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ADIPOSE TISSUE

Macrophage retention inhibits beige adipogenesis in obesity

Inflammation of adipose tissue, which is characterized by the infiltration and retention of pro-inflammatory M1 macrophages, and reductions in beige adipogenesis and in the energy-dissipating capacity of white adipose tissue (WAT) are hallmarks of metabolic dysregulation in obesity. However, whether inflammation of adipose tissue inhibits beige adipogenesis in obesity was unclear.

In new research published in *Nature Immunology*, Chung *et al.* show that macrophage retention in obese adipose tissue is mediated by macrophage–adipocyte adhesion and that this interaction directly inhibits beige adipogenesis. "We were interested in identifying molecules that mediate the chronic retention of macrophages in obese adipose tissue and focused our attention on the $\alpha_4\beta_1$ integrin, which mediates the adhesion of monocytes and macrophages to target cells," explains lead investigator Triantafyllos Chavakis.

> "…macrophage retention in obese adipose tissue is mediated by macrophage–adipocyte adhesion…"

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The team first generated mice with inducible knockout of *Itga4* (which encodes α_4 integrin), to bypass the embryonic lethality of *Itga4* deletion. Following isolation of monocytes from the bone marrow of *Itga4*-knockout mice and their *Itga4*-sufficient control littermates, wild-type mice with diet-induced obesity (DIO) were simultaneously injected with both monocyte populations in a 1:1 mixture. 7 days after injection, considerably more *Itga4*-sufficient macrophages had accumulated in visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) than had *Itga4*-knockout macrophages, which suggests that macrophage accumulation in obese adipose tissue is dependent on macrophage expression of α_4 integrin.

The team next showed that expression of *Vcam1*, which encodes vascular cell adhesion molecule 1 (the counter-receptor for $\alpha_4\beta_1$ integrin), was markedly upregulated in both VAT and SAT of mice with DIO, predominantly in adipocytes. Subsequent experiments confirmed that direct macrophage–adipocyte adhesion was dependent on the $\alpha_4\beta_1$ integrin–VCAM1 interaction and that this interaction was required for retention of macrophages in obese adipose tissue. Moreover, macrophage–adipocyte adhesion reduced *Ucp1* expression in adipocytes and inhibited beige adipogenesis in obesity, thereby leading to adipose tissue dysfunction and insulin resistance. Crucially, this adhesion also exacerbated proinflammatory activation of macrophages and resultant increased production of tumour necrosis factor, which in turn increased expression of VCAM1 on adipocytes, thereby sustaining the direct macrophage–adipocyte interaction and perpetuating inflammation of adipose tissue and inhibition of adipocyte UCP1 expression and beige adipogenesis. The findings establish a self-sustaining cycle that links (and perpetuates) inflammation of adipose tissue with impaired beige adipogenesis, thus contributing to obesity-related metabolic dysfunction.

As beiging of WAT has been proposed as a possible strategy to treat obesity, the researchers investigated the therapeutic potential of inhibiting $\alpha_4\beta_1$ integrin. Wild-type mice with DIO administered an inhibitor of $\alpha_4\beta_1$ integrin for 6 weeks had improved insulin sensitivity and lower serum levels of insulin, glucose and cholesterol than vehicle-treated mice. Inhibition of $\alpha_4\beta_1$ integrin also reduced the number of M1 macrophages in SAT and increased beige adipogenesis. Similar metabolically beneficial effects were obtained with pharmacologic inhibition of $\alpha_4\beta_1$ integrin in *ob/ob* mice, a model of genetically induced obesity.

"Blockade of $\alpha_4\beta_1$ integrin with the monoclonal antibody natalizumab is a well-established therapeutic strategy in multiple sclerosis, albeit associated with an increased risk of progressive multifocal leukoencephalopathy," explains Chavakis. "Although risk of progressive multifocal leukoencephalopathy could render $\alpha_4\beta_1$ integrin blockade in obesity impractical, we believe that interfering with the direct adhesive interaction or with yet to be identified further interactions between inflammatory cells and adipocytes in obese adipose tissue could be a promising approach to trigger beige adipogenesis and promote metabolic homeostasis in obesity."

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ORIGINAL ARTICLE Chung, K.-J. *et al.* A self-sustained loop of inflammation-driven inhibition of beige adipogenesis in obesity. *Nat. Immunol.* http://dx.doi.org/10.1038/ni.3728 (2017)