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MACROPHAGES

Preventing lipid overload

Eaten too much over the holiday season? New research shows that macrophages in the mesenteric lymph nodes (MLNs) can offset the pro-inflammatory effects of overeating saturated fats by expressing angiopoietin-like protein 4 (ANGPTL4), which inhibits the generation of free fatty acids and subsequent lipid uptake by macrophages.

After eating saturated fats, long-chain fatty acids are incorporated as triglycerides into lipoprotein particles known as chylomicrons, which travel through the lymphatics before entering the blood. The triglycerides in chylomicrons are then hydrolysed by the enzyme lipoprotein lipase (LPL), which is highly expressed by endothelial cells and macrophages, to generate free fatty acids that fuel tissues such as the heart and muscles. Based on the knowledge that saturated fatty acids have potent pro-inflammatory effects and that ANGPTL4 is an inhibitor of LPL activity, the authors examined the effects of ANGPTL4 on diet-induced obesity and its metabolic consequences. They observed that feeding mice that are deficient for ANGPTL4 (*Angptl4*$^{-/-}$ mice) a diet rich in saturated fats had lethal consequences, associated with fibrinopurulent peritonitis, intestinal inflammation, a wasting disease and fat-laden ascites fluid. Further analysis showed that these mice had an abundance of chylomicrons in ascites fluid and a marked leukocyte infiltration of the intestine and mesenteric adipose tissues. These abnormalities were preceded by a massive acute-phase response, suggesting that fat-induced systemic inflammation was the cause.

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The authors also noted that the MLNs of *Angptl4*$^{-/-}$ mice on a high-fat diet were dramatically enlarged compared with *Angptl4*$^{-/-}$ mice on a diet of medium-chain fatty acids, which are not incorporated into chylomicrons and do not flow through the lymphatics. Consistent with chylomicrons having a direct pro-inflammatory effect, the MLNs of *Angptl4*$^{-/-}$ mice fed a high-fat diet contained a large number of lipid-laden macrophages, known as foam cells, and incubation of peritoneal macrophages from *Angptl4*$^{-/-}$ mice with an emulsion of chylomicrons led to foam cell formation and the induction of inflammatory gene expression. These effects were shown to be the result of loss of ANGPTL4-mediated inhibition of LPL, as they could be reproduced by incubation with a synthetic inhibitor of LPL and prevented by treatment with recombinant ANGPTL4. Finally, the mechanism of inflammation induced by excess chylomicrons was found to involve activation of endoplasmic reticulum stress pathways, which have previously been linked to inflammation.

Together, the findings suggest that ANGPTL4, the expression of which is upregulated in macrophages by chylomicron-derived fatty acids, is part of a feedback mechanism that protects MLN-resident macrophages from lipid overload and associated inflammation.

Lucy Bird

ORIGINAL RESEARCH PAPER Lichtenstein, L. *et al.* Angptl4 protects against severe proinflammatory effects of saturated fat by inhibiting fatty acid uptake into mesenteric lymph node macrophages. *Cell Metab.* **12**, 580–592 (2010)

FURTHER READING Osborn, O., Sears, D. D. & Olefsky, J. M. Fat-induced inflammation unchecked. *Cell Metab.* **12**, 553–554 (2010)