Inflammatory lipid mediators in adipocyte function and obesity

Abishek Iyer, David P. Fairlie, Johannes B. Prins, Bruce D. Hammock and Lindsay Brown

Abstract | Survival of multicellular organisms depends on their ability to fight infection, metabolize nutrients, and store energy for times of need. Unsurprisingly, therefore, immunoregulatory and metabolic mechanisms interact in human conditions such as obesity. Both infiltrating immunoinflammatory cells and adipocytes play critical roles in the modulation of metabolic homeostasis, so it is important to understand factors that regulate both adipocyte and immune cell function. A currently favored paradigm for obesity-associated metabolic dysfunction is that chronic macronutrient and/or lipid overload (associated with adiposity) induces cellular stress that initiates and perpetuates an inflammatory cycle and pathophysiological signaling of immunoinflammatory cells and adipocytes. Many lipid mediators exert their biological effects by binding to cognate receptors, such as G-protein-coupled receptors and Toll-like receptors. This process is tightly regulated under normal physiological conditions, and any disruption can initiate disease processes. Observations that cellular lipid loading (associated with adiposity) initiates inflammatory events has encouraged studies on the role of lipid mediators. In this review, we speculate that lipid mediators act on important immune receptors to induce low-grade tissue inflammation, which leads to adipocyte and metabolic dysfunction.

Iyer, A. *et al. Nat. Rev. Endocrinol.* **6**, 71–82 (2010); doi:10.1038/nrendo.2009.264

Introduction

Obesity—a medical condition in which excessive fat storage occurs in tissues—is closely associated with metabolic dysfunction, which is a major cause of morbidity and mortality in most societies.[1,2] (Box 1) Clinical features of obesity, especially centrally distributed abdominal fat, combined with hyperglycemia, hyperlipidemia and hypertension, form the basis for varying definitions of the metabolic syndrome.[3–5] Resultant abnormalities in glucose, lipid and fluid homeostasis commonly manifest as cardiovascular disease, insulin resistance and/or type 2 diabetes mellitus.[2] Lifestyle changes, such as an excessive caloric intake, are indicated as one of the most important factors in initiating obesity and associated metabolic and cardiovascular disorders. Clinical studies have suggested that excessive macronutrient intake promotes signs of cellular stress and leads to metabolic dysfunction.[6,7] A better molecular understanding of the biochemical mechanisms that underpin metabolic dysfunction has the potential to uncover new therapeutic strategies for the treatment of obesity and the metabolic syndrome. This Review aims to stimulate debate by providing some mechanistic insights and hypotheses for how excess macronutrient intake might induce the initiation and propagation of the metabolic syndrome.

Competing interests
J. B. Prins declares an association with the following company: Adipogen Pty Ltd. B. D. Hammock declares an association with the following company: Arête Therapeutics. See the article online for full details of the relationships. The other authors declare no competing interests.

Obesity and inflammation

The idea that chronic low-grade inflammation underlies obesity and metabolic dysfunction[8–12] has become credible in recent years (Figure 1, Table 1). Excessive nutrient consumption or storage has the potential to overload signaling networks, and this overload affects both the immune and metabolic systems because these systems are closely linked and interdependent.[13] Many hormones, cytokines, signaling proteins, transcription factors and bioactive lipids have both immune and metabolic roles.[14] Unsurprisingly, therefore, metabolic and immune regulatory mechanisms interact in human disease. Five sets of clinical observations supported by evidence from *in vitro* studies and/or studies of animal models (Table 1) demonstrate that obesity and metabolic dysfunction are associated with a low-grade chronic inflammatory state. These five observations are discussed below.

Increased inflammation and oxidative stress

Metabolic dysfunction is associated with increased tissue and systemic inflammation and oxidative stress. Increased levels of pro-inflammatory proteins are found in the circulation and metabolically relevant tissues of obese individuals.[2] Adipose tissue releases many bioactive mediators, including inflammatory cytokines, that influence body weight homeostasis and induce changes in cardiovascular structure and function, glucose metabolism, blood pressure, lipid metabolism, coagulation, fibrinolysis and inflammation; these changes lead to endothelial dysfunction and atherosclerosis.[2,15,16]

Plasma concentrations of inflammatory markers (for example intercellular cell adhesion molecule 1, vascular

School of Biomedical Sciences (**A. Iyer**), Institute for Molecular Bioscience (**D. P. Fairlie**), Diamantina Institute for Cancer, Immunology and Metabolic Medicine (**J. B. Prins**), The University of Queensland, Brisbane, Qld 4072, Australia. Department of Entomology and Cancer Center, University of California, Davis, CA 95616, USA (**B. D. Hammock**). Faculty of Sciences, University of Southern Queensland, Toowoomba, Qld 4350, Australia (**L. Brown**).

Correspondence to:
L. Brown
l.brown@uq.edu.au

Key points

- The idea that chronic low-grade inflammation underlies obesity and metabolic dysfunction has become credible in recent years
- Clinical studies have shown that excess macronutrient intake promotes signs of inflammatory stress and leads to metabolic dysfunction
- Metabolic dysfunction may not be just a disease of obesity but a disease of dysfunctional adipocytes, induced either by excess feeding (obesity), malnutrition, starvation or possibly an immunoinflammatory disorder
- Elevation of the concentration of circulating and adipose-tissue-localized inflammatory lipid mediators contributes to inflammatory cell activation, adipocyte growth, development and dysfunction, which leads to metabolic disturbances
- Lipid mediators might induce adipocyte dysfunction in obesity by over-stimulating or inhibiting cognate receptors, such as G-protein-coupled receptors and Toll-like receptors
- Immune system modulation might provide a means to intervene and re-establish tolerance to the abnormal metabolic homeostasis that occurs in obesity

Box 1 | Clinical perspective

The prevalence of obesity and the metabolic syndrome has escalated throughout the developed world; the growing incidence of childhood obesity being especially worrying

In 2005, it was estimated that nearly 3.24 million Australians (approximately 16%) were obese including 280,000 young Australians aged 5–19 years. Furthermore, it is predicted that this number of obese Australians will escalate to nearly 7.2 million by 2025 and that nearly 50% will have type 2 diabetes mellitus

Environmental factors, including high-calorie diets and sedentary lifestyles have contributed to the obesity epidemic

The therapeutic potential of anti-inflammatory drug regimes will become clearer with ongoing clinical trials with NSAID drugs and soluble epoxide hydrolase inhibitors for obesity, type 2 diabetes mellitus and metabolic dysfunction

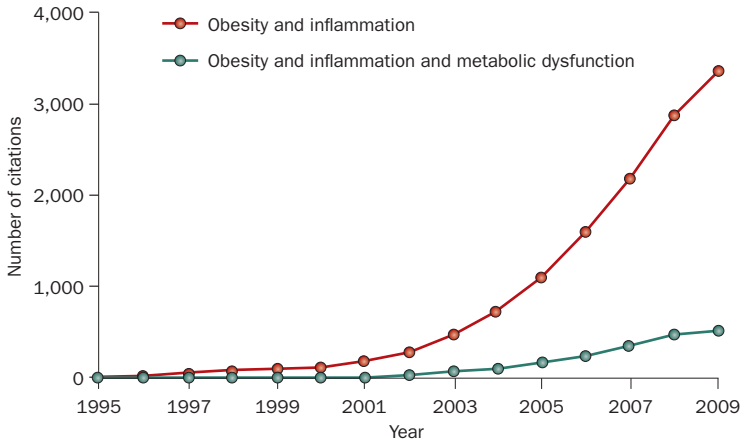

Figure 1 | Obesity, metabolic syndrome and inflammation citations as a function of year from 1995. The plot shows cumulative PubMed citations to keywords "Obesity & inflammation" and "Obesity & inflammation & metabolic dysfunction". This plot highlights the increasingly accepted relationship between obesity and inflammation, as well as the poor link between metabolic dysfunction in obesity and chronic inflammation.

cell adhesion molecule 1, C-reactive protein, asymmetric dimethyl-L-arginine, secretory phospholipase A_2 and lipoprotein-associated phospholipase A_2) and metabolic markers (such as homeostatic model assessment of insulin resistance) correlate with BMI in morbidly obese patients.[17–19] Some markers are nonspecific, such as C-reactive protein. This marker is elevated in cardiovascular and renal diseases. Other pro-inflammatory molecules, such as tumor necrosis factor (TNF), interleukin (IL)-6 and plasminogen activator inhibitor 1, are also elevated in inflammatory states unrelated to obesity.

An increased population of tissue inflammatory cells may promote production of reactive free radicals and perpetuate the state of chronic oxidative stress found in patients with obesity and metabolic dysfunction.[20] Chronic inflammatory and oxidative stress occur together and feed-forward in metabolic dysfunction. To fuel this process, inflammatory cells such as leukocytes increase expression and activity of pro-oxidant enzymes including myeloperoxidase and NADPH oxidases.[20–22]

Altered insulin sensitivity

Chronic inflammation is associated with altered insulin sensitivity in obesity and metabolic dysfunction. Increased plasma concentrations of pro-inflammatory cytokines, adipokines, and lipids such as nonesterified fatty acids in obese individuals may reduce insulin action and initiate insulin resistance, hyperglycemia and metabolic dysfunction.[2] Insulin alone possesses anti-inflammatory properties in contrast to the pro-inflammatory effects of glucose.[23] Acute oral challenge with glucose in healthy humans increases superoxide radical generation in leukocytes and also activates redox-sensitive pro-inflammatory transcription factors, including nuclear factor κB and activator protein 1.[7,24] In patients with acute myocardial infarction, insulin infusion reduces plasma C-reactive protein concentrations.[23] Furthermore, in patients with type 2 diabetes mellitus, insulin infusion suppresses expression of immune inflammatory receptors such as Toll-like receptors (TLR) 2 and 4.[23]

Anti-inflammatory intervention

Anti-inflammatory intervention is helpful in metabolic dysfunction. Pre-clinical and clinical data suggest that metabolic dysfunction can be improved by treatment with anti-inflammatory agents such as NSAIDs, salicylates and aspirin.[25–29] This observation is supported by NIH reports that list 13 ongoing human clinical trials with anti-inflammatory drug intervention for the treatment of obesity and metabolic dysfunction.

Chronic inflammatory conditions

Diseases involving chronic inflammation are known to be associated with premature and/or more severe metabolic dysfunction, and the drugs used in these varying conditions are not causative. Such diseases include rheumatoid arthritis, inflammatory bowel disease and cystic fibrosis.[30,31]

Pleiotropic anti-inflammatory effects

The final observation that links chronic low-grade inflammation, obesity and metabolic dysfunction is that drugs with pleiotropic anti-inflammatory effects are effective in metabolic disorders. The beneficial metabolic effects on morbidity and mortality of angiotensin receptor blockers,[32] statins,[33,34] angiotensin-converting enzyme inhibitors[35] and peroxisome proliferator-activated receptor (PPAR) agonists[36,37] cannot be fully explained by their respective lipid lowering, insulin sensitizing and blood-pressure-lowering effects. These classes of drugs have pleiotropic functions and bring about considerable reductions in tissue and systemic inflammation.

The five observations show prominent relationships between inflammation, obesity and metabolic dysfunction; however, some issues remain unresolved. For example, obesity without metabolic dysfunction ('fit fat') is not uncommon and, conversely, some lean people have severe metabolic disease. Reasons behind this paradox remain to be identified. A logical hypothesis is that metabolic disease is not just a disease of obesity, but a disease of dysfunctional adipocytes induced either by excess feeding (obesity), malnutrition, starvation or possibly an immunoinflammatory disorder. Hence, identification of the factors that regulate adipocyte function is crucial in order to understand metabolic dysfunction. The roles of lipid mediators in adipocyte dysfunction and obesity will, therefore, now be described, as this knowledge provides an essential framework upon which to conduct research to identify new targets for treatment.

Table 1 | Key conceptual advances

Year of publication	Study (times cited)
2000	Yudkin *et al.*[132] (613)
2003	Weisberg *et al.*[44] (1142) Xu *et al.*[133] (834) Ridker *et al.* [19] (800) Esposito *et al.*[18] (459) Wang *et al.*[134] (419) Rajala *et al.*[135] (242)
2004	Dandona *et al.*[136] (302)
2005	Cai *et al.*[137] (333) Arkan *et al.*[138] (252) Dandona *et al.*[5] (188) Masoudi *et al.*[139] (99) Christiansen *et al.*[140] (19)
2006	Bastard *et al.*[15] (131)
2007	Shoelson *et al.*[141] (66) Kim *et al.*[142] (33)
2008	Heilbronn *et al.*[143] (12) Cani *et al.*[144] (12) Rocha *et al.*[145] (3)

Table shows citations that have linked obesity, metabolic dysfunction and inflammation in the past decade. Times cited quoted from Essential Science Indicators®, ISI Web of Science (Thomson Reuters, Philadelphia, PA).

Adipocyte dysfunction and inflammation

Obesity is a condition of energy imbalance between intake and expenditure. When an organism encounters excess food, it conserves the nutrients either as glycogen for short-term storage or as lipids for longer storage duration. Lipids are major constituents of cellular membranes, and lipid combustion yields more energy than almost any other source.[13,38] During evolution, limited or spasmodic nutrient supply forced organisms to manage the need for portable energy with the need to efficiently store fatty acids, and to develop effective transcriptional machineries such as PPARs that are activated by fatty acids and regulate the cellular response.[13] For 21st century humans, however, dietary calories are no longer limited for most individuals in developed societies, which has led to an epidemic of obesity and associated metabolic disturbances.

The currently favored paradigm for obesity-associated metabolic dysfunction is that a chronic cellular energy and/or lipid overload characterized particularly by abdominal obesity induces cellular stress. In turn, this stress initiates and perpetuates oxidative and inflammatory cascades, with the consequence of continuous pathophysiological signaling of adipocytes.

Adipocytes provide an important reversible storage depot for excess energy as lipids.[38] In obesity, excessive adipose tissue growth is associated with hypertrophy and hyperplasia of adipocytes.[39] Excess energy intake or decreased expenditure results in excess triacylglyceride accumulation in adipose tissue, which results in hypertrophy.[40] Adipose tissue mass expands and redistributes throughout adult life, proliferative adipocyte precursor cells standing ready to respond to increased demands for energy storage.[41] Thus, hyperplasia results from recruitment of new adipocytes, which involves the proliferation and differentiation of pre-adipocytes (adipogenesis).[42] However, whether hypertrophy and hyperplasia coexist or whether hypertrophy precedes hyperplasia is unclear.[43] Although adipocytes have specifically evolved to store excess energy, the morphological changes associated with adipocyte fat uptake and homeostasis have many consequences for the organism. In storing excess energy as fat, adipocyte function can become compromised. The production of various endocrine, paracrine and autocrine factors by mature adipocytes could play important roles in recruitment of new adipocytes.

Like other organs, adipose tissue contains a resident population of cells of the innate immune system, in particular macrophages and T lymphocytes.[15,44–46] These resident inflammatory cells are spatially and temporally associated with adiposity and may also alter adipocyte secretory profiles.[44] In general, both mammalian liver and adipose tissue have comparable structural blueprints in which metabolic cells such as adipocytes and hepatocytes are in close proximity to immunoregulatory cells such as Kupffer cells and/or macrophages and/or T cells and with immediate access to a vast network of blood vessels.[47] This environment encourages both of these cell types to sustain continuous dynamic interactions between immune and metabolic responses and regulate signaling networks that communicate with sites such as pancreatic islets and muscle.[47]

Alteration in both population and function of adipose tissue T cells occurs early during the development of obesity.[48] The majority of resident T cells in adipose

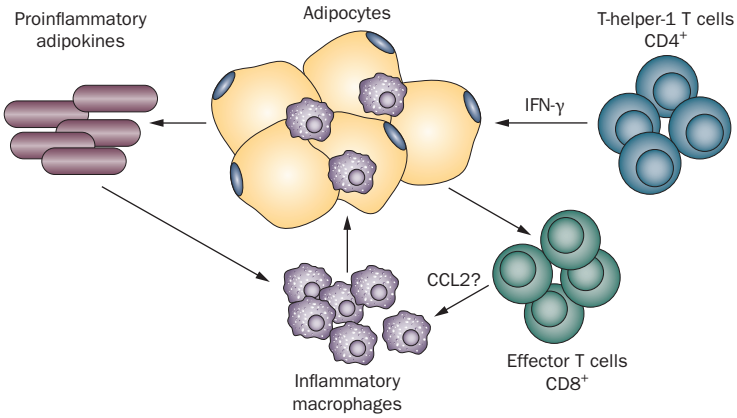

Figure 2 | Inflammatory cells and adipocytes in adipose tissue in obesity. Alteration in the population of adipose tissue T cells occurs early during obesity and is currently understood as the tipping point in propagating the inflammatory cycle. In adipose tissue of obese individuals, the decrease in the number of T_{REG} cells and the early appearance of $CD8^+$ effector T cells, which aid infiltration of pro-inflammatory macrophages, may disrupt adipocyte homeostasis and trigger an immune response that results in further recruitment of circulating pro-inflammatory macrophages. This recruitment (possibly triggered via chemokines such as CCL2) is then followed by macrophage activation and induction of the expression and release of cytokines and adhesion molecules. In addition, T-helper-1 T cells secrete IFN-γ and aid inflammatory macrophage recruitment and activation.

tissue of lean individuals are T-regulatory (T_{REG}) cells and T-helper-2 cells[49] that, together with resident macrophages, produce IL-10 and impede inflammation.[49] T_{REG} cells regulate innate immunity and express chemokine receptors that may respond to cytokines produced by adipocytes.[49] Conversely, the predominant resident T cells in adipose tissue of obese individuals are T-helper-1 and $CD8^+$ effector T cells.[50]

In adipose tissue of obese individuals, the decrease in the number of T_{REG} cells and the early appearance of $CD8^+$ effector T cells, which aid infiltration of pro-inflammatory macrophages, together may disrupt adipocyte homeostasis and trigger an immune response that leads to further recruitment of circulating pro-inflammatory macrophages.[48] This recruitment is then followed by macrophage activation, chemoattraction and induction of the expression and release of cytokines and adhesion molecules.[51,52] These inflammatory effectors can also act in a paracrine manner (i.e. by being transferred from macrophages to adipocytes), which further stimulates other pro-inflammatory cytokines, macrophages and adipokines and hence links inflammation to adipocyte dysfunction (Figure 2).[2,15,44]

Interestingly, in a macrophage environment, preadipocytes can be effectively converted into macrophages, which suggests cellular plasticity in adipocyte precursors.[53] Macrophage infiltration into the adipose tissue of obese individuals alters the expression of genes that encode proteins involved in inflammatory processes in those cells.[15,44] Of note, reduction in body weight in humans is accompanied by a decrease or even a normalization of pro-inflammatory effectors including cytokines, adhesion molecules and eicosanoids.[54–56] Macrophages, apart from playing a role in the local adipocyte pro-inflammatory environment, alter and potentiate systemic inflammation especially in chronic inflammatory states.[57]

The first report on the infiltration of macrophages into adipose tissue was published in 2003,[44] but we still do not know whether a specific immune cell type, and which one, is mainly responsible for metabolic dysfunction. Evidence available to date suggest that many different types of immune cells including macrophages, monocytes, leukocytes, platelets, T cells, T_{REG} and mast cells may contribute important roles to the development of metabolic diseases, particularly in the context of obesity and type 2 diabetes mellitus. Further studies are clearly necessary to tease out the roles of individual immunoinflammatory cells in metabolic dysfunction.

Adipocytes produce many signaling proteins such as TNF, adipsin, angiotensinogen and leptin, and lipids including fatty acids, prostaglandins and short-chain acylglycerols (for example, monobutyrin), all of which may be involved directly in adipocyte hypertrophy and adipogenesis.[42,58–60] Many endocrine factors, such as insulin, catecholamines, insulin-like growth factor I, growth hormones, glucocorticoids and thyroid hormones, influence lipolysis and promote proliferation and differentiation of pre-adipocytes.[61–64] Although regulation of adipocyte homeostasis by these endocrine factors has been extensively studied, the local regulation of triglyceride accumulation and differentiation of preadipocytes by autocrine and paracrine factors is not well understood. Observations that cellular lipid loading is an initiator of inflammation have encouraged studies of the underlying mechanisms; lipid mediators being key suspects in this initiation process given their precursor status to inflammatory pathways.

Inflammatory lipid mediators

Lipid mediators are involved in many human diseases, including rheumatoid and other forms of arthritis, multiple sclerosis, reproductive disorders, intestinal polyposis, bronchial asthma, pulmonary and cardiac fibrosis, and numerous chronic inflammatory diseases.[65] Historically, lipid mediators were considered to be energy sources, but more recently the importance of lipid mediators as intracellular signaling molecules in immune defense has become appreciated. Prostaglandins, thromboxane, leukotrienes, lipoxins, epoxyeicosatrienoic acids, other fatty acid epoxides, platelet-activating factor (PAF), lysophosphatidic acid, sphingosine-1-phosphate, 2-arachidonoylglycerol and other lipid amides are now collectively referred to as lipid mediators (Table 2). Some of the enzymes involved in the production of these mediators are phospholipase A_2, lysophospholipid acyltransferases, PAF acetyltransferase, cyclooxygenases, lipoxygenases and cytochrome P450 enzymes.

Lipid mediators can act as ligands for important immune receptors such as class A G-protein-coupled receptors and TLRs, and this receptor activation can initiate and perpetuate an innate immune response.[65] In relation to obesity and metabolic dysfunction, we speculate that lipid mediators localized in the circulation and adipose tissue bind to these immune receptors

and induce low-grade tissue inflammation. This process leads to adipocyte and metabolic dysfunction, without overt signs of inflammation. In support of this hypothesis, a recent study suggests that high fat, high carbohydrate feeding induces oxidative and inflammatory stress and an increase in plasma endotoxin concentrations together with increased expression of TLR2, TLR4 and suppressor of cytokine signaling 3 in healthy lean individuals.[66] Hence, it has become increasingly important to investigate the nexus between lipids, inflammation and adipocyte function in order to clarify the emerging roles of circulating lipid mediators in obesity and metabolic dysfunction.

Inflammatory fatty acids

Obesity and insulin resistance are associated with high circulating concentrations of free fatty acids, particularly post-prandially.[67–69] A potential link between adipose tissue fatty acid composition and obesity has been highlighted in several studies.[70–72] Arachidonate is the primary source of fatty acids that mediate inflammatory responses (Table 2). In human studies, high levels of arachidonate in adipose tissue correlate with a 20-fold increase in the likelihood of abdominal obesity.[70] In obese children from the Mediterranean region, arachidonate levels are increased in adipose tissue compared to those in lean children.[73] Infant piglets fed 0.5% arachidonate for 2 weeks show a 27% increase in body weight without change in body length, which suggests an increase in fat mass.[74] Plasma arachidonate concentrations and human infant body weight at 4 months are correlated, consistent with a role of arachidonate in adipose tissue development.[43,75] Taken together, these findings link arachidonate level in adipose tissue with obesity (Figure 3).

Since arachidonate and fatty acid products in adipose tissue are important in regulating lipolysis, lipogenesis and adipogenesis, it is probable that phospholipase A enzymes that release arachidonate from membrane phospholipids may be directly involved in these three processes (Figure 3b).[39] Of interest is the discovery of an adipose-tissue-specific phospholipase A_2 enzyme (Group XVI phospholipase A_2 or AdPLA), which has been characterized in white adipose tissue in mice.[76] This enzyme is a small (18 kDa), membrane-associated, calcium-dependent, intracellular phospholipase A_2 that fairly selectively processes phosphatidylcholine at the SN-2 position of the acyl chain. Knockout of the gene that encodes Group XVI phospholipase A_2 in mice increases the rate of lipolysis by markedly reducing prostaglandin E_2 levels. These mice also show reduced tissue mass, triglyceride levels, insulin resistance and increased fatty acid oxidation in adipocytes in response to either a high fat diet or leptin deficiency.[39]

Group IV phospholipases are calcium-dependent enzymes and are commonly referred to as cytosolic phospholipase A_2. One member of this group—Group IVA phospholipase A_2—is also involved in the storage of lipids in the adipose tissue. Mice devoid of group IVA phospholipase A_2 show a marked decrease in adipocyte size and the ratio of epididymal fat pad weight to body weight compared with wild type animals.[77] Furthermore,

Table 2 | Classification of lipid mediators

Class	Lipid mediators
Fatty acids	Prostaglandins Thromboxane Leutrotrienes Lipoxins Protectins Resolvins Epoxyeicosatrienoic acids Other fatty acid epoxides
Phospholipids	Platelet-activating factor Oxidized lipids
Lysophospholipids	Lysophosphatidic acid Sphingosine-1-phosphate
Others	2-Arachidonylglycerol Other lipid amides

Group V secretory phospholipase A_2 enzymes play an important part in the release of arachidonate and subsequent production of cysteinyl leukotrienes, prostaglandin E_2 and other inflammatory eicosanoids from macrophages, which contributes to the inflammatory cascade.[78] Phospholipase A_2 may also be important in releasing arachidonate from inflammatory cells to be later metabolized by other cells such as adipocytes. As a result, adipocytes may become chronically energy overloaded, which may alter their secretory profiles. Secretory phospholipases such as secretory phospholipase A_2 IIA from platelets and inflammatory cells could act to release arachidonate from neighboring cells including adipocytes.[79]

Previous studies have shown that inhibition of secretory phospholipase A_2 IIA in young spontaneously hypertensive rats does not affect cardiac tissue macrophage infiltration but inhibits cardiac fibrosis.[80] These findings are consistent with the concept that inflammatory cells provide a source of phospholipase A_2 and associated inflammatory fatty acids.[80] Cytosolic phospholipase $A_2\alpha$ is involved in arachidonate release induced by secretory phospholipase A_2 and is also responsible for arachidonate release from neutrophils.[81] As we shall show herein, evidence is emerging for specific roles of arachidonate and fatty acid metabolites as factors that mediate the inflammatory state that occurs in adipocyte dysfunction and obesity.

Prostaglandins and thromboxanes

The metabolism of arachidonate by cyclooxygenase 1 and cyclooxygenase 2 is an essential step in the synthesis of prostanoids, which include the prostaglandins (Figure 3a). Prostanoids exert autocrine or paracrine actions on a family of prostanoid membrane receptors.[82] At least nine types of human prostanoid receptor exist.[83] Prostanoid responses are mediated by nuclear receptors such as PPARα, γ or δ,[84,85] or by specific cell-surface G-protein-coupled receptors,[86,87] Prostaglandins bind to prostanoid receptors coupled with G-protein-coupled receptors to increase cyclic AMP concentrations and, thereby, activate a number of signaling transduction cascades.[88,89] Several studies have suggested that prostanoids modulate differentiation and maturation in

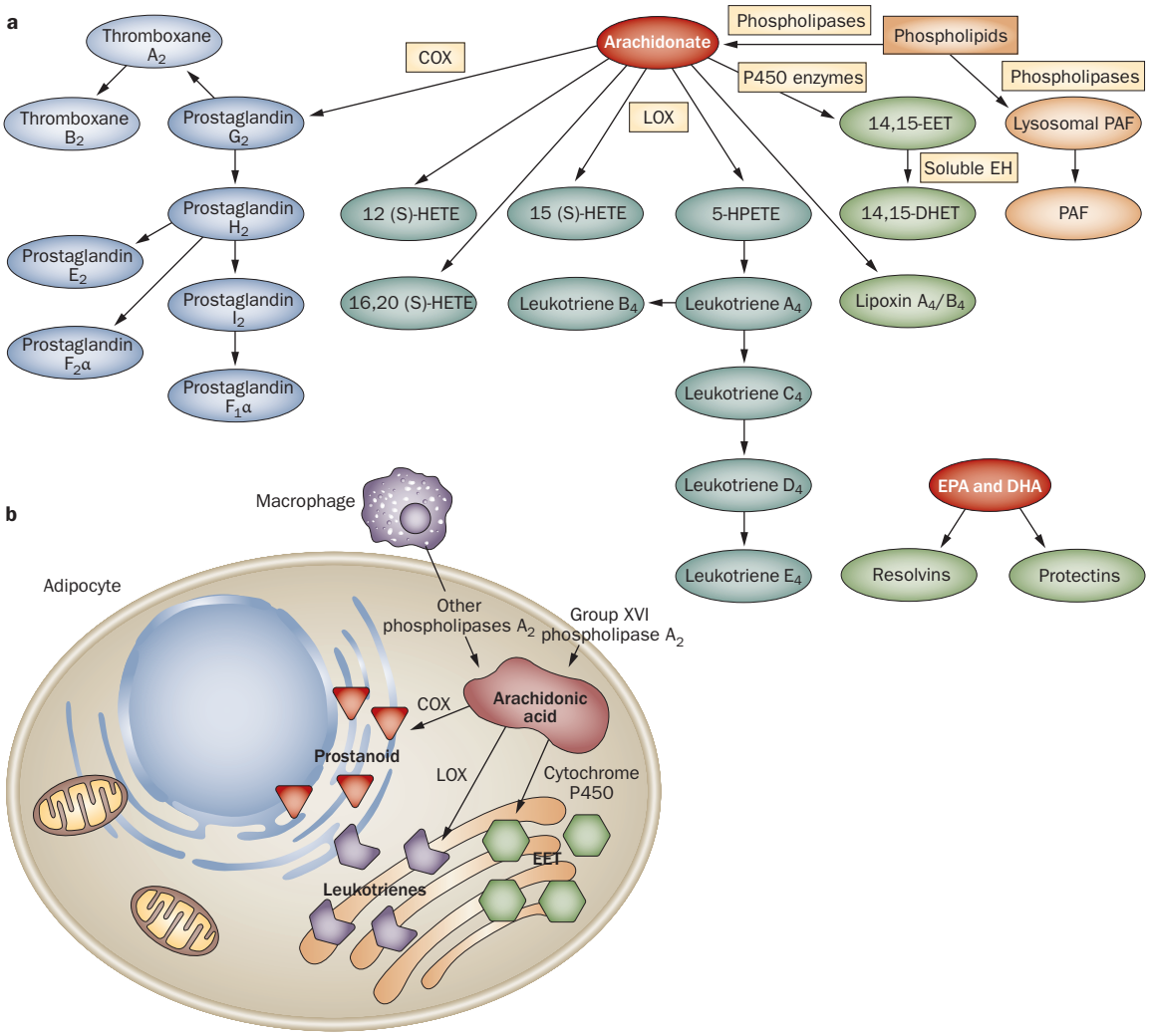

Figure 3 | Important lipid mediators in obesity and metabolic dysfunction. **a** | Arachidonate and fatty acid products in adipose tissue are important in regulating lipolysis, lipogenesis and adipogenesis. Phospholipids are broken down into arachidonate by phosholipase enzymes. The biosynthesis of fatty acid products from arachidonate are regulated by three major enzymes—cycloxygenases, lipoxygenases and cytochrome P450s. Cyclooxygenase 1 and 2 metabolize arachidonate to form prostanoids, including the prostaglandins. Lipoxygenases metabolize arachidonate into hydroperoxyeicosatetraenoic acids that are converted into many bioactive eicosanoids including leukotriene A_4. Cytochrome P450 epoxygenases metabolize arachidonate to either epoxyeicosatrienoic acids or hydroxyeicosatrienoic acids or other fatty acid epoxides. Of these fatty acid metabolites, lipoxin A_4/B_4, 14,15 epoxyeicosatrienoic acids, resolvins and protectins may aid in resolution and active reduction in inflammation compared to the others. **b** | Adipocyte dysfunction induced by intracellular inflammatory lipid signaling. In the adipose tissue, the production of archidonate fatty acid products can be catalyzed by membrane-associated group XVI phospholipase A_2, or by other types of phospholipases A_2 released from macrophages and other inflammatory cells. Increased prostanoids and leukotrienes probably initiate adipocyte dysfunction while EETs help re-establish adipocyte homeostasis. Abbreviations: COX, cyclooxygenases; EETs, epoxyeicosatrienoic acids; LOX, lipoxygenases.

adipocytes.[90,91] Of these prostanoids, increased concentrations of both prostaglandin E_2 and prostaglandin I_2 induce adipocyte dysfunction.[90] Prostaglandin E_2 acts on E-prostanoid-3 receptors to decrease lipolysis by decreasing cAMP concentrations and, thereby, contributes to the hypertrophic development of adipocytes.[39] Prostaglandin E_2 also increases leptin production in mouse adipose tissue primary culture.[92] In general, leptin is a circulating signal protein that reduces appetite.[1] Obese people have unusually high circulating concentrations of leptin, probably because they have enlarged adipose stores with increased prostaglandin E_2 concentrations that result in increased leptin production. However, the high sustained concentrations of leptin mean that leptin desensitization occurs and these individuals are resistant to the appetite-suppressing effects of leptin.[1,93] Furthermore, administration of prostaglandin E_2 to rats and stimulation of rat hepatocytes with prostaglandin E_2 induces an increase in triglycerides in the liver and other cells, which suggests that prostaglandin E_2 participates in deposition of triglycerides in adipocytes and liver. These responses contribute to the complexity of the pathogenesis of obesity and the symptoms of the metabolic syndrome.[2,94,95]

Both prostaglandin I_2 (prostacyclin) and its stable analog carbaprostacyclin activate PPAR δ and γ and, therefore, induce adipogenesis and adipocyte differentiation.[96] In addition, a report has clearly shown that another prostaglandin, 15-deoxyprostaglandin J_2, contributes to the storage of triglycerides in an autocrine manner.[97] By contrast, prostaglandin F_2α inhibits adipocyte differentiation in rats.[98,99] To date, no direct evidence links thromboxanes to adipocyte dysfunction. However, thromboxane A_2 levels are increased in obese experimental animals and impair vascular function.[100] Thus, most cyclooxygenase metabolites (prostanoids) are essential for adipocyte differentiation, and elevated prostanoid levels are associated with the lipid abnormalities that occur in adipose tissue in obesity. By contrast, PGF_2α inhibits adipocyte differentiation.

Leukotrienes, resolvins and protectins

The lipoxygenase pathway involves the conversion of arachidonate to 5-, 12- or 15-hydroperoxyeicosatetraenoic acids by 5-, 12- or 15-lipoxygenases (Figure 3a).[101] Arachidonate 5-lipoxygenase-activating protein, also called FLAP, presents free arachidonate to 5-lipoxygenase, the key enzyme in the synthesis of leukotriene A_4.[101] Leukotrienes—metabolites of the lipoxygenase pathway—act by binding to specific leukotriene receptors located in the plasma membrane of leukocytes and structural cells. Members of the two arms of the leukotriene cascade exert their different biological actions through activation of specific G-protein-coupled receptors to trigger downstream effects.[102,103]

To date, very limited evidence directly links metabolites of the lipoxygenase pathway to adipocyte dysfunction. However, incidental evidence associates the 5-, 12- and 15-lipoxygenase pathways with adipocyte dysfunction. FLAP mRNA levels are upregulated approximately eightfold in adipose tissue derived from obese *ob/ob* mice compared with the levels in wild type mice.[104] Moreover, adipocyte differentiation of a preadipocyte cell line *in vitro* is inhibited by a general lipoxygenase inhibitor and the 12/15-lipoxygenase selective inhibitor, baicalein.[105] Mice devoid of the 12-lipoxygenase gene and fed a Western diet show reduced macrophage infiltration and monocyte chemoattractant protein-1 expression in visceral fat tissues compared with wild-type, Western-diet-fed mice, which suggests that 12-lipoxygenase activation plays a critical role in Western-diet-induced damage in visceral fat.[106]

Lipid bodies (lipid droplets) are emerging as dynamic organelles with roles in lipid metabolism and inflammation.[107] Increased leptin concentrations associated with obesity can directly activate macrophages and also induce the formation of adipose-protein-enriched lipid bodies that are related to adipose tissue differentiation.[107] These newly formed lipid bodies are sites of 5-lipoxygenase localization and their presence correlates with an enhanced capacity of leukotriene B_4 production in phosphoinositide 3-kinase knockout mice.[107] Thus, circumstantial evidence suggests the involvement of FLAP and the products of the lipoxygenase enzymes in both macrophage activation and adipocyte dysfunction associated with obesity. By contrast, the recently described alternative products of the lipoxygenase pathway, lipoxins, protectins and resolvins, have anti-inflammatory properties.[65,108–111]

A key conceptual advance of Serhan and colleagues is that resolution as well as propagation of inflammation can be an active process.[111,112] Thus, a shift in the pattern of eicosanoids and in particular increases in lipoxins, protectins and resolvins as well as shifts in patterns of cytokines, chemokines and other regulatory molecules can lead to active reduction in inflammation.[111,112] A more detailed review of the cellular and molecular mechanisms involved in this process is given elsewhere.[111,112]

Epoxyeicosatrienoic acids

Cytochrome P450 epoxygenases metabolize arachidonate to either epoxyeicosatrienoic acids, hydroxyeicosatetraenoic acids or other epoxide fatty acids including epoxides of ω-3 fatty acids.[113] The epoxyeicosatrienoic acids are then rapidly metabolized to the less active dihydroxyeicosatrienoates by the enzyme soluble epoxide hydrolase.[113] To date, no selective epoxyeicosatrienoic acid receptor has been characterized. The great diversity of biological effects resulting from increased levels of epoxyeicosatrienoic acids suggests the presence of multiple receptors. Many researchers assume that at least some G-protein-coupled receptors are involved.[113]

Epoxyeicosatrienoic acids and other epoxylipids seem to be regulated by both biosynthesis by cytochrome P450s and by degradation by soluble epoxide hydrolase.[114] The activity of soluble epoxide hydrolase increases dramatically during the maturation of adipocytes,[115] and thus reduces the level of anti-inflammatory epoxyeicosatrienoic acids and other epoxides in the ω-3 and ω-6 series. Soluble epoxide hydrolase is also induced by angiotensin II, leading to a cascade of pro-inflammatory effects.[116] Thus angiotensin receptor blockers and angiotensin-converting enzyme inhibitors may exert some of their pleiotropic effects by reducing the expression and/or activity of soluble epoxide hydrolase and increasing the concentration of epoxyeicosatrienoic acids. PPARα agonists have long been known to increase levels of soluble epoxide hydrolases in rodents,[117] and recently PPARγ agonists such as the glitazones have been shown to induce activity of this enzyme in adipose tissue.[115]

Unlike the cyclooxygenase and lipoxygenase metabolites, epoxyeicosatrienoic acids and other epoxylipids decrease inflammation. In addition, epoxyeicosatrienoic acids and other epoxylipids regulate vascular tone, in part by preventing the activation of nuclear factor κB.[118,119] These molecules transcriptionally downregulate the induced cyclooxygenase 2 and 5-lipoxygenase pathways resulting in synergism with NSAIDs, aspirin and also other cascade modulators in reducing the levels of inflammatory eicosanoids.[120] Increased levels of epoxyeicosatrienoic acids or epoxyeicosanoids are associated with a downregulation of prostaglandin E_2, because they transcriptionally downregulate induction of cyclooxygenase. Thus they could be considered to reduce adipocyte dysfunction.[113,115]

Box 2 | Therapeutic opportunities

- Since metabolic and immune systems are closely linked and interdependent, manipulation of either system for therapeutic purposes whilst avoiding severe adverse consequences is a formidable challenge
- In preclinical settings, targeting inflammatory signaling pathways improves metabolic conditions such as insulin resistance and impaired glucose tolerance
- In light of the roles played by lipid mediators in obesity, the manipulation of lipid mediator signaling, through either enzyme inhibitors or receptor antagonists and agonists, has potential as a therapeutic approach to metabolic disease
- A wide array of clinically tested and readily available drugs target enzymes and receptors of various inflammatory fatty acids including arachidonate
- The design of novel drugs that are more lipophilic than those currently available that target enzymes and receptors of inflammatory fatty acids might prove useful in selectively targeting adipose tissue without compromising innate immunity
- The inflammatory response observed in obesity and metabolic dysfunction is milder and more chronic than the classic description of inflammation (pain, swelling, redness, fever and loss of function). One approach would be to titre optimum (low) anti-inflammatory doses to counter this chronic state of inflammation with minimal effects on innate immunity
- Arachidonate is now being manipulated in the food chain both by removing it by classical genetics in some oil crops to reduce the speed with which these oils go rancid, and by adding arachidonate and ω-3 lipids to baby and other foods
- Since lipid signaling is tightly regulated under normal physiological conditions, the major challenge is chalking out the intricacies of lipid signaling and function to validate these new antiobesity targets for therapeutic intervention

As expected, the inhibitors of soluble epoxide hydrolases also synergize with NSAIDs.[120] Nanomolar concentrations of 11,12-epoxyeicosatrienoic acid, or overexpression of cytochrome P2J2, decreases upregulation of cell adhesion molecules, vascular adhesion molecule-1, intercellular adhesion molecule-1 and E-selectin induced by tumor necrosis factor, IL-1α and lipopolysaccharide in cultured endothelial cells. This finding further validates their anti-inflammatory effects.[119] It remains to be seen if these biological effects also occur in the pancreas and in adipose tissue. Interestingly, in patients with type 2 diabetes mellitus, single nucleotide polymorphisms in the gene that encodes soluble epoxide hydrolase are associated with an increased risk of cardiovascular disease,[121] insulin resistance[122] and hypertension.[123]

If epoxyeicosatrienoic acids act as agonists at cannabinoid 2 receptors, stabilization of the cytochrome P450 pathway with soluble epoxide hydrolase inhibitors to increase epoxyeicosatrienoic acid concentrations should act only on peripheral cannabinoid 2 receptors. This could provide a new antiobesity strategy that would not result in psychotropic adverse effects (see section Endocannabinoids below) based on the anti-inflammatory actions of the products of the cytochrome 450 pathway. A recent study has reported expression and regulation of soluble epoxide hydrolases in adipose tissue from mice fed either a normal or high-fat diet.[115] Although soluble epoxide hydrolase mRNA and protein levels in adipose tissue did not differ between normal and fat-fed animals, total adipose soluble epoxide hydrolase activity was increased in obese mice.[115] Given the involvement of soluble epoxide hydrolase in inflammation, this study suggests that mimicking or increasing epoxyeicosatrienoic acid concentrations may be potentially important in controlling obesity and the symptoms of the metabolic syndrome.

As discussed earlier, anti-inflammatory agents such as NSAIDs, salicylates and aspirin seem to reduce the severity of metabolic dysfunction.[25–27] However, the very high doses necessary can lead to a variety of adverse effects ranging from gastrointestinal problems to tinnitus. Soluble epoxide hydrolase inhibitors synergize the anti-inflammatory actions of these compounds, which suggests that low doses could be used in combination to reduce the symptoms of metabolic syndrome possibly without affecting innate immunity.[113,120]

Other lipid mediators

Studies on the underlying mechanisms that link metabolic dysfunction in obesity to chronic inflammation are still in their infancy. Until now, relatively few studies other than those described in this review have focused on other inflammatory lipid mediators such as PAF, oxidized phospholipids, lysophosphatidic acid and sphingosine-1-phosphate. Only circumstantial evidence exists that PAF and sphingosine-1-phosphate are involved in adipocyte function and obesity.[124,125] On the other hand, the role of endocannabinoids such as 2-arachidonoylglycerol and anandamide in obesity is an expanding field of research.[126]

Platelet activating factor

Lysosomal PAF acetyltransferase metabolizes lysophospholipids with an alkyl–ether bond at the SN-1 position into PAF. The receptor of PAF, PAFR, is a relatively small G-protein-coupled receptor that is involved in a variety of intracellular pathways with various biological functions.[65] PAF activity, as measured by its surrogate PAF acetylhydrolase, is increased in obese hypercholesterolemic individuals compared with lean individuals, which implicates PAF metabolism in dyslipidemia and insulin resistance.[127] In abdominally obese children, PAF acetylhydrolase concentrations are also elevated with increasing degree of abdominal obesity.[128] TNF induces PAF synthesis in many inflammatory cells.[124] Furthermore, in adipocytes and pre-adipocytes, TNF increases PAF synthesis and might enhance adipocyte differentiation. The TNF-induced PAF synthesis in adipocytes was sevenfold higher than in pre-adipocytes.[124] Together, these studies suggest that PAF metabolism may be involved in the pathogenesis of obesity.

Sphingosine-1-phosphate

Type 1 and 2 sphingosine kinases convert sphingosine into sphingosine-1-phosphate.[65] Among the many prominent roles of sphingosine-1-phosphate, its involvement in immune responses suggests that it might be a potential therapeutic target in obesity and metabolic dysfunction. FTY720, a pro-drug of a potent sphingosine-1-phosphate 1 agonist (a functional antagonist), is currently undergoing clinical trials as an immunosuppressant in multiple sclerosis and for use following

kidney transplantation.[65] By contrast, sphingolipids contribute to the prothrombotic and pro-inflammatory phenotype of obese adipose tissue.[123] In diabetic *ob*/*ob* mice, plasma concentrations of total sphingomyelin, ceramide, sphingosine and sphingosine-1-phosphate, as well as adipose tissue sphingosine concentrations were elevated compared with those in lean control mice.[125]

Endocannabinoids

The G-protein-coupled cannabinoid receptors cannabinoid receptor type 1 and cannabinoid receptor type 2 have been identified as potential therapeutic targets for obesity and have been extensively reviewed.[126,129,130] Endogenous cannabinoids such as anandamide and related compounds have been identified as their endogenous ligands.[126,129] In general, cannabinoid receptor type 1 is present in both peripheral sites and in the brain.[130,131] On the other hand, cannabinoid receptor type 2, though detectable at low levels in the brain, is mainly expressed at peripheral sites including inflammatory cells.[130,131] Clinical trials with cannabinoid receptor type 1 modulators for obesity have been terminated because of psychotropic adverse effects.[129,131]

Conclusions

The adipocyte—a capricious cell that has evolved to provide mammalian energy storage—regulates itself depending on the environment. Alteration in the population of immune cells (for example, T cells and macrophages) resident in adipose tissue early during the development of obesity is currently thought to propagate oxidative and inflammatory cascades. What initiates immune cell activation in adipose tissue remains unknown. A growing body of evidence suggests that lipid mediators produced locally by adipocytes and/or inflammatory cells can, at least in part, participate in inflammatory cell activation, adipocyte growth, development and dysfunction and, therefore, contribute to metabolic disturbances. If lipid loading influences these disturbances, then it is reasonable to suspect that the effects of lipid mediators on inflammatory pathways and adipocyte signaling can be modulated with anti-inflammatory agents. Modulation of the immune system by drugs might be able to re-establish tolerance to the abnormal environment of adipose tissue in obesity and re-establish normal adipocyte function (Box 2). Advances in our understanding of lipid signaling and function are certain to advance our understanding of the links between inflammation and obesity, and may uncover new antiobesity targets for therapeutic intervention.

Review criteria

A search for original articles published between 1975 and 2009 that focused on obesity, inflammation and metabolic dysfunction was performed in PubMed. The search terms used were "obesity", "inflammation", "T-cells", "macrophages", "metabolic syndrome", "metabolic dysfunction", "adipocyte", "adipose tissue", "lipid mediators", "arachidonate", "GPCRs", "TLRs", "prostaglandins", "thromboxanes", "leukotrienes", "lipoxins", "epoxyeicosatrienoic acids", "epoxides", "platelet activating factor", " sphingosine 1-phosphate" and "endocannabinoids". Some citations were from personal experience, but should be available in PubMed using most of the above keywords.

1. Powell, K. Obesity: the two faces of fat. *Nature* **447**, 525–527 (2007).
2. Van Gaal, L. F., Mertens, I. L. & De Block, C. E. Mechanisms linking obesity with cardiovascular disease. *Nature* **444**, 875–880 (2006).
3. Eckel, R. H., Grundy, S. M. & Zimmet, P. Z. The metabolic syndrome. *Lancet* **365**, 1415–1428 (2005).
4. Alberti, K. G., Zimmet, P. & Shaw, J. The metabolic syndrome—a new worldwide definition. *Lancet* **366**, 1059–1062 (2005).
5. Dandona, P., Aljada, A., Chaudhuri, A., Mohanty, P. & Garg, R. Metabolic syndrome: a comprehensive perspective based on interactions between obesity, diabetes, and inflammation. *Circulation* **111**, 1448–1454 (2005).
6. Mohanty, P. *et al.* Glucose challenge stimulates reactive oxygen species (ROS) generation by leucocytes. *J. Clin. Endocrinol. Metab.* **85**, 2970–2973 (2000).
7. Aljada, A. *et al.* Glucose intake induces an increase in activator protein 1 and early growth response 1 binding activities, in the expression of tissue factor and matrix metalloproteinase in mononuclear cells, and in plasma tissue factor and matrix metalloproteinase concentrations. *Am. J. Clin. Nutr.* **80**, 51–57 (2004).
8. Das, U. N. Is obesity an inflammatory condition? *Nutrition* **17**, 953–966 (2001).
9. Unger, R. H. Lipid overload and overflow: metabolic trauma and the metabolic syndrome. *Trends Endocrinol. Metab.* **14**, 398–403 (2003).
10. Pickup, J. C. Inflammation and activated innate immunity in the pathogenesis of type 2 diabetes. *Diabetes Care* **27**, 813–823 (2004).
11. Duncan, B. B. *et al.* Low-grade systemic inflammation and the development of type 2 diabetes: the atherosclerosis risk in communities study. *Diabetes* **52**, 1799–1805 (2003).
12. Odegaard, J. I. *et al.* Macrophage-specific PPARγ controls alternative activation and improves insulin resistance. *Nature* **447**, 1116–1120 (2007).
13. Plutzky, J. Expansion and contraction: the mighty, mighty fatty acid. *Nat. Med.* **15**, 618–619 (2009).
14. Wellen, K. E. & Hotamisligil, G. S. Inflammation, stress, and diabetes. *J. Clin. Invest.* **115**, 1111–1119 (2005).
15. Bastard, J. P. *et al.* Recent advances in the relationship between obesity, inflammation, and insulin resistance. *Eur. Cytokine Netw.* **17**, 4–12 (2006).
16. Caballero, A. E. Endothelial dysfunction in obesity and insulin resistance: a road to diabetes and heart disease. *Obes. Res.* **11**, 1278–1289 (2003).
17. Visser, M., Bouter, L. M., McQuillan, G. M., Wener, M. H. & Harris, T. B. Elevated C-reactive protein levels in overweight and obese adults. *JAMA* **282**, 2131–2135 (1999).
18. Esposito, K. *et al.* Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. *JAMA* **289**, 1799–1804 (2003).
19. Ridker, P. M., Buring, J. E., Cook, N. R. & Rifai, N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14,719 initially healthy American women. *Circulation* **107**, 391–397 (2003).
20. Dandona, P. *et al.* Inhibitory effect of a two day fast on reactive oxygen species (ROS) generation by leucocytes and plasma ortho-tyrosine and meta-tyrosine concentrations. *J. Clin. Endocrinol. Metab.* **86**, 2899–2902 (2001).
21. Serpillon, S. *et al.* Superoxide production by NAD(P)H oxidase and mitochondria is increased in genetically obese and hyperglycemic rat heart and aorta before the development of cardiac dysfunction. The role of glucose-6-phosphate dehydrogenase-derived NADPH. *Am. J. Physiol. Heart Circ. Physiol.* **297**, H153–H162 (2009).
22. Nijhuis, J. *et al.* Neutrophil activation in morbid obesity, chronic activation of acute inflammation. *Obesity* **17**, 2014–2018 (2009).
23. Dandona. P., Chaudhuri, A., Ghanim, H. & Mohanty, P. Insulin as an anti-inflammatory and antiatherogenic modulator. *J. Am. Coll. Cardiol.* **53** (Suppl. 1), S14–S20 (2009).
24. Dhindsa, S. *et al.* Differential effects of glucose and alcohol on reactive oxygen species generation and intranuclear nuclear factor-kappaB in mononuclear cells. *Metabolism* **53**, 330–334 (2004).
25. Yuan, M. *et al.* Reversal of obesity- and diet-induced insulin resistance with salicylates or targeted disruption of Ikkβ. *Science* **293**, 1673–1677 (2001).

26. Renna, N. F., Vazquez, M. A., Lama, M. C., Gonzalez, E. S. & Miatello, R. M. Effect of chronic aspirin administration on an experimental model of metabolic syndrome. *Clin. Exp. Pharmacol. Physiol.* **36**, 162–168 (2009).
27. Van Kerckhoven, R., Kalkman, E. A., Saxena, P. R. & Schoemaker, R. G. Altered cardiac collagen and associated changes in diastolic function of infarcted rat hearts. *Cardiovasc. Res.* **46**, 316–323 (2000).
28. Larsen, C. M. *et al.* Interleukin-1-receptor antagonist in type 2 diabetes mellitus. *N. Engl. J. Med.* **356**, 1517–1526 (2007).
29. Larsen, C. M. *et al.* Sustained effects of interleukin-1 receptor antagonist treatment in type 2 diabetes. *Diabetes Care* **32**, 1663–1668 (2009).
30. Wilson, P. W. Evidence of systemic inflammation and estimation of coronary artery disease risk: a population perspective. *Am. J. Med.* **121** (Suppl. 1), S15–S20 (2008).
31. Libby, P. Role of inflammation in atherosclerosis associated with rheumatoid arthritis. *Am. J. Med.* **121** (Suppl. 1), S21–S31 (2008).
32. Dandona, P. *et al.* Angiotensin II receptor blocker valsartan suppresses reactive oxygen species generation in leukocytes, nuclear factor-kappa B, in mononuclear cells of normal subjects: evidence of an antiinflammatory action. *J. Clin. Endocrinol. Metab.* **88**, 4496–4501 (2003).
33. Koh, K. K., Han, S. H. & Quon, M. J. Inflammatory markers and the metabolic syndrome: insights from therapeutic interventions. *J. Am. Coll. Cardiol.* **46**, 1978–1985 (2005).
34. Paraskevas, K. I., Stathopoulos, V. & Mikhailidis, D. P. Pleiotropic effects of statins: implications for a wide range of diseases. *Curr. Vasc. Pharmacol.* **6**, 237–239 (2008).
35. Jankowski, P., Safar, M. E. & Benetos, A. Pleiotropic effects of drugs inhibiting the renin–angiotensin–aldosterone system. *Curr. Pharm. Des.* **15**, 571–584 (2009).
36. Aljada, A. *et al.* Troglitazone reduces the expression of PPARγ while stimulating that of PPARα in mononuclear cells in obese subjects. *J. Clin. Endocrinol. Metab.* **86**, 3130–3133 (2001).
37. Mohanty, P. *et al.* Evidence for a potent antiinflammatory effect of rosiglitazone. *J. Clin. Endocrinol. Metab.* **89**, 2728–2735 (2004).
38. Singh, R. *et al.* Autophagy regulates lipid metabolism. *Nature* **458**, 1131–1135 (2009).
39. Jaworski, K. *et al.* AdPLA ablation increases lipolysis and prevents obesity induced by high-fat feeding or leptin deficiency. *Nat. Med.* **15**, 159–168 (2009).
40. Duncan, R. E., Ahmadian, M., Jaworski, K., Sarkadi-Nagy, E. & Sul, H. S. Regulation of lipolysis in adipocytes. *Annu. Rev. Nutr.* **27**, 79–101 (2007).
41. Park, K. W., Halperin, D. S. & Tontonoz, P. Before they were fat: adipocyte progenitors. *Cell. Metab.* **8**, 454–457 (2008).
42. Pages, C., Simon, M. F., Valet, P. & Saulnier-Blache, J. S. Lysophosphatidic acid synthesis and release. *Prostaglandins Other Lipid Mediat.* **64**, 1–10 (2001).
43. Ailhaud, G., Guesnet, P. & Cunnane, S. C. An emerging risk factor for obesity: does disequilibrium of polyunsaturated fatty acid metabolism contribute to excessive adipose tissue development? *Br. J. Nutr.* **100**, 461–470 (2008).
44. Weisberg, S. P. *et al.* Obesity is associated with macrophage accumulation in adipose tissue. *J. Clin. Invest.* **112**, 1796–1808 (2003).
45. Cinti, S. The adipose organ. *Prostaglandins Leukot. Essent. Fatty Acids* **73**, 9–15 (2005).
46. Winer, S. *et al.* Normalization of obesity-associated insulin resistance through immunotherapy. *Nat. Med.* **15**, 921–929 (2009).
47. Hotamisligil, G. S. Inflammation and metabolic disorders. *Nature* **444**, 860–867 (2006).
48. Lumeng, C. N., Maillard, I. & Saltiel, A. R. T-ing up inflammation in fat. *Nat. Med.* **15**, 846–847 (2009).
49. Feuerer, M. *et al.* Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. *Nat. Med.* **15**, 930–939 (2009).
50. Nishimura, S. *et al.* CD8+ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. *Nat. Med.* **15**, 914–920 (2009).
51. Nathan, C. Points of control in inflammation. *Nature* **420**, 846–852 (2002).
52. Medzhitov, R. Origin and physiological roles of inflammation. *Nature* **454**, 428–435 (2008).
53. Charriere, G. *et al.* Preadipocyte conversion to macrophage. Evidence of plasticity. *J. Biol. Chem.* **278**, 9850–9855 (2003).
54. Clement, K. *et al.* Weight loss regulates inflammation-related genes in white adipose tissue of obese subjects. *FASEB J.* **18**, 1657–1669 (2004).
55. van Dielen, F. M., Buurman, W. A., Hadfoune, M., Nijhuis, J. & Greve, J. W. Macrophage inhibitory factor, plasminogen activator inhibitor-1, other acute phase proteins, and inflammatory mediators normalize as a result of weight loss in morbidly obese subjects treated with gastric restrictive surgery. *J. Clin. Endocrinol. Metab.* **89**, 4062–4068 (2004).
56. Cottam, D. R. *et al.* The chronic inflammatory hypothesis for the morbidity associated with morbid obesity: implications and effects of weight loss. *Obes. Surg.* **14**, 589–600 (2004).
57. Nawrocki, A. R. & Scherer, P. E. Keynote review: the adipocyte as a drug discovery target. *Drug Discov. Today* **10**, 1219–1230 (2005).
58. Spiegelman, B. M. PPAR-gamma: adipogenic regulator and thiazolidinedione receptor. *Diabetes* **47**, 507–514 (1998).
59. Amri, E. Z., Bertrand, B., Ailhaud, G. & Grimaldi, P. Regulation of adipose cell differentiation. I. Fatty acids are inducers of the *AP2* gene expression. *J. Lipid Res.* **32**, 1449–1456 (1991).
60. Aubert, J., Ailhaud, G. & Negrel, R. Evidence for a novel regulatory pathway activated by (carba) prostacyclin in preadipose and adipose cells. *FEBS Lett.* **397**, 117–121 (1996).
61. Ailhaud, G., Grimaldi, P. & Negrel, R. Cellular and molecular aspects of adipose tissue development. *Annu. Rev. Nutr.* **12**, 207–233 (1992).
62. Ailhaud, G. Some new aspects on adipose tissue development. *Diabetes Metab. Rev.* **8**, 3–7 (1992).
63. Spiegelman, B. M. & Flier, J. S. Adipogenesis and obesity: rounding out the big picture. *Cell* **87**, 377–389 (1996).
64. Hauner, H. *et al.* Promoting effect of glucocorticoids on the differentiation of human adipocyte precursor cells cultured in a chemically defined medium. *J. Clin. Invest.* **84**, 1663–1670 (1989).
65. Shimizu, T. Lipid mediators in health and disease: enzymes and receptors as therapeutic targets for the regulation of immunity and inflammation. *Annu. Rev. Pharmacol. Toxicol.* **49**, 123–150 (2009).
66. Ghanim, H. *et al.* Increase in plasma endotoxin concentrations and the expression of Toll like receptors and suppressor of cytokine signaling-3 in mononuclear cells following a high fat high carbohydrate meal: implications for insulin resistance. *Diabetes Care* **32**, 2281–2287 (2009).
67. Dandona, P., Chaudhuri, A., Ghanim, H. & Mohanty, P. Anti-inflammatory effects of insulin and pro-inflammatory effects of glucose: relevance to the management of acute myocardial infarction and other acute coronary syndromes. *Rev. Cardiovasc. Med.* **7** (Suppl. 2), S25–S34 (2006).
68. Dandona, P. The link between insulin resistance syndrome and inflammatory markers. *Endocr. Pract.* **9** (Suppl. 2), 53–57 (2003).
69. Dandona, P., Aljada, A., Chaudhuri, A. & Bandyopadhyay, A. The potential influence of inflammation and insulin resistance on the pathogenesis and treatment of atherosclerosis-related complications in type 2 diabetes. *J. Clin. Endocrinol. Metab.* **88**, 2422–2429 (2003).
70. Williams, E. S., Baylin, A. & Campos, H. Adipose tissue arachidonic acid and the metabolic syndrome in Costa Rican adults. *Clin. Nutr.* **26**, 474–482 (2007).
71. Garaulet, M. *et al.* Site-specific differences in the fatty acid composition of abdominal adipose tissue in an obese population from a Mediterranean area: relation with dietary fatty acids, plasma lipid profile, serum insulin, and central obesity. *Am. J. Clin. Nutr.* **74**, 585–591 (2001).
72. Decsi, T., Molnar, D. & Koletzko, B. Long-chain polyunsaturated fatty acids in plasma lipids of obese children. *Lipids* **31**, 305–311 (1996).
73. Savva, S. C. *et al.* Association of adipose tissue arachidonic acid content with BMI and overweight status in children from Cyprus and Crete. *Br. J. Nutr.* **91**, 643–649 (2004).
74. Weiler, H. A. Dietary supplementation of arachidonic acid is associated with higher whole body weight and bone mineral density in growing pigs. *Pediatr. Res.* **47**, 692–697 (2000).
75. Jensen, C. L. *et al.* Effect of dietary linoleic/alpha-linolenic acid ratio on growth and visual function of term infants. *J. Pediatr.* **131**, 200–209 (1997).
76. Duncan, R. E., Sarkadi-Nagy, E., Jaworski, K., Ahmadian, M. & Sul, H. S. Identification and functional characterization of adipose-specific phospholipase A_2 (AdPLA). *J. Biol. Chem.* **283**, 25428–25436 (2008).
77. Ii, H., Hatakeyama, S., Tsutsumi, K., Sato, T. & Akiba, S. Group IVA phospholipase A_2 is associated with the storage of lipids in adipose tissue and liver. *Prostaglandins Other Lipid Mediat.* **86**, 12–17 (2008).
78. Satake, Y. *et al.* Role of group V phospholipase A_2 in zymosan-induced eicosanoid generation and vascular permeability revealed by targeted gene disruption. *J. Biol. Chem.* **279**, 16488–16494 (2004).
79. Balsinde, J., Winstead, M. V. & Dennis, E. A. Phospholipase A_2 regulation of arachidonic acid mobilization. *FEBS Lett.* **531**, 2–6 (2002).
80. Levick, S. *et al.* Antifibrotic activity of an inhibitor of group IIA secretory phospholipase A_2 in young spontaneously hypertensive rats. *J. Immunol.* **176**, 7000–7007 (2006).
81. Degousee, N. *et al.* Groups, IV, V, and X phospholipases A_2s in human neutrophils: role in eicosanoid production and gram-negative bacterial phospholipid hydrolysis. *J. Biol. Chem.* **277**, 5061–5073 (2002).
82. Harizi, H., Corcuff, J. B. & Gualde, N. Arachidonic-acid-derived eicosanoids: roles in biology and immunopathology. *Trends Mol. Med.* **14**, 461–469 (2008).

83. Narumiya, S. & FitzGerald, G. A. Genetic and pharmacological analysis of prostanoid receptor function. *J. Clin. Invest.* **108**, 25–30 (2001).
84. Gupta, R. A. *et al.* Prostacyclin-mediated activation of peroxisome proliferator-activated receptor delta in colorectal cancer. *Proc. Natl Acad. Sci. USA* **97**, 13275–13280 (2000).
85. Forman, B. M. *et al.* 15-Deoxy-delta 12, 14-prostaglandin J2 is a ligand for the adipocyte determination factor PPAR gamma. *Cell* **83**, 803–812 (1995).
86. Pierce, K. L. & Regan, J. W. Prostanoid receptor heterogeneity through alternative mRNA splicing. *Life Sci.* **62**, 1479–1483 (1998).
87. Sugimoto, Y. & Narumiya, S. Prostaglandin E receptors. *J. Biol. Chem.* **282**, 11613–11617 (2007).
88. Vane, J. R., Bakhle, Y. S. & Botting, R. M. Cyclooxygenases 1 and 2. *Annu. Rev. Pharmacol. Toxicol.* **38**, 97–120 (1998).
89. Bos, C. L., Richel, D. J., Ritsema, T., Peppelenbosch, M. P. & Versteeg, H. H. Prostanoids and prostanoid receptors in signal transduction. *Int. J. Biochem. Cell Biol.* **36**, 1187–1205 (2004).
90. Kim, S. & Moustaid-Moussa, N. Secretory, endocrine and autocrine/paracrine function of the adipocyte. *J. Nutr.* **130** (Suppl.), S3110–S3115 (2000).
91. Shillabeer, G., Kumar, V., Tibbo, E. & Lau, D. C. Arachidonic acid metabolites of the lipoxygenase as well as the cyclooxygenase pathway may be involved in regulating preadipocyte differentiation. *Metabolism* **47**, 461–466 (1998).
92. Fain, J. N., Leffler, C. W. & Bahouth, S. W. Eicosanoids as endogenous regulators of leptin release and lipolysis by mouse adipose tissue in primary culture. *J. Lipid Res.* **41**, 1689–1694 (2000).
93. Fain, J. N. & Bahouth, S. W. Regulation of leptin release by mammalian adipose tissue. *Biochem. Biophys. Res. Commun.* **274**, 571–575 (2000).
94. Enomoto, N. *et al.* Kupffer cell-derived prostaglandin E_2 is involved in alcohol-induced fat accumulation in rat liver. *Am. J. Physiol. Gastrointest. Liver Physiol.* **279**, G100–G106 (2000).
95. Perez, S., Aspichueta, P., Ochoa, B. & Chico, Y. The 2-series prostaglandins suppress VLDL secretion in an inflammatory condition-dependent manner in primary rat hepatocytes. *Biochim. Biophys. Acta* **1761**, 160–171 (2006).
96. Massiera, F. *et al.* Arachidonic acid and prostacyclin signaling promote adipose tissue development: a human health concern? *J. Lipid Res.* **44**, 271–279 (2003).
97. Mazid, M. A. *et al.* Endogenous 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 synthesized by adipocytes during maturation phase contributes to upregulation of fat storage. *FEBS Lett.* **580**, 6885–6890 (2006).
98. Vassaux, G., Negrel, R., Ailhaud, G. & Gaillard, D. Proliferation and differentiation of rat adipose precursor cells in chemically defined medium: differential action of anti-adipogenic agents. *J. Cell Physiol.* **161**, 249–256 (1994).
99. Liu, L. & Clipstone, N. A. Prostaglandin F2α inhibits adipocyte differentiation via a Gαq-calcium-calcineurin-dependent signaling pathway. *J. Cell Biochem.* **100**, 161–173 (2007).
100. Goodwill, A. G., James, M. E. & Frisbee, J. C. Increased vascular thromboxane generation impairs dilation of skeletal muscle arterioles of obese Zucker rats with reduced oxygen tension. *Am. J. Physiol. Heart Circ. Physiol.* **295**, H1522–H1528 (2008).
101. Homaidan, F. R., Chakroun, I., Haidar, H. A. & El-Sabban, M. E. Protein regulators of eicosanoid synthesis: role in inflammation. *Curr. Protein Pept. Sci.* **3**, 467–484 (2002).
102. Brink, C. Leukotriene receptors: state of the art. *Adv. Exp. Med. Biol.* **525**, 7–10 (2003).
103. Camara, N. O., Martins, J. O., Landgraf, R. G. & Jancar, S. Emerging roles for eicosanoids in renal diseases. *Curr. Opin. Nephrol. Hypertens.* **18**, 21–27 (2009).
104. Back, M., Sultan, A., Ovchinnikova, O. & Hansson, G. K. 5-Lipoxygenase-activating protein: a potential link between innate and adaptive immunity in atherosclerosis and adipose tissue inflammation. *Circ. Res.* **100**, 946–949 (2007).
105. Madsen, L. *et al.* Adipocyte differentiation of 3T3-L1 preadipocytes is dependent on lipoxygenase activity during the initial stages of the differentiation process. *Biochem. J.* **375**, 539–549 (2003).
106. Nunemaker, C. S. *et al.* 12-Lipoxygenase-knockout mice are resistant to inflammatory effects of obesity induced by Western diet. *Am. J. Physiol. Endocrinol. Metab.* **295**, E1065–E1075 (2008).
107. Maya-Monteiro, C. M. *et al.* Leptin induces macrophage lipid body formation by a phosphatidylinositol 3-kinase- and mammalian target of rapamycin-dependent mechanism. *J. Biol. Chem.* **283**, 2203–2210 (2008).
108. József, L., Zouki, C., Petasis, N. A., Serhan, C. N. & Filep, J. G. Lipoxin A4 and aspirin-triggered 15-epi-lipoxin A4 inhibit peroxynitrite formation, NF-kappa B and AP-1 activation, and IL-8 gene expression in human leukocytes. *Proc. Natl Acad. Sci. USA* **99**, 13266–13271 (2002).
109. Perretti, M. *et al.* Endogenous lipid- and peptide-derived anti-inflammatory pathways generated with glucocorticoid and aspirin treatment activate the lipoxin A_4 receptor. *Nat. Med.* **8**, 1296–1302 (2002).
110. Serhan, C. N. *et al.* Resolvins: a family of bioactive products of omega-3 fatty acid transformation circuits initiated by aspirin treatment that counter proinflammation signals. *J. Exp. Med.* **196**, 1025–1037 (2002).
111. Serhan, C. N. & Savill, J. Resolution of inflammation: the beginning programs the end. *Nat. Immunol.* **6**, 1191–1197 (2005).
112. Serhan, C. N., Chiang, N. & Van Dyke, T. E. Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. *Nat. Rev. Immunol.* **8**, 349–361 (2008).
113. Inceoglu, B., Schmelzer, K. R., Morisseau, C., Jinks, S. L. & Hammock, B. D. Soluble epoxide hydrolase inhibition reveals novel biological functions of epoxyeicosatrienoic acids (EETs). *Prostaglandins Other Lipid Mediat.* **82**, 42–49 (2007).
114. Spector, A. A. & Norris, A. W. Action of epoxyeidosatrienoic acids on cellular function. *Am. J. Physiol. Cell. Physiol.* **292**, C996–C1012 (2007).
115. De Taeye, B. M. *et al.* Expression and regulation of soluble epoxide hydrolase in adipose tissue. *Obesity* doi:10.1038/oby.2009.227.
116. Ai, D. *et al.* Angiotensin II up-regulates soluble epoxide hydrolase in vascular endothelium *in vitro* and *in vivo*. *Proc. Natl Acad. Sci. USA* **104**, 9018–9023 (2007).
117. Hammock, B. D. & Ota, K. Differential induction of cytosolic epoxide hydrolase, microsomal epoxide hydrolase, and glutathione S-transferase activities. *Toxicol. App. Pharmacol.* **71**, 254–265 (1983).
118. Campbell, W. B. New role for epoxyeicosatrienoic acids as anti-inflammatory mediators. *Trends Pharmacol. Sci.* **21**, 125–127 (2000).
119. Node, K. *et al.* Anti-inflammatory properties of cytochrome P450 epoxygenase-derived eicosanoids. *Science* **285**, 1276–1279 (1999).
120. Schmelzer, K. R. *et al.* Enhancement of antinociception by coadministration of nonsteroidal anti-inflammatory drugs and soluble epoxide hydrolase inhibitors. *Proc. Natl Acad. Sci. USA* **103**, 13646–13651 (2006).
121. Lee, C. R. *et al.* Genetic variation in soluble epoxide hydrolase (EPHX2) and risk of coronary heart disease: The Atherosclerosis Risk in Communities (ARIC) study. *Hum. Mol. Genet.* **15**, 1640–1649 (2006).
122. Ohtoshi, K. *et al.* Association of soluble epoxide hydrolase gene polymorphism with insulin resistance in type 2 diabetic patients. *Biochem. Biophys. Res. Commun.* **331**, 347–350 (2005).
123. Burdon, K. P. *et al.* Genetic analysis of the soluble epoxide hydrolase gene, *EPHX2*, in subclinical cardiovascular disease in the Diabetes Heart Study. *Diab. Vasc. Dis. Res.* **5**, 128–134 (2008).
124. Gountopoulou, A., Leondaritis, G., Galanopoulou, D. & Mavri-Vavayanni, M. TNFα is a potent inducer of platelet-activating factor synthesis in adipocytes but not in preadipocytes. Differential regulation by PI3K. *Cytokine* **41**, 174–181 (2008).
125. Samad, F., Hester, K. D., Yang, G., Hannun, Y. A. & Bielawski, J. Altered adipose and plasma sphingolipid metabolism in obesity: a potential mechanism for cardiovascular and metabolic risk. *Diabetes* **55**, 2579–2587 (2006).
126. Di Marzo, V. Targeting the endocannabinoid system: to enhance or reduce? *Nat. Rev. Drug Discov.* **7**, 438–455 (2008).
127. Kudolo, G. B., Bressler, P. & DeFronzo, R. A. Plasma PAF acetylhydrolase in non-insulin dependent diabetes mellitus and obesity: effect of hyperinsulinemia and lovastatin treatment. *J. Lipid Mediat. Cell Signal.* **17**, 97–113 (1997).
128. Okada, T. *et al.* Platelet-activating factor acetylhydrolase concentration in children with abdominal obesity. *Arterioscler. Thromb. Vasc. Biol.* **26**, e40–e41 (2006).
129. Jones, D. End of the line for cannabinoid receptor 1 as an anti-obesity target? *Nat. Rev. Drug Discov.* **7**, 961–962 (2008).
130. Cooke, D. & Bloom, S. The obesity pipeline: current strategies in the development of anti-obesity drugs. *Nat. Rev. Drug Discov.* **5**, 919–931 (2006).
131. Janero, D. R. & Makriyannis, A. Cannabinoid receptor antagonists: pharmacological opportunities, clinical experience, and translational prognosis. *Expert Opin. Emerg. Drugs* **14**, 43–65 (2009).
132. Yudkin, J. S., Kumari, M., Humphries, S. E. & Mohamed-Ali, V. Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link? *Atherosclerosis* **148**, 209–214 (2000).
133. Xu, H. *et al.* Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J. Clin. Invest.* **112**, 1821–1830 (2003).
134. Wang, Y. X. *et al.* Peroxisome-proliferator-activated receptor delta activates fat metabolism to prevent obesity. *Cell* **113**, 159–170 (2003).

135. Rajala, M. W., Obici, S., Scherer, P. E. & Rossetti, L. Adipose-derived resistin and gut-derived resistin-like molecule-beta selectively impair insulin action on glucose production. *J. Clin. Invest.* **111**, 225–230 (2003).
136. Dandona, P., Aljada, A. & Bandyopadhyay, A. Inflammation: the link between insulin resistance, obesity and diabetes. *Trends Immunol.* **25**, 4–7 (2004).
137. Cai, D. *et al.* Local and systemic insulin resistance resulting from hepatic activation of IKK-β and NF-kB. *Nat. Med.* **11**, 183–190 (2005).
138. Arkan, M. C. *et al.* IKK-β links inflammation to obesity-induced insulin resistance. *Nat. Med.* **11**, 191–198 (2005).
139. Masoudi, F. A. *et al.* Thiazolidinediones, metformin, and outcomes in older patients with diabetes and heart failure: an observational study. *Circulation* **111**, 583–590 (2005).
140. Christiansen, T., Richelsen, B. & Bruun, J. M. Monocyte chemoattractant protein-1 is produced in isolated adipocytes, associated with adiposity and reduced after weight loss in morbid obese subjects. *Int. J. Obes. (Lond.)* **29**, 146–150 (2005).
141. Shoelson, S. E., Herrero, L. & Naaz, A. Obesity, inflammation, and insulin resistance. *Gastroenterology* **132**, 2169–2180 (2007).
142. Kim, F. *et al.* Toll-like receptor-4 mediates vascular inflammation and insulin resistance in diet-induced obesity. *Circ. Res.* **100**, 1589–1596 (2007).
143. Heilbronn, L. K. & Campbell, L. V. Adipose tissue macrophages, low grade inflammation and insulin resistance in human obesity. *Curr. Pharm. Des.* **14**, 1225–1230 (2008).
144. Cani, P. D. *et al.* Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. *Diabetes* **57**, 1470–1481 (2008).
145. Rocha, V. Z. *et al.* Interferon-gamma, a Th1 cytokine, regulates fat inflammation: a role for adaptive immunity in obesity. *Circ. Res.* **103**, 467–476 (2008).