*Proceedings of the Nutrition Society* (2009), **68**, 378–384 doi:10.1017/S0029665109990218

*A Meeting of the Nutrition Society, hosted by the Scottish Section, was held at the Royal Society of Edinburgh, Edinburgh on 7 and 8 April 2009*

## Symposium on ‘Frontiers in adipose tissue biology’

# Chemotactic cytokines, obesity and type 2 diabetes: *in vivo* and *in vitro* evidence for a possible causal correlation?

Henrike Sell and Jürgen Eckel*
*Institute of Clinical Biochemistry and Pathobiochemistry, German Diabetes Center, Düsseldorf, Germany*

A strong causal link between increased adipose tissue mass and insulin resistance in tissues such as liver and skeletal muscle exists in obesity-related disorders such as type 2 diabetes. Increased adipose tissue mass in obese patients and patients with diabetes is associated with altered secretion of adipokines, which also includes chemotactic proteins. Adipose tissue releases a wide range of chemotactic proteins including many chemokines and chemerin, which are interesting targets for adipose tissue biology and for biomedical research in obesity and obesity-related diseases. This class of adipokines may be directly linked to a chronic state of low-grade inflammation and macrophage infiltration in adipose tissue, a concept intensively studied in adipose tissue biology in recent years. The inflammatory state of adipose tissue in obese patients may be the most important factor linking increased adipose tissue mass to insulin resistance. Furthermore, chemoattractant adipokines may play an important role in this situation, as many of these proteins possess biological activity beyond the recruitment of immune cells including effects on adipogenesis and glucose homeostasis in insulin-sensitive tissues. The present review provides a summary of experimental evidence of the role of adipose tissue-derived chemotactic cytokines and their function in insulin resistance *in vivo* and *in vitro*.

**Chemokine: Chemerin: Insulin resistance: Adipose tissue: Obesity**

Obesity with increased adipose tissue mass is associated with insulin resistance, hyperglycaemia, dyslipidaemia, hypertension and other components of the metabolic syndrome(1,2). Type 2 diabetes has markedly increased in prevalence; 50 % of men and 70 % of women with diabetes are obese and obesity predisposes strongly to diabetes(3). Furthermore, type 2 diabetes is becoming a serious health issue in overweight or obese children and adolescents(4). Indeed, there is clearly a strong causal link between increased adipose tissue mass and insulin resistance in tissues such as liver and skeletal muscle in patients with diabetes(5,6).

Adipocytes, the predominant cell type in adipose tissue, are insulin-sensitive cells that store TAG, but in addition to their storage function they are also active endocrine cells that produce and release various proteins termed adipokines. Increased adipose tissue mass in obese patients and patients with diabetes has been found to be associated with altered secretion of adipokines, the most important of which are TNFα, IL-6 and adiponectin(7). Adipose tissue also releases a wide range of chemotactic proteins including many chemokines, which are becoming increasingly interesting in relation to adipose tissue biology as well as biomedical research in obesity and obesity-related diseases. This class of adipokines may be directly linked to a chronic state of low-grade inflammation and macrophage infiltration in adipose tissue, a concept that has been intensively studied in adipose tissue biology in recent years. The inflammatory state of adipose tissue in obese patients may be the most important factor linking increased adipose tissue mass to insulin resistance, and chemoattractant adipokines might play an important role in this

---

**Abbreviations:** CCR, chemokine CC motif receptor; CMKLR1, chemokine-like receptor 1; CXCL, chemokine CXC motif ligand; MCP, monocyte chemoattractant protein.

***Corresponding author:** Professor Jürgen Eckel, fax +49 211 3382697, email eckel@uni-duesseldorf.de

**Table 1.** Clinical data showing the association between chemotactic cytokines and obesity and type 2 diabetes

| Chemotactic cytokine | Clinical data related to obesity and type 2 diabetes | References |
|---|---|---|
| MCP-1 (CCL2) | Increased in obesity and diabetes | Christiansen *et al.*(11), Kim *et al.*(12), Herder *et al.*(13), Malavazos *et al.*(14), Huber *et al.*(15), Piemonti *et al.*(16), Simeoni *et al.*(17) |
| RANTES (CCL5) | Associated with diabetes | Herder *et al.*(26) |
| MCP-3 (CCL7) | Elevated in obesity | Jiao *et al.*(25) |
| MCP-2 (CCL8) | Elevated in obesity | Huber *et al.*(15), Murdolo *et al.*(24) |
| Eotaxin (CCL11) | Increased in obesity but not associated with insulin resistance | Hashimoto *et al.*(23), Vasudevan *et al.*(27) |
| MCP-4 (CCL13) | Elevated in obesity | Hashimoto *et al.*(23) |
| CXCL5 | Linking obesity and insulin resistance | Chavey *et al.*(32) |
| IL-8 (CXCL8) | Increased in obesity and diabetes | Kim *et al.*(12), Herder *et al.*(13) |
| IP-10 (CXCL10) | Increased in obesity but not associated with insulin resistance | Herder *et al.*(26,31) |
| Chemerin | Increased in obesity but not related to type 2 diabetes | Bozaoglu *et al.*(9) |

MCP, monocyte chemoattractant protein; CCL, chemokine CC motif ligand; CXCL, chemokine CXC motif ligand; IP-10, 10 kDa interferon γ-induced protein.

scenario. The present review provides a summary of experimental evidence of the role of adipose tissue-derived chemoattractant proteins and their function in insulin resistance *in vivo* and *in vitro*. The aim is to provide an overview of known relationships between the chemokines and chemotactic cytokines being released from adipose tissue and obesity and type 2 diabetes. Mechanisms of obesity-related disorders that underlie adipose tissue inflammation and that may be related to chemotactic cytokines are also discussed.

## Chemotactic proteins in obesity and type 2 diabetes

Chemotactic proteins, particularly those of the chemokine family, have been shown to be related *in vivo* to the metabolic syndrome, obesity and type 2 diabetes (Table 1) and to be adipokines secreted from adipocytes or other cell types residing in adipose tissue. Chemokines are small proteins that attract various immune cells such as monocytes, neutrophils, T lymphocytes, basophils or eosinophils (each chemokine activating one or more target cell types)(8). Chemokines are characterized by the presence of four highly-conserved cysteine residues. CXC chemokines have two amino-terminal cysteine residues separated by only one amino acid. In CC chemokines, the other main subfamily of chemokines, the amino-terminal cysteine residues are adjacent(8). In addition, other chemoattractant proteins such as chemerin, which has been shown to attract macrophages and dendritic cells but is not structurally related to any chemokine family, comprise the adipokines and factors shown to be involved in obesity and obesity-related pathologies(9).

Monocyte chemoattractant protein (MCP)-1 is a chemokine and a member of the small inducible cytokine family that plays a role in the recruitment of monocytes and T lymphocytes to sites of injury and infection(10). Its main receptor is the chemokine CC motif receptor (CCR) 2. Plasma MCP-1 levels are markedly higher in obese patients(11,12) and patients with diabetes(13), and in relation to these pathologies MCP-1 is one of the most studied chemokines. In obese patients different depots of adipose tissue such as visceral, subcutaneous and epicardial adipose tissue show increased expression of MCP-1(14,15). Clinical data provide good evidence for a relationship between serum MCP-1 levels and insulin resistance, as well as type 2 diabetes. Several studies have demonstrated that patients with type 2 diabetes display elevated MCP-1 levels(13,16,17). High MCP-1 levels have been shown to contribute to diabetes risk independently of previously-described clinical, metabolic and immunological risk factors(13). Conversely, diabetes treatments such as exercise(18), pioglitazone(19) and weight loss(20), all of which improve insulin sensitivity in obese patients, reduce MCP-1 plasma concentrations. Expression of MCP-1 has been found to be higher in visceral adipose tissue than in subcutaneous tissue and is closely related to the number of resident macrophages(21). Conversely, obese patients that lose weight after bariatric surgery show decreased levels of MCP-1(20), probably in parallel with lower macrophage infiltration in adipose tissue(22).

Fewer data are available for other MCP such as MCP-2, -3 and -4 but it is clear that these adipokines are elevated in obese patients(15,23–25). Measurement of these factors in adipose tissue has shown a marked increase in expression together with an increased expression of the corresponding receptors in obese patients(15).

Other CC chemokines such as RANTES (or chemokine CC motif ligand 5) and eotaxin (or chemokine CC motif ligand 11) are also elevated in the serum of obese patients as compared with lean controls(23,26,27). Eotaxin is overexpressed in visceral adipose tissue of obese patients as compared with lean controls and subcutaneous fat. While RANTES has also been found to be associated with type 2 diabetes in a large German study cohort, eotaxin is not associated with insulin resistance(26).

IL-8 and 10 kDa interferon γ-induced protein (or chemokine CXC motif ligand (CXCL) 10) are CXC chemokines. IL-8 is secreted from adipose tissue and its plasma levels are increased in obesity(28–30). However, a correlation between higher levels of IL-8 in obesity and increased insulin resistance has not yet been fully established, as the association between IL-8 and diabetes(13) is attenuated by

**Table 2.** *In vitro* evidence that chemotactic cytokines are adipokines with a possible role in insulin resistance

| Chemotactic cytokine | Adipokine | *In vitro* evidence for a relationship with insulin resistance | References |
|---|---|---|---|
| MCP-1 (CCL2) | Yes | Linked to insulin resistance in mouse models, adipocytes and skeletal muscle cells | Sell *et al.*(36), Gerhardt *et al.*(37), Kanda *et al.*(42), Kamei *et al.*(44) |
| MIP-1α (CCL3) | Yes | Regulated by adiponectin | Gerhardt *et al.*(37), Dietze-Schroeder *et al.*(38) |
| MIP-1β (CCL4) | Yes | Regulated by adiponectin and inducer of insulin resistance in skeletal muscle cells | Sell *et al.*(36), Dietze-Schroeder *et al.*(38) |
| RANTES (CCL5) | Yes | Increased in visceral adipocytes | Skurk *et al.*(73), Madani *et al.*(75) |
| Eotaxin (CCL11) | Yes (SV fraction) | Increased release in obesity | Vasudevan *et al.*(27) |
| GRO-α (CXCL1) | Yes | Regulated by adiponectin | Dietze-Schroeder *et al.*(38) |
| CXCL5 | Yes (SV fraction) | Induces insulin resistance in skeletal muscle | Chavey *et al.*(32) |
| IL-8 (CXCL8) | Yes | Regulated by adiponectin and induces insulin resistance in skeletal muscle cells | Sell *et al.*(36), Dietze-Schroeder *et al.*(38) |
| IP-10 (CXCL10) | Yes | Regulated by interferon-γ | Herder *et al.*(76) |
| Chemerin | Yes | Induces insulin resistance in adipocytes | Kralisch *et al.*(55) |

MCP, monocyte chemoattractant protein; CCL, chemokine CC motif ligand; MIP-1, macrophage inflammatory protein 1; GRO-α, growth-regulated oncogene α; SV, stroma vascular; CXCL, chemokine CXC motif ligand; IP-10, 10 kDa interferon γ-induced protein.

multivariable adjustment for BMI and other metabolic and immunological risk factors. Another study has demonstrated that IL-8 expression is markedly increased in human fat cells from individuals who are insulin-resistant(30). Serum levels of 10 kDa interferon γ-induced protein are increased in obese patients but are not associated with insulin resistance(26,31). CXCL5 has very recently been revealed to be a new adipokine that is present in markedly increased levels in obese subjects as compared with lean controls(32). The same study has also shown that the serum concentration of this chemokine decreases in obese subjects after weight reduction.

Recently, the rapidly-growing adipokine family has expanded to include chemerin, a secretory chemoattractant protein. Initially discovered in body fluids associated with inflammatory processes(33), chemerin and its receptor chemokine-like receptor 1 (CMKLR1) (or ChemR23) are also highly expressed in adipose tissue(9,34). *In vivo* data have shown that chemerin is elevated in adipose tissue of diabetic *Psammomys obesus* (sand rat; an animal model of obesity and type 2 diabetes) compared with controls(9). However, there is no difference in chemerin levels between patients with diabetes and control patients despite a correlation between chemerin levels and BMI, blood TAG and blood pressure(9).

## Chemotactic adipokines: data from animal models and cell culture

Many chemokines have been shown to possess biological activity beyond the recruitment of immune cells, which also applies to adipose tissue-derived chemokines such as MCP-1, for which insulin resistance-inducing capacity is postulated(35,36) (Table 2). MCP-1 is secreted from adipocytes in rodents(35,37) and human subjects(11,38). Large adipocytes release higher levels of MCP-1 together with other pro-inflammatory cytokines(39). It appears, however, that adipocytes only partly contribute to the MCP-1 output from adipose tissue(40). *In vitro*, MCP-1 expression and secretion is highly regulated in adipocytes, i.e. increased by insulin, TNFα, growth hormone and IL-6(41), all of which are increased in obese patients. Conversely, treatment of 3T3-L1 adipocytes with MCP-1 impairs glucose uptake, indicating that this cytokine may contribute to the pathogenesis of insulin resistance(35). MCP-1 does not, however, cause insulin resistance by acting only in an autocrine or paracrine manner. In primary human skeletal muscle cells it has been shown that even hypophysiological levels of MCP-1 induce robust insulin resistance(36).

The use of mouse models has revealed that specific overexpression of MCP-1 in adipose tissue alone can mimic the effects of diet-induced obesity such as insulin resistance, macrophage infiltration into adipose tissue and liver steatosis, which occurs in the absence of any increase in body weight(42). The same study has also shown that in contrast to MCP-1 overexpression, MCP-1 deficiency in diet-induced obese mice or inhibition of MCP-1 expression in *db/db* mice ameliorates insulin resistance and reduces the number of macrophages in adipose tissue(42). On the other hand, conflicting data from another group suggest that MCP-1 deficiency does not reduce obesity-induced inflammation in adipose tissue(43). Another study using mice with adipose tissue overexpression of MCP-1 has demonstrated that MCP-1 can reduce insulin sensitivity in an endocrine manner in skeletal muscle(44).

Thus, the role of MCP-1 in adipose tissue inflammation is not fully understood, which is also the case for its receptor CCR2. One study with CCR2-knock-out mice has demonstrated that disruption of MCP-1 signalling does not prevent obesity induced by a high-fat diet(45). Another study, however, has found that when CCR2 is lacking the efficiency of diet-induced obesity is decreased concomitantly with reduced macrophage number and an ameliorated inflammatory profile together with reduced insulin resistance(46). Furthermore, pharmacological inhibition of CCR2 has been shown to improve glucose homeostasis and inflammatory markers both dependently and independently of adipose tissue(47,48).

The release of the chemokines MCP-1, macrophage inflammatory protein 1α and β, growth-regulated oncogene α and IL-8 is inhibited by adiponectin(38). Adiponectin is a prominent adipokine that is decreased in obesity and that positively influences insulin sensitivity(49). Accordingly, low plasma adiponectin levels observed in obesity are good indicators of insulin resistance and the development of diabetes(50). It has been demonstrated that adiponectin acts as an autocrine regulator of adipocyte secretion and by decreasing the release of adipokines simultaneously prevents insulin resistance in myocytes undergoing co-culture with adipocytes(38). In addition, several chemokines, including IL-8, macrophage inflammatory protein 1β and MCP-1, induce insulin resistance in skeletal muscle cells(36) and thereby may represent a link between obesity and type 2 diabetes. In the case of eotaxin there are no data to suggest that it is regulated by adiponectin, but one clinical study has demonstrated a link between high eotaxin levels and hypoadiponectinaemia(51). Eotaxin is also released from adipose tissue but stroma vascular cells appear to be the major source of this chemokine(27).

CXCL5, a very recent addition to the adipokines(32), is mainly secreted by the macrophage fraction of adipose tissue. Like MCP-1 this chemokine induces insulin resistance in muscle, pointing to a link between adipose tissue inflammation and insulin resistance in peripheral tissues. In addition, blocking CXCL5 signalling in insulin-resistant mice using either an anti-CXCL5 antibody or an antagonist for the corresponding receptor, chemokine CXC motif receptor 2, improves insulin sensitivity without changing body weight or food intake. Also, chemokine CXC motif receptor 2-knock-out mice display enhanced insulin responsiveness when compared with wild-type mice. It should be mentioned that CXCL5 has only been studied by one group so far, so these results need verification by other studies. Furthermore, in light of the varying phenotypes of CCR2-knock-out mice it is difficult to discuss the role of CXCL5 and its receptor chemokine CXC motif receptor 2 definitively at this point.

Chemerin and CMKLR1 are necessary for adipogenesis, as viral knockdown of expression of both proteins completely inhibits this process(34). Chemerin mRNA expression increases with adipogenesis(9,34,52). In human adipocytes a comparison of chemerin and CMKLR1 mRNA expression before and after differentiation shows a more pronounced increase in CMKLR1 than in chemerin(34). Human adipocytes also release measurable amounts of chemerin, the secretion of which is up regulated by TNFα (H Sell and J Eckel, unpublished results). In adipose tissue chemerin can also be found in the stroma vascular fraction, suggesting a contribution of various adipose tissue cell types to chemerin production. It has been demonstrated that macrophages express CMKLR1 and are chemerin responsive(53). A comparison of different animal models of obesity and diabetes reveals that chemerin expression is not increased in adipose tissue of genetically-obese mice(34), is lower in *db/db* mice(54) but is higher in obese insulin-resistant *P. obesus*(9). A single study in human subjects has reported a correlation between blood chemerin levels and BMI that is independent of glucose tolerance(9). However, it is difficult to speculate on the overall contribution of adipocyte-derived chemerin to serum levels of this chemokine. Concentrations and the origin of chemerin in the liver, lung and other chemerin-producing organs have to be taken into account. Surprisingly, chemerin itself increases glucose uptake in 3T3-adipocytes(54), although another study has reported the opposite effect on adipocytes(55) and it has been demonstrated that chemerin induces insulin resistance in skeletal muscle cells (H Sell and J Eckel, unpublished results). Chemerin expression in adipocytes is up regulated by IL-1β(55). Thus, chemerin may exert different effects by its endocrine and paracrine or autocrine actions.

The current knowledge of chemerin is complicated because the actions of this protein involve targets other than chemerin and its receptor CMKLR1. New receptors have been identified as well as peptides derived from chemerin that have been shown to have completely different modes of action. Chemerin is synthesized as prochemerin, which has a low affinity to CMKLR1(33). Prochemerin is converted rapidly to a CMKLR1 agonist by proteolytic cleavage of a carboxy-terminal peptide involving serine proteases of the coagulation and inflammation cascades(33). Carboxy-terminal peptides derived from chemerin by cysteine protease cleavage bind to CMKLR1 with much higher affinity than chemerin itself and exert potent anti-inflammatory effects on activated macrophages(56,57). This divergent effect of chemerin and chemerin-derived peptides can be explained by binding to receptors other than CMKLR1, which have been identified recently. Chemerin binds to two G-protein-coupled receptors, GPR1 and CCR-like 2(57,58). More specifically, chemerin binds with its carboxy-terminal domain to CMKLR1, directly activating cells; however, chemerin can also bind to CCR-like 2 with its amino-terminal domain and present the carboxy-terminal domain to CMKLR1 on neighbouring cells. In contrast, chemerin-derived peptides only binding to CMKLR1 inhibit an inflammatory response, a process that is comparable with that for other chemokines such as MCP-1 or RANTES(59,60). The role of the novel chemerin receptors and chemerin-derived peptides in the context of obesity and type 2 diabetes is not known.

## Mechanisms of adipose tissue inflammation with a potential role for chemoattractants

Obesity is associated with a state of chronic inflammation in adipose tissue. In addition to increased release of pro-inflammatory markers, macrophage infiltration has recently been shown to be characteristic of expanding adipose tissue(61). However, obesity is not associated with increased macrophage numbers in muscle or liver. It has been proposed that the main source of pro-inflammatory adipokines is in fact macrophages, although other cells in adipose tissue such as adipocytes, preadipocytes and vascular cells contribute to adipose tissue secretion(62). Clinical studies have provided evidence for a good correlation between BMI and macrophage infiltration into adipose tissue, particularly in relation to the visceral fat depot(63). Paracrine and endocrine signals as well as adipocyte hypertrophy and hyperplasia might contribute to macrophage infiltration into adipose tissue. In adipose tissue of obese patients crown-like structures of macrophages surrounding apoptotic adipocytes have been found(64). The expression of several chemotactic cytokines is increased in the obese state concomitantly with increased expression of chemokine receptors such as CCR2 in newly-recruited macrophages, making it possible that ligands for this receptor contribute to macrophage attraction and activation(65). Characterization of adipose tissue-resident macrophages has shown that the latter express surface markers for alternatively activated macrophages (M2) that are able to secrete anti-inflammatory cytokines in addition to pro-inflammatory cytokines, a process that may be necessary for the uptake of large, apoptotic or necrotic adipocytes(65). Weight reduction in human subjects is accompanied by the occurrence of more M2-like macrophages in adipose tissue(66) while diet-induced obesity is characterized by switching the macrophage phenotype towards classical inflammatory M1 status(67). However, it must be emphasized that the mechanisms of macrophage recruitment to adipose tissue in obesity are not yet understood.

The study of hypoxia in adipose tissue in the context of obesity is timely, as some very enlightening studies have put this theory in a physiological context in recent years(68). Hypoxia has been observed in both physiological and pathological situations. In relation to adipose tissue, it has been demonstrated in mice that oxygenation is comparable with general tissue oxygenation in lean animals, while their obese littermates are characterized by an approximately 60 % lower $O_2$ pressure in fat(69). In adipose tissue of mice hypoxia underlies the increased production of adipokines and the development of obesity and the metabolic syndrome(70). Furthermore, it has been demonstrated in human subjects that hypoxia occurs in the obese state(22). Mechanistically, hypoxia leads to activation of the transcription factor hypoxia inducible factor 1$\alpha$, which has a key role in the adaptive response to decreased $O_2$ availability in tissues. Hypoxia inducible factor 1$\alpha$ increases the transcription of various genes that affect, for example, cell proliferation, angiogenesis, glucose metabolism and the extracellular matrix(71). Hypoxia studies in isolated adipocytes have shown that hypoxia causes various changes in protein expression and secretory behaviour in this cell type. Hypoxia in isolated adipocytes leads to the same dysregulation of secretory function as that observed in expanded adipose tissue, including increased release of IL-6, leptin and vascular endothelial growth factor(72). In contrast, the release of adiponectin is decreased in hypoxia, possibly through activation of endoplasmic reticulum stress(70). The release of RANTES is increased by hypoxia(73), while MCP-1 secretion is slightly decreased (72). The regulation of other chemotactic proteins by hypoxia is not yet known.

Another mechanism of adipose tissue inflammation associated with hypoxia currently under investigation is endoplasmic reticulum stress. There are several explanations of why endoplasmic reticulum stress occurs particularly in fat in obesity, including increased protein synthesis as a result of increased energy availability or even glucose deprivation as a result of insulin resistance in adipose tissue(74). Hypoxia has also been proposed to be a cause of endoplasmic reticulum stress(70). Furthermore, hypoxia and endoplasmic reticulum stress might be closely related, as signalling pathways for both forms of stress merge in common pathways such as activation of mammalian target of rapamycin or c-Jun N-terminal kinase(70).

## Conclusion

Research on adipose tissue secretory function has opened up a new vision on the pathophysiological relationships between increased adipose tissue mass in obesity, inflammation, insulin resistance and type 2 diabetes. The observation that macrophages infiltrate expanded adipose tissue in obesity has led to new perspectives in both clinical and basic science for a better understanding of the pathophysiology of obesity and for the development of new therapeutic strategies. Adipose tissue secretes many chemotactic proteins, chemokines and other proteins such as chemerin that correlate with obesity and also with type 2 diabetes *in vivo*. These adipokines participate in a low-grade chronic inflammatory state that could play a key role in insulin resistance. Analysis of adipokine and chemokine release could eventually provide new potential therapeutic targets and also serve to define new biomarkers that may be helpful in optimizing the prevention of insulin resistance and type 2 diabetes in the future. Finally, understanding adipose tissue inflammation and hypoxic events occurring in adipose tissue might lead to a better understanding of the pathophysiology of obesity and facilitate targeting involved pathways for the treatment of obesity-related diseases.

## Acknowledgements

This work was supported by the Ministerium für Wissenschaft und Forschung des Landes Nordrhein-Westfalen, the Bundesministerium für Gesundheit, the EU European Cooperation in the field of Scientific and Technical Research (COST) Action BM0602 (Adipose tissue: A key target for prevention of the metabolic syndrome) and the Commission of the European Communities (Collaborative Project ADAPT, contract no. HEALTH-F2–2008–201100). The secretarial assistance of Birgit Hurow is gratefully acknowledged. The authors declare no conflict of interest. H. S. and J. E. both reviewed the existing literature and contributed to writing the article.

## References

1. Dandona P, Aljada A, Chaudhuri A *et al.* (2005) Metabolic syndrome: a comprehensive perspective based on interactions between obesity, diabetes, and inflammation. *Circulation* **111**, 1448–1454.
2. Despres JP (2006) Is visceral obesity the cause of the metabolic syndrome? *Ann Med* **38**, 52–63.
3. Jones DB & Gill GV (1997) Non-insulin-dependent diabetes mellitus. In *Textbook of Diabetes*, 2nd ed., pp. 17.1–17.13 [JC Pickup and G Williams, editors]. Oxford: Blackwell Science.
4. Goran MI, Ball GD & Cruz ML (2003) Obesity and risk of type 2 diabetes and cardiovascular disease in children and adolescents. *J Clin Endocrinol Metab* **88**, 1417–1427.

5. Argiles JM, Lopez-Soriano J, Almendro V *et al.* (2005) Cross-talk between skeletal muscle and adipose tissue: a link with obesity? *Med Res Rev* **25**, 49–65.
6. Krebs M & Roden M (2005) Molecular mechanisms of lipid-induced insulin resistance in muscle, liver and vasculature. *Diabetes Obes Metab* **7**, 621–632.
7. Coppack SW (2005) Adipose tissue changes in obesity. *Biochem Soc Trans* **33**, 1049–1052.
8. Rollins BJ (1997) Chemokines. *Blood* **90**, 909–928.
9. Bozaoglu K, Bolton K, McMillan J *et al.* (2007) Chemerin is a novel adipokine associated with obesity and metabolic syndrome. *Endocrinology* **148**, 4687–4694.
10. Baggiolini M (1998) Chemokines and leukocyte traffic. *Nature* **392**, 565–568.
11. Christiansen T, Richelsen B & Bruun JM (2005) 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.
12. Kim CS, Park HS, Kawada T *et al.* (2006) Circulating levels of MCP-1 and IL-8 are elevated in human obese subjects and associated with obesity-related parameters. *Int J Obes (Lond)* **30**, 1347–1355.
13. Herder C, Baumert J, Thorand B *et al.* (2006) Chemokines as risk factors for type 2 diabetes: results from the MONICA/KORA Augsburg study, 1984–2002. *Diabetologia* **49**, 921–929.
14. Malavazos AE, Ermetici F, Coman C *et al.* (2006) Influence of epicardial adipose tissue and adipocytokine levels on cardiac abnormalities in visceral obesity. *Int J Cardiol* **121**, 132–134.
15. Huber J, Kiefer FW, Zeyda M *et al.* (2008) CC chemokine and CC chemokine receptor profiles in visceral and subcutaneous adipose tissue are altered in human obesity. *J Clin Endocrinol Metab* **93**, 3215–3221.
16. Piemonti L, Calori G, Mercalli A *et al.* (2003) Fasting plasma leptin, tumor necrosis factor-alpha receptor 2, and monocyte chemoattracting protein 1 concentration in a population of glucose-tolerant and glucose-intolerant women: impact on cardiovascular mortality. *Diabetes Care* **26**, 2883–2889.
17. Simeoni E, Hoffmann MM, Winkelmann BR *et al.* (2004) Association between the A-2518G polymorphism in the monocyte chemoattractant protein-1 gene and insulin resistance and Type 2 diabetes mellitus. *Diabetologia* **47**, 1574–1580.
18. Troseid M, Lappegard KT, Claudi T *et al.* (2004) Exercise reduces plasma levels of the chemokines MCP-1 and IL-8 in subjects with the metabolic syndrome. *Eur Heart J* **25**, 349–355.
19. Di Gregorio GB, Yao-Borengasser A, Rasouli N *et al.* (2005) Expression of CD68 and macrophage chemoattractant protein-1 genes in human adipose and muscle tissues: association with cytokine expression, insulin resistance, and reduction by pioglitazone. *Diabetes* **54**, 2305–2313.
20. Schernthaner GH, Kopp HP, Kriwanek S *et al.* (2006) Effect of massive weight loss induced by bariatric surgery on serum levels of interleukin-18 and monocyte-chemoattractant-protein-1 in morbid obesity. *Obes Surg* **16**, 709–715.
21. Bruun JM, Lihn AS, Pedersen SB *et al.* (2005) Monocyte chemoattractant protein-1 release is higher in visceral than subcutaneous human adipose tissue (AT): Implication of macrophages resident in the AT. *J Clin Endocrinol Metab* **90**, 2282–2289.
22. Cancello R, Henegar C, Viguerie N *et al.* (2005) Reduction of macrophage infiltration and chemoattractant gene expression changes in white adipose tissue of morbidly obese subjects after surgery-induced weight loss. *Diabetes* **54**, 2277–2286.
23. Hashimoto I, Wada J, Hida A *et al.* (2006) Elevated serum monocyte chemoattractant protein-4 and chronic inflammation in overweight subjects. *Obesity (Silver Spring)* **14**, 799–811.
24. Murdolo G, Hammarstedt A, Sandqvist M *et al.* (2007) Monocyte chemoattractant protein-1 in subcutaneous abdominal adipose tissue: characterization of interstitial concentration and regulation of gene expression by insulin. *J Clin Endocrinol Metab* **92**, 2688–2695.
25. Jiao P, Chen Q, Shah S *et al.* (2009) Obesity-related upregulation of monocyte chemotactic factors in adipocytes: involvement of nuclear factor-kappaB and c-Jun NH2-terminal kinase pathways. *Diabetes* **58**, 104–115.
26. Herder C, Haastert B, Muller-Scholze S *et al.* (2005) Association of systemic chemokine concentrations with impaired glucose tolerance and type 2 diabetes: results from the Cooperative Health Research in the Region of Augsburg Survey S4 (KORA S4). *Diabetes* **54**, Suppl. 2, S11–S17.
27. Vasudevan AR, Wu H, Xydakis AM *et al.* (2006) Eotaxin and obesity. *J Clin Endocrinol Metab* **91**, 256–261.
28. Bruun JM, Pedersen SB & Richelsen B (2001) Regulation of interleukin 8 production and gene expression in human adipose tissue in vitro. *J Clin Endocrinol Metab* **86**, 1267–1273.
29. Straczkowski M, Dzienis-Straczkowska S, Stepien A *et al.* (2002) Plasma interleukin-8 concentrations are increased in obese subjects and related to fat mass and tumor necrosis factor-alpha system. *J Clin Endocrinol Metab* **87**, 4602–4606.
30. Rotter V, Nagaev I & Smith U (2003) Interleukin-6 (IL-6) induces insulin resistance in 3T3-L1 adipocytes and is, like IL-8 and tumor necrosis factor-alpha, overexpressed in human fat cells from insulin-resistant subjects. *J Biol Chem* **278**, 45777–45784.
31. Herder C, Schneitler S, Rathmann W *et al.* (2007) Low-grade inflammation, obesity, and insulin resistance in adolescents. *J Clin Endocrinol Metab* **92**, 4569–4574.
32. Chavey C, Lazennec G, Lagarrigue S *et al.* (2009) CXC ligand 5 is an adipose-tissue derived factor that links obesity to insulin resistance. *Cell Metab* **9**, 339–349.
33. Wittamer V, Franssen JD, Vulcano M *et al.* (2003) Specific recruitment of antigen-presenting cells by chemerin, a novel processed ligand from human inflammatory fluids. *J Exp Med* **198**, 977–985.
34. Goralski KB, McCarthy TC, Hanniman EA *et al.* (2007) Chemerin, a novel adipokine that regulates adipogenesis and adipocyte metabolism. *J Biol Chem* **282**, 28175–28188.
35. Sartipy P & Loskutoff DJ (2003) Monocyte chemoattractant protein 1 in obesity and insulin resistance. *Proc Natl Acad Sci USA* **100**, 7265–7270.
36. Sell H, Dietze-Schroeder D, Kaiser U *et al.* (2006) Monocyte chemotactic protein-1 is a potential player in the negative cross-talk between adipose tissue and skeletal muscle. *Endocrinology* **147**, 2458–2467.
37. Gerhardt CC, Romero IA, Cancello R *et al.* (2001) Chemokines control fat accumulation and leptin secretion by cultured human adipocytes. *Mol Cell Endocrinol* **175**, 81–92.
38. Dietze-Schroeder D, Sell H, Uhlig M *et al.* (2005) Autocrine action of adiponectin on human fat cells prevents the release of insulin resistance-inducing factors. *Diabetes* **54**, 2003–2011.
39. Skurk T, Alberti-Huber C, Herder C *et al.* (2007) Relationship between adipocyte size and adipokine expression and secretion. *J Clin Endocrinol Metab* **92**, 1023–1033; Epublication 12 December 2006.
40. Fain JN & Madan AK (2005) Regulation of monocyte chemoattractant protein 1 (MCP-1) release by explants of human visceral adipose tissue. *Int J Obes (Lond)* **29**, 1299–1307.

41. Fasshauer M, Klein J, Kralisch S *et al.* (2004) Monocyte chemoattractant protein 1 expression is stimulated by growth hormone and interleukin-6 in 3T3-L1 adipocytes. *Biochem Biophys Res Commun* **317**, 598–604.
42. Kanda H, Tateya S, Tamori Y *et al.* (2006) MCP-1 contributes to macrophage infiltration into adipose tissue, insulin resistance, and hepatic steatosis in obesity. *J Clin Invest* **116**, 1494–1505.
43. Inouye KE, Shi H, Howard JK *et al.* (2007) Absence of CC chemokine ligand 2 does not limit obesity-associated infiltration of macrophages into adipose tissue. *Diabetes* **56**, 2242–2250.
44. Kamei N, Tobe K, Suzuki R *et al.* (2006) Overexpression of monocyte chemoattractant protein-1 in adipose tissues causes macrophage recruitment and insulin resistance. *J Biol Chem* **281**, 26602–26614.
45. Chen A, Mumick S, Zhang C *et al.* (2005) Diet induction of monocyte chemoattractant protein-1 and its impact on obesity. *Obes Res* **13**, 1311–1320.
46. Weisberg SP, Hunter D, Huber R *et al.* (2006) CCR2 modulates inflammatory and metabolic effects of high-fat feeding. *J Clin Invest* **116**, 115–124.
47. Tamura Y, Sugimoto M, Murayama T *et al.* (2008) Inhibition of CCR2 ameliorates insulin resistance and hepatic steatosis in db/db mice. *Arterioscler Thromb Vasc Biol* **28**, 2195–2201.
48. Yang SJ, IglayReger HB, Kadouh HC *et al.* (2009) Inhibition of the chemokine (C-C motif) ligand 2/chemokine (C-C motif) receptor 2 pathway attenuates hyperglycaemia and inflammation in a mouse model of hepatic steatosis and lipoatrophy. *Diabetologia* **52**, 972–981.
49. Lihn AS, Pedersen SB & Richelsen B (2005) Adiponectin: action, regulation and association to insulin sensitivity. *Obes Rev* **6**, 13–21.
50. Tschritter O, Fritsche A, Thamer C *et al.* (2003) Plasma adiponectin concentrations predict insulin sensitivity of both glucose and lipid metabolism. *Diabetes* **52**, 239–243.
51. Herder C, Hauner H, Haastert B *et al.* (2006) Hypoadiponectinemia and proinflammatory state: two sides of the same coin?: results from the Cooperative Health Research in the Region of Augsburg Survey 4 (KORA S4). *Diabetes Care* **29**, 1626–1631.
52. Roh SG, Song SH, Choi KC *et al.* (2007) Chemerin – a new adipokine that modulates adipogenesis via its own receptor. *Biochem Biophys Res Commun* **362**, 1013–1018.
53. Zabel BA, Ohyama T, Zuniga L *et al.* (2006) Chemokine-like receptor 1 expression by macrophages in vivo: regulation by TGF-beta and TLR ligands. *Exp Hematol* **34**, 1106–1114.
54. Takahashi M, Takahashi Y, Takahashi K *et al.* (2008) Chemerin enhances insulin signaling and potentiates insulin-stimulated glucose uptake in 3T3-L1 adipocytes. *FEBS Lett* **582**, 573–578.
55. Kralisch S, Weise S, Sommer G *et al.* (2009) Interleukin-1beta induces the novel adipokine chemerin in adipocytes in vitro. *Regul Pept* **154**, 102–106.
56. Wittamer V, Gregoire F, Robberecht P *et al.* (2004) The C-terminal nonapeptide of mature chemerin activates the chemerin receptor with low nanomolar potency. *J Biol Chem* **279**, 9956–9962.
57. Cash JL, Hart R, Russ A *et al.* (2008) Synthetic chemerin-derived peptides suppress inflammation through ChemR23. *J Exp Med* **205**, 767–775.
58. Zabel BA, Nakae S, Zuniga L *et al.* (2008) Mast cell-expressed orphan receptor CCRL2 binds chemerin and is required for optimal induction of IgE-mediated passive cutaneous anaphylaxis. *J Exp Med* **205**, 2207–2220.
59. Zhang Y & Rollins BJ (1995) A dominant negative inhibitor indicates that monocyte chemoattractant protein 1 functions as a dimer. *Mol Cell Biol* **15**, 4851–4855.
60. Proudfoot AE, Power CA, Hoogewerf AJ *et al.* (1996) Extension of recombinant human RANTES by the retention of the initiating methionine produces a potent antagonist. *J Biol Chem* **271**, 2599–2603.
61. Weisberg SP, McCann D, Desai M *et al.* (2003) Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest* **112**, 1796–1808.
62. Fain JN (2006) Release of interleukins and other inflammatory cytokines by human adipose tissue is enhanced in obesity and primarily due to the nonfat cells. *Vitam Horm* **74**, 443–477.
63. Zeyda M, Farmer D, Todoric J *et al.* (2007) Human adipose tissue macrophages are of an anti-inflammatory phenotype but capable of excessive pro-inflammatory mediator production. *Int J Obes (Lond)* **31**, 1420–1428.
64. Murano I, Barbatelli G, Parisani V *et al.* (2008) Dead adipocytes, detected as crown-like structures, are prevalent in visceral fat depots of genetically obese mice. *J Lipid Res* **49**, 1562–1568.
65. Lumeng CN, Deyoung SM, Bodzin JL *et al.* (2007) Increased inflammatory properties of adipose tissue macrophages recruited during diet-induced obesity. *Diabetes* **56**, 16–23.
66. Clement K, Viguerie N, Poitou C *et al.* (2004) Weight loss regulates inflammation-related genes in white adipose tissue of obese subjects. *FASEB J* **18**, 1657–1669.
67. Lumeng CN, Bodzin JL & Saltiel AR (2007) Obesity induces a phenotypic switch in adipose tissue macrophage polarization. *J Clin Invest* **117**, 175–184.
68. IS Wood, F Pérez de Heredia, B Wang *et al.* (2009) Cellular hypoxia and adipose tissue dysfunction in obesity. *Proc Nutr Soc* **68** (In the Press).
69. Ye J, Gao Z, Yin J *et al.* (2007) Hypoxia is a potential risk factor for chronic inflammation and adiponectin reduction in adipose tissue of ob/ob and dietary obese mice. *Am J Physiol Endocrinol Metab* **293**, E1118–E1128.
70. Hosogai N, Fukuhara A, Oshima K *et al.* (2007) Adipose tissue hypoxia in obesity and its impact on adipocytokine dysregulation. *Diabetes* **56**, 901–911.
71. Semenza GL (2003) Targeting HIF-1 for cancer therapy. *Nat Rev Cancer* **3**, 721–732.
72. Wang B, Wood IS & Trayhurn P (2007) Dysregulation of the expression and secretion of inflammation-related adipokines by hypoxia in human adipocytes. *Pflugers Arch* **455**, 479–492.
73. Skurk T, Mack I, Kempf K *et al.* (2009) Expression and secretion of RANTES (CCL5) in human adipocytes in response to immunological stimuli and hypoxia. *Horm Metab Res* **41**, 183–189.
74. Gregor MF & Hotamisligil GS (2007) Adipocyte stress: the endoplasmic reticulum and metabolic disease. *J Lipid Res* **48**, 1905–1914.
75. Madani R, Karastergiou K, Ogston N *et al.* (2009) Rantes release by human adipose tissue in vivo and evidence for depot specific differences. *Am J Physiol Endocrinol Metab* **296**, E1262–E1268.
76. Herder C, Hauner H, Kempf K *et al.* (2007) Constitutive and regulated expression and secretion of interferon-gamma-inducible protein 10 (IP-10/CXCL10) in human adipocytes. *Int J Obes (Lond)* **31**, 403–410.