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# RESISTIN AND VISFATIN: REGULATORS OF INSULIN SENSITIVITY, INFLAMMATION AND IMMUNITY

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*

Adipokines play a significant role in the pathogenesis of a low-grade inflammation associated with obesity and metabolic syndrome, and in chronic inflammatory and autoimmune diseases such as rheumatoid arthritis. Among variety of adipokines, resistin and visfatin are proposed as important pro-inflammatory mediators, which also interfere with the central regulation of insulin sensitivity. Resistin has been initially postulated as a risk factor for insulin resistance, however, the subsequent available data on it have revealed contradictory findings in both humans and rodents. On the other hand, visfatin has been suggested to be a beneficial adipokine with insulin-mimicking/-sensitizing effects, but regulation of visfatin production and its physiological importance in the conditions of obesity and type 2 diabetes mellitus are still not completely understood. Despite the opposing effects of resistin and visfatin on the regulation of insulin sensitivity, both adipokines have pro-inflammatory properties. Clinical and experimental studies have shown that the expression and secretion of resistin and visfatin are up-regulated during inflammation and in response to pro-inflammatory cytokines. It has also become increasingly evident that resistin as well as visfatin itself can contribute to the inflammatory processes by triggering cytokine production and NF-kappaB activation. New insight into the role of adipokines makes them attractive targets for novel therapeutic strategies in chronic inflammatory diseases or subclinical inflammation relating to obesity and various metabolic abnormalities.

**Key words:** resistin, visfatin, obesity, insulin resistance, inflammation, autoimmunity, atherosclerosis, arthritis

## Resistin: Production and biological actions

Resistin, also called FIZZ3 (found in inflammatory zone) or ADSF (adipocyte-specific secretory factor), was identified as a 12.5 kDa polypeptide expressed and secreted by white adipose tissue. The term "resistin" was originally proposed for its role as a mediator of insulin resistance (Steppan et al. 2001). Resistin belongs to the family of cysteine-rich proteins, termed RELMs (resistin-like molecules). In its structure, cysteine residues comprise 11 of 94 (12%) amino acids (Banerjee et al. 2001).

Resistin may be involved in sensing the nutritional status as its mRNA level is decreasing during fasting and increasing after food consumption (Kim et al. 2001; Steppan et al. 2001; Nogueiras et al. 2003; Valsamakis et al. 2004). Interestingly, its dramatic induction was found during 3T3-L1 and primary preadipocyte differentiation into adipocytes, and also was found its inhibitory effect on it, suggesting that resistin acts

**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, e-mail: andrea.stofkova@lf3.cuni.cz; Phone: +420 224902718; Fax: +420 224916896.

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as a regulator of adipogenesis (Holcomb et al. 2000; Kim et al. 2001). In addition, resistin gene expression was significantly up-regulated by glucose and mediators known to increase plasma glucose levels such as glucocorticoids (Haugen et al. 2001; Shojima et al. 2002). The role of insulin in the regulation of resistin production has also been investigated, but there are conflicting data from studies. Kim et al. (2001) have shown increased resistin mRNA expression in adipose tissue of streptozotocin-diabetic mice upon insulin administration. On the contrary, other studies demonstrated that insulin administration resulted in suppressed resistin gene expression (Haugen et al. 2001; Shojima et al. 2002; Kawashima et al. 2003; Liu et al. 2008). Furthermore, antidiabetic drugs thiazolidinediones (TZDs), which lower blood glucose by activating the nuclear receptor, peroxisome proliferator-activated receptor γ (PPARγ), have been shown to also modulate resistin expression. However, both down-regulation (Steppan et al. 2001; Haugen et al. 2001; Shojima et al. 2002) and up-regulation (Way et al. 2001; Fukui et al. 2002) of resistin gene expression have been reported after treatment with TZDs. Therefore, the modulation of resistin levels is presumably irrelevant for the antidiabetic effects of TZDs.

The most widely discussed biological effect of resistin has been the regulation of glucose homeostasis and insulin sensitivity. Although some studies confirmed impaired glucose tolerance and insulin action in response to resistin as well as positive correlation of increased circulating resistin levels with hyperinsulinemia and hyperglycemia (Steppan et al. 2001; Rajala et al. 2004), these observations are not without controversy. In various models of rodent obesity associated with impaired insulin sensitivity, there was shown reduced resistin mRNA expression in adipose tissue (Way et al. 2001; Juan et al. 2001; Milan et al. 2002; Fukui et al. 2002, Maebuchi et al. 2003; Haluzik et al. 2006) or in isolated adipocytes (Le Lay et al. 2001). In human studies, resistin circulating levels or gene expression have varied from increased to unchanged in obesity or type 2 diabetes mellitus (Degawa-Yamauchi et al. 2003; Savage et al. 2001; Baranova et al. 2006; Nagaev et al. 2001; Heilbronn et al. 2004; Chen et al. 2006; Anderlova et al. 2007).

According to currently available data, the potential mechanisms of the resistin pro-diabetic effects could involve: (1) inhibition of the intrinsic activity of cell surface glucose transporters (Moon et al. 2003); (2) suppression of GLUT4 translocation (Palanivel et al. 2006) or its gene expression (Fu et al. 2006); (3) induction of inhibitor of insulin signaling, suppressor of cytokine signaling 3 (Steppan et al. 2005; Brown et al. 2007); (4) blockade of insulin signal transduction pathways (Sheng et al. 2008); (5) stimulation of hepatic glucose production probably through decreased activity of AMP-activated protein kinase and increased expression of gluconeogenic enzymes in liver (Banerjee et al. 2004); and (6) activation of free fatty acids release from adipose tissue (Pravenec et al. 2006). Nevertheless, resistin receptor and its downstream signaling pathways have not yet been identified.

Current evidence documents that resistin is also involved in food intake control at the central level. It has been reported that resistin is also expressed in the hypothalamus (Morash et al. 2002) and is able to activate hypothalamic neurons (Brunetti et al. 2004). Further study showed that central administration of resistin resulted in increased number of cells expressing Fos in the arcuate nucleus and promoted short-term satiety in rats (Tovar et al. 2005). Interestingly, anorectic effect of central resistin has been associated with decreased mRNA expression of orexigenic neuropeptides, neuropeptide Y (NPY) and agouti-related peptide (AgRP), and increased mRNA expression of anorexigenic cocaine and amphetamine-regulated transcript (CART) in the arcuate nucleus, as well as inhibition of hypothalamic fatty acid metabolism (Vazquez et al. 2008). These findings demonstrate that resistin could be one of the factors involved in the hypothalamic anorexigenic pathway, similarly like leptin and insulin.

### Resistin in inflammation and autoimmunity

Recent studies showed that resistin can also play a role in inflammation and autoimmunity. While in rodents resistin is predominantly expressed in adipocytes, analyses of resistin gene expression across a wide array of human tissues revealed that peripheral blood mononuclear cells (PBMCs), macrophages and bone marrow cells are a major source of human resistin (Kaser et al. 2003; Patel et al. 2003). Therefore, in humans, resistin may be rather involved in the inflammatory processes than in the modulation of adiposity and glucose homeostasis.

Several studies demonstrated that inflammatory stimuli mediate resistin production. In human PBMCs, pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α, as well as LPS have strongly induced resistin mRNA expression (Kaser et al. 2003). On the other hand,

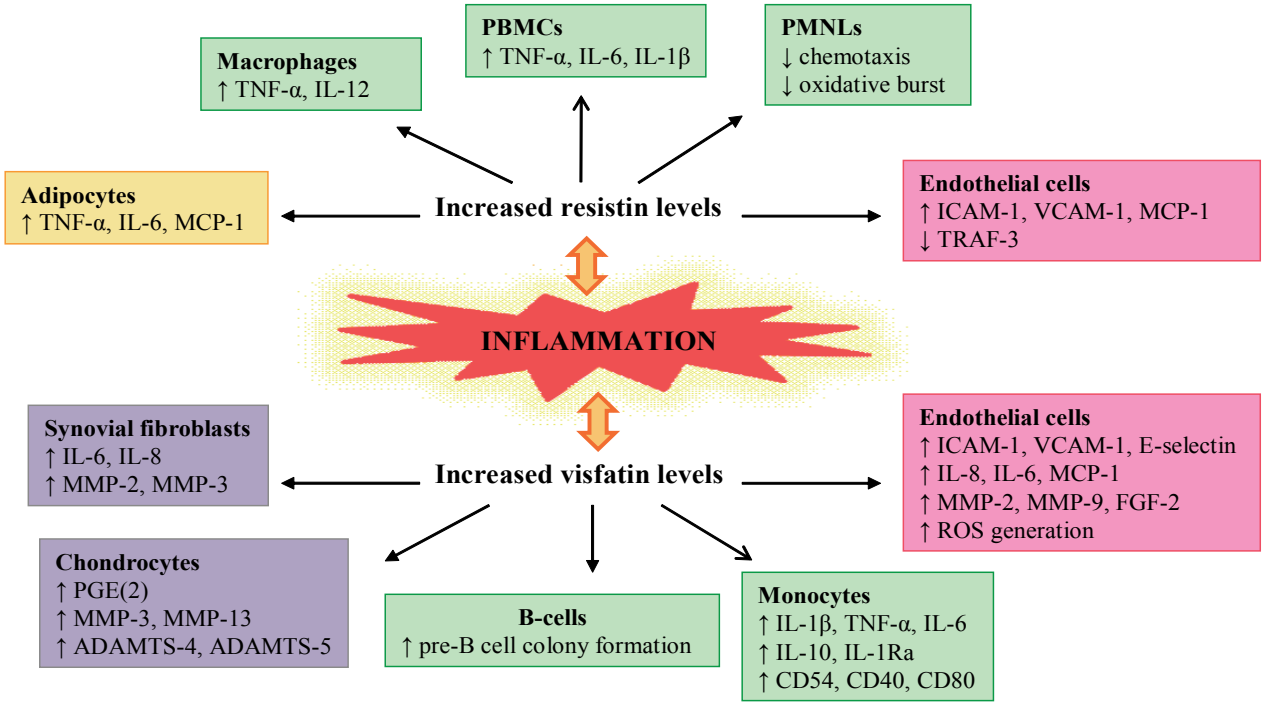


**Figure 1: Involvement of resistin and visfatin in inflammation.**
**Inflammatory stimuli increase resistin and visfatin production. These adipokines act as specific immunomodulatory factors generating pro-inflammatory responses. Resistin stimulates adipocytes, macrophages and peripheral blood mononuclear cells (PBMCs) to produce pro-inflammatory cytokines, and innibits chemotaxis and oxidative burst of activated polymorphonuclear leukocytes (PMNLs). On endothelial cells, resistin induces expression of VCAM-1, ICAM-1 and monocyte chemoattractant protein-1 (MCP-1), and reduces expression of TNF receptor-associated factor-3 (TRAF-3). Visfatin, originally identified as pre-B-cell colony enhancing factor (PBEF), up-regulates the production of pro- and anti-inflammatory cytokines IL-1β, TNF-α, IL-6, IL-10 and IL-1 receptor antagonist (IL-1Ra) in monocytes, and enhances the surface expression of the co-stimulatory molecules CD54, CD40 and CD80 in these cells. In joint inflammation, visfatin exhibits pro-inflammatory and matrix degrading effects by affecting the synthesis of metalloproteinases (MMPs), ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs), and PGE(2) in chondrocytes as well as pro-inflammatory cytokines and MMPs in synovial fibroblasts. Visfatin with its pro-inflammatory effects on endothelial cells may also influence the process of atherosclerosis inducing ICAM-1, VCAM-1, E-selectin, IL-8, IL-6, MCP-1, fibroblast growth factor-2 (FGF-2), and metalloproteinases MMP-2/-9 production as well as ROS (reactive oxygen species) generation.**

in adipocytes and preadipocytes, TNF-α administration significantly decreased resistin mRNA expression (Fasshauer et al. 2001; Li et al. 2003). Interestingly, LPS stimulated resistin mRNA levels in both types of cells, adipocytes and white blood cells in vivo and in vitro (Lu et al. 2002; Lehrke et al. 2004).

Resistin, per se, acts as a pro-inflammatory factor (Fig. 1). In human as well as macrophage culture resistin enhanced secretion of pro-inflammatory cytokines, TNF- α and IL-12, and was able to induce the nuclear translocation of NF-kappaB transcription factor (Silswal et al. 2005). In 3T3-L1 adipocytes resistin potentiated TNF-α, IL-6 and monocyte chemoattractant protein-1 (MCP-1) production (Fu at al. 2006). Moreover, stimulation of human PBMC with recombinant resistin led to a marked up-regulation of the genes for TNF-α, IL-6, IL-1β, and resistin itself, showing that resistin induces a positive feedback mechanism on its own expression (Bokarewa et al. 2005). Resistin also suppressed chemotaxis of human polymorphonuclear leukocytes (PMNLs) and decreased the oxidative burst stimulated by Escherichia coli and by phorbol myristate acetate, but did not affect PMNL phagocytosis (Cohen et al. 2008). In addition, exposure of cultured human hepatic stellate cells to recombinant resistin caused increased expression of MCP-1 and IL-8 through activation of $Ca^{2+}$/NF-

κB dependent pathway (Bertolani et al. 2006). Finally, resistin significantly enhanced hepatic inflammation and necrosis in LPS-induced liver damage in mice. This effect of resistin was presumably mediated via activation of mechanisms involving the coagulation cascade and fibrin accumulation (Beier et al. 2008).

Recent studies indicate that the pathogenesis of atherosclerosis is highly connected with resistin-induced inflammatory process. Resistin has been demonstrated to directly induce expression of VCAM-1, ICAM-1 and MCP-1, and concomitantly reduce TNF receptor-associated factor-3 (TRAF-3) expression on endothelial cells (Verma et al. 2003; Kawanami et al. 2004). Calabro et al. (2004) reported that resistin also activates human aortic smooth muscle cells through both extracellular signal-related kinase 1/2 and Akt signaling pathways. Moreover, resistin promotes macrophage-foam cell formation by affecting class A scavenger receptor, CD 36 and ATP-binding cassette transporter-A1 in macrophages (Lee et al. 2009).

Resistin likely plays an important role in chronic inflammatory and autoimmune diseases. In inflammatory bowel disease, it has been shown that circulating resistin levels were elevated and correlated with white blood cell count, C-reactive protein (CRP) levels and disease activity (Konrad et al. 2007). The increased circulating resistin levels were also observed in patients with chronic pancreatitis suggesting its impact on pancreatic fibrosis development (Adrych et al. 2008). In patients with SLE, similar serum resistin levels to those in controls were reported. However, circulating resistin level was clearly associated with general inflammation, renal disease, treatment with glucocorticoids, and bone loss in SLE patients (Almehed et al. 2008).

There are also data which clearly indicate a pro-inflammatory effect of resistin in pathogenesis of arthritis. Healthy mice injected with recombinant mouse resistin into knee joints developed arthritis and showed infiltration of synovial tissue with leucocytes associated with hypertrophy of synovial lining layer and panus formation (Bokarewa et al. 2005). In human RA, there were revealed increased synovial fluid resistin levels, correlated with elevated resistin expression in synovial sublining layers, abundant accumulation of inflammatory cells or IL-6 synovial fluid levels (Bokarewa et al. 2005; Senolt et al. 2007). However, existing studies differ in results on circulating resistin levels in RA patients. While some studies showed unaltered resistin serum levels in RA patients compared to controls (Bokarewa et al. 2005; Otero et al. 2006; Forsblad d'Elia et al. 2008), Migita et al. (2006) found higher serum resistin levels, correlated with RA disease activity markers, CRP, TNF-α, and erythrocyte sedimentation rate. In rat model of RA, adjuvant arthritis (AA), we observed unchanged circulating resistin levels compared to controls in the clinical phase of the disease (Jurcovicova et al. 2009).

At the joint cartilage level, Lee et al. (2009) have reported direct effect of resistin in stimulation of proteoglycan degradation in mouse cartilage cultures, and in proteoglycan biosynthesis inhibition in human cartilage explants. Furthermore, treatment of mouse cartilage cultures with recombinant resistin induced pro-inflammatory cytokines and PGE(2) production (Lee et al., 2009). With regard to these findings, increased systemic and local cartilage resistin levels during arthritis may enhance joint inflammation.

## Visfatin: Production and biological actions

Visfatin, an adipokine isolated by Fukuhara et al. (2005), corresponds to a protein identified previously as pre-B cell colony-enhancing factor (PBEF), a 52 kDa cytokine expressed and secreted by lymphocytes (Samal et al. 1994). Visfatin is also called NAMPT because of its significant sequence and functional homology with nicotinamide phosphoribosyltransferase (NAmPRTase), an enzyme involved in nicotinamide adenine dinucleotide (NAD) biosynthesis from nicotinamide (Rongvaux et al. 2002). The term "visfatin" was adopted for this protein because of its predominant production in visceral adipose tissue (Fukuhara et al. 2005; Pagano et al. 2006). However this observation was not always confirmed by further studies; e.g. Berndt et al. (2005) reported no differences in visfatin mRNA expression between visceral and subcutaneous adipose tissue in humans.

The biological role of visfatin is not entirely understood, but several studies indicated glucose lowering and insulin-mimicking/-sensitizing effects of visfatin. Mice heterozygous for a target mutation in the visfatin gene had modestly higher levels of plasma glucose (Fukuhara et al. 2005), impaired glucose tolerance and reduced glucose-stimulated insulin secretion relative to control mice (Revollo et al. 2007). Initial studies showed that visfatin exerted insulin-mimetic effects in various insulin-sensitive cell cultures through binding to insulin receptor at a site distinct from insulin and stimulated phosphorylation of insulin receptor, insulin receptor substrate-1 and -2 (IRS-1 and IRS-2), and

downstream signaling kinases: protein kinase B (Akt) and mitogen-activated protein kinase (MAPK). In vitro, visfatin treatment enhanced glucose uptake in 3T3-L1 adipocytes and L6 myocytes, and suppressed glucose release in hepatocytes (Fukuhara et al. 2005). Interestingly, the transfection of visfatin plasmid enhanced plasma visfatin level, improved insulin sensitivity or displayed hypocholesterolemic effects in normal-chow rats and rats on high-fat diet (Qin et al. 2008; Sun et al. 2009). These effects were mediated at least partially through up-regulation of the tyrosine phosphorylation of IRS-1 protein, and the mRNA levels of PPAR-γ and sterol regulatory element-binding proteins 2 (Sun et al. 2009). Insulin-like effects of visfatin have been also described on human osteoblasts where visfatin induced tyrosine phosphorylation of insulin receptor, IRS-1 and IRS-2 (Xie at al. 2007). However, another study described that visfatin does not have insulin-mimetic effects, but rather functions as an extracellular NAD biosynthetic enzyme (NAMPT) critical for glucose-stimulated insulin secretion in pancreatic β-cells (Revollo et al. 2007). Moreover, stimulation of GLUT1 protein expression and migration into cellular membranes has been also described as one of mechanisms of visfatin actions on mesangial cells (Song et al. 2008).

According to above mentioned beneficial effects of visfatin on glucose homeostasis, visfatin has been speculated to provide a compensatory mechanism in response to hyperglycemia in conditions of insulin resistance. The in vitro experiments demonstrated direct effect of glucose on visfatin release from adipocytes that depended on the PI3-kinase/Akt pathway activation (Haider at al. 2006b). However, it seems that visfatin production is regulated by glucose upon time-dependent stimulation since short-time period of glucose elevation, observed at 60 and 120 minute of the oral glucose tolerance test, did not altered circulating visfatin levels in humans (Marcinkowska et al. 2007). Up-regulation of visfatin levels in states of hyperglycaemia for a prolonged period, i.e. in patients with diabetes mellitus, has been observed in several studies (Chen et al. 2006; Hammarstedt et al. 2006; Lopez-Bermejo et al. 2006). However, Berndt et al. (2005) did not found significant correlation of plasma visfatin levels and parameters of insulin sensitivity, including fasting insulin, fasting plasma glucose concentrations, and the glucose infusion rate during the steady state of a euglycemic-hyperinsulinemic clamp independent of percent body fat. There are also conflicting data on visfatin circulating levels in obese humans. Some studies confirmed the increased levels of circulating visfatin (Haider et al. 2006a; Zahorska-Markiewicz et al. 2007; Jin et al. 2008; Davutoglu et al. 2009), but there is also a study which showed reduced plasma visfatin levels in obese subjects (Pagano et al. 2006). Paradoxically, both weight reduction (Haider et al. 2006c; Manco et al. 2007; De Luis et al. 2008; Sheu et al. 2008) as well as overnutrition down-regulated circulating visfatin concentrations in humans (Sun et al. 2007). The controversial findings on visfatin levels, reaching the increased (Fukuhara et al. 2005), unchanged (Kloting and Kloting 2005; Stofkova et al. 2009) or decreased levels (Mercader et al. 2008) during the obesity and metabolic syndrome were also reported in various rat or mouse models of obesity. According to these observations in humans and animals, the regulation of visfatin production under the conditions of obesity and diabetes mellitus is not completely clear and also seems to differ across the species and genetic background.

### Visfatin in inflammation and autoimmunity

Visfatin is not only an adipocyte-specific protein. The expression of visfatin gene was originally found in human peripheral blood lymphocytes, and was termed pre-B cell colony-enhancing factor (PBEF) as it increased the effect of IL-7 and stem-cell factor on pre-B-cell colony formation (Samal et al. 1994).

Visfatin appears to be an important mediator of inflammation (Fig. 1). Moschen et al. (2007) demonstrated that recombinant visfatin induced dose-dependent production of pro-inflammatory IL-1β, TNF-α, and IL-6 as well as anti-inflammatory cytokines like IL-10, and IL-1 receptor antagonist in human monocytes. Moreover, visfatin enhanced the surface expression of the co-stimulatory molecules important to activate T cells, such as CD54 (ICAM-1), CD40 and CD80 in monocytes, and was able to act as a potent chemotactic factor for $CD14^+$ monocytes and $CD19^+$ B cells. In vivo, i.p. injection of recombinant murine visfatin significantly increased circulating IL-6 levels and IL-6 mRNA expression in the small intestine in mice (Moschen et al. 2007). Other study demonstrated that visfatin was also synthesized and released by neutrophils in response to inflammatory stimuli and that it functioned as an inhibitor of apoptosis resulting from variety of inflammatory stimuli. For example, visfatin was expressed at high levels in neutrophils harvest from septic critically ill patients and contributed to prolonged neutrophil survival in clinical sepsis (Jia et al. 2004).

Interestingly, pharmacological inhibition of visfatin reduced the intracellular concentration of NAD in inflammatory cells and circulating TNF-α level during endotoxemia in mice. Thus, visfatin links NAD metabolism to inflammatory cytokine secretion by leukocytes (Busso et al. 2008). In addition, lack of visfatin expression strongly affected the development of both T and B lymphocytes and deteriorated cellular resistance to genotoxic/oxidative stress. These findings indicate that visfatin may confer to cells of the immune system the ability to survive during stressful situations such as inflammation (Rongvaux et al. 2008).

Visfatin with its pro-inflammatory effects could promote the process of atherosclerosis. In vitro, visfatin increased leukocyte adhesion to endothelial cells by induction of the cell adhesion molecules ICAM-1, VCAM-1 and E-selectin, and expression of IL-6 and IL-8 in the conditioned medium of endothelial cells (Kim et al. 2008; Lee et al. 2009). Additionally, visfatin treatment led to ROS (reactive oxygen species) generation (Kim et al. 2008), and activation of a potent angiogenic factors including endothelial fibroblast growth factor-2 (FGF-2) (Bae et al. 2009), and matrix metalloproteinase (MMP) -2 and -9 (Adya et al. 2008) as well as MCP-1 and its putative receptor CCR2 in endothelial cells (Adya et al. 2009). Further data also suggest a potential role of visfatin in plaque destabilization. Visfatin gene expression was markedly enhanced in carotic plaques from symptomatic individuals (Dahl et al. 2007). Importantly, both oxidized low-density lipoprotein and TNF-α increased visfatin expression in THP-1 monocytes (Dahl et al. 2007). On the other hand, visfatin gene expression in adipocytes has been found to be negatively regulated by TNF-α and IL-6 (Kralisch et al. 2005a; Kralisch et al. 2005b; Li et al. 2009).

Notably, several inflammatory conditions including acute lung injury (Ye et al. 2005), chronic obstructive pulmonary disease (Liu et al. 2009), inflammatory bowel disease (Moschen et al. 2007), psoriasis (Koczan et al. 2005) and rheumatoid arthritis (Otero et al. 2006; Matsui et al. 2008) are accompanied by visfatin up-regulation. Significantly higher visfatin gene expression was found in synovial tissue, PBMC and peripheral blood granulocytes (PBG) in patients with RA compared to healthy controls (Matsui et al. 2008). Nowell et al. (2006) described regulation of visfatin production via STAT-3-dependent IL-6 trans-signaling in synovial fibroblasts in RA. Brentano et al. (2007) reported that the TLR-2 ligand bacterial lipoprotein, the TLR-4 ligand LPS, IL-1β, TNF-α, and visfatin itself up-regulated visfatin mRNA in RA synovial fibroblasts. Moreover, visfatin itself activated NF-kappaB and activator protein 1, and induced IL-6, IL-8, MMP-1 and MMP-3 in RA synovial fibroblasts (Brentano et al. 2007). Additionally, visfatin serum and synovial fluid levels positively correlated with the degree of inflammation and clinical disease activity in RA patients (Brentano et al. 2007).

Visfatin may also have a possible inflammatory influence on osteoarthritis (OA). Although visfatin circulating levels were found lower in OA patients than in RA patients (Matsui et al. 2008), visfatin was highly produced in human OA chondrocytes (Gosset et al. 2008). In searching for the functions of visfatin in OA-affected human chondrocytes, Gosset et al. (2008) found that visfatin, similarly like IL-1β, triggers excessive release of PGE(2), due to increase of microsomal PGE synthase 1 and decrease of $NAD^+$-dependent 15-hydroxy-PG dehydrogenase synthesis. In this study, visfatin also stimulated MMP-3 and MMP-13 synthesis and expression of a disintegrin and metalloproteinase (ADAMTS) -4 and -5 that indicated catabolic function of visfatin in chondrocytes (Gosset et al. 2008). The increased visfatin circulating levels were also confirmed in adjuvant arthritic rats (Jurcovicova et al. 2009) and mice with collagen-induced arthritis compared to healthy controls (Busso et al. 2008). Moreover, the severity of arthritis in mice was reduced by a specific inhibitor of NAMPT/visfatin enzymatic function (Busso et al. 2008). Overall, these observations provide the evidence that visfatin could be considered as a pro-inflammatory and destructive mediator in arthritis. Thus, visfatin quantification may serve as a marker of the degree of inflammation and disease activity.

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