Review

Role of Resistin in Inflammation and Inflammation-Related Diseases

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Resistin is a newly identified adipocyte secreted hormone belonging to a cysteine-rich protein family. It is expressed in white adipose tissues in rodents and has also been found in several other tissues in human. Insulin, glucose, many cytokines and anti-diabetic thiazolidinediones are regulators of resistin gene expression. Resistin was firstly proposed to be involved in insulin resistance and type 2 diabetes. Recently, it was found to be relevant to inflammation and inflammation-related diseases like atherosclerosis and arthritis. *Cellular & Molecular Immunology*. 2006;3(1):29-34.

Key Words: resistin, insulin resistance, inflammation, atherosclerosis, arthritis

Introduction

Resistin is an adipokine that was independently identified by three groups. Kim et al. identified resistin as an adipose tissue-specific secreted factor by microarray analysis (1). Holcomb et al. identified resistin as "found in inflammatory zone 3" (FIZZ3) by a homology search of the expressed sequence tag (EST) database against a related protein induced during lung inflammation which is known as FIZZ1 (2). Steppan et al. identified resistin by a screen for genes that are induced during adipocyte differentiation but downregulated in mature adipocytes when exposed to thiazolidinediones (TZDs), a class of common used anti-diabetic drugs (3). The first functional study on resistin revealed that it is an important factor linking obesity to type 2 diabetes (3). After that, several follow-up studies have explored the role of resistin in obesity and type 2 diabetes and its underlying mechanisms. Recently, several studies showed that resistin may also play a pivotal role in inflammation and process of inflammation-related diseases. This review will summarize the current understanding of the biology and physiology of resistin, with emphasis on its role in inflammation and inflammation-related diseases.

Molecular and cellular biology of resistin

Resistin is a member of a secretory protein family, known as resistin-like molecules (RELMs). The family is characterized by a highly conserved, cysteine-rich C terminus in which the spacing of the cysteines is invariant. There are four members in the mouse RELMs family: resistin, RELMα, RELMβ and RELMγ. Only two counterparts were found in human: resistin and RELMβ. Mouse resistin gene is localized to chromosome 8 and human resistin gene to chromosome 19. Mouse and human resistin share 64.4% sequence homology at mRNA level and 59% identity at the amino acid level (4). Mouse resistin is a 108 amino acid peptide with a molecular weight of 12.5 kD (3). It is secreted as a disulfide-linked homodimer. A cysteine residue (Cys26), closest to its N-terminus, is critical for this dimerization, because when Cys26 was mutated to alanine, mouse resistin was secreted as a monomer. The remaining 10 cysteines probably participate in intramolecular disulfide bonds (5). Besides homodimer, mouse resistin can also interact with its family members, mouse RELMα and mouse RELMβ, through non-covalent interactions regardless of the presence of Cys26. Furthermore, mouse resistin and mouse RELMβ can form multimers, probably with a dimmer as subunit (6).

Mouse resistin is almost exclusively expressed in white adipose tissue with high level, whereas human resistin expressed in adipose tissue is significantly lower, even undetectable under some conditions. Besides adipose tissue, human resistin is also expressed in other tissues. A scan of a

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Abbreviations: FIZZ, found in inflammatory zone; GH, growth hormone; ICAM-1, intercellular cell-adhesion molecule-1; IL, interleukin; LPS, lipopolysaccharide; MCP-1, monocyte chemotactic protein-1; PBMC, peripheral blood mononuclear cells; RELMs, resistin-like molecules; TNF, tumor necrosis factor; TZDs, thiazolidinediones; VCAM-1, vascular cell adhesion molecule-1.

variety of human tissues by real-time PCR showed that human resistin was expressed at the highest level in bone marrow followed by lung (7). Human resistin mRNA has also been detected in the nonfat cells of adipose depots (8). Additionally, human resistin has been detected in placental tissue (9) and pancreatic islet cells (10). Interestingly, resistin mRNA levels were found to be higher in males than that in females in rats (11, 12), whereas human plasma resistin was found to be higher in females than in males (13), which indicated that gender may be one of the factors influencing resistin expression and function.

Regulation of resistin gene expression

Many hormones and molecules can regulate resistin gene expression, such as TZDs, insulin, glucose, glucocorticoid, and growth hormone.

Since resistin was firstly identified as a downregulated gene by TZDs, its expression in response to TZDs under different conditions has been investigated. Consistent with the first observation (3), resistin mRNA and protein levels were suppressed by TZDs in 3T3-L1 adipocytes (14-16). Overexpression of peroxisome proliferators-activated receptor-γ which is strongly activated by TZDs markedly reduced resistin gene expression (17). However, there are also conflicting data from *in vivo* studies. Both upregulation (18, 19) and dowregulation (3, 20, 21) of resistin gene expression induced by TZDs have been reported, suggesting that downregulation of resistin is not necessary for the antidiabetic effects of TZDs in all models.

The regulation of resistin gene expression has been investigated in adipocytes in response to insulin and glucose both *in vitro* and *in vivo*. Insulin administration can suppress resistin gene expression in 3T3-L1 adipocytes (14, 16, 22). This inhibitory effect by insulin is independent of phosphatidylinositol 3-kinase, extracellular signal-regulated kinase or p38-mitogen-activatied protein kinase pathways. However, a previous study *in vivo* described the contrary results that insulin can induce resistin expression (1). Another group also reported the increased resistin protein level induced by acute and chronic insulin stimulation in 3T3-L1 adipocytes (23). High glucose concentration significantly upregulated resistin in 3T3-L1 adipocytes (14). Resistin mRNA level increased in response to hyperglycemia *in vivo* (24). In wild type C57 mice, plasma resistin level increased after feeding, consistent with insulin level. During fasting, both mRNA and protein levels of resistin reduced, which was concordant with insulin and glucose level. These conflict results may be due to different detailed experimental processes.

Cushing's syndrome, a clinical syndrome of glucocorticoid excess, is associated with glucose intolerance, obesity and hypertension (25). Dexamethasone, one of potent synthetic glucocorticoids, increased expression of resistin at both mRNA and protein levels by 2.5- to 3.5-fold in 3T3-L1 adipocytes and by approximately 70% in white adipose tissue from mice (14, 16), which indicated that resistin may be a possible link between such syndrome and insulin resistance.

Growth hormone (GH), an important regulator of metabolism, is also a regulator of resistin. Resistin gene expression was significantly suppressed in GH-deficient rats compared with controls. Acute treatment or continuous infusion of recombinant human growth hormone both caused marked increases of resistin gene expression in white adipose tissue (26).

Besides these regulators, other factors have also been reported to regulate resistin gene expression, such as β-adrenoceptor agonist (27), thyroid hormones (12, 28), vitamin A (29), epigalocatechin-3-gallate, etc. (30). Overall, further work is needed to understand the mechanisms of these regulators on resistin expression and the underlying physiological and pathophysiological significance.

Involvement of resistin in insulin resistance

An abundance of evidence has emerged linking resistin to insulin resistance. In mice, neutralization of resistin by antibody improved glucose and insulin action in diet-induced obesity (3). Two independent groups reported that administration of recombinant resistin impaired glucose tolerance and insulin action (3, 31). In an *in vitro* study, L6 myocytes that were stimulated by mouse resistin showed impaired glucose uptake induced by insulin (32, 33). Besides glucose metabolism, chronic incubation of L6 myocytes with resistin can inhibit fatty acid uptake and metabolism *via* a pathway involving CD36, Fatty Acid Transport Protein 1, Acetyl-CoA carboxylase, and AMP-activated protein kinase (34).

The role of resistin in insulin resistance was also investigated in mice engineered to knockdown or overexpress resistin. Knockdown of resistin can completely reverse the hepatic insulin resistance in diet-induced insulin resistance mice (35). Resistin knockout mice exhibited low blood glucose levels after fasting, due to reduced hepatic glucose production, and showed dramatically better glucose tolerance when fed a high-fat diet (36). Overexpression of resistin in circulation by adenovirus-mediated gene expression led to glucose intolerance, hyperinsulinemia, and hypertriglyceridemia associated with impaired insulin signaling in skeletal muscle, liver, and adipose tissue (37). Resistin transgenic mice showed increased adiposity and enlarged adipocyte size. These mice also exhibited improved glucose tolerance and insulin sensitivity either on chow or high-fat diets (38). Resistin gene single nucleotide polymorphisms have been linked to obesity and diabetes (39-42).

All of these findings clearly suggest a pivotal role of resistin in insulin resistance and type 2 diabetes. However, the receptor and relevant intracellular signaling pathway of resistin have not been completely understood yet.

Resistin and inflammation

Although resistin was firstly postulated to contribute to insulin resistance, more and more evidence indicated that it may also be involved in inflammatory process. Some pro-inflammatory agents, such as tumor necrosis factor-α

(TNF-α), interleukin 6 (IL-6) and lipopolysaccharide (LPS), can regulate resistin gene expression. Resistin mRNA was strongly increased by TNF-α in human peripheral blood mononuclear cells (PBMC) (43). However, treatment of TNF-α in 3T3-L1 adipocytes downregulated resistin at both mRNA and protein levels (14, 24, 44). The explanation for this paradox may be due to the different types of cells used. IL-6 also increased resistin expression in PBMC (43), but had no effect in 3T3-L1 adipocytes (24). LPS has been reported to upregulate the resistin mRNA levels in white adipose tissue and white blood cells in rats as well as in 3T3-L1 adipocytes (20). In contrast, Rajala et al. reported that LPS had no effect on resistin expression in 3T3-L1 adipocytes and downregulated resistin expression in adipose tissue in FVB mice (24). These contradictory results may be due to the differences in methodology, cell types and animals.

Recent studies have shown the regulation of pro-inflammatory cytokine expression by resistin. Resistin strongly upregulated IL-6 and TNF-α in human PBMC *via* NF-κB pathway (45). Addition of recombinant human resistin protein to macrophages from both mouse and human resulted in enhanced secretion of pro-inflammatory cytokines, TNF-α and IL-12 (46). LPS was reported to induce resistin gene expression in primary human macrophages *via* a cascade involving the secretion of inflammatory cytokines (47).

Other evidence linking resistin to inflammation is that plasma resistin levels were found associated with many inflammatory markers in some pathophysiological conditions. A study found that persons with clinical signs of severe inflammation showed significantly higher concentrations of resistin than healthy individuals. In people with severe inflammations, a significant positive correlation between resistin and inflammatory markers was showed (48). IL-6 and intercellular cell-adhesion molecule-1 (ICAM-1) were also significantly correlated with resistin in patients with obstructive sleep apnoea syndrome (49). Resistin level was also positively associated with levels of inflammatory markers, including soluble TNF-α receptor-2, IL-6 and lipoprotein-associated phospholipase A2 in atherosclerosis patients (50). More recently, the inflammatory markers were shown to be independently associated with circulating resistin levels in patients with chronic kidney disease (51). C-reactive protein, a marker of inflammation, was reported to be positively correlated with resistin levels in several pathophysiological conditions (51-54).

In summary, resistin was undoubtedly involved in inflammation, although further study should be conducted to clarify its exact role in these conditions.

Role of resistin in inflammation-related diseases

Resistin and atherosclerosis

Inflammatory process has recently been connected with the pathogenesis of atherosclerosis. Recent studies indicate that resistin may promote the initiation or perpetuation of the atherosclerotic state by activating vascular endothelial cells. Verma et al. found that resistin promoted endothelial cell activation by promoting endothelin-1 release, partly by inducing endothelin-1 promoter activity. Furthermore, resistin upregulated adhesion molecule vascular cell adhesion molecule-1 (VCAM-1) and monocyte chemotactic protein-1 (MCP-1), and downregulated TNF-receptor-associated factor-3, an inhibitor of CD40 ligand signaling which can induce MCP-1 production (55). Other investigators observed that resistin could induce adhesion molecules VCAM-1 and ICAM-1, and long pentraxin 3, a marker of inflammation in vascular endothelial cell (56). Moreover, besides endothelial cells, resistin induced human aortic smooth muscle cell proliferation through both ERK1/2 and Akt signaling pathways (57). These results were further confirmed by another two groups (58, 59).

Besides cell culture studies, other studies found that resistin protein was present in both murine and human atherosclerotic lesions, and its mRNA levels progressively increased in the aortas of mice developing atherosclerosis (59). Immunohistochemical staining of human vessels showed that aortic aneurysms exhibited resistin-positive staining areas along macrophage infiltration, while normal arteries and veins did not (58).

In population studies, resistin levels were also associated with increasing coronary artery calcification, a quantitative index of atherosclerosis (50). All these data indicate a pivotal role of resistin in the development of atherosclerosis, but the underlying mechanisms are still unclear.

Resistin and arthritis

Healthy NMRI mice intra-articularly injected with recombinant mouse resistin in the knee joints showed arthritis compared with mice injected with albumin. These mice showed infiltration of synovial tissue with leukocytes in the knee joints, which were associated with hypertrophy of synovial lining layer and panus formation. Arthritis were also caused when recombinant mouse resistin was injected in the knee points of C57/6J mice (45) .

In human study, synovial fluid from patients with rheumatoid arthritis (RA) showed significantly higher level of resistin compared with control samples. Moreover, resistin level in RA synovial fluid positively correlated with synovial leukocyte count and IL-6 level (45). However, plasma resistin concentrations were not different between RA patients and healthy counterparts (45, 60). Thus, the role of resistin in RA is apparent, but the underlying mechanism needs further investigations.

Resistin and other inflammation-related diseases

Type 1 diabetes is an autoimmune disease. Plasma resistin levels were firstly found not to be different between patients with type 1 diabetes and healthy controls (61). However, a recent study showed that healthy people had significantly higher plasma resistin levels than patients with type 1 diabetes (62). Plasma resistin levels were measured in healthy people and patients with type 1 diabetes pre- and post-islet transplantation. Interestingly, plasma resistin levels were significantly higher in patients with type 1 diabetes

before transplantation compared with healthy controls, but reduced to normal levels after islet transplantation (63). Thus, human resistin may be involved in the pathophysiology of type 1 diabetes.

More recently, a study reported that plasma resistin was higher in nonalcoholic fatty liver disease patients compared with control and obese patients. Increased resistin mRNA was also found in adipose tissue of nonalcoholic fatty liver disease patients compared with controls and obese subjects. In these patients, a positive correlation was found between resistin and histological inflammatory score (64).

Overexpression of resistin in mesenteric adipose tissue of patients with Crohn's disease has recently been reported (65). Serum resistin levels in patients with inflammatory bowel disease, such as ulcerative colitis and Crohn's disease, increased when compared with healthy controls (66).

Although increased levels of resistin have been associated with these inflammation-related diseases, further studies are needed to elucidate the role of resistin in these pathophysiological conditions.

Perspectives

The involvement of resistin in inflammation and inflammation-related diseases is just studied at the very beginning. Much more needs to be studied and clarified. Identification of resistin receptor and its downstream signaling pathway will be much helpful for exploring its physiological roles. Resistin knockout and transgenic mice will be helpful to investigate the roles of resistin in inflammation and inflammation-related diseases. Finally, since the expression pattern of resistin in mouse and human is different, experiments with human cells and epidemiological studies are critical to clarify the exact roles of resistin in human inflammation-related diseases.

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