Metabolism Select

Cell

The role of adipose tissue, or fat, in the development and treatment of metabolic disease is the subject of this issue's Select. A cluster of new studies in mice suggest that dysregulation of lymphocytes and other inflammatory cells in adipose tissue contributes to obesity and metabolic diseases such as type 2 diabetes. Elucidation of how the inflammatory response affects different types of adipose tissue may shed light on new strategies for treating diseases associated with obesity.

T Cells Send Fat a Mixed Message

The increase in metabolic diseases worldwide has been linked to a spike in obesity. Chronic inflammation of adipose tissue is known to be associated with obesity and to contribute to insulin resistance, a major feature of metabolic diseases, but how this process begins is unclear. Three recent papers (Feuerer et al., 2009; Winer et al., 2009; Nishimura et al., 2009) now address this issue.

Do T Cells Fight Flab?

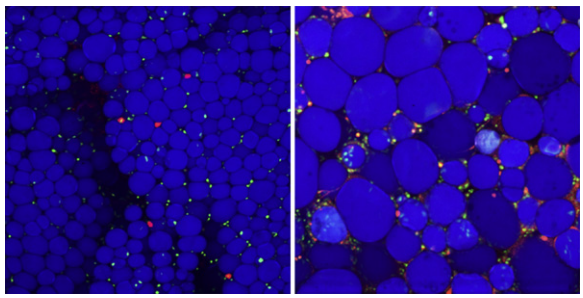
Given the role of $CD4^+$ regulatory T cells (Tregs) in controlling inappropriate immune responses, Feuerer et al. (2009) examine the part played by these cells in the inflammatory response in adipose tissue from lean mice. They find that Tregs are enriched in visceral adipose tissue (VAT), but not in subcutaneous adipose tissue (SAT) or other tissues. They also analyze obese mice and observe a strong correlation between insulin resistance and a lower proportion of Tregs in VAT but not other tissues. Systemic depletion of Tregs in mice induces the expression of genes encoding proinflammatory cytokines mainly in VAT, and triggers insulin resistance. On the other hand, expansion of Tregs in vivo leads to lower blood glucose concentrations and reduced glucose intolerance in mice fed a high-fat diet. Thus Tregs appear to protect against excessive inflammation of VAT and may block progression to metabolic disease. Tregs produce the cytokine interleukin-10, which inhibits the expression of proinflammatory mediators from adipocytes. Hence, this Treg-derived cytokine may directly regulate adipocyte function in VAT.

In a related study, Winer et al. (2009) assess the broader $CD4^+$ T lymphocyte population in VAT. The authors examine T cell populations from both SAT and VAT of obese and lean mice and observe increased numbers of $CD4^+$ T cells after diet-induced obesity. Within the $CD4^+$ T cell population, the authors find a rising bias toward proinflammatory T helper 1 (Th1) cells relative to Tregs in VAT from obese humans and mice, which appears to be antigen-driven. They find that mutant mice lacking lymphocytes and fed a high-fat diet are more prone to weight gain and developing insulin resistance than wild-type mice, suggesting that T lymphocytes may be important regulators of metabolism. Further, when these mutant mice are reconstituted with $CD4^+$ T cells, they display less weight gain, lower serum levels of obesity-associated adipokines such as leptin, normalized glucose tolerance, and improved insulin sensitivity in response to a high-fat diet. Through additional cellular reconstitution and depletion experiments, the investigators demonstrate that it is the Tregs together with anti-inflammatory T helper 2 cells that help to control obesity and the development of insulin resistance until overwhelmed by expanding Th1 cells. Immunotherapy that decreases the ratio of Th1 cells to Tregs in VAT results in long-lasting improved glucose tolerance of mice fed a high-fat diet.

But is the decrease in Treg proportions in the VAT of obese mice a cause or consequence of inflammation? Regardless, an upstream initiating event must trigger their loss. The nature of such an event is unclear, but it could be associated with hypoxia, or adipocyte stress or death. The studies establish a role for the adaptive immune system in reducing adipose tissue inflammation and insulin resistance and also suggest that stimulation of $CD4^+$ T cells by autoantigen may contribute to the accumulation of these cells in VAT. If so, identifying the antigenic epitopes in VAT may enable development of a vaccine against metabolic diseases like type 2 diabetes.

Initiating Inflammation and Insulin Resistance

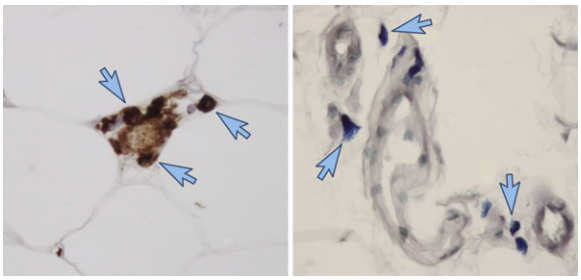
But why is there an inflammatory response in adipose tissue in the first place? Nishimura et al. (2009) address this question in their new study. They also analyze immune cell populations from the VAT of obese and lean mice to identify local immunological changes induced by obesity. Along with an increase in macrophages, they observe that the $CD8^+$ T cell fraction is elevated in the VAT of obese mice. In contrast, the $CD8^+$ T cell counts are the same or lower in other tissues from obese mice compared to lean mice, suggesting that $CD8^+$ T cells are selectively recruited to the VAT of obese animals. The authors perform a time course to evaluate the changes in immune cell populations during the progression of diet-induced obesity in the mice. They find that the increase in $CD8^+$ T cells in VAT occurs prior to the accumulation of macrophages or the reduction in Tregs. Further, whereas



Increased $CD8^+$ T cells (red) in visceral adipose tissue (blue, lipid droplets; green, nuclei) from diet-induced obese mice (right) compared to control mice (left). Photo courtesy of S. Nishimura.

systemic depletion of the $CD8^+$ T cell population has no effect on body weight or food intake in mice fed a high-fat diet, it does reduce the infiltration of macrophages in VAT, lowers production of proinflammatory cytokines, and ameliorates the insulin resistance and glucose intolerance induced by the high-fat diet. The authors also show that $CD8^+$ T cells and adipose tissue cooperate to induce macrophage differentiation and activation, thus initiating an inflammatory cascade. Further studies may reveal what cues within obese VAT initiate the accumulation of $CD8^+$ T cells and whether this accumulation plays a part in the reduction of Tregs in the VAT of obese animals.

Feuerer et al. (2009). Nat. Med. ***15***, 930–939.
Winer et al. (2009). Nat. Med. ***15***, 921–929.
Nishimura et al. (2009). Nat Med. ***15***, 914–920.



Macrophages (left, arrows) and mast cells (right, arrows) in white adipose tissue from obese humans. Photo courtesy of G.-P. Shi.

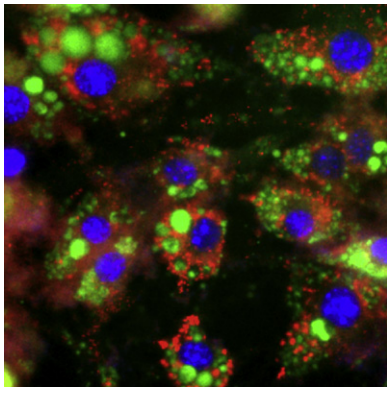
WAT's UP with Mast Cells?

The white adipose tissue (WAT) of mammals is known to contain macrophages and lymphocytes, but according to new work by Liu et al. (2009), it also harbors mast cells. These inflammatory cells are important not only in wound healing, allergy, and autoimmune disease, but also, as Liu et al. elegantly demonstrate, in obesity and diabetes. The authors find that there are more mast cells in WAT from obese humans and animals than from lean subjects. Further, when fed a high-fat diet, mice lacking mast cells have less total fat, lower body weight, increased glucose tolerance, and increased insulin sensitivity compared to wild-type mice. Pharmacological inhibition of mast cell activation has the same effect on metabolism, and more interestingly also reverses pre-established obesity and diabetes in mice fed a high-fat diet. The authors find that a lack of mast cells or their inactivation reduces blood vessel formation (angiogenesis) in WAT and hence formation of more adipose tissue. Indeed, they provide evidence that the mast cell-derived cytokines interleukin-6 and interferon-γ contribute to angiogenesis by stimulating cysteine protease cathepsin production by adipocytes, which leads to the release of proangiogenic peptides. These findings suggest that allergy drugs, which combat mast cell activity, may provide a new therapeutic approach for treating obesity.

Liu et al. (2009). Nat. Med. ***15***, 940–945.

When the Good Twin Wins

White adipose tissue (WAT), which stores energy as triglycerides, has a good twin, brown adipose tissue (BAT), which releases energy in the form of heat. In new work, Kajimura et al. (2009) reveal how to make BAT. The transcriptional regulator PRDM16 is known to control the switch between brown fat formation and muscle cell differentiation from a common precursor cell. Using a proteomics approach, the authors now isolate factors that cooperate with PRDM16 to regulate this developmental switch. They identify the transcription factor C/EBP-β as a critical binding partner in the PRDM16 transcriptional complex and show that it is required for PRDM16 to convert immature muscle cells into brown adipocytes. Surprisingly, the two factors are sufficient to induce the expression of brown fat-specific genes by mouse embryonic fibroblasts (MEFs), causing them to differentiate into adipocytes. Indeed, when transplanted into mice, MEFs expressing both factors form ectopic fat pads with the characteristics of BAT. For instance, by monitoring glucose uptake with positron emission tomography, the authors show that the engineered BAT acts like a sink for active disposal of glucose. This pathway might offer a new strategy to counteract obesity and metabolic disease by using BAT to dissipate stored energy.



Brown fat cells derived from mouse skin fibroblasts (red, mitochondria; green, lipid droplets; blue, nuclei). Photo courtesy of S. Kajimura.

Kajimura et al. (2009). Nature. ***460***, 1154–1158.

Angela Andersen