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

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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 TNF α , 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.

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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 <i>et al.</i> ⁽¹¹⁾ , Kim <i>et al.</i> ⁽¹²⁾ , Herder <i>et al.</i> ⁽¹³⁾ , Malavazos <i>et al.</i> ⁽¹⁴⁾ , Huber <i>et al.</i> ⁽¹⁵⁾ , Piemonti <i>et al.</i> ⁽¹⁶⁾ , Simeoni <i>et al.</i> ⁽¹⁷⁾
RANTES (CCL5)	Associated with diabetes	Herder <i>et al.</i> ⁽²⁶⁾
MCP-3 (CCL7)	Elevated in obesity	Jiao <i>et al.</i> ⁽²⁵⁾
MCP-2 (CCL8)	Elevated in obesity	Huber <i>et al.</i> ⁽¹⁵⁾ , Murdolo <i>et al.</i> ⁽²⁴⁾
Eotaxin (CCL11)	Increased in obesity but not associated with insulin resistance	Hashimoto <i>et al.</i> ⁽²³⁾ , Vasudevan <i>et al.</i> ⁽²⁷⁾
MCP-4 (CCL13)	Elevated in obesity	Hashimoto <i>et al.</i> ⁽²³⁾
CXCL5	Linking obesity and insulin resistance	Chavey <i>et al.</i> ⁽³²⁾
IL-8 (CXCL8)	Increased in obesity and diabetes	Kim <i>et al.</i> ⁽¹²⁾ , Herder <i>et al.</i> ⁽¹³⁾
IP-10 (CXCL10)	Increased in obesity but not associated with insulin resistance	Herder <i>et al.</i> ^(26,31)
Chemerin	Increased in obesity but not related to type 2 diabetes	Bozaoglu <i>et al.</i> ⁽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 over-expressed 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	<i>In vitro</i> 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 <i>et al.</i> ⁽³⁶⁾ , Gerhardt <i>et al.</i> ⁽³⁷⁾ , Kanda <i>et al.</i> ⁽⁴²⁾ , Kamei <i>et al.</i> ⁽⁴⁴⁾
MIP-1 α (CCL3)	Yes	Regulated by adiponectin	Gerhardt <i>et al.</i> ⁽³⁷⁾ , Dietze-Schroeder <i>et al.</i> ⁽³⁸⁾
MIP-1 β (CCL4)	Yes	Regulated by adiponectin and inducer of insulin resistance in skeletal muscle cells	Sell <i>et al.</i> ⁽³⁶⁾ , Dietze-Schroeder <i>et al.</i> ⁽³⁸⁾
RANTES (CCL5)	Yes	Increased in visceral adipocytes	Skurk <i>et al.</i> ⁽⁷³⁾ , Madani <i>et al.</i> ⁽⁷⁵⁾
Eotaxin (CCL11)	Yes (SV fraction)	Increased release in obesity	Vasudevan <i>et al.</i> ⁽²⁷⁾
GRO- α (CXCL1)	Yes	Regulated by adiponectin	Dietze-Schroeder <i>et al.</i> ⁽³⁸⁾
CXCL5	Yes (SV fraction)	Induces insulin resistance in skeletal muscle	Chavey <i>et al.</i> ⁽³²⁾
IL-8 (CXCL8)	Yes	Regulated by adiponectin and induces insulin resistance in skeletal muscle cells	Sell <i>et al.</i> ⁽³⁶⁾ , Dietze-Schroeder <i>et al.</i> ⁽³⁸⁾
IP-10 (CXCL10)	Yes	Regulated by interferon- γ	Herder <i>et al.</i> ⁽⁷⁶⁾
Chemerin	Yes	Induces insulin resistance in adipocytes	Kralisch <i>et al.</i> ⁽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, TNF α , 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 1 α 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 1 β 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 TNF α (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-1 β ⁽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 O₂ 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 α , which has a key role in the adaptive response to decreased O₂ availability in tissues. Hypoxia inducible factor 1 α 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.

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