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

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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 diabetess (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
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 (ob/ob) mice in response to Coxsackie 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 (db/db) 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- (Fagginoni 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 (Lava Cav and Materese 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 (Lava Cav and Materese 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 coinoculated 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; Warzech et al. 2002). Moreover, leptin has been also...
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-\(\gamma\) and TNF secretion (LA CA V A and MATA RE SE, 2004). Further effect of leptin involves suppression of CD4+CD25\(^\dagger\) 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 CA V A and MATA RE SE, 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-\(\alpha\), 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-\(\alpha\) 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 (Lava 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 Th1 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 Th2-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 state (Anders et al. 1999; Nishiya et al. 2002; Pova 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 chondrocytes. 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; Keldsen-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 Th2 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+ Th1 cell and decreasing CD4+ Th2 cells activity (Lord et al. 1998; Rodriguez et al. 2007), its reduction during fasting might result in shift towards Th2 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
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 adip/o−/− mice, but only when these mice were placed on 2 weeks high fat diet. In other study, adip/o−/− 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 adip/o−/− 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 (Coote 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 adip/o- 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 et 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...
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-inflamm-
matory cytokines (Lee et al. 2008; Ehina 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.

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