REVIEWS

Adipokines in inflammation and metabolic disease

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Abstract | The worldwide epidemic of obesity has brought considerable attention to research aimed at understanding the biology of adipocytes (fat cells) and the events occurring in adipose tissue (fat) and in the bodies of obese individuals. Accumulating evidence indicates that obesity causes chronic low-grade inflammation and that this contributes to systemic metabolic dysfunction that is associated with obesity-linked disorders. Adipose tissue functions as a key endocrine organ by releasing multiple bioactive substances, known as adipose-derived secreted factors or adipokines, that have pro-inflammatory or anti-inflammatory activities. Dysregulated production or secretion of these adipokines owing to adipose tissue dysfunction can contribute to the pathogenesis of obesity-linked complications. In this Review, we focus on the role of adipokines in inflammatory responses and discuss their potential as regulators of metabolic function.

Insulin resistance
A condition characterized by the inability of cells (in the muscle, liver and fat) to respond appropriately to endogenous insulin, resulting in increased blood glucose levels.

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Obesity has become a major worldwide health problem, not least because it is strongly associated with a number of diseases, including insulin resistance, type 2 diabetes, atherosclerosis and ischaemic heart disease, that reduce life expectancy and together have huge economic and societal consequences. Increasing evidence indicates that obesity is causally linked to a chronic low-grade inflammatory state[1,2], which contributes to the development of obesity-linked disorders, in particular to metabolic dysfunction. It is now well established that adipose tissue is not only involved in energy storage but also functions as an endocrine organ that secretes various bioactive substances[3,4]. The dysregulated expression of these factors, caused by excess adiposity and adipocyte dysfunction, has been linked to the pathogenesis of various disease processes through altered immune responses. As such, much attention has been paid to developing a better understanding of the immunoregulatory functions of adipose tissue. New factors secreted by adipose tissue have been identified that either promote inflammatory responses and metabolic dysfunction or contribute to the resolution of inflammation and have beneficial effects on obesity-linked metabolic disorders. These findings lend additional support to the notion that an imbalance of pro- and anti-inflammatory adipokines secreted by adipose tissue contributes to metabolic dysfunction.

Obesity and inflammation

Clinical observations. Obesity — in particular, excess visceral adiposity — is strongly associated with insulin resistance, hypertension and dyslipidaemia, which contribute to high rates of mortality and morbidity. Accumulating evidence indicates that a state of chronic inflammation has a crucial role in the pathogenesis of obesity-related metabolic dysfunction[1,2]. Indeed, clinical and epidemiological studies have described a clear connection between the development of low-grade inflammatory responses and metabolic diseases, particularly in the context of obesity and type 2 diabetes. Excess adipose mass (as occurs in obese individuals) is associated with increased levels of the pro-inflammatory marker C-reactive protein (CRP) in the blood[5]. Increased levels of CRP, and its inducer interleukin-6 (IL-6), are predictive of the development of type 2 diabetes in various populations[5,6]. In addition, interventions aimed at causing weight loss lead to reductions in the levels of pro-inflammatory proteins, including CRP and IL-6 (REF. 7).

The adipokine concept. Adipose tissue was traditionally considered to be a long-term energy storage organ, but it is now appreciated that it has a key role in the integration of systemic metabolism. This metabolic function is mediated, in part, by its ability to secrete numerous proteins. Factors that are secreted by adipose tissue are collectively

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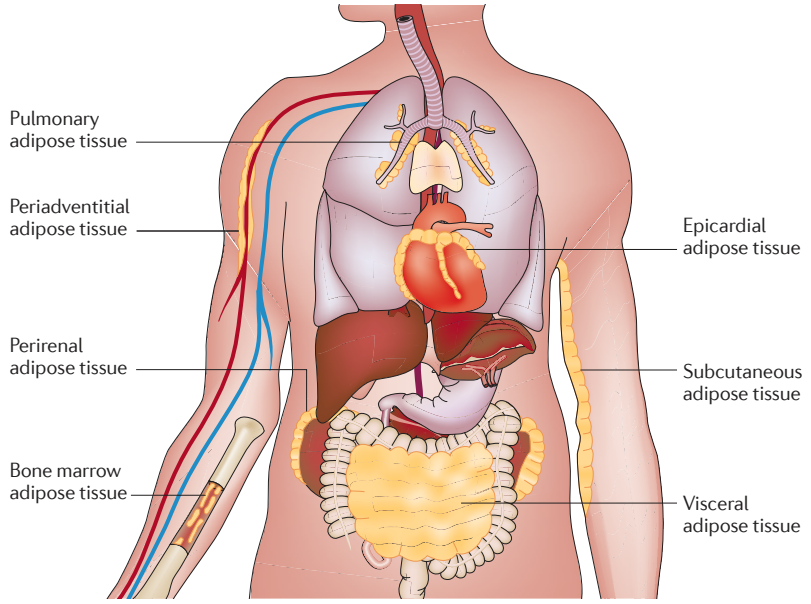

Figure 1 | **Adipose tissue depots.** Adipose tissue is mainly found in subcutaneous and visceral depots. Under conditions of obesity, adipose tissue expands in these and other depots throughout the body. Common sites of adipose tissue accumulation include the heart, the kidneys and the adventitia of blood vessels. Differential adipokine secretion by various adipose tissue depots may selectively affect organ function and systemic metabolism.

referred to as adipokines[3,4]. Importantly, following the onset of obesity, the secretory status of an adipose tissue depot can be modified by changes in the cellular composition of the tissue, including alterations in the number, phenotype and localization of immune, vascular and structural cells. The expression of adipokines can also vary depending on the site of an adipose tissue depot (FIG. 1). The two most abundant depots are visceral and subcutaneous adipose tissues, which produce unique profiles of adipokines[8,9]. In addition, adipocyte depots occur throughout the body in association with multiple organs, including the heart and kidneys. Adipocytes are also found in the bone marrow, lungs and the adventitia of major blood vessels. In some instances, it has been shown that high-calorie diets can promote the development of a pro-inflammatory state in these depots in a similar manner to that observed in subcutaneous and visceral adipose tissue (for example, see REF. 10). Although the functional importance of many of these individual adipose depots is generally not known, recent evidence suggests that diet-induced changes in their adipokine secretion can influence the function of the associated tissue[11]. Brown adipose tissue, which is mainly found in infants and hibernating animals, is functionally distinct from white adipose tissue, and is not covered in this Review.

Adipsin (also known as complement factor D) was identified as an adipokine in 1987 (REF. 12). In 1993, tumour necrosis factor (TNF) was identified as a pro-inflammatory product of adipose tissue that is induced in models of diabetes and obesity, providing evidence for a functional link between obesity and inflammation[13]. Subsequently, leptin was identified as an adipose tissue-specific secreted protein that regulates food intake and energy expenditure in an endocrine manner[14]. Similarly, the identification of plasminogen activator inhibitor 1 (PAI1), an inhibitor of fibrinolysis, as an adipokine that is strongly upregulated in visceral adipose depots in obesity[15] suggested a mechanistic link between obesity and thrombotic disorders. At about the same time, adiponectin (also known as ACRP30 and ADIPOQ) was identified as an adipocyte-specific adipokine[16–18]. Adiponectin expression was found to be decreased in obesity, and studies in experimental organisms showed that adiponectin protects against several metabolic and cardiovascular disorders that are associated with obesity. These results were surprising as most adipokines stimulate inflammatory responses, are upregulated in obesity and promote obesity-induced metabolic and cardiovascular diseases. Collectively, these findings have led to the notion that metabolic dysfunction that is due to excess adipose tissue mass may partly result from an imbalance in the expression of pro- and anti-inflammatory adipokines, thereby contributing to the development of obesity-linked complications. Accordingly, the concept that adipokines function as regulators of body homeostasis has received widespread attention from the research community (TABLE 1).

Infiltration of immune cells into adipose tissue. Adipose tissue is mainly comprised of adipocytes, although other cell types contribute to its growth and function, including pre-adipocytes, lymphocytes, macrophages, fibroblasts and vascular cells (FIG. 2a). Obesity can lead to changes in the cellular composition of the fat pad as well as to the modulation of individual cell phenotypes (BOX 1). Adipose tissues in obese individuals and in animal models of obesity are infiltrated by a large number of macrophages, and this recruitment is linked to systemic inflammation and insulin resistance[19,20]. Moreover, the accumulation of adipose tissue macrophages is proportional to adiposity in both humans and mice[19,20], and sustained weight loss results in a reduction in the number of adipose tissue macrophages that is accompanied by a decrease in the pro-inflammatory profiles of obese individuals[21]. Macrophages are also more abundant in visceral than subcutaneous adipose tissue[22], and this is in line with the belief that visceral adipose tissue has a more important role in the development of insulin resistance. However, it has been recently reported that macrophages accumulate in adipose tissues during the early phase of weight loss, presumably as a result of adipose tissue lipolysis[23].

Adipose tissue also contains fibroblasts, which produce extracellular matrix components. Recently, it has been shown that metabolically dysfunctional adipose tissue produces excess matrix components that may interfere with adipose mass expansion and contribute to metabolic dysregulation[24]. Thus, it is becoming increasingly evident that intercellular communication within adipose tissue is required for normal metabolic function. Examples of such intercellular communication include the counter-regulation between the adipocyte-derived anti-inflammatory factors adiponectin and secreted frizzled-related protein 5 (SFRP5) and the macrophage-derived pro-inflammatory factors TNF and WNT5a. Under conditions of obesity, TNF and WNT5a are upregulated, whereas adiponectin and SFRP5 are downregulated[3,4,25] (FIG. 2b).

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Table 1 | **Sources and functions of key adipokines**

Adipokine	Primary source(s)	Binding partner or receptor	Function
Leptin	Adipocytes	Leptin receptor	Appetite control through the central nervous system
Resistin	Peripheral blood mononuclear cells (human), adipocytes (rodent)	Unknown	Promotes insulin resistance and inflammation through IL-6 and TNF secretion from macrophages
RBP4	Liver, adipocytes, macrophages	Retinol (vitamin A), transthyretin	Implicated in systemic insulin resistance
Lipocalin 2	Adipocytes, macrophages	Unknown	Promotes insulin resistance and inflammation through TNF secretion from adipocytes
ANGPTL2	Adipocytes, other cells	Unknown	Local and vascular inflammation
TNF	Stromal vascular fraction cells, adipocytes	TNF receptor	Inflammation, antagonism of insulin signalling
IL-6	Adipocytes, stromal vascular fraction cells, liver, muscle	IL-6 receptor	Changes with source and target tissue
IL-18	Stromal vascular fraction cells	IL-18 receptor, IL-18 binding protein	Broad-spectrum inflammation
CCL2	Adipocytes, stromal vascular fraction cells	CCR2	Monocyte recruitment
CXCL5	Stromal vascular fraction cells (macrophages)	CXCR2	Antagonism of insulin signalling through the JAK–STAT pathway
NAMPT	Adipocytes, macrophages, other cells	Unknown	Monocyte chemotactic activity
Adiponectin	Adipocytes	Adiponectin receptors 1 and 2, T-cadherin, calreticulin–CD91	Insulin sensitizer, anti-inflammatory
SFRP5	Adipocytes	WNT5a	Suppression of pro-inflammatory WNT signalling

ANGPTL2, angiopoietin-like protein 2; CCL2, CC-chemokine ligand 2; CXCL5, CXC-chemokine ligand 5; IL, interleukin; JAK, Janus kinase; NAMPT, nicotinamide phosphoribosyltransferase; RBP4, retinol-binding protein 4; SFRP5, secreted frizzled-related protein 5; STAT, signal transducer and activator of transcription; TNF, tumour necrosis factor.

Crown-like structure
An aggregation of single or fused macrophages (also referred to as multinucleated giant cells) around a single adipocyte in adipose tissue. These structures are typically associated with obesity, adipose tissue dysfunction and chronic inflammation.

M1 or 'classically activated' macrophage
A macrophage that is activated by Toll-like receptor ligands (such as lipopolysaccharide) and interferon-γ, and that expresses inducible nitric oxide synthase and nitric oxide, as well as other pro-inflammatory factors.

M2 or 'alternatively activated' macrophage
A macrophage that is stimulated by interleukin-4 (IL-4) or IL-13, and that expresses arginase 1, the mannose receptor CD206 and the IL-4 receptor α-chain.

It has become evident that in addition to absolute fat quantity, qualitative aspects of adipose tissue function and cellular composition have an important effect on the systemic metabolic phenotype[26]. Indeed, body mass-matched obese individuals can be divided into two categories: those that have fully dysfunctional metabolic control and those that have mildly dysfunctional metabolic control (FIG. 3). Obese individuals with the latter intermediate metabolic phenotype have lower levels of inflammatory marker expression and reduced cardiovascular risk compared with metabolically dysfunctional obese individuals[27]. In the same study, the classification of metabolically dysfunctional obese individuals correlated with the presence of crown-like structures, which are histological features that represent an accumulation of macrophages around dead adipocytes in inflamed adipose tissue[28,29]. Because a key function of macrophages is to remove apoptotic cells in an immunologically silent manner to prevent the release of noxious substances, it is reasonable to speculate that the presence of crown-like structures in adipose tissue reflects a pro-inflammatory state that is due, in part, to an impairment of the macrophage-mediated phagocytic process. Consistent with this notion is the finding that the induction of adipocyte apoptosis in an inducible mouse model of lipoatrophy leads to macrophage accumulation in adipose tissues[30]. However, the process may be more complex as a recent paper has reported that adipocyte death is not increased by obesity in humans[31].

Different subsets of macrophages are involved in obesity-induced adipose tissue inflammation. Macrophages that accumulate in the adipose tissues of obese mice mainly express genes associated with an M1 or 'classically activated' macrophage phenotype, whereas adipose tissue macrophages from lean mice express genes associated with an M2 or 'alternatively activated' macrophage phenotype[32]. Stimulation with T helper 1 (T_H1)-type cytokines, including interferon-γ (IFNγ), or with bacterial products leads to the generation of M1 macrophages, which produce pro-inflammatory cytokines (including TNF and IL-6), express inducible nitric oxide synthase (iNOS) and produce reactive oxygen species (ROS) and nitrogen intermediates[33]. By contrast, macrophages are polarized to the M2 phenotype by T_H2-type cytokines such as IL-4 and IL-13. M2 macrophages upregulate production of the anti-inflammatory cytokine IL-10 and downregulate synthesis of pro-inflammatory cytokines. The transcription of several genes, including those encoding arginase 1, macrophage mannose receptor 1 and IL-1 receptor antagonist, is upregulated in M2 macrophages, through a programme that is reported to be regulated by the transcription factors peroxisome proliferator-activated receptor-γ (PPARγ)

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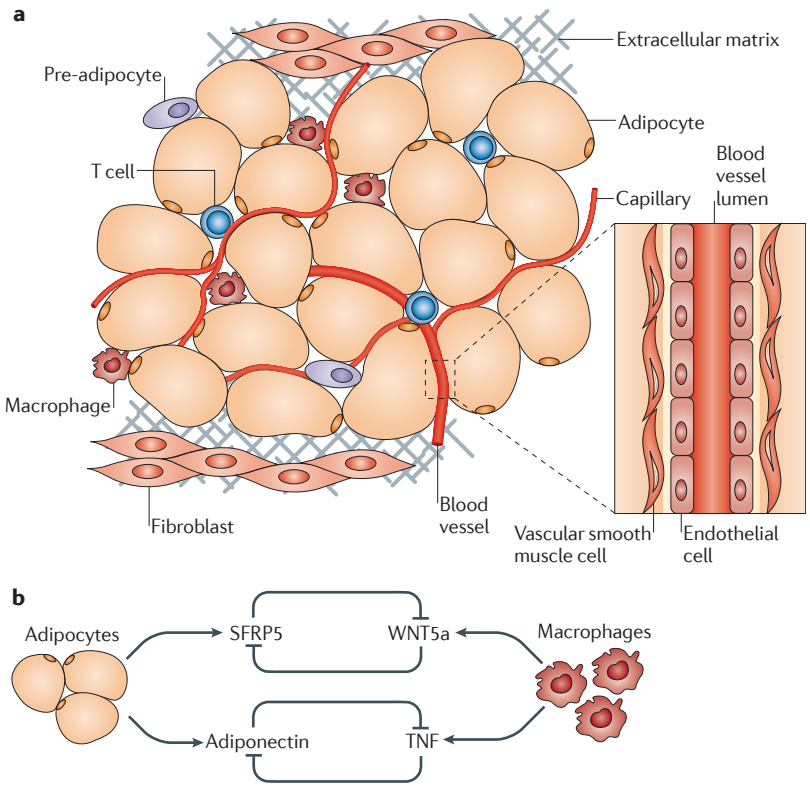

Figure 2 | **Components of adipose tissue. a** | Adipocytes are the main cellular component of adipose tissue, and they are crucial for both energy storage and endocrine activity. The other cell types that are present are precursor cells (including pre-adipocytes), fibroblasts, vascular cells and immune cells, and these cells constitute the stromal vascular fraction of adipose tissue. Vascular cells include both endothelial cells and vascular smooth muscle cells, which are associated with the major blood vessels. The blood vessels in adipose tissue are required for the proper flow of nutrients and oxygen to adipocytes, and they are the conduits that allow for the distribution of adipokines. Vascular cells also secrete, and are responsive to, adipose tissue-secreted proteins. Other active adipose tissue components include macrophages and T cells, which have major roles in determining the immune status of adipose tissue. The fibroblast-derived extracellular matrix functions to provide mechanical support, and excess matrix can lead to adipose tissue dysfunction. Factors that are secreted by these different cellular components are critical for maintaining homeostasis in adipose tissue and throughout the body. **b** | Examples of intercellular communication between different adipose tissue cell types include the counter-regulation between adiponectin and tumour necrosis factor (TNF), and between secreted frizzled-related protein 5 (SFRP5) and WNT5a. Under conditions of obesity the pro-inflammatory factors (TNF and WNT5a) predominate.

and PPARδ[34]. Functionally, M2 macrophages are associated with the repair of injured tissues and the resolution of inflammation[33]. So, it has been suggested that M1 macrophages promote insulin resistance and M2 macrophages protect against obesity-induced insulin resistance[35].

Recent studies have described subsets of T cells that are present in adipose tissues and seem to be involved in the regulation of macrophage phenotype. $CD4^+$ regulatory T cells are more abundant in the adipose tissues of lean mice and have a protective effect by inhibiting pro-inflammatory macrophages, leading to the suppression of insulin resistance[36]. $CD8^+$ effector T cells and T_H1 cell-associated factors can initiate the recruitment and activation of macrophages in adipose tissues and promote a pro-inflammatory cascade that is associated with insulin resistance[37,38]. Thus, obesity-induced perturbations in the balance between T_H1- and T_H2-type signals may influence the recruitment and activation of macrophages in adipose tissues, thereby generating either a pathogenic and inflammatory environment or a non-inflammatory and protective environment. However, the changes in the adipose tissue microenvironment that initiate T cell recruitment and macrophage activation are not fully understood. Nevertheless, it is important to bear in mind that obesity-associated changes in the cellular composition of adipose tissue complicates our understanding of whether a putative adipokine is expressed entirely by adipocytes or by recruited inflammatory cells (TABLE 1).

Pro-inflammatory adipokines

The production of most adipokines is upregulated in the obese state, and these pro-inflammatory proteins typically function to promote obesity-linked metabolic diseases. In addition to leptin, TNF and IL-6, more recently identified adipokines that promote inflammation include resistin, retinol-binding protein 4 (RBP4), lipocalin 2, IL-18, angiopoietin-like protein 2 (ANGPTL2), CC-chemokine ligand 2 (CCL2), CXC-chemokine ligand 5 (CXCL5) and nicotinamide phosphoribosyltransferase (NAMPT) (TABLE 1), and this subset of factors is discussed in more detail below. It is the upregulation of these factors (as well as others) that leads to the development of a chronic inflammatory state and contributes to metabolic dysfunction. Below, we briefly describe adipose tissue-derived proteins that generally have pro-inflammatory effects and discuss their metabolic regulatory properties.

Leptin. The adipokine leptin is the product of the obese gene (*ob*; also known as *Lep*), which was identified in *ob/ob* mice by positional cloning[14]. Leptin regulates feeding behaviour through the central nervous system. Mice that lack leptin (*ob/ob* mice) show hyperphagia (abnormally increased feeding), obesity and insulin resistance, and the administration of leptin to *ob/ob* mice reverses these changes[39]. The administration of leptin to lipoatrophic mice (which lack subcutaneous adipose tissue and thus have low levels of leptin) also improves metabolic abnormalities, including insulin resistance and hyperlipidaemia[40]. Leptin has also been shown to be effective at improving metabolic dysfunction in patients with lipodystrophy or congenital leptin deficiency[41,42]. However, leptin levels in the blood positively correlate with adipose mass, indicating the occurrence of leptin resistance, and obese individuals have high levels of leptin without the expected anorexic responses[39].

Leptin is structurally similar to the family of helical cytokines that includes IL-2 and growth hormone 1, and is thought to have pro-inflammatory activities. Indeed, leptin increases the production of TNF and IL-6 by monocytes and stimulates the production of CC-chemokine ligands (namely, CCL3, CCL4 and CCL5) by macrophages by activating the JAK2 (Janus kinase 2)–STAT3 (signal transducer and activator of

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Box 1 | **Vascular function in adipose tissue**

Recent interest has been paid to the status of the vasculature in adipose tissue. It has been shown that obesity can lead to capillary rarefaction in adipose tissue leading to localized hypoxia[146,147]. Theoretically, reductions in blood flow in obese adipose tissue could limit the delivery of nutrients, thereby contributing to insulin resistance. Perhaps more importantly, a restriction of blood flow in adipose tissue could contribute to an inflammatory state, possibly as a result of ischaemia-induced adipocyte necrosis and the subsequent recruitment of macrophages. Furthermore, obesity leads to the downregulation of anti-inflammatory factors, such as adiponectin, that pacify the vascular endothelium, and the upregulation of pro-inflammatory factors that activate endothelial cells and promote a dysfunctional phenotype[11]. In turn, the activated vascular endothelium expresses adhesion molecules and chemotactic factors that accelerate and localize inflammatory processes. Thus, the status of endothelial cell function may have an integral role both in mediating the effects of metabolic disease on the cardiovascular system and in controlling the metabolic state of the organism by influencing, either positively or negatively, the microenvironment in adipose tissue. Therefore, it can be posited that obesity favours a vicious cycle whereby endothelial cell dysfunction in the adipose tissue leads to metabolic dysfunction, reflected by adipokine dysregulation, adipocyte necrosis and inflammation[120]. In turn, metabolic dysfunction promotes endothelial cell dysfunction, both in the adipose tissue and systemic circulation, putting further stress on adipocytes. However, in contrast to these considerations, it has been reported that obese mice receiving anti-angiogenic reagents have a reduced body weight and adipose mass, and show increased metabolic rates[148]. Because there is a close interplay between adipogenesis and angiogenesis in obesity[149], further analysis of the role of adipokines in controlling vascular growth and metabolic function during adipose tissue expansion should be of interest.

transcription 3) pathway[43,44]. In monocytes, leptin also stimulates the production of ROS and promotes cell proliferation and migratory responses[43,45]. Leptin levels in the serum and adipose tissues are increased in response to pro-inflammatory stimuli, including TNF and lipopolysaccharide (LPS)[46]. Furthermore, leptin increases the production of the T_H1-type cytokines IL-2 and IFNγ and suppresses the production of the T_H2-type cytokine IL-4 by T cells or mononuclear cells[47], thus polarizing T cells towards a T_H1 cell phenotype. Consistent with these findings, leptin deficiency protects against liver damage in models of T cell-mediated hepatitis[48]. In addition, *ob/ob* mice are resistant to the induction of experimental autoimmune encephalomyelitis, owing to the polarization of T cells towards the T_H2-type phenotype rather than the pathogenic T_H1-type phenotype[47,49]. Thus, it is generally accepted that leptin acts as a pro-inflammatory adipokine.

Resistin. Resistin is a member of the cysteine-rich family of resistin-like molecules (RELMs) that are associated with the activation of inflammatory processes. Resistin has been shown to induce insulin resistance in mice[50], and mice lacking resistin have low blood glucose levels post-fasting owing to low hepatic glucose production[51]. Resistin deficiency in *ob/ob* mice leads to increased obesity, but these severely obese mice have improved glucose tolerance and insulin sensitivity[52]. The ability of resistin to modulate glucose metabolism is associated with the activation of suppressor of cytokine signalling 3 (SOCS3), an inhibitor of insulin signalling, in adipocytes[53]. Although studies in animal models consistently show that resistin promotes insulin resistance, evidence for this effect in humans is less clear[54,55].

Resistin is present in two quaternary forms: an abundant high-molecular weight hexamer and a less abundant, but more bioactive, trimer, which strongly induces hepatic insulin resistance[56]. Although originally identified in adipose tissue, further analyses have shown a broader pattern of expression and led to controversy about the regulation of this adipokine. In mice, resistin protein synthesis is restricted to adipocytes[50], whereas in humans, resistin is mainly produced by macrophages and monocytes, and it is not detectable in adipocytes[57]. In human mononuclear cells, transcription of the resistin gene (*RETN*) is induced by pro-inflammatory cytokines, including IL-1, IL-6 and TNF[58], and in white adipose tissue it is inhibited by the PPARγ agonist rosiglitazone, suggesting that the anti-inflammatory effect of rosiglitazone is mediated in part by the attenuation of *RETN* transcription[59]. More recently, studies of mice that lack endogenous resistin expression in adipocytes but express a human *RETN* transgene in macrophages indicate that the pro-inflammatory properties of macrophage-derived resistin contribute to insulin resistance *in vivo*[60]. The pro-inflammatory properties of resistin in human mononuclear cells are evident, as resistin promotes the expression of TNF and IL-6 by these cells[61]. In addition, resistin directly counters the anti-inflammatory effects of adiponectin on vascular endothelial cells by promoting the expression of the pro-inflammatory adhesion molecules vascular cell adhesion molecule 1 (VCAM1), intercellular adhesion molecule 1 (ICAM1) and pentraxin 3 in these cells, thereby enhancing leukocyte adhesion[62,63].

RBP4. Serum RBP4 is a hepatocyte-secreted factor that is responsible for the transport of retinol (vitamin A) throughout the body[64]. Recently, RBP4 was also found to be secreted by both adipocytes[65] and macrophages[66]. The expression of RBP4 is inversely related to that of glucose transporter type 4 (GLUT4; also known as SLC2A4), and administration of recombinant RBP4 to normal mice decreases insulin sensitivity[65]. RBP4 is released by adipocytes and inhibits insulin-induced phosphorylation of insulin receptor substrate 1 (IRS1) in an autocrine or paracrine manner[67]. These data implicate RBP4 as an adipose tissue-secreted factor that is important for the regulation of glucose homeostasis in models of type 2 diabetes. Studies in human populations have supported this concept: increased serum RBP4 levels were found to associate with features of the metabolic syndrome, including high blood pressure, low levels of high-density lipoprotein, high levels of cholesterol and triglycerides, and increased body mass index[68]. RBP4 is preferentially produced by visceral adipose tissues in states of obesity and insulin resistance, and it is a marker of intra-abdominal adipose tissue expansion[69] and subclinical inflammation[70]. Recent studies suggest that high levels of RBP4 may be specifically associated with nephropathy[71,72]. Accordingly, approaches that lower the levels of RBP4 or reduce its stability by inhibiting its interaction with transthyretin may be beneficial for the treatment of insulin resistance[73].

The metabolic syndrome
A disorder characterized by the presence of at least three of the following features: large waist circumference (men: ≥40 inches; women: ≥35 inches), high levels of circulating triglycerides (≥150 mg dl^{-1}), low levels of high-density lipoprotein (men: <40 mg dl^{-1}; women: <50 mg dl^{-1}), high fasting blood glucose (≥100 mg dl^{-1}) and high blood pressure (≥130/85 mm Hg). Together, these conditions increase the risk of heart disease, stroke and type 2 diabetes.

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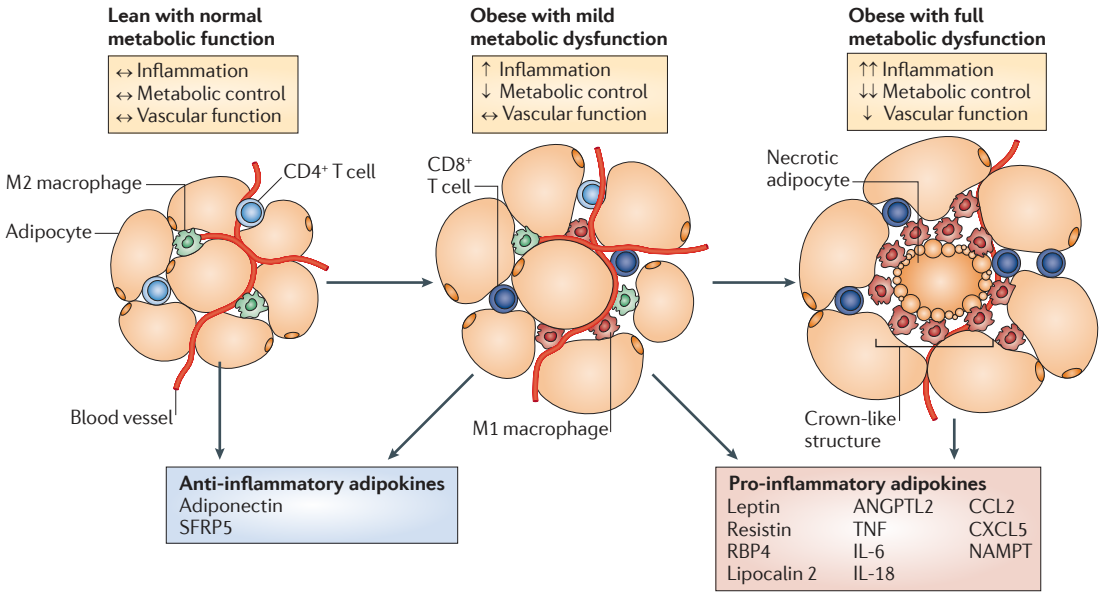

Figure 3 | **Phenotypic modulation of adipose tissue.** Adipose tissue can be described by at least three structural and functional classifications: lean with normal metabolic function, obese with mild metabolic dysfunction and obese with full metabolic dysfunction. As obesity develops, adipocytes undergo hypertrophy owing to increased triglyceride storage. With limited obesity, it is likely that the tissue retains relatively normal metabolic function and has low levels of immune cell activation and sufficient vascular function. However, qualitative changes in the expanding adipose tissue can promote the transition to a metabolically dysfunctional phenotype. Macrophages in lean adipose tissue express markers of an M2 or alternatively activated state, whereas obesity leads to the recruitment and accumulation of M1 or classically activated macrophages, as well as T cells, in adipose tissue. Anti-inflammatory adipokines, including adiponectin and secreted frizzled-related protein 5 (SFRP5), are preferentially produced by lean adipose tissue. In states of obesity, adipose tissue generates large amounts of pro-inflammatory factors, including leptin, resistin, retinol-binding protein 4 (RBP4), lipocalin 2, angiopoietin-like protein 2 (ANGPTL2), tumour necrosis factor (TNF), interleukin-6 (IL-6), IL-18, CC-chemokine ligand 2 (CCL2), CXC-chemokine ligand 5 (CXCL5) and nicotinamide phosphoribosyltransferase (NAMPT). Obese individuals with adipose tissue in a metabolically intermediate state have improved metabolic parameters, diminished inflammatory marker expression and better vascular function compared with individuals that have metabolically dysfunctional adipose tissue. Metabolically dysfunctional adipose tissue can be associated with higher levels of adipocyte necrosis, and M1 macrophages are arranged around these dead cells in crown-like structures.

Lipocalin 2. Lipocalin 2 (also known as neutrophil gelatinase-associated lipocalin and 24p3) belongs to the lipocalin protein superfamily, which also includes RBP4 (REFS 74,75). Lipocalins bind and transport various small lipophilic substances such as retinoids, arachidonic acid and steroids. Lipocalin 2 can bind weakly to some of the common ligands of lipocalins, including leukotriene B_4 and platelet activating factor, although its high-affinity endogenous ligands have not been identified.

Lipocalin 2 is abundantly expressed in adipose tissue[74,75] and is induced by inflammatory stimuli through activation of nuclear factor-κB (NF-κB)[76]. Indeed, lipocalin 2 is found at high levels in the adipose tissues of diet-induced or genetically obese mice[74], as well as those of obese individuals[77,78]. Serum concentrations of lipocalin 2 are positively associated with adiposity, hyperglycaemia, insulin resistance and CRP levels[77]. Lipocalin 2-deficient mice have improved insulin sensitivity compared with control littermates under conditions of ageing or obesity[79]. The improved metabolic properties are attributed to the inhibition of arachidonate 12-lipoxygenase, an enzyme that is linked to inflammation and insulin resistance. However, another study reported that lipocalin 2 deficiency potentiates diet-induced obesity and insulin resistance, which is accompanied by the increased expression of pro-inflammatory mediators[80]. The reason for these discrepant findings in lipocalin 2-deficient mice is currently unknown.

ANGPTL2. It was recently reported that ANGPTL2 functions as an adipokine that promotes inflammation and insulin resistance[81]. ANGPTL2 levels in adipose tissues and plasma are higher in diet-induced obese mice than in control mice, and circulating ANGPTL2 levels are positively associated with adiposity, markers of insulin resistance and CRP levels in humans.

ANGPTL2 deficiency leads to a reduction in inflammation, including downregulation of pro-inflammatory cytokines in adipose tissues and the amelioration of systemic insulin resistance in diet-induced obese mice. Conversely, ANGPTL2 overexpression in adipose tissue leads to exacerbation of adipose tissue inflammation and insulin resistance. Overexpression of ANGPTL2 in the epidermis also stimulates the attachment of leukocytes to the blood vessel walls in the skin and increases vascular permeability, leading to enhanced vascular inflammation[81]. Moreover, ANGPTL2 activates inflammatory responses by endothelial cells, monocytes and macrophages through the activation of integrin signalling[81].

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TNF. TNF is a pro-inflammatory cytokine that is mainly produced by monocytes and macrophages and has a central role in inflammatory and autoimmune diseases. TNF expression is increased in the adipose tissues of experimental animal models of obesity and type 2 diabetes[13]. Accordingly, neutralization of TNF-induced signalling in obese animals leads to an improvement in insulin sensitivity, which is associated with an enhancement of insulin signalling in muscle and adipose tissues[13,82,83]. At a mechanistic level, TNF attenuates insulin-stimulated tyrosine phosphorylation of the insulin receptor and IRS1 in muscle and adipose tissues, thus promoting insulin resistance[82]. These data support the notion that TNF functions as a pro-inflammatory cytokine that has a crucial role in obesity-related insulin resistance.

TNF levels are increased in the adipose tissue and plasma of obese individuals, and a reduction of body weight in these individuals is associated with a decrease in TNF expression[84,85]. TNF levels in the blood were also found to positively correlate with markers of insulin resistance in a community-based cohort study[86]. However, clinical trials that have tested the ability of TNF antagonism to improve insulin sensitivity have not provided consistent results. For example, short-term administration of TNF blocking reagents to obese patients with type 2 diabetes led to a reduction in systemic inflammatory markers, but did not ameliorate insulin resistance[87,88]. Similarly, blockade of TNF in patients with the metabolic syndrome resulted in an increase in muscle adiposity, indicating a lack of effect on insulin sensitivity[89]. On the other hand, blockade of TNF in patients with severe inflammatory diseases, including rheumatoid arthritis and psoriasis, is reported to promote insulin sensitivity[90,91], suggesting that inhibition of TNF might be effective at improving insulin resistance under certain conditions (such as severe inflammatory states). A recent report also shows that a prolonged period of TNF neutralization in patients with the metabolic syndrome improves fasting glucose levels[92], and this supports the notion that increased TNF levels in obesity contribute to impaired glucose homeostasis in humans.

IL-6. IL-6 is a pro-inflammatory cytokine that may also be involved in obesity-related insulin resistance. Clinically, plasma IL-6 levels positively correlate with adiposity in human populations[9], such that increased levels of IL-6 are observed in obese subjects and weight loss leads to a reduction in IL-6 levels[7,85]. Furthermore, plasma levels of IL-6 are increased in patients with type 2 diabetes, and increased IL-6 levels are predictive of the development of type 2 diabetes[6]. It is estimated that approximately one-third of total circulating IL-6 is produced by adipose tissues[9], and it is possible that increased secretion of IL-6 under conditions of obesity contributes to metabolic dysfunction. However, the role of IL-6 in insulin resistance has been controversial. IL-6 has been shown to suppress insulin-stimulated metabolic actions in hepatocytes through a mechanism that is mediated by the induction of SOCS3 expression[93]. Similarly, infusion of IL-6 into mice abolishes the ability of insulin to suppress glucose production in the liver[94]. By contrast, IL-6 deficiency exacerbates hepatic insulin resistance and inflammation in mice on a high-calorie diet[95], whereas reduction of IL-6 in adipose tissue (by ablation of JNK) protects against the development of insulin resistance through modulation of SOCS3 expression in the liver[96]. Thus, the different actions of IL-6 on insulin signalling may be due to its disparate actions in different organs (liver versus muscle) or the different sources of IL-6 (muscle versus fat)[97,98].

IL-18. IL-18 is a pro-inflammatory cytokine, and it is now recognized that it is produced by adipose tissues[99]. Serum levels of IL-18 are increased in obese individuals, and they decline following weight loss[100]. High levels of IL-18 have also been detected in atherosclerotic lesions in humans and may indicate plaque instability[101]. Overexpression of IL-18 in rats results in increased expression of endothelial cell adhesion molecules, macrophage infiltration of the blood vessel wall and vascular abnormalities[102], whereas IL-18 deficiency led to smaller lesions in a mouse model of atherosclerosis[103]. Despite the pro-inflammatory nature of IL-18, mice that are deficient in IL-18 or its receptor show hyperphagia and have features of the metabolic syndrome, including insulin resistance, hyperglycaemia and obesity[104]. Similar results were found in mice that overexpress IL-18 binding protein, which reversibly binds and inactivates IL-18. Thus, IL-18 seems to have complex roles in coordinating inflammation and metabolism.

CCL2. The expression of CCL2 (also known as MCP1) has been shown to be increased in adipose tissues under conditions of glucose deprivation[105]. In addition, genetically obese (*ob/ob*) mice and diet-induced obese mice have high levels of CCL2 expression in their white adipose tissue, and this observation has been extended to humans[106]. In mice, high levels of circulating CCL2 (originating from adipose tissues) are sufficient to induce macrophage recruitment to, and inflammation in, adipose tissues, as well as to promote glucose intolerance and insulin insensitivity[105]. Accordingly, somatic deletion of *Ccl2* protects mice against adipose tissue inflammation and macrophage recruitment, as well as metabolic perturbations, following the initiation of a high-fat diet. Conversely, another study found no differences in adipose tissue inflammation or macrophage accumulation in CCL2-deficient mice[107]. Studies of mice with a somatic deletion of CC-chemokine receptor 2 (*Ccr2*), the receptor for CCL2, gain as much weight as their wild-type littermates but fail to show adipose tissue inflammation, and maintain insulin sensitivity on a high-fat diet[108,109]. As CCR2 functions as a receptor for several chemokines, there may be additional inflammatory chemokines that compensate for the absence of CCL2 (REF. 110).

CXCL5. CXCL5 is secreted by macrophages within the stromal vascular fraction, and has been shown to be linked to adipose tissue inflammation and insulin resistance[111]. Circulating levels of CXCL5 are higher in obese, insulin-resistant individuals than in obese insulin-sensitive individuals, and CXCL5 levels decrease after a 4-week period on a low-calorie diet. Mechanistically, CXCL5 interferes

Stromal vascular fraction
Non-adipocyte components of adipose tissue, including monocytes, macrophages, vascular cells, pre-adipocytes, T cells and mesenchymal stem cells.

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with insulin signalling in muscles by activating the JAK–STAT pathway through its receptor CXC-chemokine receptor 2 (CXCR2). Administration of neutralizing antibodies specific for CXCL5 increases insulin sensitivity in both genetic and diet-induced models of obesity. In addition, genetic loss of *Cxcr2* improves insulin sensitivity in mice that are fed a high-fat diet. The expression of *CXCL5* is controlled through TNF signalling by direct promoter activation, associated with increased occupancy of the *CXCL5* promoter by NF-κB[111].

NAMPT. NAMPT (also known as pre-B cell colony enhancing factor and visfatin) was originally identified as a modulator of B cell differentiation that is expressed in lymphocytes, bone marrow, muscle and liver[112]. Subsequently, it was reported to be mainly expressed and secreted by adipose tissues (in particular, visceral adipose tissue) through a non-classical secretory pathway[113]. It has been reported that NAMPT expression correlates with visceral adiposity in humans and in an experimental model of obesity, and that NAMPT regulates glucose levels in mice, possibly by activating insulin receptors; however, this latter claim was retracted[114]. High circulating levels of NAMPT are also found in patients with obesity and type 2 diabetes[115,116], and in inflammatory bowel disease[117], and its expression positively correlates with serum levels of IL-6 and CRP[118].

NAMPT is thought to function in the NAD biosynthetic pathway and to have an important role in insulin secretion by pancreatic β-cells[113]. Heterozygous NAMPT-deficient mice have reduced NAD biosynthesis and glucose-stimulated insulin secretion in the pancreas, and this contributes to glucose intolerance[113]. NAMPT stimulates the p38 mitogen-activated protein kinase (p38 MAPK) and extracellular signal-regulated kinase (ERK) pathways, leading to the production of IL-1β, TNF and IL-6. These factors increase human monocyte chemotactic activity; thus these observations support the idea that NAMPT has a pro-inflammatory role[117]. Overall, NAMPT seems to be involved in inflammation and pancreatic function. However, further studies are required to understand its physiological functions with regard to obesity-linked metabolic disorders.

Anti-inflammatory adipokines

In addition to the numerous pro-inflammatory adipokines described above, adipose tissues also secrete a smaller number of anti-inflammatory factors, such as adiponectin, which has been the subject of intense investigation[3,4], and SFRP5, which has been recently identified as an adipokine[25].

Adiponectin. Adiponectin is almost exclusively synthesized by adipocytes and is present at high levels (3 to 30 μg ml^{-1}) in the blood[3]. Adiponectin has a collagen-like domain followed by a globular domain that is similar to complement factor C1q. Similarly to C1q, adiponectin forms trimers, through collagen-like domain interactions, that can further associate to form stable multimeric oligomers (hexamers and a high molecular weight form)[3], and all three forms are detectable in the blood.

Adiponectin levels in the plasma and adipose tissue are decreased in obese individuals compared with lean individuals[119]. Consistent with this, the production of adiponectin by adipocytes is inhibited by pro-inflammatory factors, such as TNF and IL-6 (REFS 3,4), as well as by hypoxia and oxidative stress[120]. PPARγ agonists promote adipocyte differentiation, and adiponectin secretion is stimulated in adipocytes by the activation of PPARγ[3,4].

Several clinical observations support an association between adiponectin levels and obesity-linked metabolic dysfunction: first, plasma adiponectin levels negatively correlate with visceral fat accumulation[119]; second, plasma adiponectin levels are decreased in patients with type 2 diabetes; and third, high adiponectin levels are associated with a lower risk for developing type 2 diabetes[3,121]. Thus, in view of the pro-inflammatory adipokines discussed previously, adiponectin is unique in that it is expressed at the highest levels by the functional adipocytes that are found in lean organisms but its expression is downregulated in the dysfunctional adipocytes that are associated with obesity.

Metabolic actions of adiponectin. Much evidence from experimental models indicates that adiponectin protects against obesity-linked metabolic dysfunction. Administration of adiponectin to diabetic mice has been shown to reduce hyperglycaemia by enhancing insulin activity[4] and, when given to obese mice, it increases fatty acid oxidation in muscle tissue and reduces plasma levels of glucose, free fatty acids and triglycerides[122]. In line with these observations, adiponectin-deficient mice develop exacerbated diet-induced insulin resistance[123,124], whereas transgene-mediated overexpression of adiponectin in *ob/ob* mice improves glucose metabolism independently of weight loss[26].

The beneficial effects of adiponectin on insulin sensitivity seem to be mediated in part by its ability to activate AMP-activated protein kinase (AMPK) in skeletal muscle and liver[125,126], because AMPK activation leads to an increase in fatty acid oxidation and glucose uptake in muscle tissue, and inhibition of gluconeogenesis in the liver. Adiponectin is thought to mediate AMPK activation through interactions with its cell surface receptors: adiponectin receptor 1 and adiponectin receptor 2 (REF. 127). Accordingly, adiponectin receptor 1 deficiency results in reduced adiponectin-induced AMPK activation, increased glucose production and impaired insulin resistance, whereas adiponectin receptor 2 deficiency causes decreased activity of PPARα signalling pathways and enhanced insulin resistance[128]. The disruption of both receptors abolishes adiponectin binding and actions, leading to exacerbation of glucose intolerance.

In skeletal muscle cells, adiponectin was found to increase intracellular Ca^{2+} concentration and the activities of calcium/calmodulin-dependent protein kinase kinase (CaMKK), AMPK and sirtuin 1 (SIRT1), resulting in enhanced expression and activity of PPARγ co-activator 1α (PPARγC1α; also known as PGC1α). This pathway is associated with insulin sensitivity, and thus disruption of adiponectin receptor 1 expression specifically in muscle cells was shown to prevent these adiponectin-mediated changes and cause insulin resistance[129].

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However, another study reported the opposite phenotype in adiponectin receptor 2-deficient mice, showing that they are resistant to metabolic alterations that are caused by a high-fat diet[130], and a third study showed that deletion of adiponectin receptor 2 attenuates high-fat diet-induced insulin resistance, but exacerbates glucose intolerance after long-term exposure to a high-fat diet, presumably owing to the dysfunction of pancreatic β-cells[131]. Thus, the roles of adiponectin receptors in mediating the metabolic actions of adiponectin *in vivo* are controversial and incompletely understood.

Adiponectin and inflammation. Several studies have investigated the association between adiponectin levels and pro-inflammatory markers in various disease settings. Plasma adiponectin levels are negatively correlated with CRP levels in obese or diabetic patients, and low adiponectin levels are associated with higher CRP levels in non-diabetic or healthy subjects[3,132]. Adiponectin-deficient mice have higher levels of *Tnf* mRNA in adipose tissue and TNF protein in the blood[123], and these parameters were restored to normal levels on administration of adiponectin. Transgenic overexpression of adiponectin in *ob/ob* mice leads to morbid obesity, but there is marked improvement in glucose metabolism, accompanied by a reduction in macrophage numbers in adipose tissue and decreased expression of TNF in fat pads[26]. Similarly, the acute administration of adiponectin to *ob/ob* mice improves fatty liver disease through suppression of TNF production[133]. Therefore, it seems that the ability of adiponectin to suppress pro-inflammatory cytokine production may be an important feature in its ability to reverse metabolic dysfunction. Similarly, these anti-inflammatory activities contribute to the protective actions of adiponectin in cardiovascular tissues (BOX 2).

Accumulating evidence suggests that adiponectin-mediated modulation of macrophage function and phenotype contributes to its role in controlling inflammation. Adiponectin inhibits the transformation of macrophages into foam cells, and reduces intracellular cholesteryl ester content in human macrophages by suppressing the expression of class A scavenger receptors (SR-A)[134]. It also abrogates LPS-stimulated TNF production by macrophages[135] and inhibits Toll-like receptor-mediated NF-κB activation in mouse macrophages[136]. Furthermore, adiponectin stimulates the production of the anti-inflammatory cytokine IL-10 by human macrophages[137]. Peritoneal macrophages and adipose tissue stromal vascular fraction cells of adiponectin-deficient mice show increased expression of pro-inflammatory M1-type markers and decreased expression of anti-inflammatory M2-type markers[138]. Conversely, the systemic delivery of adiponectin to mice stimulates arginase 1 expression by peritoneal macrophages and stromal vascular fraction cells, and stimulation of cultured macrophages with recombinant adiponectin results in an increase in the levels of M2-type markers and a reduction in ROS generation[138].

Similar to other members of the collectin family, including C1q and surfactant proteins A and D[135], adiponectin can bind to apoptotic cells and facilitate their uptake by macrophages[139]. Accordingly, macrophages in adiponectin-deficient mice display a reduced ability to

Box 2 | **Cardiovascular effects of adiponectin**

Clinical studies have identified an association between low serum levels of adiponectin and coronary artery disease[150], hypertension[151], left ventricular hypertrophy[152] and a greater risk of myocardial infarction[153]. Early experimental studies showed that adiponectin reduces tumour necrosis factor (TNF)-stimulated expression of interleukin-8 (IL-8) and vascular endothelial cell adhesion molecules (such as vascular cell adhesion molecule 1 (VCAM1)) through the suppression of nuclear factor-κB (NF-κB) activation, and thus diminishes monocyte attachment[154–156]. Consistent with these *in vitro* findings, overexpression of adiponectin inhibits the formation of atherosclerotic lesions and decreases the expression of class A scavenger receptors (SR-A), TNF and VCAM1 in the aorta in a model of atherosclerosis[157,158], whereas the ablation of adiponectin leads to augmented atherosclerosis that is associated with increased T cell accumulation in atheratoma[159]. However, a recent study did not find an association between atherosclerosis and levels of circulating adiponectin, such that in a low-density lipoprotein receptor (LDLR)-deficient mouse model, atherosclerosis was not altered in states of adiponectin deficiency or chronic overexpression[160]. Related studies have shown that adiponectin also promotes vascular homeostasis through its ability to activate endothelial nitric oxide synthase (eNOS), a key determinant of endothelial cell function. Adiponectin promotes eNOS activation in endothelial cells through AMP-activated protein kinase (AMPK)-dependent phosphorylation of this enzyme[161,162]. In addition, adiponectin stimulates endothelial cell migration and differentiation to form capillary-like structures, and prevents endothelial cell apoptosis through activation of AMPK signalling[161–163]. In keeping with these *in vitro* observations, adiponectin-deficient mice develop hypertension and impaired endothelial cell-dependent vasodilation when fed an atherogenic diet[164]. Disruption of adiponectin also leads to the enhancement of salt-induced hypertension and the reduction of eNOS expression in the aorta[165]. Adiponectin suppresses cerebral ischaemia–reperfusion injury[166] and promotes the revascularization response to chronic hindlimb ischaemia through activation of the AMPK–eNOS signalling pathway[167,168]. Finally, recent evidence has shown that adiponectin also promotes the expression of the autacoid prostaglandin I_2 (PGI_2) by endothelial cells, contributing to the improved vascular function that is attributed to this adipokine[169]. Adiponectin also inhibits pathological cardiac remodelling following pressure overload or angiotensin II infusion *in vivo*, at least in part through its ability to activate AMPK signalling in myocytes[170,171]. Adiponectin protects the heart from detrimental remodelling (such as fibrosis) and heart failure after myocardial infarction[172], and a recent study has shown that aldosterone-infused adiponectin-deficient mice show exacerbated diastolic dysfunction[173]. Of particular interest, the glycosylphosphatidylinositol (GPI)-anchored cell surface glycoprotein T-cadherin has been shown to be required for localizing adiponectin to the lumenal surface of the vascular endothelium[174] and for conferring the cardioprotective action of adiponectin[175]. Overall, adiponectin is a protective adipokine against the development of obesity-linked heart diseases, and it is a molecular link between adipose and cardiovascular tissues.

Foam cell
A macrophage in the arterial wall that ingests oxidized low-density lipoprotein and assumes a foamy appearance. These cells secrete various substances involved in atherosclerotic plaque growth.

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clear early apoptotic cells in the peritoneal cavity. Because phagocytosis of early apoptotic cells promotes an M2-like phenotype in macrophages[140], these data suggest that adiponectin can protect the organism from systemic inflammation at least in part through its ability to function as a collectin protein. Collectin proteins have important roles in suppressing inflammation in the lungs, and a number of studies have recently documented inflammatory lung disorders in adiponectin-deficient mice (BOX 3). Similar to C1q and other collectin proteins, adiponectin binds to calreticulin on the cell surface of macrophages[139]. Calreticulin and its adaptor protein CD91 act as a co-receptor system for the uptake and removal of apoptotic cells by macrophages. Adiponectin facilitates the uptake of dead cells through a pathway involving calreticulin and CD91, but not adiponectin receptor 1 or 2 (REF. 139).

Overall, adiponectin can modulate macrophage phenotype through multiple mechanisms, but the receptor-mediated signalling pathways in macrophages that contribute to the anti-inflammatory actions of adiponectin are poorly understood. Furthermore, adiponectin levels are increased, rather than decreased, in a number of chronic inflammatory and autoimmune diseases[141]. The upregulation of adiponectin in severe inflammatory diseases may represent a compensatory response as it has been shown that increasing adiponectin levels by treatment with a PPARγ agonist ameliorates disease in a mouse model of lupus[142]. Thus, the clinical significance of adiponectin in the context of inflammatory diseases requires future investigation.

SFRP5. We reported in a recent study the identification of SFRP5 as a new adipokine with anti-inflammatory properties that has beneficial effects on metabolic dysfunction[25]. SFRPs act as soluble modulators that sequester WNT proteins, preventing them from binding to their receptors. SFRP5 is expressed at high levels in mouse white adipose tissue[25] but is downregulated in the adipose tissues of various obese rodents, as well as in the visceral adipose tissue of obese individuals with adipose tissue inflammation and insulin resistance. WNT5a, which is antagonized by SFRP5, is upregulated in the fat depots of obese rodents, and the WNT5a/SFRP5 protein expression ratio in adipose tissue is also increased by obesity. WNT5a has previously been implicated in a variety of inflammatory disorders.

SFRP5-deficient mice have normal glucose tolerance when kept on a regular diet, but show impaired insulin sensitivity and increased fatty liver disease compared with control mice[25]. Exacerbation of metabolic dysfunction induced by SFRP5 deficiency is associated with increased accumulation of macrophages and enhanced production of pro-inflammatory cytokines (including TNF and IL-6) in adipose tissues. Of importance, JUN N-terminal kinase 1 (JNK1; also known as MAPK8), a downstream target of non-canonical WNT signalling, is activated in adipose tissues of SFRP5-deficient mice on a high-calorie diet. A series of *in vitro* experiments indicated that overexpression of SFRP5 inhibits WNT5a-stimulated phosphorylation of JNK1 in adipocytes, and similarly blocks WNT5a-induced JNK1 activation and the subsequent induction of pro-inflammatory cytokine production in macrophages. Furthermore, deletion of JNK1 in SFRP5-deficient mice reverses the impaired insulin sensitivity and enhanced adipose tissue inflammation observed in SFRP5-deficient mice. Thus, SFRP5 deficiency exacerbates obesity-induced adipose tissue inflammation and metabolic dysfunction through activation of JNK1 in adipose tissue, and this is consistent with the previously described role for JNK1 in the regulation of insulin resistance and inflammation[96,143–145]. Notably, systemic administration of SFRP5 to obese mice improved metabolic parameters, such as insulin resistance and fatty liver disease. Taken together, these observations indicate that the balance between SFRP5 and WNT5a in adipose tissue has an important role in the regulation of JNK1 activity in adipocytes and adipose tissue macrophages, thereby modulating inflammation and metabolic function. Thus, SFRP5 in adipose tissue is a potential target for the control of obesity-linked abnormalities in glucose homeostasis. Future studies are required to address the role of SFRP5 in the regulation of obesity-linked inflammatory disorders, including atherosclerosis and ischaemic heart disease.

Box 3 | **Adiponectin and inflammatory lung disease**

A baseline phenotype of adiponectin-deficient mice is emphysema-like dilated airspaces and alveolar macrophage activation[176]. In addition, adiponectin-deficient mice develop a pulmonary hypertension phenotype that is associated with perivascular inflammation[177,178]. Obesity is a risk factor for the development of asthma, and micro-pump administration of recombinant adiponectin is reported to reduce allergic lung inflammation in an asthma model of ovalbumin sensitization and challenge[179]. Little is known about the mechanisms by which adiponectin suppresses inflammation in the lungs. Adiponectin receptor 1 is expressed by lung epithelial cells[180], and T-cadherin seems to be required to facilitate the entry of adiponectin into the lungs[181]. Whereas expression of adiponectin is reduced in subjects who smoke cigarettes, increased levels are found in those with chronic obstructive pulmonary disease[180] and high levels of adiponectin are associated with mortality in patients with respiratory failure[182].

Concluding remarks

Adipose tissues can influence and communicate with many other organs, including the brain, heart, vasculature, liver and muscle, through the production of various secretory factors or adipokines. Adipokines have both pro-inflammatory and anti-inflammatory activities, and the balance between the different factors is crucial for determining homeostasis throughout the body based on nutritional status. When adipocyte dysfunction occurs as a result of adipose tissue expansion (which may be due to over-nutrition or physical inactivity, for example), dysregulation of adipokine production can have local or systemic effects on inflammatory responses, thereby contributing to the initiation and progression of obesity-induced metabolic and cardiovascular complications. Thus, further elucidation of the functions and mechanisms of key adipokines will lead to a better understanding of the pathogenesis of obesity-linked disorders. Moreover, therapeutic strategies that counteract the imbalance of pro-inflammatory and anti-inflammatory adipokines could be an attractive and useful means for preventing and/or treating obesity-related metabolic and cardiovascular diseases.

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