doi:10.4149/endo_2009_04_157

LEPTIN AND ADIPONECTIN: FROM ENERGY AND METABOLIC DYSBALANCE TO INFLAMMATION AND AUTOIMMUNITY

STOFKOVA A

Department of Normal, Pathological and Clinical Physiology, Third Faculty of Medicine, Charles University in Prague, Czech Republic
e-mail: andrea.stofkova@lf3.cuni.cz

There is a growing evidence that both overnutrition and undernutrition negatively interfere with immune system. The overnutrition has been found to increase susceptibility to the development of inflammatory or autoimmune diseases. On the other hand, starvation or malnutrition has been more associated with increased susceptibility to infections. In the regulation of immune and inflammatory processes, white adipose tissue plays a critical role as an endocrine organ which produces number of active peptides, called adipokines. The adipokines, leptin and adiponectin represent a critical link among nutritional status, metabolism and immunity. Leptin is primarily known as a satiety factor regulating body weight by suppression of appetite and stimulation of energy expenditure, and its serum levels and gene expression in adipocytes strongly correlate with proportion of body fat stores. On the other hand, leptin is a pro-inflammatory adipokine inducing T helper 1 cells and may contribute to the development and progression of autoimmune responses. Adiponectin plays an important role as an insulin-sensitizing adipokine which production is decreased in obesity and in conditions associated with insulin resistance. Adiponectin also acts as an anti-inflammatory factor especially with regard to atherosclerosis, but in some chronic inflammatory/autoimmune diseases adiponectin may have pro-inflammatory effects and its production correlates with inflammatory markers and disease activity. This review discusses the main biological activities of leptin and adiponectin as well as their contribution to inflammatory and autoimmune processes with particular focus on rheumatoid arthritis and its experimental models.

Key words: Leptin – Adiponectin – Obesity – Inflammation – Autoimmunity – Rheumatoid arthritis – Adjuvant arthritis

Leptin: Production and Biological Actions

Leptin, the 16kDa adipocyte-derived protein, was identified as a product of the obesity (*ob*) gene which recessive mutation resulted in food intake and energy expenditure defects (ZHANG et al. 1994). Leptin is structurally classified as a member of the long-chain helical cytokine family, which also includes IL-6, IL-11, IL-12 or LIF (ZHANG et al. 1997). The leptin receptor (OB-R), a product of diabetes (*db*) gene (TARTAGLIA et al. 1995), belongs to the class I cytokine receptor family, which uses gp130 as a signal-transduction component in its receptor complex (HELDIN 1995). There were identified six alternatively spliced isoforms of OB-R, which contain identical extracellular binding domain but differ by the length of cytoplasmic domains: A long isoform (OB-Rb), 4 short isoforms (OB-Ra, OB-Rc, OB-Rd and OB-Rf), and soluble isoform (OB-Re). However, only the OB-Rb isoform is suggested to be

Corresponding Author: PharmDr. Andrea Stofkova, Department of Normal, Pathological, and Clinical Physiology, Third Faculty of Medicine, Charles University in Prague, Ke Karlovu 4, 120 00 Prague, Czech Republic, Phone: +420 224902718, Fax: +420 224916896 e-mail: andrea.stofkova@lf3.cuni.cz

the major signaling form having an extended intracellular domain of approx. 300 cytoplasmic residues for efficient activation of the JAK-STAT signaling pathway (Wang et al. 1996; Houseknecht et al. 1998).

Leptin is predominantly produced by white adipose tissue (WAT) and its circulating levels directly correlate with body fat mass as well as adipocyte size, and are altered by nutritional status, i.e., falling with starvation and rising with obesity (Houseknecht et al. 1998). There is also a strong relationship between leptin pattern and meal timing. The shift of meal timing led to the shift of plasma leptin peak in both humans (Schoeller et al. 1997) and rodents (Bodosi et al. 2004). Furthermore, the expression of leptin can be directly up-regulated by insulin and glucocorticoids (Fried et al., 2000).

Leptin as an adiposity signal acts on the specialized hypothalamic pathways, repressing anabolic neuronal circuits that stimulate appetite and inhibit energy expenditure, while simultaneously activating catabolic neuronal circuits that inhibit appetite and increase energy expenditure. These effects of leptin include stimulation of the expression of anorexigenic factors, pro-opiomelanocortin (POMC) and cocaine and amphetamine-regulated transcript (CART), and inhibition of the expression of orexigenic factors, neuropeptide Y (NPY) and agouti-related peptide (AgRP) via its receptor OB-Rb in neurons located in the arcuate nucleus (Schwartz et al. 2000). In addition to regulation of energy balance, leptin is a crucial factor for normal development of reproductive system. Congenital leptin deficiency has been associated with hypogonadotropic hypogonadism and infertility, which was corrected by exogenous leptin administration. However, these effects of leptin depend upon functional hypothalamic NPY neurons of the arcuate nucleus and Y1 receptor (the subtype of NPY receptors) pathway downstream to convey leptin signals on GnRH neurons, the key activators of the reproductive neuroendocrine axis (Gamba et al. 2006).

Leptin: A cytokine-like hormone

Leptin is a potent modulator of immune responses (Fig. 1). The initial study, which comes from 1976, a long time before the identification of leptin and its receptor, described increased mortality of leptin receptor deficient (*db/db*) mice in response to Coxackie virus group B inoculation. These mice had defective cellular immunity and showed thymic and lymphoid atrophy (Webb et al. 1976). Similar features have been further described in leptin deficient (*ob/ob*) mice (Meade et al. 1979; Chandra 1980), but exogenous leptin administration protected these mice from marked reduction in the size and cellularity of the thymus (Howard et al. 1999), enhanced protection to LPS- (Faggioni et al. 1999) and TNF- (Takahashi et al. 1999) induced lethality, and up-regulated phagocytosis of macrophages (Loffreda et al. 1998). The dramatic fall in leptin production induced by starvation also causes immunosuppression which can be reversed by leptin replacement therapy. Several studies reported protection from the lymphoid atrophy (Howard et al. 1999), and enhanced activation of $CD4^+$ and $CD8^+$ T helper 1 (T_H1) cells producing pro-inflammatory cytokines such as IL-2 and IFN-γ while decreased the percentage of $CD4^+$ and $CD8^+$ T helper 2 (T_H2) cells producing IL-4 and IL-10 after leptin administration during starvation (Lord et al. 1998; Rodriguez et al. 2007). Nevertheless, these immunomodulatory effects of leptin require direct interactions with functional OB-Rb receptor as leptin therapy failed to restore immune responses in *db/db* mice (Lord et al. 1998; Loffreda et al. 1998). Interestingly, OB-Rb is expressed by monocytes/macrophages, natural killers (NK) cells, T and B lymphocytes, and $CD34^+$ haematopoietic bone-marrow precursors (La Cava and Matarese 2004).

The main effects of leptin in innate immunity involve activation of proliferation and phagocytosis of monocytes/macrophages, chemotaxis of neutrophils and the release of oxygen radicals by these cells, and activation of NK cells (La Cava and Matarese 2004). Additionally, leptin stimulates synthesis of leukotrienes by alveolar macrophages, and production of nitric oxide and growth hormone by peripheral blood mononuclear cells (PBMCs). However, the effect of leptin on cytokine production is still controversial. Some studies have shown enhanced pro-inflammatory cytokine production including TNF-α, IL-6, IL-8 or IFN-γ by mice or human monocytes/macrophages incubated with leptin alone or coincubated with leptin and endotoxin (Loffreda et al. 1998; Santos-Alvarez et al. 1999; Zarkesh-Esfahani et al. 2001). In contrast to these findings, in vivo study performed on endotoxin injected primates has shown significant reduction of TNF-α and IL-6 after leptin treatment indicating leptin anti-inflammatory effects to promote survival during sepsis (Xiao et al. 2003). Consistently, leptin administration attenuated experimental pancreatitis in rats by increasing anti-inflammatory cytokine IL-4 and decreasing pro-inflammatory cytokines TNF-α and IL-1β production (Jaworek et al. 2002; Warzecha et al. 2002). Moreover, leptin has been also

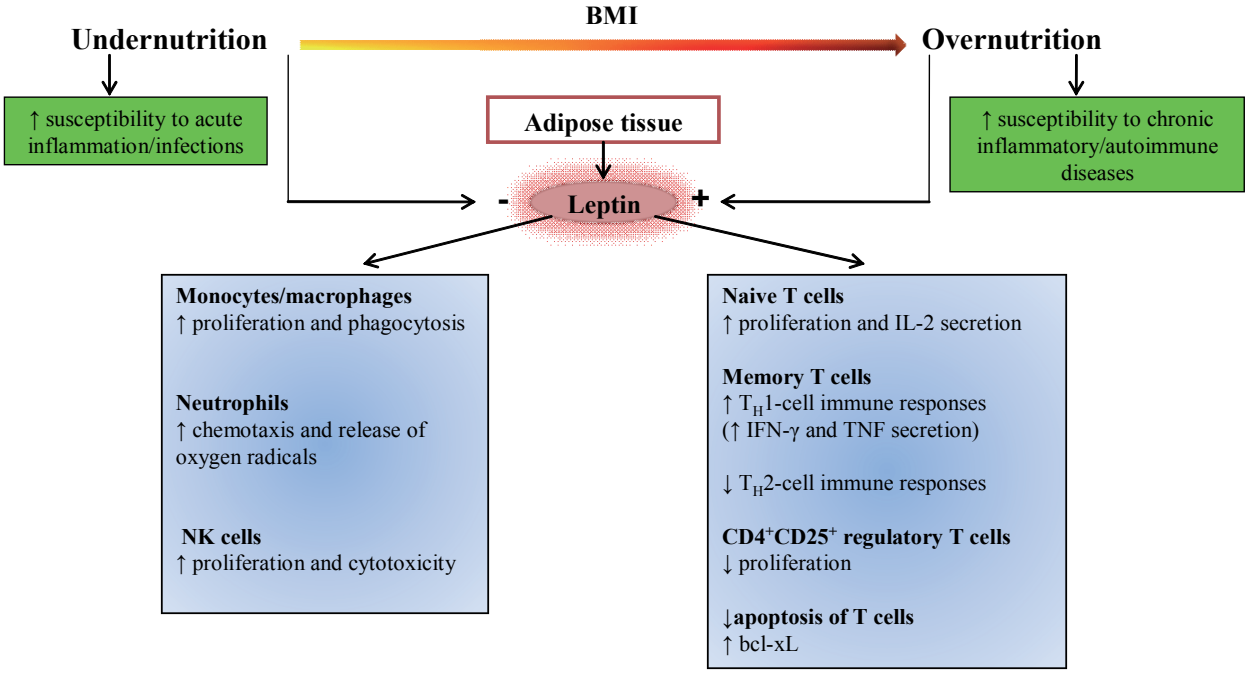

Figure 1: Leptin, a factor through which nutritional status affects immune responses.
Leptin production reflects the amount of energy stores in the adipose tissue. Expression of leptin is increased in conditions that are associated with expansion of the adipose tissue during overnutrition, and decreased with a fall in amount of the adipose tissue during undernutrition. Leptin modulates both innate and adaptive immunity. It activates proliferation and phagocytosis of monocytes/macrophages and cytotoxicity of natural killer (NK) cells. In neutrophils, leptin stimulates chemotaxis and the production of oxygen radicals, such as hydrogen peroxide and superoxide. In adaptive immunity, leptin induces proliferation of naive T cells and IL-2 secretions by these cells. On memory T cells, leptin up-regulates T helper (T_H1)-cell immune responses and down-regulates T helper (T_H2)-cell immune responses. Leptin inhibits $CD4^+CD25^+$ regulatory T cells proliferation, and also prevents apoptosis of T cells through up-regulation of anti-apoptotic protein bcl-xL.

reported to increase IL-1-receptor antagonist secretion from human monocytes in vitro (Gabay et al. 2001). Although these observations on leptin immunomodulatory effects are not always consistent, in summary they indicate that leptin is an active participant of innate immunity and its deficiency increases susceptibility to deleterious effects of infectious diseases.

In adaptive immunity, leptin markedly stimulates proliferation of naive T cells and secretion of IL-2 by these cells, whereas it minimally affects the proliferation of memory T cells. On memory T cells, leptin promotes the switch towards T helper 1 (T_H1)-cell immune responses by IFN-γ and TNF secretion (La Cava and Matarese, 2004). Further effect of leptin involves suppression of $CD4^+CD25^+$ regulatory T cells proliferation (De Rosa et al. 2007). Leptin also prevents apoptosis of T cells that normally accompanies fasting through up-regulation of anti-apoptotic protein bcl-xL via leptin receptors on lymphocytes (La Cava and Matarese, 2004).

Although leptin is well known for its regulatory effects on immune cells, its expression and release is reciprocally under the control of different inflammatory stimuli. It has been shown that acute inflammation and pro-inflammatory cytokines, such as TNF-α, IL-1, IL-6, and LIF positively regulate leptin expression in adipose tissue and circulating leptin levels (Gualillo et al. 2000; Grunfeld et al. 1996; Sarraf et al. 1997), whereas long-term exposition to IL-1 or TNF-α negatively regulated leptin levels (Bruun et al. 2002; Sato et al. 2003).

Leptin: Chronic Inflammation and Autoimmunity

As mentioned above, the absence of leptin causes impaired immune responses resulting in increased susceptibility to infections. On the other hand, leptin deficient (*ob/ob*) mice are resistant to T_H1-mediated experimental autoimmune diseases including encephalomyelitis,

arthritis, glomerulonephritis, colitis and hepatitis (La Cava and Matarese, 2004). Therefore, leptin might have a dual nature in immunity: first, leptin prevents from lethality of infectious diseases and second, leptin can be involved in the development and progression of autoimmunity.

Leptin as a stimulator of T_H1 immune responses appears to regulate susceptibility to experimental autoimmune encephalomyelitis (EAE) in mice. Leptin surge has been occurred before the clinical manifestation of EAE and consequently potentiated progression of the disease. It is important to note, that the decrease in serum leptin levels induced by acute starvation was able to delay EAE onset and attenuated clinical symptoms by promoting a T_H2-mediated cytokine switch (Sanna et al. 2003). Moreover, leptin replacement to *ob/ob* mice, which are normally resistant to both active and adoptive EAE, results in development of the disease. In normal mice leptin administration worsened the progression of EAE (Matarese et al. 2001).

The role of leptin in the pathogenesis of rheumatoid arthritis (RA) is still questionable. Some studies demonstrated increased circulating leptin levels in RA patients compared to controls (Bokarewa et al. 2003; Otero et al. 2006; Gunaydin et al. 2006) or confirmed that there exists an important dependence between the risk of aggressive course of RA and increased leptin levels (Lee et al. 2007; Targonska-Stepniak et al. 2008). On the other hand, different groups of authors showed that leptin levels of RA patients did not significantly differ from controls, and were positively correlated with body mass index (BMI) rather than disease activity stage (Anders et al. 1999; Nishiya et al. 2002; Popa et al. 2005; Hizmetli et al. 2007). There is also a study which described lower leptin levels in RA patients compared to controls and no relations of leptin to BMI or disease activity score (Tokarczyk-Knapik et al. 2002). The discrepancy found on leptin concentrations among results in human RA could be due to various treatments interfering with endocrine system that often complicate human experimental studies. However, in a rat model of human RA, adjuvant arthritis (AA), leptin plasma and adipose tissue levels have been found decreased compared to controls and corresponded to adiposity (Granado et al. 2005; Stofkova et al. 2006; Stofkova et al. 2009).

Possible role of leptin in arthritis may consist in its local effects in joint cavity. Indeed, synovial fluid samples of RA patients showed reduced leptin concentrations compared to plasma samples of the same patients but correlated with the cellularity of the synovial fluid samples, implying local consumption of leptin in joint cavity (Bokarewa et al. 2003). Leptin immunomodulatory functions during joint inflammation can involve local effects on chondrocytes possessing functional leptin receptor. Interestingly, incubation of human chondrocytes with leptin showed an increased proliferation and an enhanced synthesis of extracellular matrix (Figenschau et al. 2001). Furthermore, leptin injection into joint cavity of the rat knee strongly stimulated anabolic functions of chondrocytes via induction of insulin-like growth factor 1 (IGF-1) and transforming growth factor (TGF-β) (Dumond et al. 2003). These findings suggest that leptin might have a protective role against destructive course of arthritis. However, Otero et al. (2003; 2005) have demonstrated a pro-inflammatory and detrimental role of leptin during joint inflammation as leptin in synergy with IFN-γ or IL-1 induced nitric oxide synthase type II (NOS2) production in mouse chondocytes. Furthermore, leptin has been shown to promote concentration- and time-dependent increase in IL-8 production via OB-Rb in both RA and osteoarthritis (OA) synovial fibroblasts (Tong et al. 2008). In cartilage cultures of OA patients, leptin enhanced not only IL-8, but also NO, PGE2, and IL-6 production (Voulteenaho et al. 2009).

Several studies have shown that fasting or special dietary regime in RA led to an improvement of the severity of arthritis (Fraser et al. 1999; Kjeldsen-Kragh 1999). Fraser et al. (1999) found attenuation of clinical symptoms associated with diminished leptin levels, decreased $CD4^+$ T-cell activation and an increased number and/or function of IL-4-producing T_H2 cells in fasting RA patients. Moreover, rat AA has also been improved by chronic food restriction induced at the onset of the disease (Jurcovicova et al. 2001). Since leptin enhances $CD4^+$ T_H1 cell and decreasing $CD4^+$ T_H2 cells activity (Lord et al. 1998; Rodriguez et al. 2007), its reduction during fasting might result in shift towards T_H2 cytokine production and subsequently suppression of the progression of arthritis. However, further studies are needed to confirm this hypothesis and also the importance of leptin in the pathogenesis of rheumatoid arthritis.

Adiponectin: Production and Biological Actions

Adiponectin was independently characterized by four groups, as a protein with alternative names: Acrp30 (adipocyte complement-related protein of 30 kDa), apM1 (adipose most abundant gene transcript

1), adipoQ or GBP28 (gelatin binding protein of 28 kDa) (Scherer et al. 1995; Maeda et al. 1996; Hu et al. 1996; Nakano et al. 1996). Adiponectin structurally belongs to the collagen super-family and shares homologies with the collagens, complement factors, TNF-α, and the brain-specific factor cerebellin. The primary structure of adiponectin contains an N-terminal signal sequence, a variable domain, a collagen-like domain, and C-terminal domain (known as globular adiponectin). Monomeric adiponectin (30 kDa) can trimerize to make a low-molecular weight (LMW) trimer that further associates through disulfide bonds to form a middle-molecular-weight (MMW) hexamer or high-molecular-weight (HMW) 12- to 18-mers. Both trimers and other oligomers of adiponectin are present in the circulation, whereas monomeric adiponectin has not been observed in the circulation and therefore it appears to be confined to the adipocyte (Tilg and Moschen 2006).

Adiponectin isoforms differ in their biological function, possibly depending on tissue and receptor subtype. AdipoR1 and AdipoR2 are two major subtypes of the adiponectin receptor that contain seven transmembrane domains, and are structurally and functionally distinct from G-protein-coupled receptors. AdipoR1 is abundantly expressed in skeletal muscle and binds with high affinity globular adiponectin, whereas AdipoR2 is predominantly expressed in the liver and binds full-length adiponectin (Kadowaki and Yamauchi 2005).

Adiponectin is most abundantly produced in WAT by both fat and non-fat cells (Fain et al. 2008). Actually, adiponectin is present in bloodstream at high concentrations under the physiological conditions. The average level of adiponectin in human plasma is 5-10μg/ml. However, obesity, type 2 diabetes mellitus (T2DM), and cardiovascular diseases are mostly associated with decreased circulating adiponectin levels. Conversely, weight loss results in significant increase of adiponectin production (Inadera et al. 2008).

Several studies demonstrated that adiponectin may serve as an insulin-sensitizing adipokine. Adiponectin administration to normal mice led to decreased plasma glucose levels and increased insulin sensitivity by inhibition of gluconeogenesis in liver and activation of free-fatty acid oxidation in skeletal muscles. Likewise, treatment with adiponectin ameliorated insulin resistance in lipoatrophic mice, but insulin resistance was completely restored only after the treatment by the combination of adiponectin and leptin. This finding indicates the mutual interplay of both leptin and adiponectin as the two major insulin-sensitizing hormones (Kadowaki and Yamauchi 2005). Adiponectin-deficient mice (*adipo-/-*) exhibited features of metabolic syndrome, however, there have been found discrepancies in their phenotypes that can be presumably related to differences in genetic background. Kubota et al. (2002) have shown that adiponectin deficiency resulted in insulin resistance, glucose intolerance and hypertriglyceridemia. Similar findings have also been reported by Maeda et al. (2002) in *adipo-/-* mice, but only when these mice were placed on 2 weeks high fat diet. In other study, *adipo-/-* mice displayed not only hepatic insulin resistance but also reduced responsiveness to peroxisome proliferators-activated receptor-γ (PPAR-γ) agonists (Nawrocki et al. 2006). On the other hand, Ma et al. (2002) did not observe impaired glucose tolerance or insulin resistance in *adipo-/-* mice under basal conditions or even after they were fed a high-fat diet for 7 months.

The regulation of metabolic state by adiponectin involves the activation of AMPK (5´-AMP-activated protein kinase) through which adiponectin inhibits gluconeogenesis in liver, and stimulates free-fatty acid oxidation in skeletal muscle and liver. However, adiponectin also acts through PPAR-α, -γ activation to stimulate fatty-acid oxidation and decrease tissue triglyceride content in muscle and liver (Kadowaki and Yamauchi 2005). Additionally, adiponectin has been shown to have direct effect on glucose uptake in skeletal muscle and adipose tissue via increasing GLUT4 translocation into plasma membrane (Ceddia et al. 2005; Fu et al. 2005).

Recently, a new role for adiponectin in the central regulation of energy homeostasis has been reported, but adiponectin's effects on food intake showed considerable diversity in different studies. Whereas Kubota et al. (2007) have found stimulatory effect of i.v. administered adiponectin on food intake through AMP-activated protein kinase in the arcuate nucleus of the hypothalamus, other authors found leptin/insulin-like anorexigenic action of centrally administered adiponectin (Coope et al. 2008). These opposite findings on adiponectin effects could be related to different isoforms of administered adiponectin, timing, concentration and route of administration. On that account, the physiological importance of adiponectin in the hypothalamic regulation of energy homeostasis remains to be defined.

Adiponectin: An Anti-inflammatory Adipokine

Adiponectin has been consistently shown to be an anti-inflammatory adipokine especially with regard to

protective effects on the vascular wall. Its deficiency in *adipo-/-* mice is manifested by increased neointimal formation in response to external cuff injury (Kubota et al. 2002) and high concentrations of TNF-α in circulation (Maeda et al. 2002). Actually, adiponectin is able to inhibit TNF-α–induced adhesion of human monocytes on endothelial cells as well as TNF-α–stimulated expression of vascular cell adhesion molecule-1 (VCAM-1), endothelial-leukocyte adhesion molecule-1 (E-selectin), and intracellular adhesion molecule-1 (ICAM-1) and IL-8 in human aortic endothelial cells (Ouchi and Walsh 2007). It has also been reported that adiponectin can inhibit the production of CXC chemokine receptor 3 ligands in LPS-stimulated macrophages and reduce T-lymphocyte recruitment in atherogenesis (Okamoto et al. 2008). Furthermore, adiponectin can modulate transformation of macrophages into foam cells, and can act as a regulator of endothelial NOS to stimulate production of nitric oxide leading to vasodilatation and to attenuate oxidative/nitrative stress (Ouchi and Walsh 2007; Li et al. 2007).

Besides acting as an anti-atherogenic factor, adiponectin exhibits also anti-inflammatory effects in response to LPS. Yokota et al. (2000) reported that recombinant adiponectin suppressed maturing and growth of macrophages as well as inhibited their functions including phagocytosis and TNF-α gene expression in response to stimulation with LPS. In addition, adiponectin significantly impaired the production of IFN-γ in LPS-stimulated human macrophages. Adiponectin also induced the production of anti-inflammatory mediators, IL-10 and IL-1-receptor antagonist, through activation of IP3-kinase in primary human monocytes, monocyte-derived macrophages, and dendritic cells. Moreover, there has been shown dual effect of HMW adiponectin on macrophages: Adiponectin alone suppressed phagocytosis of apoptotic cells and IL-8 production, while in the presence of LPS adiponectin augmented both the phagocytosis of apoptotic cells and IL-8 production. Adiponectin effects on monocytes also seem to depend on its isoform. HMW and LMW adiponectin shared some common effects, such as the activation of AMPK, the induction of apoptosis of monocytes and the suppression of macrophage scavenger receptor expression, but only LMW adiponectin displayed anti-inflammatory properties inhibiting LPS-mediated IL-6 release and stimulating IL-10 secretion. In contrast, HMW adiponectin induced the secretion of IL-6 by monocytes (Tilg and Moschen 2006).

Further anti-inflammatory effects of adiponectin involve suppression of IL-2-induced NK cell cytotoxic activity (Kim et al. 2006), and inhibition of B-cell lymphopoiesis in stromal cell culture through the induction of prostaglandin synthesis (Yokota et al. 2003).

Interestingly, pro-inflammatory cytokines, such as TNF-α and IL-6 are potent inhibitors of adiponectin gene expression or protein secretion (Ouchi and Walsh 2007). In experimental models of acute inflammation, adiponectin has been reported to either protect from inflammatory insults or not to affect inflammatory responses. Adiponectin-knockout mice treated with low dose of caerulein developed pancreatic damage and inflammation compared to wild-type mice. Moreover, the acute pancreatitis in adiponectin-knockout mice was attenuated by adenovirus-mediated over-expression of adiponectin (Araki et al. 2008). Similarly, after subtotal renal ablation in adiponectin-knockout mice, treatment with adenovirus-mediated adiponectin resulted in amelioration of albuminuria, glomerular hypertrophy, tubulointestinal fibrosis and reduction of elevated chemokines to the same levels as those in wild-type mice (Ohashi et al. 2007). On the other hand, immune responses to endotoxin and ConcanavalinA were not significantly different when compared adiponectin-knockout mice to wild-type mice (Pini et al. 2006). Additionally, in humans endotoxin-induced acute inflammation did not alter adiponectin plasma levels (Keller at al. 2003; Anderson et al. 2007).

Adiponectin: Chronic Inflammation and Autoimmunity

In contrast to reduced adiponectin levels in chronic low-grade inflammation associated with visceral obesity, metabolic syndrome or T2DM, elevated adiponectin levels are present in most of chronic inflammatory and autoimmune diseases including RA, osteoarthritis (OA), systemic lupus erythematosus, T1DM, and inflammatory bowel disease. In these patients, increased adiponectin levels were mostly independent on BMI, and rather positively then negatively correlated with inflammatory markers and disease activity (Fantuzzi 2008).

Increased adiponectin production has been reported in hypertrophic mesenteric adipose tissue of patients with Crohn's disease compared to controls or patients with ulcerative colitis. Actually, the globular form of adiponectin was able to stimulate IL-8, GM-CSF and MCP-1 secretion on colonic epithelial cells. In addition, incubation of colon cultures obtained from dextran sulfate sodium treated mice in presence of adiponectin

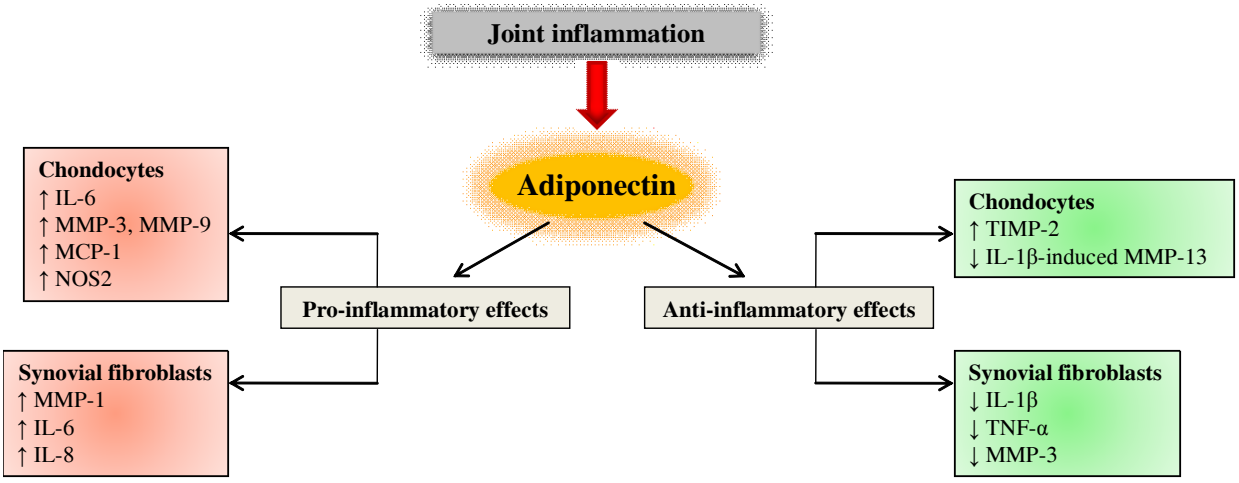

Figure 2: Dual effect of adiponectin on chondrocytes and synovial fibroblasts in joint inflammation.
Articular adipose tissue and synovium of patients with inflammatory joint diseases are a significant source of adiponectin. According to recent findings, adiponectin can modulate cartilage homeostasis in joint degenerative diseases by dual effects. On one hand, adiponectin exhibits destructive and pro-inflammatory role inducing nitric oxide synthase type II (NOS2) and IL-6, matrix metalloproteinase (MMP) -3, MMP-9, and monocyte chemoattractant protein 1 (MCP-1) in chondrocytes, on the other hand it acts as a protective factor up-regulating tissue inhibitor of metalloproteinase-2 (TIMP-2) and down-regulating IL-1beta-induced MMP-13 in chondrocytes. In synovial fibroblasts, adiponectin induces synthesis of MMP-1, IL-6 and IL-8 contributing to inflammation and matrix-degradation. Despite of these effects, adiponectin may also play an anti-inflammatory role in the pathophysiology of RA reducing TNF-α, IL-1β, and MMP-3 expressions in stimulated synovial fibroblasts.

resulted in elevated IL-6 and macrophage inflammatory protein 2 levels compared to cultures obtained from control mice. However, the opposite findings have been reported on adiponectin-knockout mice in the context of intestinal inflammation. While in the first study, adiponectin-knockout mice developed much more severe colitis compared to wild-type mice, in the second study, adiponectin-knockout mice were protected from chemically induced colitis (Karmiris et al. 2008).

The effects of adiponectin in joint inflammation such as RA and OA are controversial (Fig. 2). In RA patients, circulating adiponectin levels were significantly increased compared to healthy controls (Senolt et al. 2006; Otero et al. 2006), but synovial fluid adiponectin negatively correlated with synovial fluid leukocyte count (Senolt et al. 2006). However, examination of synovium and articular adipose tissue revealed strong expression of adiponectin, AdioR1 and AdipoR2 especially in activated synovial fibroblasts in both RA and OA patients. In addition, adiponectin has been shown to activate inflammatory process and matrix degradation in the human joints inducing IL-6 and matrix metalloproteinase-1 (MMP-1) via the p38 MAPK pathway in both arthritides (Ehling et al. 2006). Moreover, adiponectin also activated IL-8 production in rheumatoid synovial fibroblasts (Kitahara et al. 2009). Recently, there has been also growing evidence that adiponectin may play a destructive role in cartilage homeostasis inducing NOS2, IL-6, MMP-3, MMP-9, and monocyte chemoattractant protein 1 (MCP-1) in chondrocytes. The striking finding was also observation that human and murine chondrocytes express functional adiponectin receptors (Lago et al. 2008). In contrast to above mentioned detrimental activity of adiponectin, there have also been reported some beneficial properties of adiponectin on cartilage homeostasis in OA. In osteoarthritic chondrocytes, adiponectin has up-regulated tissue inhibitor of metalloproteinase-2 (TIMP-2), and down-regulated IL-1β-induced MMP-13 (Chen et al. 2006). Additionally, adiponectin was able to reduce TNF-α, IL-1β, and MMP-3 expressions in stimulated RA synovial fibroblasts (Lee et al. 2008).

Potential anti-inflammatory effects of adiponectin have been shown in mouse model of RA, collagen-induced arthritis (CIA), where adiponectin delivery significantly reduced the severity of the disease including decreasing histological scores of inflammation, cartilage damage, bone erosion, and mRNA levels of pro-inflam-

matory cytokines (Lee et al. 2008; Ebina et al. 2009). In rat AA, different groups of authors consistently reported decreased circulating adiponectin and its protein levels as well as mRNA expression in WAT compared to controls. The suppressed WAT adiponectin production can be due to the inflammatory response, since WAT produces enhanced levels of TNF-α, which negatively regulates adiponectin concentrations during AA (Haruna et al. 2007; Martin et al. 2008; Stofkova et al. 2009).

Taken together, the question whether adiponectin is protective or detrimental adipokine in inflammatory and autoimmune diseases is still a matter of debate and further studies are needed to fully elucidate its role in these pathological processes.

Acknowledgements

This work was supported by VZ 00216 208 16.

References

Anders HJ, Rihl M, Heufelder A, Loch O, Schattenkirchner M: Leptin serum levels are not correlated with disease activity in patients with rheumatoid arthritis. Metabolism 48, 745-748, 1999 doi:10.1016/S0026-0495(99)90174-9

Anderson PD, Mehta NN, Wolfe ML, Hinkle CC, Pruscino L, Comiskey LL, Tabita-Martinez J, Sellers KF, Rickels MR, Ahima RS, Reilly MP: Innate immunity modulates adipokines in humans. J Clin Endocrinol Metab 92, 2272-2279, 2007 doi:10.1210/jc.2006-2545

Araki H, Nishihara T, Matsuda M, Fukuhara A, Kihara S, Funahashi T, Kataoka TR, Kamada Y, Kiyohara T, Tamura S, Hayashi N, Shimomura I: Adiponectin plays a protective role in caerulein-induced acute pancreatitis in mice fed a high-fat diet. Gut 57, 1431-1440, 2008 doi:10.1136/gut.2007.135665

Bodosi B, Gardi J, Hajdu I, Szentirmai E, Obal F Jr., Krueger JM: Rhythms of ghrelin, leptin, and sleep in rats: effects of the normal diurnal cycle, restricted feeding, and sleep deprivation. Am J Physiol Regul Integr Comp Physiol 287, R1071-R1079, 2004 doi:10.1152/ajpregu.00294.2004

Bruun JM, Pedersen SB, Kristensen K, Richelsen B: Effects of pro-inflammatory cytokines and chemokines on leptin production in human adipose tissue in vitro. Mol Cell Endocrinol 190, 91-99, 2002 doi:10.1016/S0303-7207(02)00007-2

Bokarewa M, Bokarew D, Hultgren O, Tarkowski A: Leptin consumption in the inflamed joints of patients with rheumatoid arthritis. Ann Rheum Dis 62, 952-956, 2003 doi:10.1136/ard.62.10.952

Ceddia RB, Somwar R, Maida A, Fang X, Bikopoulos G, Sweeney G: Globular adiponectin increases GLUT4 translocation and glucose uptake but reduces glycogen synthesis in rat skeletal muscle cells. Diabetologia 48, 132-139, 2005 doi:10.1007/s00125-004-1609-y

Chandra RK: Cell-mediated immunity in nutritional imbalance. Fed Proc 39, 3088-3092, 1980

Chen TH, Chen L, Hsieh MS, Chang CP, Chou DT, Tsai SH: Evidence for a protective role for adiponectin in osteoarthritis. Biochim Biophys Acta 1762, 711-718, 2006

Coope A, Milanski M, Araujo EP, Tambascia M, Saad MJ, Geloneze B, Velloso L: AdipoR1 mediates the anorexigenic and insulin/leptin-like actions of adiponectin in the hypothalamus. FEBS Letters 582, 1471-1476, 2008 doi:10.1016/j.febslet.2008.03.037

De Rosa V, Procaccini C, Cali G, Pirozzi G, Fontana S, Zappacosta S, La Cava A, Matarese G: A key role of leptin in the control of regulatory T cell proliferation. Immunity 26, 241-255, 2007 doi:10.1016/j.immuni.2007.01.011

Dumond H, Presle N, Terlain B, Mainard D, Loeuille D, Netter P, Pottie P: Evidence for a key role of leptin in osteoarthritis. Arthritis Rheum 48, 3118-31129, 2003 doi:10.1002/art.11303

Ebina K, Oshima K, Matsuda M, Fukuhara A, Maeda K, Kihara S, Hashimoto J, Ochi T, Banda NK, Yoshikawa H, Shimomura I: Adenovirus-mediated gene transfer of adiponectin reduces the severity of collagen-induced arthritis in mice. Biochem Biophys Res Commun 378, 186-91, 2009 doi:10.1016/j.bbrc.2008.11.005

Ehling A, Schaffler A, Herfarth H, Tarner IH, Anders S, Distler O, Paul G, Distler J, Gay S, Scholmerich J, Neumann E, Muller-Ladner U: The potential of adiponectin in driving arthritis. J Immunol 176, 4468-4478, 2006

Faggioni R, Fantuzzi G, Gabay C, Moser A, Dinarello CA, Feingold KR, Grunfeld C: Leptin deficiency enhances sensitivity to endotoxin-induced lethality. Am J Physiol 276, R136-R142, 1999

Fain JN, Buehrer B, Tichansky DS, Madan AK: Regulation of adiponectin release and demonstration of adiponectin mRNA as well as release by the non-fat cells of human omental adipose tissue. Int J Obes (Lond) 32, 429-435, 2008 doi:10.1038/sj.ijo.0803745

Fantuzzi G: Adiponectin and inflammation: consensus and controversy. J Allergy Clin Immunol 121, 326-330, 2008 doi:10.1016/j.jaci.2007.10.018

Figenschau Y, Knutsen G, Shahazeydi S, Johansen O, Sveinbjornsson B: Human articular chondrocytes express functional leptin receptors. Biochem Biophys Res Commun 287, 190-197, 2001 doi:10.1006/bbrc.2001.5543

Fraser DA, Thoen J, Reseland JE, Forre O, Kjeldsen-Kragh J: Decreased CD4+ lymphocyte activation and increased interleukin-4 production in peripheral blood of rheumatoid arthritis patients after acute starvation. Clin Rheumatol 18, 394-401, 1999 doi:10.1007/s100670050125

Fried SK, Ricci MR, Russell CD, Laferrere B: Regulation of leptin production in humans. J Nutr 130, 3127S-3131S, 2000

Fu Y, Luo N, Klein RL, Garvey WT: Adiponectin promotes adipocyte differentiation, insulin sensitivity, and lipid accumulation. J Lipid Res 46, 1369-1379, 2005 doi:10.1194/jlr.M400373-JLR200

Gabay C, Dreyer M, Pellegrinelli N, Chicheportiche R, Meier CA: Leptin directly induces the secretion of interleukin 1 receptor antagonist in human monocytes. J Clin Endocrinol Metab 86, 783-791, 2001 doi:10.1210/jc.86.2.783

Gamba M, Pralong FP: Control of GnRH neuronal activity by metabolic factors: The role of leptin and insulin. Mol Cell Endocrinol 254-255, 133-139, 2006 doi:10.1016/j.mce.2006.04.023

Granado M, Priego T, Martin AI, Villanua MA, Lopez-Calderon A: Anti-inflammatory effect of the ghrelin agonist growth hormone-releasing peptide-2 (GHRP-2) in arthritic rats. Am J Physiol Endocrinol Metab 288, E486-492, 2005 doi:10.1152/ajpendo.00196.2004

Grunfeld C, Zhao C, Fuller J, Pollack A, Moser A, Friedman J, Feingold KR:Endotoxin and cytokines induce expression of leptin, the ob gene product, in hamsters. J Clin Invest 97, 2152-2157, 1996 doi:10.1172/JCI118653

Gualillo O, Eiras S, Lago F, Dieguez C, Casanueva FF: Elevated serum leptin concentrations induced by experimental acute inflammation. Life Sci 67, 2433-2441, 2000 doi:10.1016/S0024-3205(00)00827-4

Gunaydin R, Kaya T, Atay A, Olmez N, Hur A, Koseoglu M: Serum leptin levels in rheumatoid arthritis and relationship with disease activity. South Med J 99, 1078-1083, 2006

Haruna Y, Morita Y, Yada T, Satoh M, Fox DA, Kashihara N: Fluvastatin reverses endothelial dysfunction and increased vascular oxidative stress in rat adjuvant-induced arthritis. Arthritis Rheum 56, 1827-1835, 2007 doi:10.1002/art.22632

Heldin CH: Dimerization of cell surface receptors in signal transduction. Cell 80, 213-223, 1995 doi:10.1016/0092-8674(95)90404-2

Hizmetli S, Kisa M, Gokalp N, Bakici MZ: Are plasma and synovial fluid leptin levels correlated with disease activity in rheumatoid arthritis? Rheumatol Int 27, 335-338, 2007 doi:10.1007/s00296-006-0264-7

Houseknecht KL, Baile CA, Matteri RL, Spurlock ME: The biology of leptin: a review. J Anim Sci 76, 1405-1420, 1998

Howard JK, Lord GM, Matarese G, Vendetti S, Ghatei MA, Ritter MA, Lechler RI, Bloom SR: Leptin protects mice from starvation-induced lymphoid atrophy and increases thymic cellularity in ob/ob mice. J Clin Invest 104, 1051-1059, 1999 doi:10.1172/JCI6762

Hu E, Liang P, Spiegelman BM: AdipoQ is a novel adipose-specific gene dysregulated in obesity. J Biol Chem 271, 10697–10703, 1996 doi:10.1074/jbc.271.18.10697

Inadera H: The usefulness of circulating adipokine levels for the assessment of obesity-related health problems. Int J Med Sci 5, 248-262, 2008

Jaworek J, Bonior J, Pierzchalski P, Tomaszewska R, Stachura J, Sendur R, Leja A, Jachimczak B, Konturek PC, Bielański W, Pawlik W, Konturek SJ: Leptin protects the pancreas from damage induced by caerulein overstimulation by modulating cytokine production. Pancreatology 2, 89-99, 2002 doi:10.1159/000055897

Jurcovicova J, Stancikova M, Svik K, Ondrejickova O, Krsova D, Seres J, Rokyta R: Stress of chronic food restriction attenuates the development of adjuvant arthritis in male Long Evans rats. Clin Exp Rheum 19, 371-376, 2001

Kadowaki T, Yamauchi T: Adiponectin and adiponectin receptors. Endocr Rev 26, 439-451, 2005 doi:10.1210/er.2005-0005

Karmiris K, Koutroubakis IE, Kouroumalis EA: Leptin, adiponectin, resistin, and ghrelin implications for inflammatory bowel disease. Mol Nutr Food Res 52, 855-866, 2008 doi:10.1002/mnfr.200700050

Keller P, Moller K, Krabbe KS, Pedersen BK: Circulating adiponectin levels during human endotoxaemia. Clin Exp Immunol 134, 107-110, 2003 doi:10.1046/j.1365-2249.2003.02264.x

Kim KY, Kim JK, Han SH, Lim JS, Kim KI, Cho DH, Lee MS, Lee JH, Yoon DY, Yoon SR, Chung JW, Choi I, Kim E, Yang Y: Adiponectin is a negative regulator of NK cell cytotoxicity. J Immunol 176, 5958-5964, 2006

Kitahara K, Kusunoki N, Kakiuchi T, Suguro T, Kawai S: Adiponectin stimulates IL-8 production by rheumatoid synovial fibroblasts. Biochem Biophys Res Commun 378, 218-223, 2009 doi:10.1016/j.bbrc.2008.11.017

Kjeldsen-Kragh J: Rheumatoid arthritis treated with vegetarian diets. Am J Clin Nutr 71, 1211-1213, 1999

Kubota N, Terauchi Y, Yamauchi T, Kubota T, Moroi M, Matsui J, Eto K, Yamashita T, Kamon J, Satoh H, Yano W, Froguel P, Nagai R, Kimura S, Kadowaki T, Noda T: Disruption of adiponectin causes insulin resistance and neointimal formation. J Biol Chem 277, 25863-25866, 2002 doi:10.1074/jbc.C200251200

Kubota N, Yano W, Kubota T, Yamauchi T, Kumagai H, Kozono H, Takamoto I, Okamoto S, Shiuchi T, Suzuki R, Satoh H, Tsuchida A, Moroi M, Sugi K, Noda T, Ebinuma H, Ueta Y, Kondo T, Araki E, Ezaki O, Nagai R, Tobe K, Terauchi Y, Ueki K, Minokoshi Y, Kadowaki T: Adiponectin stimulates AMP-activated protein kinase in the hypothalamus and increases food intake. Cell Metab 6, 55-68, 2007 doi:10.1016/j.cmet.2007.06.003

La Cava A, Matarese G: The weight of leptin in immunity. Nat Rev Immunol 4, 371-379, 2004 doi:10.1038/nri1350

Lago R, Gomez R, Otero M, Lago F, Gallego R, Dieguez C, Gomez-Reino JJ, Gualillo O: A new player in cartilage homeostasis: adiponectin induces nitric oxide synthase type II and pro-inflammatory cytokines in chondrocytes. Osteoarthritis Cartilage 16, 1101-1109, 2008 doi:10.1016/j.joca.2007.12.008

Lee SW, Park MC, Park YB, Lee SK: Measurement of the serum leptin level could assist disease activity monitoring in rheumatoid arthritis. Rheumatol Int 27, 537-540, 2007 doi:10.1007/s00296-006-0253-x

Lee SW, Kim JH, Park MC, Park YB, Lee SK: Adiponectin mitigates the severity of arthritis in mice with collagen-induced arthritis. Scand J Rheumatol 37, 260-268, 2008 doi:10.1080/03009740801910346

Li R, Wang WQ, Zhang H, Yang X, Fan Q, Christopher TA, Lopez BL, Tao L, Goldstein BJ, Gao F, Ma XL: Adiponectin improves endothelial function in hyperlipidemic rats by reducing oxidative/nitrative stress and differential regulation of eNOS/iNOS activity. Am J Physiol Endocrinol Metab 293, E1703-E1708, 2007 doi:10.1152/ajpendo.00462.2007

Loffreda S, Yang SQ, Lin HZ, Karp CL, Brengman ML, Wang DJ, Klein AS, Bulkley GB, Bao C, Noble PW, Lane MD, Diehl AM: Leptin regulates proinflammatory immune responses. FASEB 12, 57-65, 1998

Lord GM, Matarese G, Howard JK, Baker RJ, Bloom SR, Lechler RI: Leptin modulates the T-cell immune responses and reverses starvation-induced immunosuppression. Nature 394, 897-901, 1998 doi:10.1038/29795

Ma K, Cabrero A, Saha PK, Kojima H, Li L, Chang BH, Paul A, Chan L: Increased beta -oxidation but no insulin resistance or glucose intolerance in mice lacking adiponectin. J Biol Chem 277, 34658-34661, 2002 doi:10.1074/jbc.C200362200

Maeda K, Okubo K, Shimomura I, Funahashi T, Matsuzawa Y, Matsubara K: cDNA cloning and expression of a novel adipose specific collagen-like factor, apM1 (AdiPose Most abundant Gene transcript 1). Biochem Biophys Res Commun 221, 286-289, 1996 doi:10.1006/bbrc.1996.0587

Maeda N, Shimomura I, Kishida K, Nishizawa H, Matsuda M, Nagaretani H, Furuyama N, Kondo H, Takahashi M, Arita Y, Komuro R, Ouchi N, Kihara S, Tochino Y, Okutomi K, Horie M, Takeda S, Aoyama T, Funahashi T, Matsuzawa Y: Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. Nat Med 8, 731-737, 2002 doi:10.1038/nm724

Meade CJ, Sheena J, Mertin J: Effects of the obese (ob/ob) genotype on spleen cell immune function. Int Arch Allergy Appl Immunol 58, 121-127, 1979 doi:10.1159/000232183

Martin AI, Castillero E, Granado M, Lopez-Menduina M, Villanúa MA, Lopez-Calderon A: Adipose tissue loss in adjuvant arthritis is associated with a decrease in lipogenesis, but not with an increase in lipolysis. J Endocrinol 197, 111-119, 2008 doi:10.1677/JOE-07-0491

Matarese G, Di Giacomo A, Sanna V, Lord GM, Howard JK, Di Tuoro A, Bloom SR, Lechler RI, Zappacosta S, Fontana S: Requirement for leptin in the induction and progression of autoimmune encephalomyelitis. J Immunol 166, 5909-5916, 2001

Nakano Y, Tobe T, Choi-Miura NH, Mazda T, Tomita M: Isolation and characterization of GBP28, a novel gelatin-binding protein purified from human plasma. J Biochem (Tokyo) 120, 803–812, 1996

Nawrocki AR, Rajala MW, Tomas E, Pajvani UB, Saha AK, Trumbauer ME, Pang Z, Chen AS, Ruderman NB, Chen H, Rossetti L, Scherer PE: Mice lacking adiponectin show decreased hepatic insulin sensitivity and reduced responsiveness to peroxisome proliferator-activated receptor gamma agonists. J Biol Chem 281, 2654-2660, 2006 doi:10.1074/jbc.M505311200

Nishiya K, Nishiyama M, Chang A, Shinto A, Hashimoto K: Serum leptin levels in patients with rheumatoid arthritis are correlated with body mass index. Rinsho Byori 50, 524-527, 2002

Ohashi K, Iwatani H, Kihara S, Nakagawa Y, Komura N, Fujita K, Maeda N, Nishida M, Katsube F, Shimomura I, Ito T, Funahashi T: Exacerbation of albuminuria and renal fibrosis in subtotal renal ablation model of adiponectin-knockout mice. Arterioscler Thromb Vasc Biol 27, 1910-1917, 2007 doi:10.1161/ATVBAHA.107.147645

Okamoto Y, Folco EJ, Minami M, Wara AK, Feinberg MW, Sukhova GK, Colvin RA, Kihara S, Funahashi T, Luster AD, Libby P: Adiponectin inhibits the production of CXC receptor 3 chemokine ligands in macrophages and reduces T-lymphocyte recruitment in atherogenesis. Circ Res 102, 218-225, 2008 doi:10.1161/CIRCRESAHA.107.164988

Otero M, Gomez Reino JJ, Gualillo O: Synergistic induction of nitric oxide synthase type II: in vitro effect of leptin and interferon-gamma in human chondrocytes and ATDC5 chondrogenic cells. Arthritis Rheum 48, 404-409, 2003 doi:10.1002/art.10811

Otero M, Lago R, Lago F, Reino JJ, Gualillo O: Signalling pathway involved in nitric oxide synthase type II activation in chondrocytes: synergistic effect of leptin with interleukin-1. Arthritis Res Ther 7, R581-R591, 2005 doi:10.1186/ar1708

Otero M, Lago R, Gomez R, Lago F, Dieguez C, Gomez-Reino JJ, Gualillo O: Changes in plasma levels of fat-derived hormones adiponectin, leptin, resistin and visfatin in patients with rheumatoid arthritis. Ann Rheum Dis 65, 1198-1201, 2006 doi:10.1136/ard.2005.046540

Ouchi N, Walsh K: Adiponectin as an anti-inflammatory factor. Clin Chim Acta 380, 24-30, 2007 doi:10.1016/j.cca.2007.01.026

Pini M, Sennello JA, Chan L, Fantuzzi G: Adiponectin deficiency does not affect the inflammatory response to endotoxin or concanavalin a in mice. Endocrinology 147, 5019-5022, 2006 doi:10.1210/en.2006-0855

Popa C, Netea MG, Radstake TR, van Riel PL, Barrera P, van der Meer JW: Markers of inflammation are negatively correlated with serum leptin in rheumatoid arthritis. Ann Rheum Dis 64, 1195-1198, 2005 doi:10.1136/ard.2004.032243

Rodriguez L, Graniel J, Ortiz R: Effect of leptin on activation and cytokine synthesis in peripheral blood lymphocytes of malnourished infected children. Clin Exp Immunol 148, 478-485, 2007

Sanna V, Di Giacomo A, La Cava A, Lechler RI, Fontana S, Zappacosta S, Matarese G: Leptin surge precedes onset of autoimmune encephalomyelitis and correlates with development of pathogenic T cell responses. J Clin Invest 111, 241-250, 2003

Santos-Alvarez J, Goberna R, Sanchez-Margalet V: Human leptin stimulates proliferation and activation of human circulating monocytes. Cell Immunol 194, 6-11, 1999 doi:10.1006/cimm.1999.1490

Sarraf P, Frederich RC, Turner EM, Ma G, Jaskowiak NT, Rivet DJ 3rd, Flier JS, Lowell BB, Fraker DL, Alexander HR: Multiple cytokines and acute inflammation raise mouse leptin levels: potential role in inflammatory anorexia. J Exp Med 185, 171-175, 1997 doi:10.1084/jem.185.1.171

Sato T, Laviano A, Meguid MM, Chen C, Rossi-Fanelli F, Hatakeyama K: Involvement of plasma leptin, insulin and free tryptophan in cytokine-induced anorexia. Clin Nutr 22, 139-146, 2003 doi:10.1054/clnu.2002.0609

Scherer PE, Williams S, Fogliano M, Baldini G, Lodish HF: A novel serum protein similar to C1q, produced exclusively in adipocytes. J Biol Chem 270, 26746–26749, 1995 doi:10.1074/jbc.270.45.26746

Schoeller DA, Cella LK, Sinha MK, Caro JF: Entrainment of the diurnal rhythm of plasma leptin to meal timing. J Clin Invest 100, 1882-1887, 1997 doi:10.1172/JCI119717

Schwartz MW, Woods SC, Porte D Jr, Seeley RJ, Baskin DG: Central nervous system control of food intake. Nature 404, 661-671, 2000

Senolt L, Pavelka K, Housa D, Haluzik M: Increased adiponectin is negatively linked to the local inflammatory process in patients with rheumatoid arthritis. Cytokine 35, 247-252, 2006 doi:10.1016/j.cyto.2006.09.002

Stofkova A, Skurlova M, Tybitanclova K, Veselsky L, Zelezna B, Jurcovicova J: Relationship among nitric oxide, leptin, ACTH, corticosterone, and IL-1 , in the early and late phases of adjuvant arthritis in male Long Evans rats. Life Sci 79, 2486-2491, 2006 doi:10.1016/j.lfs.2006.08.015

Stofkova A, Haluzik M, Zelezna B, Kiss A, Skurlova M, Lacinova Z, Jurcovicova J: Enhanced expressions of mRNA for neuropeptide-Y and IL-1 beta in hypothalamic arcuate nuclei during adjuvant arthritis-induced anorexia in Lewis rats. Neuroimmunomodulation 16, 377-384, 2009 doi:10.1159/000228912

Takahashi N, Waelput W, Guisez Y: Leptin is an endogenous protective protein against the toxicity exerted by tumor necrosis factor. J Exp Med 1, 207-212, 1999 doi:10.1084/jem.189.1.207

Targonska-Stepniak B, Majdan M, Dryglewska M: Leptin serum levels in rheumatoid arthritis patients: relation to disease duration and activity. Rheumatol Int 28, 585-591, 2008 doi:10.1007/s00296-007-0480-9

Tartaglia LA, Dembski M, Weng X, Deng N, Culpepper J, Devos R, Richards GJ, Campfield LA, Clark FT, Deeds J, Muir C, Sanker S, Moriarty A, Moore KJ, Smutko JS, Mays GG, Wool EA, Monroe CA, Tepper RI: Identification and expression cloning of a leptin receptor, OB-R. Cell 83, 1263-1271, 1995 doi:10.1016/0092-8674(95)90151-5

Tilg H, Moschen AR: Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol 6, 772-783, 2006 doi:10.1038/nri1937

Tokarczyk-Knapik A, Nowicki M, Wyroslak J: The relation between plasma leptin concentration and body fat mass in patients with rheumatoid arthritis. Pol Arch Med Wewn 108, 761-767, 2002

Tong KM, Shieh DC, Chen CP, Tzeng CY, Wang SP, Huang KC, Chiu YC, Fong YC, Tang CH: Leptin induces IL-8 expression via leptin receptor, IRS-1, PI3K, Akt cascade and promotion of NF-kappaB/p300 binding in human synovial fibroblasts. Cell Signal 20, 1478-1488, 2008 doi:10.1016/j.cellsig.2008.04.003

Vuolteenaho K, Koskinen A, Kukkonen M, Nieminen R, Päivärinta U, Moilanen T, Moilanen E. Leptin enhances synthesis of proinflammatory mediators in human osteoarthritic cartilage--mediator role of NO in leptin-induced PGE2, IL-6, and IL-8 production. Mediators Inflamm 2009:345838. Epub 2009 Aug 13

Wang MY, Zhou YT, Newgard CB, Unger RH: A novel leptin receptor isoform in rat. FEBS Lett 26, 87-90, 1996 doi:10.1016/0014-5793(96)00790-9

Warzecha Z, Dembinski A, Ceranowicz P, Jaworek J, Konturek PC, Dembinski M, Bilskl J, Konturek SJ: Influence of leptin administration on the course of acute ischemic pancreatitis. J Physiol Pharmacol 53, 775-790, 2002

Webb SR, Loria RM, Madge GE, Kibrick S: Susceptibility of mice to group B coxsackie virus is influenced by the diabetic gene. J Exp Med 143, 1239-1248, 1976 doi:10.1084/jem.143.5.1239

Xiao E, Xia-Zhang L, Vulliémoz NR, Ferin M, Wardlaw SL: Leptin modulates inflammatory cytokine and neuroendocrine responses to endotoxin in the primate. Endocrinology 144, 4350-4353, 2003

Yokota T, Oritani K, Takahashi I, Ishikawa J, Matsuyama A, Ouchi N, Kihara S, Funahashi T, Tenner AJ, Tomiyama Y, Matsuzawa Y: Adiponectin, a new member of the family of soluble defense collagens, negatively regulates the growth of myelomonocytic progenitors and the functions of macrophages. Blood 96, 1723-1732, 2000

Yokota T, Meka CS, Kouro T, Medina KL, Igarashi H, Takahashi M, Oritani K, Funahashi T, Tomiyama Y, Matsuzawa Y, Kincade PW: Adiponectin, a fat cell product, influences the earliest lymphocyte precursors in bone marrow cultures by activation of the cyclooxygenase-prostaglandin pathway in stromal cells. J Immunol 171, 5091-5099, 2003

Zarkesh-Esfahani H, Pockley G, Metcalfe RA, Bidlingmaier M, Wu Z, Ajami A, Weetman AP, Strasburger CJ, Ross RJ: High-dose leptin activates human leukocytes via receptor expression on monocytes. J Immunol 167, 4593-4599, 2001

Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM: Positional cloning of the mouse obese gene and its human homologue. Nature 372, 425-432, 1994 doi:10.1038/372425a0

Zhang F, Basinski MB, Beals JM, Briggs SL, DiMarchi RD, Furman TC, Hale JE, Hsiung HM, Schoner BE, Smith DP, Zhang XY, Wery JP, Schevitz RW: Crystal structure of the obese protein leptin-E 100. Nature 387, 206-209, 1997 doi:10.1038/387206a0