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Bloodless revolution

Subtle paracrine interactions between minor depots and contiguous tissues are restoring the reputation of adipose tissue, best known for its bulk and disease-causing properties. Micromanagement of fatty acids supports fast, efficient immune responses that avoid competition with other lipid-utilizing tissues. Such roles explain aspects of the gross anatomy of mammalian adipose tissue, long thought to be inexplicable

Aversion to adipose anatomy

Adipose tissue's 'image' has had a more thorough 'makeover' during the past 15 years than that of any other organ or tissue. For physiologists, proteomics and the enthusiasm of the pharmaceutical industry have made secreted peptides, leptin, visfatin, resistin, adiponectin and many more, the best-known aspect of this revolution. But at last, anatomists are trying to explain the tissue's organisation and anatomical relations, topics that concern surgeons, beauticians and ordinary people dissatisfied with their figures but not with their body mass.

One of the major triumphs of biology between the late eighteenth century and mid-twentieth century was showing that the arrangement of major organs in each group of animals follows a consistent body plan. In cases such as snakes and whales, where one or both pairs of limbs are absent, remnants are detectable during development and sometimes throughout life as vestigial structures. Many of the *hox* genes controlling these major anatomical changes have been identified. But many adipose depots seem to appear and disappear without such formalities, capricious variation that demoralised comparative anatomists: the topic is not addressed in Edwin Goodrich's 1930 treatise, *Studies on the Structure and Development of Vertebrates*. This omission led to the notion that its distribution and anatomical relations are without functional or phylogenetic significance. Goodrich's distaste for anatomically unruly tissues, plus the widening gap between comparative and functional anatomy and rising concern about obesity focussed attention on just one or two large, readily accessible adipose depots. Except for a few



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obvious deviants like metabolically inert, structural depots, all adipose tissue was presumed to respond similarly to blood-borne and neural signals.

Lymphoid structures of all endothermic vertebrates are closely associated with adipose tissue (Pond, 2003). In mammals, the lymph ducts run through the adipose tissue and divide into numerous fine branches near the nodes, thereby coming into contact with many of the



Figure 1. The source of the problem. 19th century prosection made for The Royal College of Surgeons' Hunterian Museum of the popliteal 'space' in the right hind leg of a dog, showing the 'important' components of the lymph and blood systems. Blood vessels and lymph nodes shorn of their adipose tissue still feature in modern textbooks, perpetuating the misleading notion that perivascular and perinodal adipose tissue are irrelevant or abnormal.

surrounding adipocytes. The omentum, a uniquely mammalian structure, is a patchwork of adipose and immune cells. Under the insidious influence of adipose-aversed anatomists (Fig. 1), most textbooks of immunology described these facts very briefly, if at all (Harvey, 2008).

In the early 1990s, the study of neurohumoral activity of perivascular adipose tissue around rat aorta was prompted by the observation that 'virtually every blood vessel in the body is surrounded to some degree by adipose tissue' (Soltis & Cassis, 1991). At about the same time, we began to investigate experimentally why epicardial and pericardial adipocytes (Marchington *et al.* 1989; Marchington & Pond, 1990) develop early in life and are not depleted in naturally lean wild animals. We were stumped by the most basic problem: laboratory rodents have variable, often negligible, quantities of cardiac adipose tissue. Advances in MRI and other scanning systems at the new millennium enabled the site-specific properties of these minor adipose depots to take centre stage in clinical and basic cardiovascular physiology (Iacobellis *et al.* 2008). Although long regarded as pathological, the cardiac depots are at last achieving respectability as integral, natural components of the heart (Fox *et al.* 2009); perinodal adipose tissue deserves similar status.

Minor depots, major players: lipids for lymph nodes

Many, possibly most, of the fatty acids incorporated into lipids in lymph node lymphoid cells that are newly formed in response to immune stimulation are derived from triacylglycerols in perinodal adipocytes (Pond, 2007, 2009). Site-specific properties of perinodal adipocytes equip them to supply

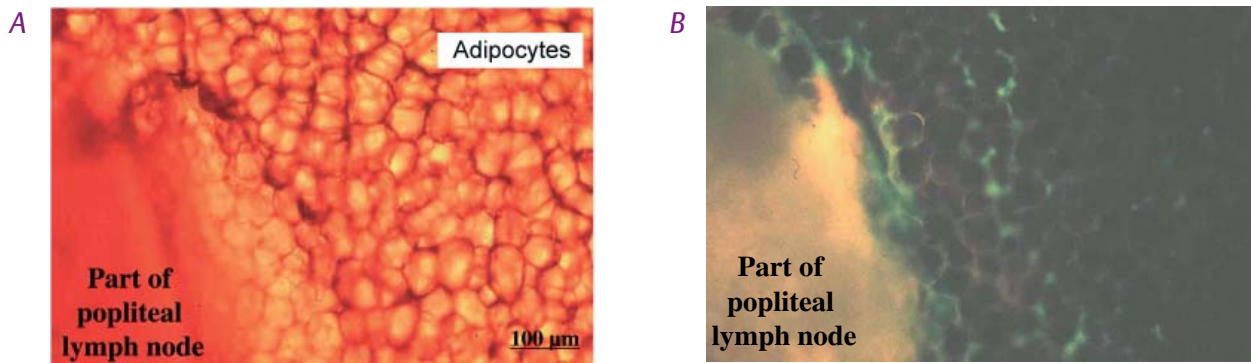


Figure 2. Perinodal adipose tissue functions as part of the lymph node. Thick section of part of a rat popliteal lymph node and its perinodal adipose tissue 1 h after subcutaneous injection of 2 mg lipopolysaccharide and staining with immunofluorescent antibody to type 1 receptors to tumour necrosis factor- α seen under (A) bright field (B) UV light. Perinodal adipocytes are indistinguishable from others until cytokine receptors appear on the surface, some within minutes of activation of the enclosed lymph node (MacQueen & Pond, 1998).

lymphoid cells. Spontaneous lipolysis in adipocytes within 2 mm of lymph node(s) draining the site of the immune stimulus increases within an hour of an experimentally elicited immune response, reaches a maximum after about 6 h and then wanes, disappearing totally after about 24 h. But the effect can be prolonged, possibly indefinitely, and elicited in adipocytes situated further from the lymph node, by repeated immune stimulation. The appearance of more receptors for tumour necrosis factor- α on perinodal adipocytes follows a similar time course (Fig. 2). Perinodal adipocytes respond much more strongly than those not anatomically contiguous to lymphoid structures to tumour necrosis factor- α , interleukin-4 and interleukin-6 and probably other cytokines. These signal molecules may mediate the paracrine

interactions between adipocytes and the lymphoid cells that they supply.

Lymph node-derived dendritic cells suppress lipolysis in perinodal adipocytes but those that permeate the adipose tissue stimulate lipolysis, especially after minor, local immune stimulation enabling lymph node lymphocytes and tissue dendritic cells to acquire fatty acids from the contiguous adipocytes. Their triacylglycerols contain more long-chain polyunsaturated fatty acids, precursors for eicosanoids and docosanoids. Chronic inflammation alters their composition, and hence that of the lymphoid cells they supply, counteracting adverse effects of dietary lipids.

The involvement of perinodal adipocytes in immune responses not only begins within minutes but can persist for months. In a rat

experiment to explore recovery from simulated low-level chronic inflammation, the numbers of dendritic cells recovered from the locally stimulating lymph node and its perinodal adipose tissue rose at least tenfold within 4 weeks and remained higher long after this regime was applied (Fig. 3). Perhaps surprisingly, perinodal adipose tissue around remote lymph nodes, especially those in the abdomen, responded similarly (Fig. 4).

Prolonged, low-level immune stimulation induces the local formation of more adipocytes, especially adjacent to the inflamed lymph node. This mechanism may contribute to hypertrophy of the mesentery and omentum in chronic inflammatory diseases such as HIV infection, and in smokers. The site-specific differences in fatty acid composition of lipids in the mesenteric adipose tissue expected from animal studies are absent from Crohn's disease patients, though they were found in similar samples from the controls (Westcott *et al.* 2005). The composition of lymphoid cells in mesenteric lymph nodes resembles that of the adjacent perinodal adipose tissue in the controls, but not in the diseased patients, which suggests that their adipocytes are not supplying fatty acids to cells in the adjacent lymph nodes. Lipids from the lymph node lymphoid cells from Crohn's disease patients contain much less of the eicosanoid precursor arachidonic acid (C20:4n-6) than the controls.

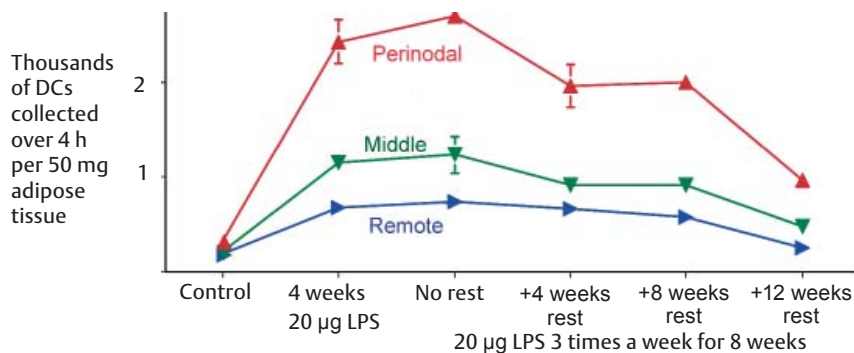


Figure 3. Perinodal adipose tissue stays alert. Mild chronic immune stimulation (local subcutaneous injection of 20 mg lipopolysaccharide (LPS) 3 times a week) increases interrelated dendritic cells (DCs) throughout the popliteal adipose depot, most in the perinodal, within 2 mm of the large popliteal lymph node, but significant in the 'middle' sample, about 5 mm from the node, and the 'remote' sample more than 10 mm away. Recovery is surprisingly slow: numbers of CCL21 (C6kine)-activated dendritic cells migrating from tissue samples are still higher more than 8 weeks after experimental inflammation ended. (Data from Sadler *et al.* 2005.)

The discrepancy between the composition of perinodal adipocytes and that of adjacent lymphoid cells contrasts with the concept of paracrine nutrition of lymphoid cells, but is consistent with reports that blood-borne mononuclear cells from Crohn's disease patients contain more, not less, n-3 polyunsaturated fatty acids. General defects in perinodal adipose tissue leading to impaired immune function could explain the association between the bowel disorders and other chronic diseases such as arthritis, eczema and rhinitis (Book *et al.* 2003). Could 'fat wrapping', the distinctive but as yet unexplained feature of Crohn's disease, be adipose tissue's long-term response to persistent signals from its client immune cells for important fatty acids that it is unable to supply?

Paracrine provision: private, personalised, potent

By ensuring that specific, possibly scarce, fatty acids reach the cells that really need them when and where required, perinodal adipocytes may be compared to tRNA that marshals amino acids into position or chaperonins that help proteins fold correctly. Local provisioning of lymphoid tissues partially

emancipates immune function from fluctuations in food quantity and composition. Energy-consuming systemic responses to immune challenges, such as fever, avoid competition for essential lipids with proliferating lymphoid cells; anorexia may help to 'put adipose tissue in charge' of lipid management during the crisis. Supplying fatty acids of slightly different composition also provides local sources of structural, and perhaps also functional, diversity of lymphoid cells that hitherto have been classified by genes and proteins (Gehring *et al.* 2008). Paracrine interactions, especially those involving only a small fraction of the total adipose tissue, cannot easily be detected as changes in blood composition. But blood supply to perinodal adipose tissue increases during inflammation so they could probably be manipulated by blood-borne drugs.

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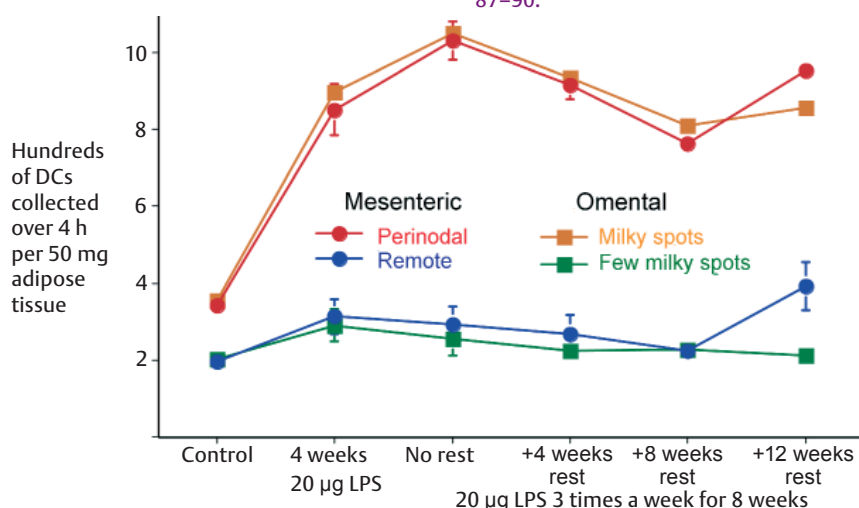


Figure 4. Even remote, mild inflammation gradually gets to the guts. Mild chronic immune stimulation of the skin over the hind leg increases interchelated dendritic cells in the adipose tissue around remote as well as local lymph nodes. This effect is substantial in the mesenteric and milky spot-rich areas of the omentum, where it persists for at least 3 months after experimental inflammation ends, but is almost undetectable in the more frequently sampled mesenteric adipose tissue located more than 10 mm from a lymph node. It may be among the ways that chronic or repeated inflammation slowly induces hypertrophy of intra-abdominal adipose tissue. (Data from Sadler *et al.* 2005.)

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