We are IntechOpen, the world's leading publisher of Open Access books
Built by scientists, for scientists

6,900
Open access books available

186,000
International authors and editors

200M
Downloads

154
Countries delivered to

Our authors are among the
TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

10

Obesity-Induced Adipose Tissue Inflammation and Insulin Resistance

Po-Shiuan Hsieh
National Defense Medical Center/ Graduate Institute of Physiology Taipei, Taiwan

1. Introduction

Obesity-induced chronic systemic inflammation has been considered as a major risk factor for the development of type 2 diabetes mellitus (T2DM). In addition, the development of inflammation in adipose tissue has been speculated to be the main resource to initialize systemic inflammation and insulin resistance in the state of obesity. However, the molecular mechanisms underlying the development of adipose tissue inflammation are not yet completely characterized, which will be of clinical importance to clarify the potential drug targets for the prevention and treatment of obesity-associated T2DM. Thereby, the aim of this chapter will focus on reviewing the recent progress and prospective related to the understanding of obesity-induced adipose tissue inflammation and insulin resistance. The content of this chapter will highlight the possible contributing factors and interplay during the different developmental stages of obesity and associated insulin resistance. Accordingly, the possible roles of adipocytes, T cells, macrophages and endothelial cells in the initiation, propagation and exacerbation of adipose tissue inflammation will be further discussed. The cross-talk between cell types in the pathogenesis of inflamed adipose tissue and adipokine overproduction will also be extensively debated. Moreover, the important molecular mediators and/or chemokine and cytokine receptors in the development of obesity-induced adipose tissue inflammation and associated insulin resistance would also be added in the text. Finally, based on the recent advances in the relevant research field, the therapeutic strategies in the treatment of obesity-associated insulin resistance and T2DM will be discussed in this chapter.

2. Obesity, adipose tissue inflammation and insulin resistance

Obesity has reached epidemic proportions in most of the industrialized countries, resulting in an increasing prevalence of the metabolic syndrome characterized by visceral obesity, dyslipidemia, and insulin resistance. Obese adipocytes characterize as the important source of inflammation mediators by producing a large number of inflammatory cytokines and chemokines, such as TNF-alpha, IL-6, monocyte chemoattractant protein-1 (MCP-1), and dysregulated production of anti-inflammatory adipokines (e.g. adiponectin). Indeed, obesity-induced adipose tissue inflammation is the key process underlying activation of proinflammatory pathways known to interfere insulin signalling and induce insulin resistance. On the other hand, activation of inflammatory pathways in adipocytes impairs

triglyceride storage and increases release of free fatty acids (FFAs), an excess of which known to induce insulin resistance in muscle and liver (Guilherme & Virbasius, 2008). In addition, it has been demonstrated that increased expression of MCP-1 in adipose tissue associated with obesity plays an important role in the pathogenesis of adipose macrophage infiltration and insulin resistance (Kanda, 2006). The infiltrated macrophages secrete a variety of chemokines and other cytokines that further promote a local inflammatory response resulting in subsequent systemic insulin resistance.

3. Immune system and obesity-induced adipose tissue inflammation

3.1 Innate immune system and the development of inflammation in adipose tissue

Macrophages are the fundamental part of the immediate innate defense mechanisms, which can promote specific adaptive immunity by inducing T-cell recruitment and activation while the body is disturbed. Macrophages have attracted considerable recent attention in adipose tissue biology following the discovery that they infiltrate the tissue in obesity and appear to play a substantial role in the inflammatory process (Haiyan, 2003; Weisberg, 2003). The majority of macrophages in obese adipose tissue aggregate in "crown- like structure" completely surrounding dead (necrotic-like) adipocytes and scavenging adipocyte debris (Cinti et al. 2005). The number of macrophages positively correlates with body mass and adipocyte size in both subcutaneous and visceral fat depots, even though macrophage infiltration is more prominent in the latter. Accumulated macrophages are considered to be the critical link between obesity and adipose tissue inflammation since they are the major source of pro- inflammatory cytokine production, notably TNF-alpha and IL-6, in adipose tissue (Cancello, 2005; Haiyan, 2003). Interestingly, the process appears reversible since macrophage infiltration and pro-inflammatory marker expression in the adipose tissue of obese subjects can be significantly reduced after weight loss (Brun, 2006; Cancello, 2005). Similarly to any immune and inflammatory responses, macrophage infiltration in expanding adipose tissue results from blood monocytes influx, likely attracted by the chemokine MCP-1 (Kanda, 2006). Indeed, it has been reported that MCP-1 secretion is markedly enhanced locally and in plasma in obese rodents and human patients. Mice with targeted deletion in the genes for monocyte MCP-1 and its receptor CCR2 both could attenuate adipose tissue macrophages (ATMs) infiltration and decrease inflammation in fat. It would subsequently protect these mice from high fat diet-induced insulin resistance (Kanda, 2006; Weisberg, 2006). Conversely, MCP-1 overexpressed mice have increased numbers of ATMs along with insulin resistance (Kamei et al., 2006). Moreover, some mechanistic insights to explain how macrophages are associated with inflammation in obesity, have emerged from the characterization of ATM activation state. Macrophage population and function have been revealed to be highly heterogeneous and dependent on the surrounding environment, which has led to their characterization and classification following the well-known classification of T-cell activation state into Th1/Th2 sub-types (Gordon, 2007). Typically, macrophages can be distinguished between the M1 phenotype, identified as the pro- inflammatory or "classically"- activated state, secreting various cytokines (e.g. TNF-alpha, IL-6), and the M2 phenotype referred as to the anti- inflammatory or "alternatively"- activated state, which produces IL-10. Following a pulse dye labelling of ATMs to discriminate newly infiltrated ATMs from the resident ATMs, it has been shown that recruited ATMs during a diet- induced obesity exhibit an inflammatory M1 profile

compared to already settled ATMs (Lumeng et al., 2007). Moreover, the same research group has also demonstrated that ATMs from lean mice retain the typical gene expression pattern of the M2 activation state, while ATMs from obese mice are characterized by enhanced expression levels of TNF-alpha and NOS2, both markers of the M1 activated state. This study supports that diet-induced obesity either converts or promotes the replacement of initial M2- polarized ATMs by M1- polarized ATMs, thereby contributing to the development of insulin resistance (Lumeng, 2007). In conclusion, ATMs are the major source of pro- inflammatory mediators in obese adipose tissue and contribute both to the local and systemic metabolic alterations and the general inflammatory state. Their number and activation states are likely crucial in the onset of obesity-associated adipose tissue inflammation and in the development of insulin resistance.

3.2 Adaptive immune system and the development of inflammation in adipose tissue

Macrophages infiltrating into adipose tissue during obesity could be largely extended by providing convincing evidence for an early participation of various cells from the adaptive immune system in the development of obesity (Kintscher, 2008; Rocha, 2008; Wu, 2007). For instance, T cells are also actively regulated in adipose tissue and contribute to obesity-induced inflammation. Previous studies have shown that specific rearrangements in the T cell receptor (TCR) are selected in adipose tissue, suggesting that antigens in fat may communicate with adaptive immune system (Nishimura et al., 2009). Several studies have pointed out that dietary (Rocha, 2008; Wu, 2007) or genetic obesity (Rausch et al., 2007) is associated with T- cell infiltration including both CD4+ and CD8+ T cells. The assessment of immune cell composition at early stage of high fat diet-induced obesity suggests that T-cell entry in adipose tissue precedes monocyte attraction and, therefore, might represent one of the processes initiating adipose tissue inflammation (Kintscher et al., 2008). Indeed, both the secretion of the chemokine C-C motif chemokine ligand (CCL) 5/ Regulated on Activation, Normal T Cell Expressed and Secreted (RANTES) and the expression level of its receptor CCR5 are enhanced in adipose tissue of obese male mice (Wu et al., 2007). Moreover, RANTES neutralization reduces T- cell migration *in vitro*. RANTES expression is not only restricted to T- cells but is also detected in mature adipocytes, more prominently in presence of TNF- alpha (Wu et al., 2007). CD4+ T cells in adipose tissue can be classified into pro-inflammatory Th1 polarized T cells secreting IFN- gamma and anti- inflammatory Th2 polarized T cells secreting IL-4 and IL-13. In lean mice, Th1 and Th2 polarized T cells are higher in visceral than in subcutaneous adipose tissue with both T- cell type being present at approximately equal amounts (Winer et al., 2009). In addition, the role of the Th1- type cytokine IFN- gamma in adipose tissue inflammation has been explored (Rocha et al., 2008). IFN- gamma mRNA expression was up-regulated in mouse adipose tissue after high fat diet feeding. 3T3-L1 adipocytes incubated with IFN- gamma exhibited a marked enhancement of the expression levels of various cytokines and chemokines. Moreover, IFN- gamma deficiency partly prevented the diet-induced increases of both ATM number and pro-inflammatory marker expression (TNF- alpha and MCP-1) in adipose tissue. On the other hand, several studies have also observed an increase in adipose tissue CD8+ T cells in the course of obesity (Nishimura, 2009; Winer, 2009). The infiltration of CD8+ T cells precedes the recruitment of macrophages in the development of adipose tissue inflammation (Nishimura et al., 2009). Depletion of CD8+ T cells before inducing obesity in mice prevents M1 macrophage infiltration into adipose tissue without changing adiposity or the number of

M2 macrophages residing in fat. In obese mice with existing inflammation, an antibody-mediated reduction of CD8+ T cells improved glucose tolerance and insulin sensitivity along with adipose tissue inflammation, providing evidence for a role of these CD8+ T cells not only in the initiation but also preservation of inflammation in adipose tissue. Furthermore, adoptive transfer of CD8+ T cells to CD8- deficient mice lead to increase adipose tissue inflammation. In summary, adipose tissue expansion is associated with changes in the number and various phenotype of lymphocytes. A pathological role of Th1 polarized T cells and CD8+ T cells in adipose could be described in the state of obesity correlating with adipose tissue inflammation and subsequent insulin resistance.

4. Adipokine dysregulation in obesity and insulin resistance

4.1 Obesity-induced upregulation of potentially deleterious adipokines
4.1.1 Leptin
Leptin is almost exclusively expressed and produced by white adipose tissue. Plasma Leptin concentration and mRNA expression in adipose tissue are directly related to the severity of obesity. An increase of fat mass is associated with the elevation of leptin (Considine et al., 1996). In animal models, expression of leptin is increased in conditions that are associated with release of pro- inflammatory cytokines such as TNF- alpha and IL-6 in monocytes and macrophages. Vice versa, TNF- alpha and IL-6 are capable of stimulating adipocyte leptin production (Antuna-Puente et al., 2008). Leptin also has significant effect on adaptive immunity, such as inducing a switch toward Th1-cell immune responses by increasing IFN-gamma, TNF- alpha secretion, and the suppression of Th2- cell responses in adipose tissue (Matareseet al., 2002). On the other hand, leptin has also been reported to improve insulin sensitivity through activation of AMP-activated protein kinase (AMPK) (Minokoshi et al., 2002). However, in human obesity, the high circulating leptin levels is exhibited secondary to the development of leptin resistance. Leptin administration has little or no effect on insulin resistance. Moreover, the leptin-signaling pathway as shown to, activate suppressor of cytokine signaling (SOCS)-3, which might opposite effect to inhibit insulin signaling (Howard & Flier, 2006). Taken together, it is suggested that leptin has proinflammatory effects and is involved in the pathogenesis of insulin resistance. However, the underlying mechanism of leptin in the etiology of obesity- associated adipose tissue inflammation and insulin resistance needs to be further elucidated.

4.1.2 Resistin
Resistin received its name from the original observation that it induced insulin resistance in mice (Steppan et al., 2001). Resistin expression has demonstrated to be increased in obese animals and has been implicated in the pathogenesis of obesity- associated insulin resistance and type 2 diabetes mellitus in mouse model (Steppan et al., 2001). Accordingly, administration of recombinant resistin to normal animal produced insulin resistance, whereas neutralizing resistin with specific antibody improved insulin sensitivity in obese animals with insulin resistance. This work was the first to illustrate resistin as a link between obesity and insulin resistance (Kim et al., 2001). On the other hand, studies indicate that stimulation of macrophages *in vitro* with endotoxin or proinflammatory cytokines leads to a marked increase in resistin production. Furthermore, administration of endotoxin to human volunteers is associated with an dramatical increase in circulating resistin levels

(Lehrke et al., 2004). Previous report regarded to the effects of resistin in the modulation of inflammatory responses has shown that resistin could upregulate expression of MCP-1 as well as cell adhesion molecule ICAM-1 in endothelial cell (Kawanami et al., 2004). However, subsequent human studies failed to link resistin to insulin resistance. In addition, this protein is not produced by human adipocytes. Further investigation is needed to characterize the role of resistin in the pathogenic link between obesity-induced adipose tissue inflammation and insulin resistance in human.

4.1.3 Visfatin

Visfatin has recently been identified as an adipokine that is secreted by adipocytes in visceral fat, decreases insulin resistance (Fukuhara et al., 2005). In both genetic and nutritional obese animal models, visfatin expression is induced predominantly in visceral adipose tissue. Similarly to insulin, visfatin could enhance glucose uptake in myocytes and adipocytes, and also inhibit hepatocyte glucose production (Fukuhara et al., 2005). Its insulin- like effects are also reported that visfatin could induce tyrosine phosphorylation of insulin receptors insulin receptor substrate-1 and 2 (IRS-1, IRS-2), and activation of PI3K. The pro-inflammatory effect of visfatin has been demonstrated in unstable lesions in patients with coronary heart disease. It showed that visfain can increase matrix metalloproteinase-9 activity in monocytes, and TNF- alpha and IL-8 in peripheral blood mononuclear cells (Dahl et al., 2007). All these studies strongly suggest that visfatin could be primarily regarded as an inflammatory mediator involved in several obesity-related pathological processes. Nevertheless, the molecule of visfatin has turned out to be previously identified as a growth factor for early B-lymphocytes termed pre-B cell colony enhancing factor(PBEF) (Samal et al., 1994). The role of visfatin in human T2DM remains debated (Chen, 2006; Sandeep, 2007).

4.1.4 TNF-alpha

TNF-alpha is a proinflammatory cytokine produced by numerous cells, but mainly by macrophages, lymphocytes and monocytes. In addition, adipocytes also produce TNF-alpha in humans and rodents. TNF-alpha is the first inflammatory cytokine shown to be produced by adipocytes (Hotamisligil et al., 1993). TNF-alpha level is increased in adipose tissue and plasma of obese patients and has been related to obesity- associated complications (Kern et al., 2001). TNF-alpha has been considered to be crucially involved in the pathophysiology of insulin resistance (Hotamisligil et al., 1993). Disruption of IRS-1 phosphorylation by TNFα has been reported to one of the possible mechanisms to interfere insulin signaling. Moreover, TNF-alpha has been shown to inhibit the conversion of pre-adipocytes to mature adipocytes, allowing further recruitment of uncommitted cells and thus possible expansion of adipose tissue mass (Kras et al., 2000). Therefore TNF-alpha is considered a likely mediator of the insulin resistance and T2DM associated with high visceral adiposity.

4.1.5 IL-6

Like TNF-alpha, the levels of IL-6 positively correlates with body mass index, especially in the state of obesity (Kern et al., 2001). It has been estimated that white adipose tissue contributes about 30% of circulating IL-6. Visceral white adipose tissue (WAT) produces. Higher levels of IL-6 compared with those in subcutaneous WAT (Fain, 2004; Fried, 1998). Most of the IL-6 comes from the stromal vascular fraction of adipose tissue. There is a

positive relationship between IL-6 levels in adipose tissue and circulating C-reactive protein levels (Maachi et al., 2004), which is an important cardiovascular risk factor. Moreover, IL-6 produced by intra-abdominal adipose tissue has been documented to directly link to visceral obesity- related hypertriglyceridaemia by stimulating hepatic secretion of triglycerides (Nonogaki et al., 1995).

4.2 Obesity-induced downregulation of potentially beneficial adipokines
4.2.1 Adiponectin

Adiponectin is a protein highly expressed in adipose tissue. In contrast to other adipokines, adiponectin is underexpressed in obese patients with insulin resistance or T2DM. Adiponectin could enhance insulin sensitivity through activation of AMPK (Yamauchi et al., 2002). In addition to its effects on insulin sensitivity, adiponectin has an anti-inflammatory effect through its anti- TNF-alpha action. For example, the in vitro study has demonstrated that macrophage activity and TNF-alpha production were significantly diminished in macrophages while cotreated with adiponectin (Ouchi et al., 2000). The anti-inflammatory activities of adiponectin extend to inhibition of IL-6 production accompanied by induction of the endogenous anti- inflammatory cytokines IL-10 and IL-1 receptor antagonist (Kumada et al., 2004). On the basis of all the above-mentioned studies, adiponectin appears to act as an anti- inflammatory molecule in adipose tissue.

5. Cellular cross- talk and molecular mediators in the development of adipose tissue inflammation

5.1 Adipocyte dysfunction and inflammation

In obesity, excessive adipose tissue growth is associated with hypertrophy and hyperplasia of adipocytes. Excess energy intake or decreased expenditure results in excess TG accumulation and adipocyte hypertrophy in adipose tissue. Adipocyte size is related to dysregulated adipokines expression and secretion in humans. The hypertrophic adipocytes change their immune balance towards the production of pro- inflammatory, atherogenic and diabetic adipokines. Reportedly, the enlarged adipocytes appear to initiate macrophages infiltration which occurs secondarily in obesity through their dysregulated adipokine production (Jiao et al., 2009). Moreover, Nishimura et al showed that CD8+ T cells accumulated in obese adipose tissue, but not presence of greater number of CD8+ T cells in the systemic circulation in the state of obesity. The findings suggested that CD8+ T cells are activated by local stimulation in the adipose tissue (Nishimura et al., 2009). It implicates that obese adipose tissue activates CD8+ T cells via dysregulated adipokine expression. Adipocyte hypertrophy is associated with altered intracellular signaling. An increase in constitutive NF-κB activity has been reported in 3T3-L1 cell line during adipocyte differentiation and hypertrophy, which may potentially lead to adipokine overproduction (Berg et al., 2004). 3T3-L1 adipocyte hypertrophy could be artificially induced by preloading with palmitate, which in turn enhance oxidative stress and increase MCP-1 production through JNK and NF-κB signaling (Takahashi et al., 2008). In brief, adipose tissue might be regarded as an important source of inflammatory products *in vivo* (e.g. TNF-alpha, IL-6, leptin and adiponectin), which are regulated by the interactions among infiltrated immune cells and residual cells, i.e. adipocytes, endothelial cells in adipose tissue. Therefore, it could actively participate to initiate and regulate immune responses in local adipose tissue and whole body.

5.2 Hypoxia

It has been speculated that the dysregulation of the production of inflammation-related adipokines in obesity, linked to the development of the metabolic syndrome and other obesity-associated disorders, is a specific response to relative hypoxia in clusters of adipocytes distant from the vasculature as adipose tissue mass expands. Hypoxia is exhibited in adipose tissue of obese individuals where oxygen partial pressure and blood flow are reduced. Moreover, the expression of hypoxia- inducible factor- 1 alpha (HIF-1 alpha)-the master regulator of oxygen homeostasis" is higher in subcutaneous adipose tissue of obese vs. lean subjects (Cancello et al., 2005). In mouse model, hypoxia indicated by elevated HIF-1 alpha protein levels in WAT has also been demonstrated in both *ob/ob* mice and in diet- induced obese mice (Rausch, 2007; Ye, 2007). The presence of immunoreactive HIF-1 alpha, its induction by hypoxia and hypoxia mimetics have been demonstrated in several cell-based studies employing either the 3T3-F422A or 3T3-L1 adipocyte clonal cell lines (Chen, 2006; Lolmedet, 2003). Recent report has first showed that the production of angiogenic factors such as VEGF, leptin and matrix metalloproteinases are increased in 3T3-F422A adipocytes in response to low O2 tension (5% O2) or chemical hypoxia. The downregulation of adiponectin gene expression by hypoxia in 3T3-L1 adipocytes has subsequently been confirmed (Hosogai et al., 2007), and occurs also in human adipocytes (Wang et al., 2007). The context of macrophage involved in adipose tissue function, with the induction of IL-6, MIF, TNF- alpha and VEGF gene expressions under hypoxia has been demonstrated in peritoneal macrophages (Ye et al., 2007). These observations suggest that there is a link between pockets of inflammation within WAT and the recruitment of macrophages into these same areas of the tissue through the hypoxia-mediated signaling and relevant adipokine production.

5.3 Inflammatory fatty acids

Obesity and insulin resistance are associated with high circulating concentrations of free fatty acids. A potential link between adipose tissue fatty acid composition and obesity has been high-lighted in several studies (Decsi, 1996; Williams, 2007). Arachidonate is the primary source of fatty acids that mediate inflammatory responses. In obese children from the Mediterranean region, arachidonate levels were increased in adipose tissue compared to those in lean children (Savvas et al., 2004). These findings link arachidonate levels in adipose tissue with obesity. Since arachidonate and fatty acid products in adipose tissue are important in regulating lipolysis, lipogenesis and adipogenesis, it is speculated that phospholipase A2 enzymes that release arachidonate from membrane phospholipids may be directly involved in these three processes. In fact, it has been demonstrated that knockout of the gene that encodes adipose-tissue specific phospholipase A2 enzyme (Group XVI phospholipase A2 or AdPLA) in mice increased the rate of lipolysis by markedly reducing prostaglandin E2 levels. These mice also showed reduced tissue mass, triglyceride levels, insulin resistance and increased fatty acid oxidation in obese adipocytes induced by either a high-fat feeding or leptin deficiency (Jaworski et al., 2009). Phospholipase A2 may also be important in releasing arachidonate from inflammatory cells to be later metabolized by other cells such as adipocytes. As a result, adipocytes may become chronically energy over-loaded, which may alter their secretory profiles. Secretory phospholipase such as secretory Phospholipase A2 from inflammatory cells could act to release arachidonate from neighboring cells including adipocytes. The cyclooxygenase 1 and cyclooxygenase 2 are

essential steps in the synthesis of prostanoids from arachidonate. Several studies have suggested that prostanoids modulate adipocyte differentiation and maturation (Shillabeer et al., 1998). The elevation in both prostaglandin E2 and prostaglandin I2 levels have been shown to induce adipocyte dysfunction (Kim & Moustaid-Moussa, 2000). Prostaglandin E2 acts on EP3 receptors to decrease lipolysis by decreasing cAMP concentration and, thereby, contributes to the hypertrophic development of adipocyte (Jaworski et al., 2009). In addition, it has been demonstrated that cyclooxygenase (COX)-2 mediated inflammation in fat plays a pivotal role in the development of adipose tissue inflammation, insulin resistance and fatty liver in high fat- induced obese rats (Hsieh et al., 2009, 2010). The time- dependent increases in plasma insulin, glucose, leptin levels and homeostasis model assessment of insulin resistance (HOMA-IR) shown in high- fat induced obese rats were significantly reversed in those co-treated with a selective COX2 inhibitor (Celecoxib or Mesulid). COX2 inhibition also significantly reversed adipocyte hypertrophy, macrophage infiltration and decreased in markers of adipocyte differentiation shown in high fat diet- induced obese rats, especially in visceral fat rather than those in subcutaneous fat (Hsieh et al., 2009, 2010). In addition, in the COX2 deficient mouse model, PPAR-gamma (an adipocyte differentiation marker) mRNA expression in epididymal adipose tissue was reduced (Ghoshal et al., 2010). Recently, COX2 has been shown to contribute to the differentiation of brown adipocytes in mice, following cold or adrenergic stimulation (Madsen, 2010 ; Vegiopoulos, 2010). They demonstrated that activating the COX2- mediated pathway in adipose tissue could trigger formation of lipid- burning brown adipose tissue and induce weight loss to treat obesity. But, the coming challenge is how to boost the pathway in adipose tissue without increasing COX2- related fat inflammation.

6. Potential therapeutic drugs and immunotherapy in the treatment of obesity -induced adipose tissue inflammation and insulin resistance

Various pharmacological interventions affect obesity-associated cardiometabolic abnormalities. The effects of these interventions depend on weight loss, changes in fat distribution and/or direct effects on adipose tissue inflammation. Furthermore, several pharmacological agents commonly used in patients with vascular diseases or diabetes mellitus also affect adipose tissue function by diverse mechanisms. Although the effects of these drugs on adipose tissue function are unintended, improving adipose tissue function of these treatments may causally link with their improving effects on vascular disease and T2DM.

6.1 Salicylates and COX2 inhibitors

Salicylates are one of the most commonly used nonsteroidal anti- inflammation drugs and have their main actions through COX inhibition. Selective COX2 inhibitors may improve obesity-associated adipose tissue abnormalities (Hsieh et al., 2009, 2010). Besides COX inhibiton, salicylates also act through inhibition of the activity of inhibitor of nuclear factor kappa-B kinase subunit beta (IKK-β) leading to a reduction in translocation of NF-kB to the nucleus, which action is crucially involved in the anti-diabetic effect of aspirin (Yin et al., 1998; Yuan et al., 2001). Accordingly, salicylate in doses of 3 and 4.5 grams per day improved insulin resistance as measured by using a hyperinsulinemic euglycemic clamp. It also decreased free fatty acid and increased adiponectin levels by 35~45% in patients with type 2 diabetes (Goldfine et al., 2008).

6.2 Beta- blockers

Several recent investigations have focused on the effects of the beta-blockers on adipose tissue dysfunction (Gress et al., 2000; Pollare et al., 1989). However, it still remains debated. For instance, a combined β1 and β2- adrenoceptor agonist is capable of downregulating adiponectin and upregulating TNF-alpha mRNA in murine adipocytes (Sharma et al., 2001). Conversely, some of the recent developed β- blockers do have beneficial effects on insulin resistance and adipokines without changes in weight. Nebivolol (5 mg daily), which has β2 intrinsic sympaticomimetic action, increases plasma adiponectin levels in overweight patients with hypertension (Celik et al., 2006). Celipprolol (up to 400 mg daily), a combined β1 antagonist and β2 agonist reduces plasma leptin levels without a change in body weight in patients with dyslipidemia (Malminiemi, 2000).

6.3 Aldosterone antagonists

Adipose tissue is capable of producing an unidentified mineralcorticoid releasing factor that may stimulate aldosterone production (Lamounier-Zepter & Ehrhart-Bornstein, 2006). In obese diabetic mice, blocking the mineralcorticoid receptor reduced the expression of pro-inflammatory cytokines in adipose tissue while it lead to an increased expression of adiponectin in cardiac and adipose tissue (Guo et al., 2008). Additional evidence for an important role of the mineralcorticoid receptor in adipose tissue comes from a study in obese mice. It showed that blocking the mineralcorticoid receptor with eplerone ameliorated insulin resistance, decreased the number of hypertrophic adipocytes and infiltrating macrophages (Hirata et al., 2009).

6.4 Angiotensin converting enzyme inhibitors (ACEI)

Angiotensin converting enzyme inhibitors (ACEI) could affect insulin resistance by reducing plasma concentration of angiotensin Ⅱ, which increases serine phosphorylation of the insulin receptor, insulin receptor substrate 1 and phosphadidylinositol-3-kinase leading to a state of insulin resistance (Folli et al., 1997). Angiotensin Ⅱ might also influence insulin resistance via a direct pro- inflammatory effect on adipocyte and subsequently change in MCP-1, IL-6 and IL-8 production via the NF-kB pathway and increase production of leptin via an ERK1/2 dependent pathway in a murine model (Skurk et al., 2004; Tsuchiya et al., 2006).

6.5 Statins

Statins might alleviate adipose tissue inflammation by inhibiting Toll- like receptor-4 triggered IFN-γ expression in macrophages, which are abundant in adipose tissue and by increasing PPAR-γ expression (Abe et al., 2008; Desjardins et al., 2008). Murine 3T3-L1 adipocytes incubated with blood samples from patients treated with parvastatin have been demonstrated to induce adiponectin production (Takagi et al., 2008). Moreover, atorvastatin, which is more lipophylic than pravasatin increases adiponectin levels in patients with coronary artery disease (CAD) or at high risk for CAD while having no effect on adiponectin in patients with diabetes (Ichida et al., 2006). Simvastatin, the most lipophylic statin, decreases adiponectin (Devaraj et al., 2007). These observations suggest that hydrophilic statins have more beneficial effect than those of lipophylic statins on adipose tissue dysfunction.

6.6 Thiazolidinediones

Thiazolidinediones (TZDs) such as pioglitazone and rosiglitazone have been suggested to be the potential drugs in preventing T2DM. Treatment with rosiglitazone for 3 years have been reported to lower the incidence of T2DM (Gerstein et al. 2006). TZDs may directly increase insulin sensitivity in the liver and adipose tissue where it is of critical importance for adipocyte differentiation. PPAR-γ agonists are thought to promote the uptake and storage of free fatty acids in adipocytes and may therefore protect the liver and muscle from the attacks of excess free fatty acids and their toxic effects. Also, PPAR-γ agonists such as pioglitazone have been shown to increase high molecular weight adiponectin and decrease TNF-αand RBP-4 levels in patients with T2DM (Aso et al., 2007).

6.7 Metformin

Apart from affecting glucose uptake in the liver and peripheral tissues, metformin has anti-inflammatory properties by inhibiting NF-kB and blocking the PI3K- Akt pathway in human vascular cells (Isoda et al., 2006). Recent study suggests that the effect of metformin on AMP-activated protein kinase (AMPK) dependent lipolysis in adipocytes may lead to lower plasma levels of fatty acids and improve adipose tissue function (Bourron et al., 2010). Moreover, metformin has been reported to reduce subcutaneous adipose tissue, total body fat percentage, BMI and waist circumference but not affect the amount of visceral adipose tissue in obese children and adolescents (Srinivasan et al., 2006). However, in a study with lean and obese patients with and without diabetes, metformin did not result in a reduction of BMI, nor did it affect plasma adiponectin levels after 4 months of treatment (Phillips et al., 2003). Thererby, the clinical implication of metformin on treatment of obesity remains controversial.

6.8 Immunotherapy

Nishimura and colleagues have shown that CD8^{+} T cells play the important role in macrophage recruitment and adipose tissue inflammation. They found that large numbers of CD8^{+} T cells infiltrated into obese epididymal adipose tissue and preceded the accumulation of macrophages in fat tissue of high-fat induced obese mice. In addition, the immunological and genetic depletion of CD8^{+} T cells have been reported to lower macrophage infiltration, adipose tissue inflammation and ameliorate systemic insulin resistance (Nishimura et al., 2009). Besides, Winer and colleagues demonstrated that immunotherapy with CD4^{+} T cell transfer into lymphocyte-free obese mice reversed weight gain and insulin resistance. Short-term treatment with CD3-specific antibody markedly reversed insulin resistance for months, despite continuation of a high-fat diet (Winer et al., 2009). Taken together, these observations not only demonstrate the importance of immune response in the development of obesity, but also identify a number of novel targets and strategies that could be harnessed to treat obesity in manners similar to the treatment of other immunological abnormalities.

7. Conclusion

Obesity-induced inflammation in adipose tissue has been considered as one of the main contributors to the development of insulin resistance and subsequent T2DM in the state of obesity. Both of the innate and adaptive immune systems have been documented to be crucially involved in the initiation and regulation of adipose tissue inflammation. In the

meantime, the adipokine dysregulation and hypoxia-mediated signaling during the development of adipocyte hypertrophy are also actively participate into the pathogenesis of adipose tissue inflammation. Recently, the role of inflammatory fatty acids such as arachidonate in the etiology of adipogenesis and lipogenesis has also been the subject of intensive investigation. Although the detail mechanisms remain incompletely understood, it could be a promising therapeutic target for prevention and treatment of obesity-induced insulin resistance and T2DM in the prospective future. Besides, several therapeutic drugs used in the patients with vescular diseases or diabetes and immunotherapy have also been shown to reduce the risk of developing insulin resistance and T2DM.

8. Acknowledgment

9. References

Abe, M.; Matsuda, M.; Kobayashi, H.; Miyata, Y.; Nakayama, Y.; Komuro, R.; Fukuhara, A.; Shimomura, I. (2008). Effects of statins on adipose tissue inflammation: their inhibitory effect on MyD88-independent IRF3/IFN-beta pathway in macrophages. *Arteriosclerosis, Thrombosis, and Vascular Biology*, Vol.28, No.5, pp. 871-877, ISSN 1079-5642

Antuna-Puente, B.; Feve, B.; Fellahi, S.; Bastard, J.P. (2008). Adipokines: the missing link between insulin resistance and obesity. *Diabetes & Metabolism*, Vol.34, No.1, pp. 2-11, ISSN 1262-3636

Aso, Y.; Yamamoto, R.; Suetsugu, M.; Matsumoto, S.; Wakabayashi, S.; Matsutomo, R.; Takebayashi, K.; Inukai, T. (2007). Comparison of the effects of pioglitazone and voglibose on circulating total and high-molecular-weight adiponectin, and on two fibrinolysis inhibitors, in patients with Type 2 diabetes. *Diabetic Medicine*, Vol.24, No.9, pp. 962-968, ISSN 0742-3071

Berg, A.H.; Lin, Y.; Lisanti, M.P.; Scherer, P.E. (2004). Adipocyte differentiation induces dynamic changes in NF-kappaB expression and activity. *American Journal of Physiology - Endocrinology and Metabolism*, Vol.287, No.6, pp. E1178-1188, ISSN 0193-1849

Bourron, O.; Daval, M.; Hainault, I.; Hajduch, E.; Servant, J.M.; Gautier, J.F.; Ferré, P.; Foufelle, F. (2010). Biguanides and thiazolidinediones inhibit stimulated lipolysis in human adipocytes through activation of AMP-activated protein kinase. *Diabetologia*, Vol.53, No.4, pp. 768-778, ISSN 0012-186X

Bruun, J.M.; Helge, J.W.; Richelsen, B.; Stallknecht, B. (2006). Diet and exercise reduce low-grade inflammation and macrophage infiltration in adipose tissue but not in skeletal muscle in severely obese subjects. *American Journal of Physiology - Endocrinology and Metabolism*, Vol.290, No.5, pp. E961-967, ISSN 0193-1849

Cancello, R.; Henegar, C.; Viguerie, N.; Taleb, S.; Poitou, C.; Rouault, C.; Coupaye, M.; Pelloux, V.; Hugol, D.; Bouillot, J.L.; Bouloumié, A.; Barbatelli, G.; Cinti, S.; Svensson, P.A.; Barsh, G.S.; Zucker, J.D.; Basdevant, A.; Langin, D.; Clément, K. (2005). Reduction of macrophage infiltration and chemoattractant gene expression

changes in white adipose tissue of morbidly obese subjects after surgery-induced weight loss. *Diabetes*, Vol.54, No.8, pp. 2277-86, ISSN 0012-1797

Celik, T.; Iyisoy, A.; Kursaklioglu, H.; Kardesoglu, E.; Kilic, S.; Turhan, H.; Yilmaz, M.I.; Ozcan, O.; Yaman, H.; Isik, E.; Fici, F. (2006). Comparative effects of nebivolol and metoprolol on oxidative stress, insulin resistance, plasma adiponectin and soluble P-selectin levels in hypertensive patients. *Journal of Hypertension*, Vol.24, No.3, pp. 591-596, ISSN 0263-6352

Chen, M.P.; Chung, F.M.; Chang, D.M.; Tsai, J.C.; Huang, H.F.; Shin, S.J.; Lee, Y.J. (2006). Elevated plasma level of visfatin/pre-B cell colony-enhancing factor in patients with type 2 diabetes mellitus. *The Journal of Clinical Endocrinology & Metabolism*, Vol.91, No.1, pp. 295-299, ISSN 0021-972X

Chen, B.; Lam, K.S.; Wang, Y.; Wu, D.; Lam, M.C.; Shen, J.; Wong, L.; Hoo, R.L.; Zhang, J.; Xu, A. (2006). Hypoxia dysregulates the production of adiponectin and plasminogen activator inhibitor-1 independent of reactive oxygen species in adipocytes. *Biochemical and Biophysical Research Communications*, Vol.341, No.2, pp. 549-556, ISSN 0006-291X

Cinti, S.; Mitchell, G.; Barbatelli, G.; Murano, I.; Ceresi, E.; Faloia, E.; Wang, S.; Fortier, M.; Greenberg, A.S.; Obin, M.S. (2005). Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans. *The Journal of Lipid Research*, Vol.46, No.11, pp. 2347-2355, ISSN 0022-2275

Considine, R.V.; Sinha, M.K.; Heiman, M.L.; Kriauciunas, A.; Stephens, T.W.; Nyce, M.R.; Ohannesian, J.P.; Marco, C.C.; McKee, L.J.; Bauer, T.L. (1996). Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *The New England Journal of Medicine*, Vol.334, No.5, pp. 292-295, ISSN 0028-4793

Dahl, T.B.; Yndestad, A.; Skjelland, M.; Øie, E.; Dahl, A.; Michelsen, A.; Damås, J.K.; Tunheim, S.H.; Ueland, T.; Smith, C.; Bendz, B.; Tonstad, S.; Gullestad, L.; Frøland, S.S.; Krohg-Sørensen, K.; Russell, D.; Aukrust, P.; Halvorsen, B. (2007). Increased expression of visfatin in macrophages of human unstable carotid and coronary atherosclerosis: possible role in inflammation and plaque destabilization. *Circulation*, Vol.115, No.8, pp. 972-980, ISSN 0009-7322

Decsi, T.; Molnár, D.; Koletzko, B. (1996). Long-chain polyunsaturated fatty acids in plasma lipids of obese children. *Lipids*, Vol.31, No.3, pp. 305-311, ISSN 0024-4201

Desjardins, F.; Sekkali, B.; Verreth, W.; Pelat, M.; De, K. D.; Mertens, A.; Smith, G.; Herregods, M.C.; Holvoet, P.; Balligand, J.L. (2008). Rosuvastatin increases vascular endothelial PPARgamma expression and corrects blood pressure variability in obese dyslipidaemic mice. *European Heart Journal*, Vol.29, No.1, pp. 128-137, ISSN 0195-668X

Devaraj, S.; Siegel, D.; Jialal, I. (2007). Simvastatin (40 mg/day), adiponectin levels, and insulin sensitivity in subjects with the metabolic syndrome. *The American journal of cardiology*, Vol.100, No.9, pp. 1397-1399, ISSN 0002-9149

Fain, J.N.; Madan, A.K.; Hiler, M.L.; Cheema, P.; Bahouth, S.W. (2004). Comparison of the release of adipokines by adipose tissue, adipose tissue matrix, and adipocytes from visceral and subcutaneous abdominal adipose tissues of obese humans. *Endocrinology*, Vol.145, No.5, pp. 2273-2282, ISSN 0013-7227

Folli, F.; Kahn, C.R.; Hansen, H.; Bouchie, J.L.; Feener, E.P. (1997). Angiotensin II inhibits insulin signaling in aortic smooth muscle cells at multiple levels. A potential role

for serine phosphorylation in insulin/angiotensin II crosstalk. *The Journal of Clinical Investigation*, Vol.100, No.9, pp. 2158-2169, ISSN 0021-9738

Fried, S.K.; Bunkin, D.A.; Greenberg, A.S. (1998). Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. *The Journal of Clinical Endocrinology & Metabolism*, Vol.83, No.3, pp. 847-850, ISSN 0021-972X

Fukuhara, A.; Matsuda, M.; Nishizawa, M.; Segawa, K.; Tanaka, M.; Kishimoto, K.; Matsuki, Y.; Murakami, M.; Ichisaka, T.; Murakami, H.; Watanabe, E.; Takagi, T.; Akiyoshi, M.; Ohtsubo, T.; Kihara, S.; Yamashita, S.; Makishima, M.; Funahashi, T.; Yamanaka, S.; Hiramatsu, R.; Matsuzawa, Y.; Shimomura, I. (2005). Visfatin: a protein secreted by visceral fat that mimics the effects of insulin. *Science*, Vol.307, No.5708, pp. 426-430, ISSN 0036-8075

Gerstein, H.C.; Yusuf, S.; Bosch, J.; Pogue, J. (2006). Effect of resiglitazone on the frequency of diabetes in patients with impaired glucose tolerence or impaired fasting glucose: a randomised controlled trial. The Lancet, Vol.368, No9541, pp. 1096-1105, ISSN 0140-6736

Ghoshal, S.; Trivedi, D.B.; Graf, G.A.; Loftin, C.D. (2011). Cyclooxygenase-2 deficiency attenuates adipose tissue differentiation and inflammation in mice. *The Journal of Biological Chemistry*, Vol.286, No.1, pp. 889-898, ISSN 0021-9258

Goldfine, A.B.; Silver, R.; Aldhahi, W.; Cai, D.; Tatro, E.; Lee, J.; Shoelson, S.E. (2008). Use of salsalate to target inflammation in the treatment of insulin resistance and type 2 diabetes. *Clinical and Translational Scienc*, Vol.1, No.1, pp. 36-43, ISSN 1752-8054

Gordon, S. (2007). Macrophage heterogeneity and tissue lipids. *The Journal of Clinical Investigation*, Vol.117, No.1, pp. 89-93, ISSN 0021-9738

Gress, T.W.; Nieto, F.J.; Shahar, E.; Wofford, M.R.; Brancati, F.L. (2000). Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. Atherosclerosis Risk in Communities Study. *New England Journal of Medicine*, Vol.342, No.13, pp. 905-912, ISSN 0028-4793

Guilherme, A.; Virbasius, J.V.; Puri, V.; Czech, M.P. (2008). Adipocyte dysfunctions linking obesity to insulin resistance and type 2 diabetes. *Nature Reviews Molecular Cell Biology,* Vol.9, No.5, pp. 367-377, ISSN 1471-0072

Guo, C.; Ricchiuti, V.; Lian, B.Q.; Yao, T.M.; Coutinho, P.; Romero, J.R.; Li, J.; Williams, G.H.; Adler, G.K. (2008). Mineralocorticoid receptor blockade reverses obesity-related changes in expression of adiponectin, peroxisome proliferator-activated receptor-gamma, and proinflammatory adipokines. *Circulation*, Vol.117, No.17, pp. 2253-2261, ISSN 0009-7322

Hirata, A.; Maeda, N.; Hiuge, A.; Hibuse, T.; Fujita, K.; Okada, T.; Kihara, S.; Funahashi, T.; Shimomura, I. (2009). Blockade of mineralocorticoid receptor reverses adipocyte dysfunction and insulin resistance in obese mice. *Cardiovascular Research*, Vol.84, No.1, pp. 164-172, ISSN 0008-6363

Hotamisligil, G.S.; Shargill, N.S.; Spiegelman, B.M. (1993). Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. *Science*, Vol.259, No.5091, pp. 87-91, ISSN 0036-8075

Hosogai, N.; Fukuhara, A.; Oshima, K.; Miyata, Y.; Tanaka, S.; Segawa, K.; Furukawa, S.; Tochino, Y.; Komuro, R.; Matsuda, M.; Shimomura, I. (2007). Adipose tissue

hypoxia in obesity and its impact on adipocytokine dysregulation. *Diabetes*, Vol.56, No.4, pp. 901-911, ISSN 0012-1797

Howard, J.K. & Flier, J.S. (2006). Attenuation of leptin and insulin signaling by SOCS proteins. *Trends in Endocrinology and Metabolism*, Vol.17, No.9, pp. 365-371, ISSN 1043-2760

Hsieh, P.S.; Jin, J.S.; Chiang, C.F.; Chan, P.C.; Chen, C.H.; Shih, K.C. (2009). COX-2-mediated inflammation in fat is crucial for obesity-linked insulin resistance and fatty liver. *Obesity*, Vol.17, No.6, pp. 1150-1157, ISSN 20900708

Hsieh, P.S.; Lu, K.C.; Chiang, C.F.; Chen, C.H. (2010). Suppressive effect of COX2 inhibitor on the progression of adipose inflammation in high-fat-induced obese rats. *European Journal of Clinical Investigation*, Vol.40, No.2, pp. 164-171, ISSN 0014-2972

Ichida, Y.; Hasegawa, G.; Fukui, M.; Obayashi, H.; Ohta, M.; Fujinami, A.; Ohta, K.; Nakano, K.; Yoshikawa, T.; Nakamura, N. (2006). Effect of atorvastatin on in vitro expression of resistin in adipocytes and monocytes/macrophages and effect of atorvastatin treatment on serum resistin levels in patients with type 2 diabetes. *Pharmacology*, Vol.76, No.1, pp. 34-39, ISSN 0031-7012

Isoda, K.; Young, J.L.; Zirlik, A.; MacFarlane, L.A.; Tsuboi, N.; Gerdes, N.; Schönbeck, U.; Libby, P. (2006). Metformin inhibits proinflammatory responses and nuclear factor-kappaB in human vascular wall cells. *Arteriosclerosis, Thrombosis, and Vascular Biology*, Vol.26, No.3, pp. 611-617, ISSN 1079-5642

Jaworski, K.; Ahmadian, M.; Duncan, R.E.; Sarkadi-Nagy, E.; Varady, K.A.; Hellerstein, M.K.; Lee, H.Y.; Samuel, V.T.; Shulman, G.I.; Kim, K.H.; de Val, S.; Kang, C.; Sul, H.S. (2009). AdPLA ablation increases lipolysis and prevents obesity induced by high-fat feeding or leptin deficiency. *Nature Medicine*, Vol.15, No.2, pp. 159-168, ISSN 1078-8956

Jiao, P.; Chen, Q.; Shah, S.; Du, J.; Tao, B.; Tzameli, I.; Yan, W.; Xu, H. (2009). Obesity-related upregulation of monocyte chemotactic factors in adipocytes: involvement of nuclear factor-kappaB and c-Jun NH2-terminal kinase pathways. *Diabetes*, Vol.58, No.1, pp. 104-115, ISSN 0012-1797

Kamei, N.; Tobe, K.; Suzuki, R.; Ohsugi, M.; Watanabe, T.; Kubota, N.; Ohtsuka-Kowatari, N.; Kumagai, K.; Sakamoto, K.; Kobayashi, M.; Yamauchi, T.; Ueki, K.; Oishi, Y.; Nishimura, S.; Manabe, I.; Hashimoto, H.; Ohnishi, Y.; Ogata, H.; Tokuyama, K.; Tsunoda, M.; Ide, T.; Murakami, K.; Nagai, R.; Kadowaki, T. (2006). Overexpression of monocyte chemoattractant protein-1 in adipose tissues causes macrophage recruitment and insulin resistance. *The Journal of Biological Chemistry*, Vol.281, No.36, pp. 26602-26614, ISSN 0021-9258

Kanda, H.; Tateya, S.; Tamori, Y.; Kotani, K.; Hiasa, K.; Kitazawa, R.; Kitazawa, S.; Miyachi, H.; Maeda, S.; Egashira, K.; Kasuga, M. (2006). MCP-1 contributes to macrophage infiltration into adipose tissue, insulin resistance, and hepatic steatosis in obesity. *The Journal of Clinical Investigation*, Vol.116, No.6, pp. 1494-505, ISSN 0021-9738

Kawanami, D.; Maemura, K.; Takeda, N.; Harada, T.; Nojiri, T.; Imai, Y.; Manabe, I.; Utsunomiya, K.; Nagai, R. (2004). Direct reciprocal effects of resistin and adiponectin on vascular endothelial cells: a new insight into adipocytokine-endothelial cell interactions. *Biochemical and Biophysical Research Communications*, Vol.314, No.2, pp. 415-419, ISSN 0006-291X

Kern, P.A.; Ranganathan, S.; Li, C.; Wood, L.; Ranganathan, G. (2001). Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. *American Journal of Physiology - Endocrinology and Metabolism*, Vol.280, No.5, pp. E745-51, ISSN 0193-1849

Kim, K.H.; Lee, K.; Moon, Y.S.; Sul, H.S. (2001). A cysteine-rich adipose tissue-specific secretory factor inhibits adipocyte differentiation. *The Journal of Biological Chemistry*, Vol.276, No.14, pp. 11252-11256, ISSN 0021-9258

Kim, S. & Moustaid-Moussa, N. (2000). Secretory, endocrine and autocrine/paracrine function of the adipocyte. *Journal of Nutrition*, Vol.130, No.12, pp. 3110S-3115S, ISSN 0022-3166

Kintscher, U.; Hartge, M.; Hess, K.; Foryst-Ludwig, A.; Clemenz, M.; Wabitsch, M.; Fischer-Posovszky, P.; Barth, T.F.; Dragun, D.; Skurk, T.; Hauner, H.; Blüher, M.; Unger, T.; Wolf, A.M.; Knippschild, U.; Hombach, V.; Marx, N. (2008). T-lymphocyte infiltration in visceral adipose tissue: a primary event in adipose tissue inflammation and the development of obesity-mediated insulin resistance. *Arteriosclerosis, Thrombosis, and Vascular Biology*, Vol.28, No.7, pp. 1304-1310, ISSN 1079-5642

Kras, K.M.; Hausman, D.B.; Martin, R.J. (2000). Tumor necrosis factor-alpha stimulates cell proliferation in adipose tissue-derived stromal-vascular cell culture: promotion of adipose tissue expansion by paracrine growth factors. *Obesity Research*, Vol.8, No.2, pp. 186-193, ISSN 1071-7323

Kumada, M.; Kihara, S.; Ouchi, N.; Kobayashi, H.; Okamoto, Y.; Ohashi, K.; Maeda, K.; Nagaretani, H.; Kishida, K.; Maeda, N.; Nagasawa, A.; Funahashi, T.; Matsuzawa, Y. (2004). Adiponectin specifically increased tissue inhibitor of metalloproteinase-1 through interleukin-10 expression in human macrophages. *Circulation*, Vol.109, No.17, pp. 2046-2049, ISSN 0009-7322

Lamounier-Zepter, V. & Ehrhart-Bornstein, M. (2006). Fat tissue metabolism and adrenal steroid secretion. *Current Hypertension Reports*, Vol.8, No.1, pp. 30-34, ISSN 1522-6417

Lehrke, M.; Reilly, M.P.; Millington, S.C.; Iqbal, N.; Rader, D.J; Lazar, M.A. (2004). An inflammatory cascade leading to hyperresistinemia in humans. *PLoS Medicine*, Vol.1, No.2, pp. e45, ISSN 1549-1277

Lolmède, K.; Durand, de S. F. V.; Galitzky, J.; Lafontan, M.; Bouloumié, A. (2003). Effects of hypoxia on the expression of proangiogenic factors in differentiated 3T3-F442A adipocytes. *International Journal of Obesity and Related Metabolic Disorders*, Vol.27, No.10, pp. 1187-1195, ISSN 0307-0565

Lumeng, C.N.; Bodzin, J.L.; Saltiel, A.R. (2007). Obesity induces a phenotypic switch in adipose tissue macrophage polarization. *The Journal of Clinical Investigation*, Vol.117, No.1, pp. 175-184, ISSN 0021-9738

Lumeng, C.N.; Deyoung, S.M.; Bodzin, J.L.; Saltiel, A.R. (2007). Increased inflammatory properties of adipose tissue macrophages recruited during diet-induced obesity. *Diabetes*, Vol.56, No.1, pp. 16-23, ISSN 0012-1797

Maachi, M.; Piéroni, L.; Bruckert, E.; Jardel, C.; Fellahi, S.; Hainque, B.; Capeau, J.; Bastard, J.P. (2004). Systemic low-grade inflammation is related to both circulating and adipose tissue TNFalpha, leptin and IL-6 levels in obese women. *International*

Journal of Obesity and Related Metabolic Disorders, Vol.28, No.8, pp. 993-997, ISSN 0307-0565

Madsen, L.; Pedersen, L.M.; Lillefosse, H.H.; Fjaere, E.; Bronstad, I.; Hao, Q.; Petersen, R.K.; Hallenborg, P.; Ma, T.; De, M. R.; Araujo, P.; Mercader, J.; Bonet, M.L.; Hansen, J.B.; Cannon, B.; Nedergaard, J.; Wang, J.; Cinti, S.; Voshol, P.; Døskeland, S.O.; Kristiansen, K. (2010). UCP1 induction during recruitment of brown adipocytes in white adipose tissue is dependent on cyclooxygenase activity. *PLoS One*, Vol.5, No.6, pp. e11391, ISSN 1932-6203

Malminiemi, K. (2000). Long-term celiprolol therapy lowers fasting plasma leptin levels. Celiprolol Multicenter Study Group. *Cardiovascular Drugs and Therapy*, Vol.14, No.1, pp. 67-75, ISSN 0920-320

Matarese, G.; La Cava. A; Sanna, V, Lord, G.M.; Lechler, R.I,; Fontana, S.; Zappacosta, S. (2002). Balancing susceptibility to infection and autoimmunity: a role for leptin? *Trends Immunology,*Vol.23, No.4, pp. 182-7, ISSN 1471-4906.

Minokoshi, Y.; Kim, Y.B.; Peroni, O.D.; Fryer, L.G.; Müller, C.; Carling, D.; Kahn, B.B. (2002). Leptin stimulates fatty-acid oxidation by activating AMP-activated protein kinase. *Nature*, Vol.415, No.6869, pp. 339-343, ISSN 0027-8424

Nishimura, S.; Manabe, I.; Nagasaki, M.; Eto, K.; Yamashita, H.; Ohsugi, M.; Otsu, M.; Hara, K.; Ueki, K.; Sugiura, S.; Yoshimura, K.; Kadowaki, T.; Nagai, R. (2009). CD8^{+} effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. *Nature Medicine*, Vol. 15, No.8, pp. 914-920, ISSN 1078-8956

Nonogaki, K.; Fuller, G.M.; Fuentes, N.L.; Moser, A.H.; Staprans, I.; Grunfeld, C.; Feingold, K.R. (1995). Interleukin-6 stimulates hepatic triglyceride secretion in rats. *Endocrinology*, Vol.136, No.5, pp. 2143-2149, ISSN 0013-7227

Ouchi, N.; Kihara, S.; Arita, Y.; Okamoto, Y.; Maeda, K.; Kuriyama, H.; Hotta, K.; Nishida, M.; Takahashi, M.; Muraguchi, M.; Ohmoto, Y.; Nakamura, T.; Yamashita, S.; Funahashi, T.; Matsuzawa, Y. (2000). Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF-kappaB signaling through a cAMP-dependent pathway. *Circulation*, Vol.102, No.11, pp. 1296-1301, ISSN 0009-7322

Phillips, S.A.; Ciaraldi, T.P.; Kong, A.P.; Bandukwala, R.; Aroda, V.; Carter, L.; Baxi, S.; Mudaliar, S.R.; Henry, R.R. (2003). Modulation of circulating and adipose tissue adiponectin levels by antidiabetic therapy. *Diabetes*, Vol.52, No.3, pp. 667-674, ISSN 0012-1797

Pollare, T.; Lithell, H.; Selinus, I.; Berne, C. (1989). Sensitivity to insulin during treatment with atenolol and metoprolol: a randomised, double blind study of effects on carbohydrate and lipoprotein metabolism in hypertensive patients. *British Medical Journal*, Vol.298, No.6681, pp. 1152-1157, ISSN 0959-8138

Rausch, M.E.; Weisberg, S.; Vardhana, P.; Tortoriello, D.V. (2008). Obesity in C57BL/6J mice is characterized by adipose tissue hypoxia and cytotoxic T-cell infiltration. *International Journal of Obesity*, Vol.32, No.3, pp. 451-463, ISSN 0307-0565

Rocha, V.Z.; Folco, E.J.; Sukhova, G.; Shimizu, K.; Gotsman, I.; Vernon, A.H.; Libby, P. (2008). Interferon-gamma, a Th1 cytokine, regulates fat inflammation: a role for adaptive immunity in obesity. *Circulation Research*, Vol.103, No.5, pp. 467-476, ISSN 0009-7300

Samal, B.; Sun, Y.; Stearns, G.; Xie, C.; Suggs, S.; McNiece, I. (1994). Cloning and characterization of the cDNA encoding a novel human pre-B-cell colony-enhancing factor. *Molecular and Cellular Biology*, Vol.14, No.2, pp. 1431-1437., ISSN 0270-7306

Sandeep, S.; Velmurugan, K.; Deepa, R.; Mohan, V. (2007). Serum visfatin in relation to visceral fat, obesity, and type 2 diabetes mellitus in Asian Indians. *Metabolism*, Vol.56, No.4, pp. 565-570

Sharma, A.M.; Pischon, T.; Hardt, S.; Kunz, I.; Luft, F.C. (2001). Hypothesis: Beta-adrenergic receptor blockers and weight gain: A systematic analysis. *Hypertension*, Vol.37, No.2, pp. 250-254, ISSN 0914-91IX

Shillabeer, G.; Kumar, V.; Tibbo, E.; Lau, D.C. (1998). Arachidonic acid metabolites of the lipoxygenase as well as the cyclooxygenase pathway may be involved in regulating preadipocyte differentiation. *Metabolism*, Vol.47, No.4, pp. 461-466

Skurk, T.; van Harmelen, V.; Hauner, H. (2004). Angiotensin II stimulates the release of interleukin-6 and interleukin-8 from cultured human adipocytes by activation of NF-kappaB. *Arteriosclerosis, Thrombosis, and Vascular Biology*, Vol.24, No.7, pp. 1199-1203, ISSN 1079-5642

Srinivasan, S.; Ambler, G.R.; Baur, L.A.; Garnett, S.P.; Tepsa, M.; Yap, F.; Ward, G.M.; Cowell, C.T. (2006). Randomized, controlled trial of metformin for obesity and insulin resistance in children and adolescents: improvement in body composition and fasting insulin. *Journal of Clinical Endocrinology & Metabolism*, Vol.91, No.6, pp. 2074-2080, ISSN 0021-972X

Steppan, C.M.; Bailey, S.T.; Bhat, S.; Brown, E.J.; Banerjee, R.R.; Wright, C.M.; Patel, H.R.; Ahima, R.S.; Lazar, M.A. (2001). The hormone resistin links obesity to diabetes. *Nature*, Vol.409, No.6818, pp. 307-312, ISSN 0028-0836

Takagi, T.; Matsuda, M.; Abe, M.; Kobayashi, H.; Fukuhara, A.; Komuro, R.; Kihara, S.; Caslake, M.J.; McMahon, A.; Shepherd, J.; Funahashi, T.; Shimomura, I. (2008). Effect of pravastatin on the development of diabetes and adiponectin production. *Atherosclerosis*, Vol.196, No.1, pp. 114-121, ISSN 0021-9150

Takahashi, K.; Yamaguchi, S.; Shimoyama, T.; Seki, H.; Miyokawa, K.; Katsuta, H.; Tanaka, T.; Yoshimoto, K.; Ohno, H.; Nagamatsu, S.; Ishida, H. (2008). JNK- and IkappaB-dependent pathways regulate MCP-1 but not adiponectin release from artificially hypertrophied 3T3-L1 adipocytes preloaded with palmitate in vitro. *American Journal of Physiology - Endocrinology and Metabolism*, Vol.294, No.5, pp. E898-909, ISSN 0193-1849

Tsuchiya, K.; Yoshimoto, T.; Hirono, Y.; Tateno, T.; Sugiyama, T.; Hirata, Y. (2006). Angiotensin II induces monocyte chemoattractant protein-1 expression via a nuclear factor-kappaB-dependent pathway in rat preadipocytes. *American Journal of Physiology - Endocrinology And Metabolism*, Vol.291, No.4, pp. E771-778, ISSN 0193-1849

Vegiopoulos, A.; Müller-Decker, K.; Strzoda, D.; Schmitt, I.; Chichelnitskiy, E.; Ostertag, A.; Berriel, D.M.; Rozman, J.; Hrabe, de A. M.; Nüsing, R.M.; Meyer, C.W.; Wahli, W.; Klingenspor, M.; Herzig, S. (2010). Cyclooxygenase-2 controls energy homeostasis in mice by de novo recruitment of brown adipocytes. *Science*, Vol.328, No.5982, pp. 1158-1161, ISSN 0036-8075

Wang, B.; Wood, I.S.; Trayhurn, P. (2007). Dysregulation of the expression and secretion of inflammation-related adipokines by hypoxia in human adipocytes. *Pflügers Archiv European Journal of Physiology*, Vol.455, No.3, pp. 479-492, ISSN 0031-6768

Weisberg, S.P.; McCann, D.; Desai, M.; Rosenbaum, M.; Leibel, R.L.; Ferrante, A.W. Jr. (2003). Obesity is associated with macrophage accumulation in adipose tissue. *The Journal of Clinical Investigation*, Vol.112, No.12, pp. 1796-1808, ISSN 0021-9738

Weisberg, S.P.; Hunter, D.; Huber, R.; Lemieux, J.; Slaymaker, S.; Vaddi, K.; Charo, I.; Leibel, R.L.; Ferrante, A.W. Jr. (2006). CCR2 modulates inflammatory and metabolic effects of high-fat feeding. *The Journal of Clinical Investigation*, Vol. 116, No.1, pp.115-124, ISSN 0021-9738

Williams, E.S.; Baylin, A.; Campos, H. (2007). Adipose tissue arachidonic acid and the metabolic syndrome in Costa Rican adults. *Clinical Nutrition*, Vol.26, No.4, pp. 474-482, ISSN 1938-3207

Winer, S.; Chan, Y.; Paltser, G.; Truong, D.; Tsui, H.; Bahrami, J.; Dorfman, R.; Wang, Y.; Zielenski, J.; Mastronardi, F.; Maezawa, Y.; Drucker, D.J.; Engleman, E.; Winer, D.; Dosch, H.M. (2009). Normalization of obesity-associated insulin resistance through immunotherapy. *Nature Medicine*, Vol. 15, No.8, pp. 921-929, ISSN 1078-8956

Wu, H.; Ghosh, S.; Perrard, X.D.; Feng, L.; Garcia, G.E.; Perrard, J.L.; Sweeney, J.F.; Peterson, L.E.; Chan, L.; Smith, C.W.; Ballantyne, C.M. (2007). T-cell accumulation and regulated on activation, normal T cell expressed and secreted upregulation in adipose tissue in obesity. *Circulation*, Vol.115, No.8, pp. 1029-1038, ISSN 0009-7322

Xu, H.; Barnes, G.T.; Yang, Q.; Tan, G.; Yang, D.; Chou, C.J.; Sole, J.; Nichols, A.; Ross, J.S.; Tartaglia, L.A.; Chen, H. (2003). Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *The Journal of Clinical Investigation*, Vol.112, No.12, pp. 1821-1830, ISSN 0021-9738

Yamauchi ,T.; Kamon, J.; Minokoshi, Y.; Ito, Y.; Waki, H.; Uchida, S.; Yamashita, S.; Noda, M.; Kita, S.; Ueki, K.; Eto, K.; Akanuma, Y.; Froguel, P.; Foufelle, F.; Ferre, P.; Carling, D.; Kimura, S.; Nagai, R.; Kahn, B.B.; Kadowaki, T. (2002). Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. *Nature Medicine*, Vol.8, No.11, pp. 1288-1295, ISSN 1078-8956

Ye, J.; Gao, Z.; Yin, J.; He, Q. (2007). Hypoxia is a potential risk factor for chronic inflammation and adiponectin reduction in adipose tissue of ob/ob and dietary obese mice. *American Journal of Physiology - Endocrinology and Metabolism*, Vol.293, No.4, pp. E1118-1128, ISSN 0193-1849

Yin, M.J.; Yamamoto, Y.; Gaynor, R.B. (1998). The anti-inflammatory agents aspirin and salicylate inhibit the activity of I(kappa)B kinase-beta. *Nature*, Vol.396, No.6706, pp. 77-80, ISSN 0028-0836

Yuan, M.; Konstantopoulos, N.; Lee, J.; Hansen, L.; Li, Z.W.; Karin, M.; Shoelson, S.E. (2001). Reversal of obesity- and diet-induced insulin resistance with salicylates or targeted disruption of Ikkbeta. *Science*, Vol.293, No.5535, pp. 1673-1677, ISSN 0036-8075

zis, C.; Kyriakakis, M.; Tsimbinos, G.; Tornaritis, M.; Kafatos, A. (2004). Association of adipose tissue arachidonic acid content with BMI and overweight status in children from Cyprus and Crete. *British Journal of Nutrition*, Vol.91, No.4, pp. 643-649, ISSN 0007-1145
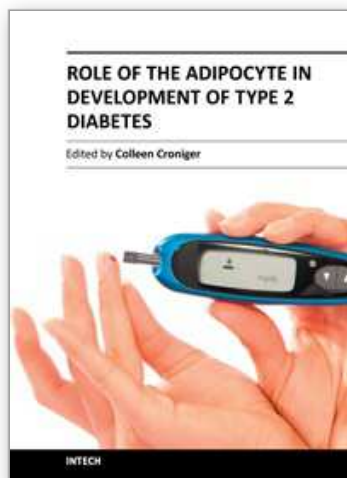
Role of the Adipocyte in Development of Type 2 Diabetes

Edited by Dr. Colleen Croniger

ISBN 978-953-307-598-3

Hard cover, 372 pages

Publisher InTech

Published online 22, September, 2011

Published in print edition September, 2011

Adipocytes are important in the body for maintaining proper energy balance by storing excess energy as triglycerides. However, efforts of the last decade have identified several molecules that are secreted from adipocytes, such as leptin, which are involved in signaling between tissues and organs. These adipokines are important in overall regulation of energy metabolism and can regulate body composition as well as glucose homeostasis. Excess lipid storage in tissues other than adipose can result in development of diabetes and nonalcoholic fatty liver disease (NAFLD). In this book we review the role of adipocytes in development of insulin resistance, type 2 diabetes and NAFLD. Because type 2 diabetes has been suggested to be a disease of inflammation we included several chapters on the mechanism of inflammation modulating organ injury. Finally, we conclude with a review on exercise and nutrient regulation for the treatment of type 2 diabetes and its co-morbidities.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Po-Shiuan Hsieh (2011). Obesity-Induced Adipose Tissue Inflammation and Insulin Resistance, Role of the Adipocyte in Development of Type 2 Diabetes, Dr. Colleen Croniger (Ed.), ISBN: 978-953-307-598-3, InTech, Available from: http://www.intechopen.com/books/role-of-the-adipocyte-in-development-of-type-2-diabetes/obesity-induced-adipose-tissue-inflammation-and-insulin-resistance

INTECH
open science | open minds