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GRANULOCYTES

A weighty role for eosinophils

New evidence published in *Science* showing that eosinophils can migrate to adipose tissue to maintain glucose homeostasis adds to our increasing appreciation of the links between immune and metabolic systems. We know that adipose tissue macrophages are an important component of the chronic low grade inflammation that characterizes the metabolic syndrome; this study now shows that eosinophils can modulate the phenotype of macrophages in adipose tissue to restrict this inflammation.

Whereas adipose tissue macrophages from obese mice have a classically activated inflammatory phenotype, those from healthy lean mice have an alternatively activated phenotype characterized by the expression of peroxisome proliferator-activated receptor-γ (PPARγ) and arginase 1 (encoded by *Arg1*). PPARγ expression in macrophages is induced by interleukin-4 (IL-4) and IL-13, so the authors set out to determine which cells express IL-4 in normal adipose tissue. In IL-4 reporter mice (in which cells that are capable of expressing IL-4 are marked by fluorescence), 90% of the IL-4-competent cells present in perigonadal white adipose tissue were eosinophils. Compared with blood eosinophils, these adipose tissue eosinophils had upregulated expression of sialic acid-binding immunoglobulin-like lectin F (Siglec-F; also known as Siglec-5), which indicated that they had migrated from the blood and were tissue-resident cells. Further flow cytometric and immunohistochemical analyses confirmed that eosinophils were present in the adipose tissue of various mouse strains, and the number of eosinophils correlated inversely with adiposity and mouse weight. Furthermore, adoptively transferred eosinophils could migrate into the adipose tissue of eosinophil-deficient mice, where their numbers remained stable, even after eosinophil numbers in the lung and spleen had decreased markedly.

As *Arg1* is a signature gene of alternatively activated macrophages and is induced by IL-4, the authors used YARG mice (which have a fluorescent reporter construct in *Arg1*) to identify these macrophages *in vivo*. They found that the numbers of *Arg1*-expressing macrophages were significantly decreased in the adipose tissue of YARG mice that lack IL-4 and IL-13. Interestingly, YARG mice crossed onto an eosinophil-deficient background also had significantly lower numbers of these macrophages in adipose tissue, but normal numbers could be restored by the adoptive transfer of bone marrow from hypereosinophilic mice (which have an increased number of eosinophils as a result of transgenic IL-5 expression). The number of eosinophils in the adipose tissue of these reconstituted mice was shown to correlate with the number of alternatively activated macrophages. However, adoptive transfer of bone marrow from hypereosinophilic mice that lack IL-4 and IL-13 did not reconstitute the *Arg1*-expressing macrophages.

So, what is the physiological significance of this role for eosinophil-derived IL-4 in sustaining an alternatively activated macrophage phenotype in adipose tissue? Hypereosinophilic mice had less visceral adipose tissue than wild-type mice when both strains were fed a normal diet, and this correlated with an improved response to a glucose challenge. Similarly, when fed a high-fat diet, eosinophil-deficient mice had increased adiposity compared with wild-type mice, and this was associated with impaired glucose tolerance as a result of decreased insulin responsiveness of the adipose tissue. These data indicate that eosinophils protect against diet-induced obesity through their effects on macrophages.

The authors speculate that eosinophils might have evolved to ensure metabolic homeostasis during chronic infection with intestinal parasites. In support of this, when mice fed a high-fat diet were infected with the helminth *Nippostrongylus brasiliensis*, increased numbers of adipose tissue eosinophils, correlating with improved insulin sensitivity and glucose tolerance, were observed long after the parasite was cleared.

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ORIGINAL RESEARCH PAPER Wu, D. *et al.* Eosinophils sustain adipose alternatively activated macrophages associated with glucose homeostasis. *Science* 24 March 2011 (doi:10.1126/science.1201475)