The role of resistin as a regulator of inflammation: Implications for various human pathologies

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Abstract

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The role of resistin as a regulator of inflammation: implications for various human pathologies

Mária Filková 1, Martin Haluzík 2, Steffen Gay 3, Ladislav Šenolt 1

1Institute of Rheumatology and Connective Tissue Research Laboratory, Department of Rheumatology and 2Third Department of Medicine of the First Faculty of Medicine, Charles University in Prague, Czech Republic, 3 Center for Experimental Rheumatology, University Hospital Zürich, Zürich, Switzerland

Short title: Resistin in various human pathologies

Corresponding author:
Ladislav Šenolt, M.D., Ph.D.
Institute of Rheumatology
Na Slupi 4
Prague 2, 128 50
Czech Republic
Tel: +420 234 075 232
Fax: +420 224 914 451
Email: seno@revma.cz
Abstract

Resistin was originally described as an adipocyte-secreted peptide that induced insulin resistance in rodents. Increasing evidence indicates its important regulatory roles in various biological processes, including several inflammatory diseases. Further studies have shown that resistin in humans, in contrast to its production by adipocytes in mice, is synthesized predominantly by mononuclear cells both within and outside adipose tissue. Possible roles for resistin in obesity-related subclinical inflammation, atherosclerosis and cardiovascular disease, non-alcoholic fatty liver disease, rheumatic diseases, malignant tumors, asthma, inflammatory bowel disease, and chronic kidney disease have already been demonstrated. In addition, resistin can modulate several molecular pathways involved in metabolic, inflammatory, and autoimmune diseases. In this review, current knowledge about the functions and pathophysiological implications of resistin in different human pathologies is summarized, although there is a significant lack of firm evidence regarding the specific role resistin plays in the “orchestra” of the numerous mediators of inflammation.

Key words: resistin, inflammation, obesity, cancer, molecular pathway
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Introduction

White adipose tissue is an active organ that secretes a large variety of proteins known as adipokines. Adipokines include several cytokines, chemokines, and hormone-like factors that participate in the regulation of physiological and pathological processes such as metabolism, immunity, and inflammation [1, 2]. Resistin, known as adipocyte-secreted factor (ADSF) or found in inflammatory zone 3 (FIZZ3), was discovered in 2001 and was proposed as a potential link between obesity and diabetes [3]. The administration of recombinant resistin to diet-induced and genetically obese mice impaired glucose tolerance. Blocking resistin action improved blood sugar in obese mice but impaired glucose tolerance in healthy ones. Moreover, resistin decreased glucose uptake in skeletal muscle cells, although this effect was independent of insulin signaling pathways [4]. An acute increase in serum resistin in rats has also been shown to result in severe hepatic insulin resistance [5].

The aim of this review was to update the reader on recent findings regarding the roles of resistin in obesity-related, inflammatory, and autoimmune diseases, as well as in cancer.

Structure of resistin

A family of resistin-like molecules (RELMs) has recently been identified. These polypeptides of 105-114 amino acids have three domains: an N-terminal signal sequence, a variable middle portion, and a highly constant C-terminal sequence that determines the signature of the molecule [6, 7]. RELM-α (FIZZ 1) is a secreted protein that is present mainly in adipose tissue and found in the inflammatory zone in murine allergic pulmonary inflammation [8]. RELM-β (FIZZ 2) is secreted only in the gastrointestinal tract from goblet and epithelial cells, and it is markedly expressed in tumors, suggesting a possible role in proliferation [7]. RELM-γ, the most recently discovered member of the RELM family, is found in hematopoietic tissue, indicating cytokine-like functions [9].
Resistin is a 12.5 kDa cysteine-rich protein that consists of 108 amino acids in humans and 114 amino acids in mice, including a 17-amino acid signal peptide, a variable region of 37 amino acids, and a conserved C terminus [7, 10, 11]. The mouse resistin gene is located on chromosome 8, and the human resistin gene is on chromosome 19. The mouse and human resistins share 46.7% similarity at the genomic DNA level, 64.4% sequence homology at the mRNA level, and 59% identity at the amino acid level [10]. Its protomer contains a disulfide-rich beta-sandwich “head” domain at the C terminus that is linked to a helical “tail” region at the N terminus. The head contains two three-stranded all-antiparallel sheets. The globular domain of resistin contains five disulfide bonds that are topologically conserved in the RELM structure. Three protomers associate through the formation of a parallel coiled coil. These trimers are further interlinked to form tail-tail hexamers, linking each protomer from one trimer to a protomer from the associated trimer and forming a short antiparallel six-helix bundle. The nature of this interface suggests that the hexamer association would be unstable. Mouse resistin exists predominantly as an α-helical form [12]. In the mouse, resistin circulates in two forms: a high-molecular weight (HMW) form that is identical to the disulfide-linked hexamer and a low-molecular weight (LMW) form that represents a smaller trimer complex that is unable to form intertrimer disulfide bonds [13]. The LMW monomeric form in mice is considered to be more bioactive and potent in terms of hepatic insulin action impairment. Indeed, resistin may have to be processed to the LMW form before it can exert its activity. In contrast to the liver, the biological action of resistin in the cardiac muscle of mice requires oligomerization [14]. Human resistin shows a concentration-dependent reversible conformational shift to the β-sheet form that may regulate its function and distinct physiological properties [15]. It circulates as an oligomer with a molecular mass >660 kDa and a trimer of 45 kDa [16]. Human resistin has a tendency to form oligomers that are, in contrast to mice, biologically
more active [15, 16, 17]. However, both the oligomeric and dimeric forms of resistin are able to activate tumor necrosis factor (TNF)-α and interleukin (IL)-12 in macrophages and monocytes [18]. The main differences between the mouse and human resistins are highlighted in Table 1. It is possible that the structural conformation of resistin may be involved in maintaining the very fine balance of various pathological conditions [15].

**Sites of resistin production**

Although murine and human resistin share more than 50% identity at the amino acid level, their expression patterns are different [19]. In mice, resistin is almost exclusively expressed in white adipose tissue in proportion to adipocyte differentiation and the amount of adipose tissue [3]. It has also been found in the pituitary gland, the hypothalamus, and in the blood circulation [20]. Resistin in rats is secreted not only by adipose tissue, but has also been found in the gastrointestinal tract, adrenal glands, skeletal muscles, pancreas, and spleen [21, 22, 23]. In contrast to mice, only a low level of expression of resistin has been found in mature adipocytes in humans [24-27]. In humans, resistin is highly expressed in the bone marrow compared to other tissues [28], but it is also present in trophoblastic cells of placenta, pancreas, primary cell leukemia, synovial fluid, synovial tissue, and circulating blood [22, 24, 28-34]. The particular cells that express resistin in white adipose tissue are monocytes and macrophages [26, 28, 35]. Based on these data, the presence of resistin in human adipose tissue is mostly due to its production by the non-fat stroma-vascular fraction of adipose tissue.

**The role of resistin in inflammation and signaling pathways**

Although resistin was first postulated to contribute to insulin resistance, it has recently been shown that resistin can trigger a proinflammatory state “in vitro” as well as “in vivo” [36].
Despite the numerous recent studies concerning resistin pathophysiology, little is known about how resistin acts in the process of inflammation.

The expression of resistin is up-regulated during monocyte-macrophage differentiation, indicating a role for resistin in monocyte-macrophage function [26, 28]. It has been demonstrated that proinflammatory mediators such as TNF-α, IL-1β, IL-6, or lipopolysaccharide (LPS) can strongly increase the expression of resistin in peripheral blood mononuclear cells (PBMCs), suggesting a role for resistin in the process of inflammation [36-39]. In addition, C-reactive protein (CRP) induced both mRNA expression and protein secretion of resistin in a dose- and time-dependent manner in PBMCs [40].

Silswal et al. incubated both human and mouse macrophages with human recombinant resistin and found increased production of the proinflammatory cytokines TNF-α and IL-12. As the authors showed, this induction was mediated through the transcription factor NF-κB [17]. Resistin induced dose-dependent NF-κB activity in PBMCs, which resulted in the translocation of both the p65 and p50 subunits of NF-κB from the cytoplasm to the nucleus [36]. This effect may occur through resistin-mediated phosphorylation of the inhibitory protein IκBα and the p65 subunit of NF-κB [40]. Resistin increased the cytosolic calcium concentration via an influx of calcium from the extracellular environment and activation of phospholipase C (PLC), leading to the release of calcium from intracellular pools [41].

Resistin is minimally expressed in human primary adipocytes, but these may be target cells for resistin. Nagaev and coworkers demonstrated that, similar to its actions in PBMCs, resistin could induce the expression of the proinflammatory cytokines IL-6, IL-8, and TNF-α by white adipose tissue in vitro [42]. Resistin targets human adipocytes and, similar to TNF-α, enhances inflammatory processes in adipose tissues. In contrast to TNF-α, resistin does not induce the suppression of adipose-specific markers (CEBPA, FABP4, and SLC2A4). This suggests that resistin's intracellular signaling pathway is distinct from that of TNF-α, even
though both activate NF-κB. Recombinant human resistin is also capable of increasing the production of the proinflammatory cytokines IL-8 and monocyte chemoattractant protein (MCP)-1 via the activation of NF-κB [42]. Both mitogen-activated protein kinases (MAPKs), such as Erk or p38, and Akt, as a downstream substrate of phosphatidylinositol 3-kinase (PI3K), can be phosphorylated by resistin in several cell lines [41, 43-45]. The intracellular signaling pathways of resistin are shown in Figure 1. In a human study, experimental endotoxemia caused a hyperresistinemic state [42]. In light of this, cytokines have been proposed to increase the levels of resistin, which may contribute to insulin resistance in obesity and several other inflammatory disorders [38, 46-54]. Potential roles for resistin in obesity, inflammatory, and other related diseases are shown in Figure 2.

Resistin, at least in humans, shares several features with proinflammatory cytokines and can play a role in the regulation of inflammation and immunity [52].

**Resistin, obesity, and markers of insulin resistance**

Resistin has been shown to be increased in the mouse models of genetic and diet-induced obesity. The administration of resistin to healthy mice impaired glucose tolerance as well as insulin action, and antibody against resistin improved blood sugar and insulin action [3]. The mechanism of how resistin modulates glucose homeostasis is of great interest. Type 2 diabetes mellitus is characterized by a progressive loss of beta-cell function. Resistin has recently been shown to induce beta-cell apoptosis in rat insulinoma. Beta-cell apoptosis induced by adipokines may thus result in beta-cell dysfunction in type 2 diabetes [55].

In 3T3-L1 adipocytes, resistin influences neither insulin binding nor the absolute levels of insulin receptor. However, it attenuates the insulin-signaling pathway upon decreased insulin-dependent phosphorylation of the insulin receptor and subsequent reduction of downstream
signals [56]. Suppressor of cytokine signaling (SOCS) proteins are well known inhibitors of insulin signaling. In adipocytes, resistin activates SOCS3 in a time- and dose-dependent manner and induces the association of SOCS3 with the insulin receptor. It is possible that SOCS3 could be a cellular mediator of the ability of resistin to antagonize insulin action in adipocytes [56].

In rat skeletal muscles, resistin inhibits insulin-stimulated glycogen synthesis and glucose uptake [4, 57]. Resistin alters neither the insulin receptor content nor its phosphorylation. Decreased glucose uptake is also independent of GLUT4 translocation from intracellular pools to the cell membrane. The inhibitory effect of resistin on glycogen synthesis may be due to a reduction in the intrinsic activity of glucose transporters [57].

Resistin also exerts its glucoregulatory effect by stimulating hepatic glucose output [5, 58, 59, 60]. Resistin decreased insulin receptor and glycogen synthase activity and increased the activity of glycogen phosphorylase at the protein level but not the mRNA level [60]. This results in lower glycogen content in the liver due to attenuated glycogenesis and enhanced glycogenolysis [60]. Recently, a hypothalamus-mediated effect of resistin on hepatic glucose homeostasis was demonstrated. The central administration of recombinant resistin impaired the inhibitory action of insulin on hepatic glycogenolysis but did not alter the hepatic expression of the key gluconeogenic enzymes [61].

Transcription factors implicated in adipogenesis include C/EBP family members and the peroxisome proliferator activated receptor γ (PPARγ), which is the main regulator. Resistin expression was enhanced by the overexpression of C/EBPα and reduced by the overexpression of PPARγ [62]. It has been shown that the mouse resistin promoter contains a C/EBPα binding site, and this binding is accompanied by a higher acetylation of histones at the resistin promoter. Moreover, PPARγ ligands reduced histone acetylation without inducing a change in C/EBPα recruitment [63].
Thus, resistin exerts its potent metabolic actions on the liver, skeletal muscles, and adipocytes through peripheral and central mechanisms. Considering this and the effect of PPARγ activation, resistin could become a target for anti-diabetic agents.

An obesity-related inflammatory state is linked to the increased risk of developing cardiovascular diseases and type 2 diabetes mellitus [64]. Immune cells infiltrating fat create a milieu that perpetuates inflammation within the adipose tissue and stimulates the adipocytes themselves to produce inflammatory mediators, including adipokines, completing a vicious circle of inflammation related to obesity [65-68].

Large fat cells and increased ectopic deposition of fat with increased intramyocellular lipids are postulated to be predictors of the development of type 2 diabetes [,69, 70]. However, it has been shown that neither fat cell size nor percent body fat is related to serum resistin [71]. There is either no difference in serum resistin levels among non-obese, obese and obese diabetic groups, despite wide variations in insulin sensitivity, or resistin is increased in obese subjects. Similarly, resistin is not a significant predictor of insulin resistance when adjusted for adiposity [71, 72]. These results suggest that resistin is neither related to adiposity nor associated with increased intramyocellular or intrahepatic lipid contents. In agreement with this, other studies have revealed no correlations between adiposity, body weight, and other metabolic parameters, including insulin sensitivity and resistin mRNA expression in isolated adipocytes [26, 27]. Resistin expression in adipose tissue from morbidly obese patients is significantly higher compared to lean subjects but does not correlate with the body mass index (BMI) [26]. A possible explanation for this could be a higher proportion of mononuclear cells expressing resistin mRNA in the adipose tissue of obese individuals. In one longitudinal study, it was observed that the percent change in serum resistin level positively correlated with the percent change in fat mass rather than the percent change in BMI [73].
In spite of great interest in how resistin impairs insulin sensitivity, there is continued uncertainty about the possible relationship between resistin and markers of insulin resistance [74]. However, the higher production of resistin by the non-fat components of adipose tissue might explain the abovementioned controversial findings in obese patients [35]. Moreover, resistin can amplify inflammatory responses in the liver via the central nervous system, which may represent a novel mechanism leading to the decrease of insulin sensitivity and related development of atherosclerosis and hyperlipidemia that are associated with metabolic syndrome [61].

**Resistin and atherosclerosis**

The cardiovascular complications of obesity have been specifically explained by endothelial and vascular dysfunction [75]. Obesity, type 2 diabetes, and cardiovascular disease have been increasingly recognized as inflammatory conditions due to an increased presence of proinflammatory mediators [51, 76]. The research on adipokines in the last 20 years has finally provided a plausible link between obesity and cardiovascular diseases [77].

Plasma resistin levels have been associated with markers of inflammation such as TNF-α, soluble TNF-α receptor-2, or IL-6 and moreover, resistin has been shown to be a predictive factor for coronary atherosclerosis in humans, independent of CRP [54, 78, 79]. It was recently shown that resistin correlates with the levels of biomarkers for cardiac injury, and it has been suggested as a marker of the severity of myocardium ischemic injury [80].

In rodents, resistin is derived largely from adipose tissue, and hyperresistinemia impairs glucose tolerance in mice. In contrast to animal models, immunocompetent cells appear to be the major source of resistin in humans, rather than adipocytes [28]. Resistin was found both intracellularly in macrophages as well as extracellularly in atheromas [81]. It contributes to glucose-dependent increases in triglyceride and cholesterol cellular mass that do not occur in
the absence of resistin [82]. Resistin also promotes foam cell formation via the up-regulation of SR-A and CD36 scavenger receptors and downregulation of the reverse cholesterol transporter ABCA1 (ATP-binding cassette transporter A1) [83].

Resistin was recently suggested as a mediator of endothelial dysfunction, and it has been shown to promote the activation of endothelial cells via the release of endothelin (ET-1). Furthermore, it induces the expression of vascular cell adhesion molecule (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), vascular endothelial growth factor receptors (VEGFR), matrix metalloproteinases (MMPs), and MCP-1; it also reduced TNF receptor-associated factor 3 (TRAF3), a key inhibitor of CD40 signaling in endothelial cells [45, 84, 85]. These “in vitro” data were confirmed by functional studies showing that resistin induces proliferation and migration of human endothelial cell and promotes capillary-like tube formation [45, 86, 87]. As it was recently reported, this could be mediated via resistin-activated TWEAK (TNF-like weak inducer of apoptosis), and it is independent of altered nitric oxide (NO) production [86, 88]. Resistin also promotes the smooth muscle cell proliferation that may account in part for the increased incidence of restenosis [43].

Angiogenesis in an atherosclerotic plaque contributes to its vulnerability, which may lead to rupture and subsequent intra-arterial occlusion [89]. In contrast, revascularization and collateral circulation is a desired process in the ischemic heart muscle and limb and is becoming the therapeutic goal [90]. However, a principle reason for the failure of angiogenic therapy could be the decreased effectiveness of growth factors due to endothelial dysfunction [91]. Although resistin was reported to promote angiogenesis [45, 86], which would be beneficial for ischemic muscle, a resistin-mediated impairment of endothelium function could diminish its angiogenic effect. Moreover, resistin has been shown to impair glucose metabolism in mouse cardiomyocytes and to worsen cardiac ischemia-reperfusion injury in rats. This could be due to stimulated cardiac TNF-α secretion and the reperfusion release of
natriuretic peptides and biochemical markers of myocardial damage [14, 87]. Furthermore, the abnormal formation of blood vessels also plays a role in other pathologies such as tumors, diabetic retinopathy, rheumatoid arthritis, or systemic lupus erythematosus. Since resistin may be a part of their pathophysiology, blocking resistin might prevent the abundant angiogenesis that is a typical sign of the abovementioned diseases.

Altogether, these data indicate that resistin may contribute to the accumulation of cholesterol and triglycerides in macrophages, arterial inflammation, endothelial dysfunction, and angiogenesis. These may contribute to accelerated atherogenesis and coronary heart disease. Moreover, resistin has been suggested as a marker of coronary atherosclerosis and the severity of myocardium ischemic injury.

**Resistin and non-alcoholic fatty liver disease**

Non-alcoholic fatty liver disease (NAFLD) is the hepatic manifestation of metabolic syndrome, which is mainly characterized by an excessive hepatic deposition of free fatty acids and triglycerides in the hepatic parenchyma. NAFLD ranges from steatosis to steatohepatitis, and potentially leads to fibrosis and end stage liver disease.

A few studies have reported that serum resistin levels did not differ between patients with NAFLD and without the disease [92, 93]. However, one study has shown that excessive ectopic accumulation of fat in the liver and skeletal muscle of insulin-resistant subjects is associated with lower concentrations of resistin in the serum, while another reports increased levels of resistin, but only in patients with severe liver disease [94, 95].

Thus, the results comparing serum resistin levels in patients with different stages of NAFLD have been controversial, and the contribution of resistin should be further explored.
**Involvement of resistin in malignancies**

Obesity has been suggested as a risk factor for the development of some types of cancer. Several recent studies have indicated that some adipose tissue-derived peptides may significantly influence the growth and proliferation of tumorous stroma and malignant cells [96]. For example, elevated levels of plasma resistin have been found in females with breast cancer, and higher levels appear related to the highest histological grade, independent of age, body mass index, serum glucose, or menopause [97]. Furthermore, resistin levels are significantly higher in lymphoma patients than in patients with other hematological malignancies [98]. Another study has reported no differences in the staining pattern between benign and neoplastic prostate tissues [99].

Although only a few studies have analyzed resistin in patients with malignancies, the general properties of resistin could contribute to tumorigenesis. For example, in choriocarcinoma, resistin induces the expression of MMPs, reduces the synthesis of tissue inhibitors of metalloproteinases (TIMP), and thereby increases the invasiveness of trophoblast-like cells [100]. Resistin has been also shown to induce production of VEGFR and the formation of endothelial cell tubes [45].

**Resistin in rheumatic diseases**

Increased resistin levels have previously been observed in synovial fluid from patients with rheumatoid arthritis (RA) compared to patients with non-inflammatory rheumatic disorders [30]. These authors observed an association of synovial fluid resistin with inflammatory markers of the disease. Moreover, the association between serum resistin levels, disease activity, and acute phase reactants, including C-reactive protein and IL-1Ra antagonizing IL-
β, suggests that resistin may be a significant mediator in the inflammatory process of RA [31, 101]. On the contrary, serum resistin levels were comparable between patients with erosive and non-erosive hand osteoarthritis and were neither associated with signs of clinical nor laboratory markers of inflammation [102]. In addition, resistin has been shown to both induce and be induced by several proinflammatory cytokines, such as TNF-α or IL-6 (via the NF-κB pathway), in peripheral blood mononuclear cells, indicating that resistin can enhance its own activity by a positive feedback mechanism. Interestingly, injection of recombinant resistin into healthy mouse joints induces infiltration of the synovial tissue with leukocytes, which resembles the pathology of rheumatoid arthritis [36]. In general, the local production of resistin at sites of inflammation could be suggested of more importance, because it has been found in numerous resident and immune cell types within the hyperplastic rheumatic synovial tissue [30, 31, 103-106].

Patients with systemic rheumatic diseases generally have an increased prevalence of atherosclerosis [107]. Very recently, a decline in serum levels of resistin after TNF-α blocking therapy has been shown; it is evident that this therapy, in addition to reducing joint inflammation, can concomitantly improve the cardiovascular prognosis in inflammatory disorders [108, 109]. An association between serum resistin levels, inflammation, bone mineral density, and renal functions has been demonstrated in patients with systemic lupus erythematosus (SLE) [110]. Increased expression of resistin corresponds to the intensity of lymphocytic inflammation in the salivary glands of patients with primary Sjogren’s syndrome [111]. Serum resistin is elevated in patients with the skin form of psoriasis but without joint involvement, and it correlates with the disease severity as assessed by the Psoriasis Area and Severity Index (PASI) [112, 113].
Resistin is associated with the laboratory findings and disease activity of several rheumatic diseases. However, its role and predictive value in autoimmune inflammatory diseases remains to be elucidated.

**Resistin and bone metabolism**

Rosen and Bouxsein asked a provocative question: does fat infiltration in the bone marrow cause low bone mass, or is it only a result of bone loss [114]? There is growing evidence that leptin as well as adiponectin can modulate bone metabolism [115, 116, 117]. Resistin expression has been found in murine preosteoblasts, preosteoclasts, and in primary human bone marrow stem cells, as well as in mature human osteoblasts [118]. Resistin stimulates osteoclast differentiation and NF-κB activity, the major signaling pathway involved in osteoclastogenesis. The observed, although weak, decrease in the RANKL/OPG mRNA ratio may indicate an indirect inhibitory effect, while an increase in IL-6 secretion may result in a stimulatory effect on osteoclastogenesis [118]. In one study, resistin levels correlated with a marker of bone metabolism, carboxyterminal cross-linked telopeptide of type I collagen (ICTP), while it was inversely related with bone mineral density [101]. These data, however, were not observed in Chinese men [119].

These findings indicate that resistin may play a role in bone remodeling.

**Resistin and inflammatory bowel diseases**

Increased serum resistin levels have been detected in both Crohn’s disease and ulcerative colitis patients [120, 121, 122]. In addition, resistin correlated with the disease activity score, white blood cell count, and CRP in patients with Crohn’s disease [121, 122]. In contrast to leptin and adiponectin, resistin significantly decreases after TNF-α blocking therapy in
patients with inflammatory bowel diseases and has been proposed as a marker of successful
therapy, similar to the patients with rheumatoid arthritis [123].

From the family of resistin-like molecules, RELM-β, as mentioned above, is predominantly
directed by goblet and epithelial cells within the colonic epithelium. It is involved in
regulating intestinal homeostasis [124, 125]. When secreted extracellularly, it can act as
a regulatory molecule in luminal molecule recognition and transportation across the epithelial
barrier and has been shown to bind to nematodes and to possess anti-chemotactic activity
against the parasites. Moreover, RELM-β-mediated dysregulation of enterocyte innate
immune mediators and IL-13-dependent expression might act in inflammatory bowel disease
pathology. Up-regulation of RELM-β in a model of mouse cystic fibrosis intestine suggests
that it also has a role in the cystic fibrosis-related disorder [126].

Resistin has been suggested as an independent predictor of disease activity in patients with
inflammatory bowel disease and has been proposed as a marker of successful therapy [121,
123]. Moreover, RELM-β has anti-parasitic effects and may play a role in the pathology of
inflammatory bowel diseases.

**Resistin and chronic kidney disease**

Resistin has been shown to be associated with both the rate of glomerular filtration and the
inflammatory status, but not insulin resistance in chronic kidney disease [127]. Increased
serum resistin has also been measured in pediatric patients with chronic renal failure and end
stage renal disease, suggesting that renal functions are an important factor in regulating the
systemic levels of resistin [128]. Resistin was also correlated with TNF-α, suggesting that it
have a role in the sub-clinical inflammatory state of chronic kidney disease [54]. Resistin may
also interfere with the chemotactic ability and oxidative burst of polymorphonuclear
leukocytes and might contribute to the disturbed immune response in conditions with increased serum resistin levels, such as uremia [129].

Resistin is associated with chronic kidney disease, which is characterized by a subclinical inflammatory state. Glomerular filtration may represent a crucial metabolic pathway for the elimination of resistin [130].

**Resistin and asthma**

Although the prevalence of asthma and obesity is increasing in recent decades, very little is known about the possible association between these two disorders. Elevated plasma resistin levels in asthmatic patients compared with control individuals as well as resistin levels that increase with disease severity have been demonstrated in the asthma cohort [131]. On the other hand, atopic asthmatic children have lower resistin levels compared to non-atopic asthma and control groups [132].

The potential of resistin and its relationship to disease activity in patients with asthma is unclear and might be the objective of further studies.

**Resistin as a potential pharmacological target**

Steppan et al. [3] suggested that resistin may be a hormone with effects on glucose metabolism, antagonizing insulin action. Thiazolidindiones (TZDs) are antidiabetic drugs that bind as ligands to PPARγ. TZDs decreased circulating resistin levels in both mice and humans and inhibited the expression of resistin in cultured 3T3-L1 adipocytes and in white adipose tissue in db/db mice [3, 133, 134, 135]. Regarding the effects of resistin on insulin sensitivity, the decrease in plasma resistin following TZD therapy may play an important role in reversing insulin resistance and its consequences in patients with type 2 diabetes [133].
Moreover, it has been recently shown that higher doses of TZDs reduced bone erosions and prevented inflammatory bone loss in an experimental model of autoimmune arthritis [136].

As mentioned above, obesity and insulin resistance are associated with higher cardiovascular risk factors. Statins (HMG CoA reductases) have been shown to reduce cardiovascular events and mortality. Statin treatment resulted in a significant reduction of plasma resistin in patients with type 2 diabetes and also downregulated mRNA resistin levels in PBMCs [40, 136]. However, niacin, another lipid-lowering drug, decreased resistin plasma levels only moderately [137]. Some of the commonly used anti-hypertensive drugs and particularly calcium channel blockers (amlodipin) have been shown to decrease plasma resistin levels in patients with arterial hypertension; to a lesser extent, an angiotensin-converting enzyme inhibitor, ramipril, and angiotensin II type 1 receptor blockade, candesartan, have been shown to do the same, but β-blockers, such as atenolol, or thiazide diuretics have not [138].

While treatment with another angiotensin II type 1 receptor blockade losartan does not modify the insulin-induced changes in plasma resistin, it attenuates the response of resistin in adipose tissue [139]. Short-term vitamin C supplementation could significantly reduce resistin serum levels, independent of changes in inflammatory or metabolic variables in healthy individuals [140]. This is interesting with regard to possible participation of resistin in oxidative stress.

Resistin significantly decreased after the TNF-α blocking therapy in patients with rheumatoid arthritis and inflammatory bowel disease [108, 109, 123]. Treatment of patients with the skin form of psoriasis with retinoids leads to a normalization of serum resistin levels [113]. This could be due to the direct effects of retinoids on resistin expression in monocytes/macrophages or adipose tissue, in accordance with the data obtained in mice [113, 141].

With respect to the multiple and rather negative involvements of resistin in various human pathologies, it is becoming a potential target for their treatment. However, to find any
effective therapeutic strategies, the exact role of resistin in their pathophysiology needs to be fully established.

**Conclusion**

Resistin was first described as a factor contributing to insulin resistance and obesity-related diseases, although there is now more (largely circumstantial) evidence that it might be involved in inflammatory, endocrine, or tumor diseases. Possible roles for resistin in obesity-related subclinical inflammation, atherosclerosis and cardiovascular disease, non-alcoholic fatty liver disease, rheumatic diseases, malignant tumors, asthma, inflammatory bowel disease, and chronic kidney disease have already been demonstrated. Resistin has been suggested as an independent predictor of the activity of several diseases. However, research on resistin has shown some conflicting results, and conclusive data await new firm evidence to elucidate the role of resistin in various disease processes.

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Table 1. The primary differences between mouse and human resistin

<table>
<thead>
<tr>
<th>Feature</th>
<th>Mouse</th>
<th>Human</th>
</tr>
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<tbody>
<tr>
<td>Chromosome location</td>
<td>8 A1; 8 0.37 cM</td>
<td>19p13.2</td>
</tr>
<tr>
<td>Genomic organization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouse</td>
<td>73 ▼ 162 ▼ 140 ▼ 763 ▼ 78 ▼ 264 ▼ 142 ▼ 2279 ▼ 150</td>
<td></td>
</tr>
<tr>
<td>Human</td>
<td>36 ▲ 195 ▲ 128 ▲ 376 ▲ 78 ▲ 320 ▲ 236</td>
<td></td>
</tr>
<tr>
<td>Number of amino acids</td>
<td>114</td>
<td>108</td>
</tr>
<tr>
<td>Secondary structure</td>
<td>predominantly α-helix</td>
<td>concentration dependent α-β shift</td>
</tr>
<tr>
<td>Active form</td>
<td>LMW in liver</td>
<td>HMW (?)</td>
</tr>
<tr>
<td></td>
<td>HMW in cardiac muscle</td>
<td></td>
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<tr>
<td>The main source</td>
<td>adipocytes</td>
<td>immune cells</td>
</tr>
</tbody>
</table>

**Abbreviations:** LMW, low molecular weight; HMW, high molecular weight; arrowheads and arrows denote the positions of the start and stop codons.
Table 2. Implication of resistin in different pathologies

<table>
<thead>
<tr>
<th>Disease/manifestation</th>
<th>Functions of resistin</th>
<th>Prognostic significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammation</td>
<td>NFκB, MAPK, PI3K activation ↑ TNFα, IL-6, IL-8, IL-12, MCP-1</td>
<td>Involvement in several inflammatory states (see below)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Specific role and prognostic value?</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>apoptosis of beta cells ↑ insulin resistance in liver, adipocytes and skeletal muscle hypothalamus-mediated effect inflammatory milieu in adipose tissue regulation via PPARγ</td>
<td>Link between obesity and DM?</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td>Link to related complications?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Obesity-associated inflammation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Potential target for treatment of DM</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>↑ proinflammatory cytokines ↑ VCAM-1, ICAM-1, VEGFR, ET-1, ↑ MCP-1, MMP, ↓ TRAF3 ↑ foam cell formation endothelial dysfunction ↑ angiogenesis smooth muscle cell proliferation</td>
<td>Implicated in the pathogenesis of atherosclerosis / cardiovascular diseases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Marker of coronary atherosclerosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Marker of myocardial ischemic injury</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Potential target for treatment?</td>
</tr>
<tr>
<td>Non-alcoholic fatty liver</td>
<td>↑ NF-κB, IL-8, MCP-1 in hepatic stellate cells ↑ lipid accumulation?</td>
<td>Association with stage of NAFLD?</td>
</tr>
<tr>
<td>disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumorigenesis</td>
<td>↑ MMP, VEGFR, ↓ TIMP ↑ angiogenesis</td>
<td>Implicated in the pathogenesis of cancer?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prognostic value?</td>
</tr>
<tr>
<td>Rheumatic diseases</td>
<td>↑ TNFα, IL-6, NF-κB activation Infiltration of synovial tissue with leukocytes, RA-like pannus formation</td>
<td>Involvement the pathogenesis of rheumatic diseases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Specific role and prognostic value?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Marker of disease activity and successful treatment?</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>↑ NF-κB activation, ↑ IL-6 ↓ RANKL/OPG Expressed in bone marrow stem cells and osteoblast-differentiated cell line</td>
<td>Osteoclastogenesis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bone remodeling</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Marker of bone metabolism?</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>↑ proinflammatory cytokines RELM-β antiparasitic effect, dysregulation of enterocyte immune mediators</td>
<td>↑ serum levels in CD and UC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Predictor of disease activity?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Marker of successful therapy?</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>↑ proinflammatory cytokines interference with chemotaxis and oxidative burst of leukocytes? ↑ inflammatory milieu</td>
<td>Proinflammatory state of chronic kidney disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Related to renal functions?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Marker of disease severity</td>
</tr>
<tr>
<td>Asthma bronchiale</td>
<td>↑ proinflammatory cytokines</td>
<td>Marker of disease severity?</td>
</tr>
</tbody>
</table>

**Abbreviations:** TNF, tumor necrosis factor; IL, interleukin; MCP-1, monocyte chemoattractant protein; PPARγ, peroxisome proliferator activated receptor γ; DM, diabetes
mellitus; ET-1, endothelium derived vasoactive factor; VCAM-1, vascular cell adhesion molecule; ICAM-1, inter-cellular adhesion molecule 1; MMPs, matrix metalloproteinases; VEGFR, vascular endothelial growth factor receptor; TRAF3, TNF receptor – associated factor-3; NAFLD, non-alcoholic fatty liver disease; TIMP, tissue inhibitors of metalloproteinases; RANKL, receptor activator of NF-κB ligand; OPG, osteoprotegerin; PPARγ, peroxisome proliferator-activated receptor γ; CD, Crohn’s disease; UC, ulcerative colitis.

Figure 1. Resistin induced intracellular signaling pathways

No receptor for resistin has yet been identified. Resistin induces NF-κB activity, resulting in the translocation of both the p65 and p50 subunits from the cytoplasm to the nucleus. This effect may be through resistin-mediated phosphorylation of the inhibitory protein IκBα and the p65 subunit of NF-κB. Resistin activates MAPKs such as Erk or p38 as well as Akt, a downstream substrate of PI3K. Resistin increases the cytosolic Ca concentration via both PLC activation, leading to the release of Ca from intracellular pools, such as the endoplasmic reticulum, and Ca influx from the extracellular environment. Activation of the abovementioned signaling pathways via resistin suggests that it has proinflammatory potential.
Abbreviations: NF-κB, nuclear factor B; IκB, inhibitor of κB; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; PI3K, phosphatidylinositol 3-kinase; Ca, calcium; PLC, phospholipase C; IP3, inositol-1,4,5-trisphosphate; IP3R, inositol trisphosphate receptor.

Figure 2. Resistin as a potential regulator of inflammation

A schematic representation of key pathophysiological signaling pathways that are mediated by resistin in immune and resident tissue cells. Resistin has many features of the proinflammatory cytokines that activate the transcription factor NF-κB. It is up-regulated during monocyte-macrophage differentiation and increases after TNF-α, IL-1β, IL-6, and LPS stimulation. Resistin can target several human cells, thereby enhancing inflammatory and autoimmune processes. It induces endothelial cell growth and migration, which are involved in angiogenesis and tumorigenesis. Together with a glucose-dependent increase in triglyceride and cholesterol cellular mass in macrophages, it can contribute to the process of atherosclerosis and its related complications. It has been also suggested that resistin can endorse osteoclastogenesis via modulation of bone turnover mediators.

Abbreviations: TNF, tumor necrosis factor; IL, interleukin; MCP-1, monocyte chemoattractant protein; ET-1, endothelium derived vasoactive factor; VCAM-1, vascular cell adhesion molecule; ICAM-1, inter-cellular adhesion molecule 1, VEGFR, vascular endothelial growth factor receptor; TRAF3, TNF receptor – associated factor-3; MMPs, matrix metalloproteinases; RANKL, receptor activator of NF-κB ligand; OPG, osteoprotegerin; PBMCs, peripheral blood mononuclear cells; LPS, lipopolysaccharide.