the spillover increases the circulating levels of lipids, which are subsequently taken up by cells in ectopic tissues.

In their recent work, Girousse *et al.* refined this spillover concept by demonstrating that adipocyte progenitors (APCs) also participate in the redistribution process [3]. The authors revealed that a subpopulation of APCs expressing the C-X-C chemokine receptor type 4 (CXCR4) are released from the ScAT in response to high-fat feeding and give rise to new adipocytes in skeletal muscle. The detachment of CXCR4$^+$ APCs is promoted by a decrease in the levels of the chemokine CXCL12 in the ScAT microenvironment and by increased secretion in skeletal muscle (Figure 1) [3]. The authors observed that the percentage of this APC subpopulation was inversely correlated with ScAT fat-pad weight. No correlation was noted for the visceral depots even though these CXCR4$^+$ APCs are present in both depots, suggesting a depot-specific response to diet. To determine the fate of the circulating APCs, Girousse *et al.* grafted a piece of ScAT from mice expressing a *Cd34–egfp* transgene (that fluorescently marks APCs – CD34 is a surface marker for APCs) to ScAT of a non-GFP recipient mouse. They demonstrated that, after 8 weeks of high-fat diet (HFD) feeding, the recipient GFP$^+$ APCs could be detected by immunohistochemistry in the quadriceps muscle [3]. This result is consistent with detachment of CD34$^+$ APCs from the graft and their relocation to skeletal muscle. The authors were not able to determine whether the ectopic APCs differentiated into adipocytes within the muscle. This required the use of another mouse ('Ad-Cre/Zs1Green') in which adipocytes could be conditionally marked with GFP by treatment with tamoxifen. As before, a piece of ScAT was grafted from the Zs1Green mouse to the ScAT of a non-GFP recipient. The grafted animals were then treated with tamoxifen 8 weeks after a HFD to induce GFP expression in all adipocytes. Zs1Green$^+$ adipocytes were detected in the quadriceps muscle, confirming not only transit of ScAT-derived APCs to muscle but their differentiation into adipocytes [3]. Accumulation of ZsGreen1$^+$ adipocytes within the quadriceps muscle could also be induced by replacing the HFD diet by weekly injections of 5 mg/kg of the CXCR4 antagonist AMD3100 for 8 weeks. The authors had previously demonstrated that AMD3100 triggered the release of APCs from ScAT [4]. Further studies showed that mice fed a normal chow diet (ND) and 8 weeks of AMD3100 treatment gained weight and increased total fat mass to the same extent as mice fed a HFD. The mass of the ScAT and perigonadal adipose tissue

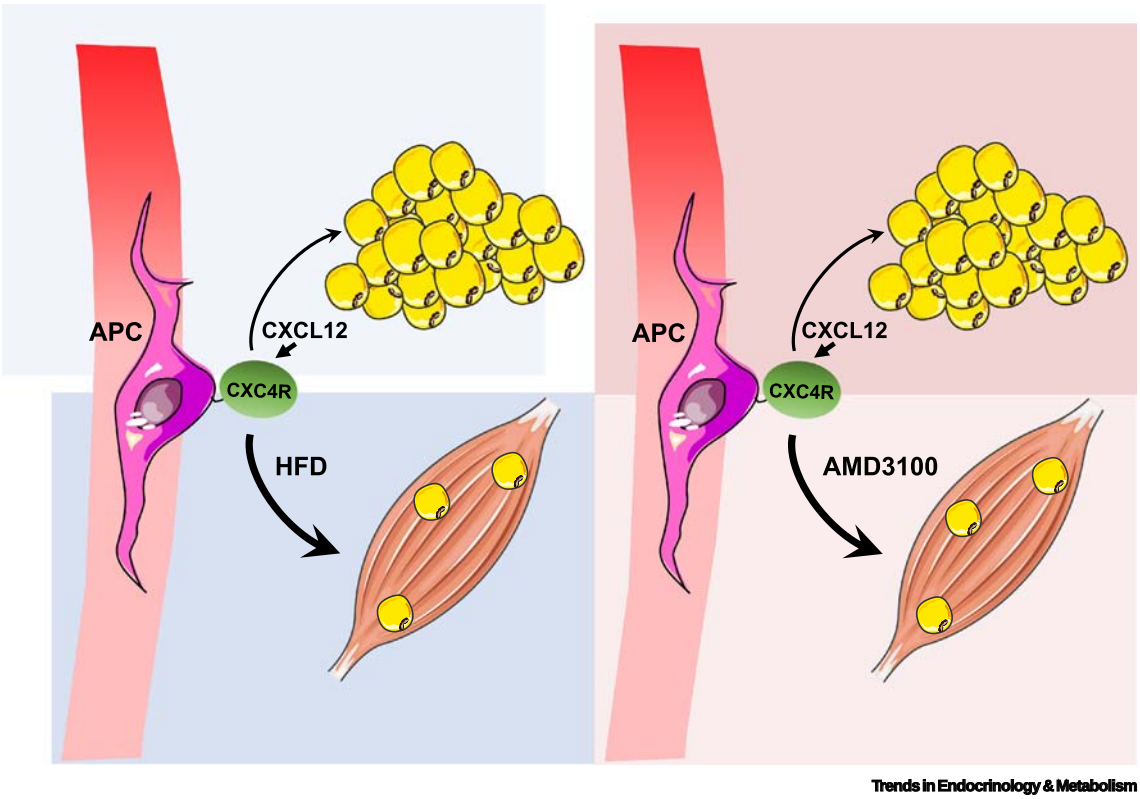

Figure 1. Adipose Progenitor Cells (APCs) Expressing CXCR4 Receptors Are Released from Subcutaneous Adipose Tissue (ScAT) in Response to a High-Fat Diet (HFD) and Migrate to Skeletal Muscle Where They Differentiate into Adipocytes. An antagonist of CXCR4, AMD3100, can mimic the effect of a HFD, thus implicating CXCR4 and its ligand CXCL12 in regulating the fate of APCs during diet-induced obesity.

(PGAT) depots did not increase, whereas ectopic depots including mesenteric, pericardiac, and periaorta were all significantly larger with AMD3100 treatment (Figure 1). Based on these data, the authors concluded that pharmacological triggering of APC release from ScAT causes ectopic adipocyte formation and metabolic imbalances independently of any dietary signals. They found that CXCR4 antagonism leads to deteriorated insulin signaling in muscle as well as whole-body insulin resistance and glucose intolerance. It should be emphasized, however, that AMD3100 could potentially impact on several physiological processes, including the function of the brown adipose tissue (BAT) as well as the pancreas, both of which could have an overall effect on energy homeostasis.

As an alternative means to perturb the CXCR4–CXCL12 axis in regulating the release of APCs from ScAT, Girousse *et al.* turned to a well-known antidiabetic drug, the peroxisome proliferator-activated receptor γ (PPAR-γ) agonist pioglitazone (Actos). Previous studies by others demonstrated that PPAR-γ agonists can reduce tumor migration via downregulation of CXCR4–CXCL12 signaling [5]. Consequently, the authors questioned whether pioglitazone could limit APC mobilization from ScAT similarly to its inhibition of cancer cell migration. They adopted an experimental strategy, however, that was unconventional for PPAR-γ agonists. Instead of giving daily injections of the agonist they administrated the drug once weekly to mimic the AMD3100 protocol. In mice fed a HFD, 8 weeks of pioglitazone treatment did not affect either body weight or the mass of ScAT or PGAT. It did, however, limit the expansion of the ectopic depots, including mesenteric, perirenal, and pericardiac adipose tissues (ATs). They further observed that pioglitazone prevented the HFD-mediated decrease in the $CXC4R^{+}$ APC population within ScAT as well as preventing the increase in quadricep muscle mass. They concluded that pioglitazone limited ectopic adipocyte formation in muscle by increasing APC retention in ScAT and reducing their migratory activity. Clinically, PPAR-γ agonists are administered daily to improve insulin sensitivity in T2D by stimulating adipogenesis, promoting fat storage in ScAT, and reducing circulating lipids, thus improving overall body insulin sensitivity [6]. Given the importance of these antidiabetic drugs, further investigations will be necessary to understand the differences

between the dosing schedules and how this affects their mechanism of action.

The work by Girousse *et al.* questioned the AT expandability theory by showing that HFD feeding induces the recruitment of a subpopulation of APC that express CXCR4 to the muscle, leading to ectopic adipocyte formation and thereby contributing to whole-body insulin resistance. The work presents an attractive model (Figure 1) which provides a framework for further investigation to determine whether it is physiologically relevant. Alternative roles for HFD-induced migration should also be considered. It is possible that depletion of APCs in ScAT might significantly reduce the pool of progenitors required for new adipocyte formation, which would also contribute to lipid spillover. Whichever mechanism is responsible for the effect of the HFD – ectopic adipocyte formation versus reduced adipogenesis in ScAT – prevention of APC mobilization could constitute a new strategy to combat obesity and its complications.

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