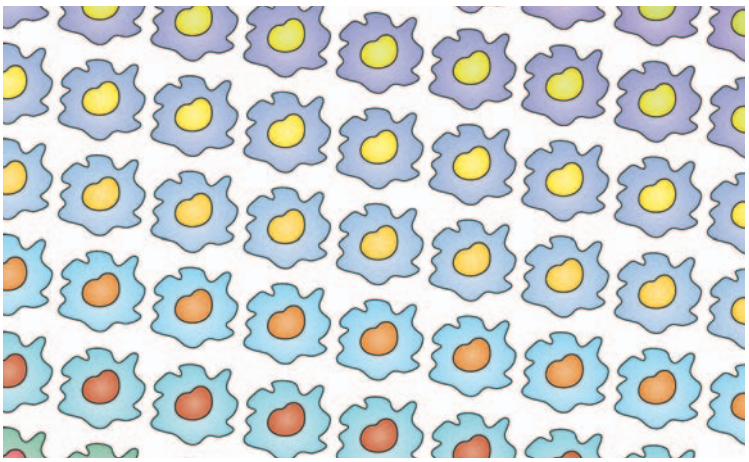
MACROPHAGES

Fat gets picky with macrophages

DOI:
10.1038/nri2026



Three studies published in *The Journal of Clinical Investigation* show that in mouse models of atherosclerosis and obesity distinct subsets of monocytes are recruited, different chemokine receptors are used and a phenotypic switch in macrophage differentiation occurs at sites of lipid accumulation. These studies provide new insights into the heterogeneity of monocyte recruitment and macrophage phenotype in lipid-rich tissues.

Atherosclerosis is an inflammatory disease that involves the accumulation of lipids and macrophages and the formation of plaques in the arteries. Mouse monocytes, the precursors of macrophages, can be divided into two main subsets on the basis of their expression of receptors that include Ly6C, GR1, CC-chemokine receptor 2 (CCR2) and CX_3C-chemokine receptor 1 (CX_3CR1). $Ly6C^{hi}$ monocytes (sometimes referred to as inflammatory monocytes) are $GR1^+CCR2^+CX_3CR1^{low}$, whereas $Ly6C^{low}$ monocytes are $GR1^-CCR2^-CX_3CR1^{hi}$. But what role do these circulating monocyte subsets have in the development of atherosclerosis?

Both Swirski *et al.* and Tacke *et al.* examined the repertoire of monocytes in apolipoprotein E (APOE)-deficient mice that were fed a high-fat diet — a mouse model of atherosclerosis. They found that the $Ly6C^{hi}$ monocyte subset continuously expanded in the periphery compared with $Ly6C^{low}$ monocytes. Interestingly, $Ly6C^{hi}$ monocytes were shown to efficiently accumulate in atherosclerotic lesions and Swirski *et al.* further showed that these cells differentiated into lesional macrophages.

Owing to the differential expression of chemokine receptors by these monocyte subsets, Tacke *et al.* examined the role of the individual receptors in the accumulation of monocytes in atherosclerotic plaques. They found that the inflammatory $Ly6C^{hi}$ monocytes used CX_3CR1 (as well as CCR2 and CCR5) to enter the plaques. $Ly6C^{low}$ monocytes could also enter atherosclerotic plaques, albeit less frequently. But unlike $Ly6C^{hi}$ monocytes, $Ly6C^{low}$ monocytes entered the plaques in a CCR2- and CX_3CR1-independent, CCR5-dependent manner and were more likely to become $CD11c^+$ dendritic-cell-like cells.

Lumeng *et al.* examined the phenotype of macrophages that migrate to adipose tissue in diet-induced obese mice compared with those in lean mice that were fed a normal diet. Macrophages isolated from adipose tissue from lean mice expressed many hallmarks of alternatively activated macrophages — that is, they expressed genes encoding the anti-inflammatory molecules interleukin-10 (IL-10) and IL-1 decoy receptor. By contrast, adipose-tissue macrophages from obese mice undergo a phenotypic switch to express pro-inflammatory molecules, such as tumour-necrosis factor (TNF) and inducible nitric-oxide synthase (iNOS). Interestingly, macrophages from CCR2-deficient obese mice expressed alternatively activated macrophage markers at levels similar to macrophages from lean mice. This indicates that, in the absence of CCR2-dependent recruitment, adipose-tissue macrophages might have reduced inflammatory capacity.

Collectively, these studies highlight potential targets to suppress the inflammatory response associated with lipid-associated diseases, such as obesity and atherosclerosis.

Olive Leavy

ORIGINAL RESEARCH PAPERS Swirski, F. K. *et al.* Ly-$6C^{hi}$ monocytes dominate hypercholesterolemia-associated monocytosis and give rise to macrophages in atheromata. *J. Clin. Invest.* **117**, 195–205 (2007) | Tacke, F. *et al.* Monocyte subsets differentially employ CCR2, CCR5, and CX_3CR1 to accumulate within atherosclerotic plaques. *J. Clin. Invest.* **117**, 185–194 (2007) | Lumeng, C. N. *et al.* Obesity induces a phenotypic switch in adipose tissue macrophage polarization. *J. Clin. Invest.* **117**, 175–184 (2007)
FURTHER READING Gordon, S. Macrophage heterogeneity and tissue lipids. *J. Clin. Invest.* **117**, 89–93 (2007)