Role of Resistin in Inflammation, Obesity and Type2 Diabetes mellitus

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Summary

Resistin is a adipocyte secreted hormone belonging to a cysteine-rich protein family. Resistin is a potential link between obesity and insulin resistance or type 2 diabetes. Several studies have subsequently been published supporting the concept that insulin resistance and obesity are actually associated with a increased resistin expression. In addition, resistin also appears to be a pro-inflammatory cytokine, inflammation can play a major role in the development of obesity and insulin resistance. Some recent genetic studies have demonstrated an association between resistin and insulin resistance and obesity. This review will place available data on resistin in the context of our current knowledge of the pathogenesis of obesity-mediated diabetes.

Introduction

Resistin is a hormone secreted by adipose tissue. It is also known as "serine/cysteine-rich adipocyte-Specific Secretory Factor" (ADSF or FIZZ3). The length of the resistin pre-peptide in human is 108 aminoacids; the molecular weight is ~12.5 kDa. Among the hormones synthesized and released from adipose tissue (adiponectin, angiotensin, estradiol, IL-6, leptin, PAI-1, TNF-α, and resistin (also known as ADSF or FIZZ3)), resistin is an adipocytokine whose physiologic role has been the subject of much controversy regarding its involvement with obesity and type II diabetes mellitus (T2DM). Resistin was originally found to be produced and released from adipose tissue to serve endocrine functions likely involved in insulin resistance. This idea primarily stems from studies demonstrating that serum resistin levels increase with obesity in several model systems (1-5). Since these observations, further research has linked resistin to other physiological systems such as inflammation and energy homeostasis (6-8).

Discovery

Resistin was discovered in 2001 by the group of Dr Mitchell A. Lazar from University of Pennsylvania School of Medicine. It was called "resistin" because of the observed insulin resistance in mice injected with resistin (5).

Structure

Crystal structures of resistin reveal an unusual composition of several subunits that are held together by non-covalent interactions which make up its structure. Each protein subunit comprises a carboxy-terminal disulfide-rich Beta-sandwich "head" domain and an amino-terminal alpha-helical "tail" segment(6) . The alpha-helical segments associate to form three-stranded coiled coils, and surface-exposed interchain disulfide linkages mediate the formation of tail-to-tail hexamers. The globular domain from resistin contains five disulfide bonds This suggests that the disulfide pattern with be conserved.

Figure:1 Ribbon diagram representation of resistin

Inflammation

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 (9). The first functional study on resistin revealed that it is an important factor linking obesity to type 2 diabetes (10). 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 (11). IL-6 and intercellular cell-adhesion molecule-1 (ICAM-1) were also significantly correlated with resistin in patients with obstructive sleep apnoea syndrome (12). 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 (13). Recently, the inflammatory markers were shown to be independently associated with circulating resistin levels in patients with chronic kidney disease (14).

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 (15). In population studies, resistin levels were also associated with increasing coronary artery calcification, a quantitative index of atherosclerosis (13). All these data indicate a pivotal role of resistin in the development of atherosclerosis, but the underlying mechanisms are still unclear.

Resistin and Arthritis

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 (16). However, plasma resistin concentrations were not different between RA patients and healthy counterparts (16, 17). Thus, the role of resistin in RA is apparent, but the underlying mechanism needs further investigations.

Resistin and other Inflammation-related diseases

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. Overexpression of resistin in mesenteric adipose tissue of patients with Crohn's disease has recently been reported (18). Serum resistin levels in patients with inflammatory bowel disease, such as ulcerative colitis and Crohn's disease, increased when compared with healthy controls (18).

Mechanism of action of Resistin

Insulin signaling is initiated with the binding of insulin to its receptor and dimerization of the receptor, leading to phosphorylation. The phosphorylated receptor then attracts the insulin receptor substrate (IRS) proteins -1 and -2. The IRS proteins are subsequently phosphorylated and initiate cascades including one involving phosphoinositide 3-kinase (PI3K) and Akt (also known as protein kinase B; PKB). Resistin decreases insulin stimulated phosphorylation of IRS-1 (19,20,21,22 ,10). In contrast, no effect of resistin on IRS-1 was found in myoblasts in culture (Moon B) and mouse liver (23). Mixed results of resistin's effect on IRS-2 have also been published. Satoh *et al.,* demonstrated reduced IRS-2 phosphorylation and protein level in skeletal muscle, adipose tissue, and liver of mice over-expressing resistin (19) while Palanivel *et al.* reported no change in IRS-2 protein in L6 myoblasts treated with resistin (22) reports indicating a lack of effect of resistin on the insulin receptor and/or IRS show no effectof resistin on PI3K activity or the subsequent phosphorylation of Akt (23). One target of active Akt is glycogen synthase kinase (GSK)-3, a protein that phosphorylates glycogen synthase thus inactivating it. Phosphorylation of GSK-3 by Akt inactivates the enzyme. both central and peripheral administration of resistin to rats resulted in reduced levels of phosphorylated GSK-3 althoughthe effect does not appear to require central signaling as hypothalamic- specific administration of an anti-resistin antibody did not alter the effect of peripherally injected resistin. A known inhibitor of insulin signaling is the suppressor of cytokine signaling (SOCS) family. Indeed, resistin treatment results in increased expression of SOCS-3 (24,25,10)both *in vitro* and *in vivo*. Both central and peripheral administration of resistin up-regulated SOCS-3 expression but central signaling was not required for resistin action (25). Pretreatment with the dominant negative SOCS-3 protein completely blocked the resistin-induced reduction in insulin receptor phosphorylation (10).Therefore, resistin appears

to up-regulate SOCS-3 expession. SOCS-3 interacts with the insulin receptor, possibly preventing its phosphorylation, and certainly inhibiting the subsequent activation of IRS-1, PI3K, and Akt . Less active Akt leads to more active GSK3 and consequently less active glycogen synthase . The decrease in glycogen synthesis, coupled with possible increases in gluconeogenesis and glycogen breakdown (activated through this or other signaling pathways) results in increased blood glucose and insulin resistance.

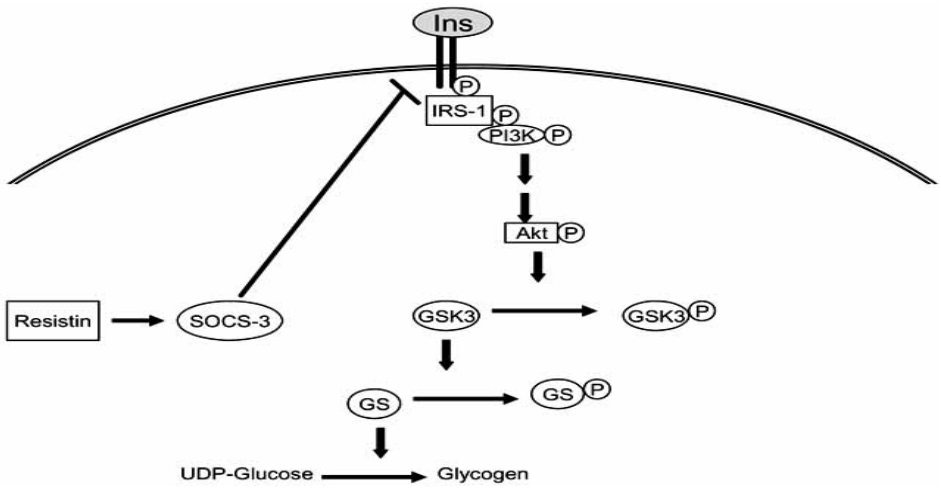

Figure: 2. Potential mechanism by which rodent resistin may interfere with insulin signaling. Resistin up-regulates the expression of SOCS-3, which may block phosphorylation of the insulin receptor and certainly blocks the activation of IRS-1. This leads to less active (phosphorylated) Akt, which results in more active (dephosphorylated) GSK3, and therefore less active (dephosphorylated) GS, and accounts for the reduction in glycogen synthesis in resistin-treated cells and animals.

Resistin in obesity

Way et al., (26) observed that resistin expression is significantly reduced in the WAT of several experimental models of obesity, including ob/ob, db/db, tub/tub and KKAy mice when compared to their lean. A correlation between obesity and the level of resistin has been reported in rodents (10) and humans (27,28). They noted that the more severe the obesity, the higher the level of resistin in humans (29). Le Lay *et al*., (30)reported decreased resistin expression in mice with different sensitivities to a high-fat diet. Janke *et al*., (31) did not find any relationship between body weight, insulin sensitivity and adipocyte resistin gene expression in humans. In a way that further complicates the link between obesity and resistin, some investigators did not find any difference between the tissue level of resistin in lean patients, obese patients and patients with type 2 diabetes (32). Human studies have highlighted increased resistin expression in adipose tissue (33), particularly abdominal depots; furthermore, positive correlations between serum resistin and body fat content have also been reported (34). On the contrary, several studies have failed to demonstrate such correlations in rodents, with groups also reporting either reduced (26,35,36,10) or no alteration (37) of resistin levels in various models of obesity. Rajala and co-workers (36), showing circulating resistin levels were significantly elevated and concordant with increasing levels of insulin, glucose and lipids; thus substantiating the initial evidence that addressed the aetiology of resistin with increasing adiposity (3). Asensio *et al*., (38) determined that high-fat-fed mice had induced adipocyte differentiation, denoted by fatty acid binding protein (AP-2) gene expression, a surrogate marker of differentiation, which positively correlated with resistin gene expression. Subsequently, previous studies (38), it was suggested that elevated resistin expression was a result of adipocyte differentiation (37). Moreover, the increase in adipocyte number may have caused a rise in local resistin production, inhibiting insulin

action on glucose uptake in adipose tissue and, thus, preventing further adipocyte differentiation (37). Recent investigations of human resistin in relation to obesity have shown higher serum resistin levels in obese subjects compared with lean subjects (39,28), which positively correlated with the changes in BMI and visceral fat area (28,40,41). The implication that resistin is important in human adipose tissue has been corroborated by studies showing increased protein expression with obesity (28), as well as protein secretion from isolated adipocytes (42). These recent observations are concomitant with initial studies that showed increased serum resistin levels and gene expression levels in abdominal depots in states of increased adiposity. A further study has shown a significant reduction in circulating resistin levels following moderate weight loss and post-gastric bypass (43). Contrary with the studies suggesting a role for resistin in obesity, (44) have reported resistin was undetectable in serum of obese mice, with the same study indicating reductions of resistin mRNA and protein expression in obesity. Others have reported no association of resistin expression with increased adiposity, despite observing elevated circulating levels (45, 36,38). However, it has been suggested recently that resistin mRNA expression does not necessarily correlate with protein expression (36).Possible explanations for such diverse observations include differences in post-transcriptional and post-translational modifications, consequently affecting secretory rates of resistin. Increased serum levels may enhance transcript degradation rates via negative feedback mechanisms, or the initiation and recruitment of inhibitors of translation. The secreted form of resistin is considered to have paracrine properties, and this may imply the majority of regulation occurs at the protein level. Similarly, Rajala and co-workers (36). Further recent human studies have shown no correlation of serum or plasma levels of resistin with any markers of adiposity (46). Heilbronn et al., reported no relationship between resistin serum levels and percentage body fat, visceral adiposity and BMI. However, the authors (47) suggested that the lack of correlation of serum resistin and increased adiposity was partly due to the confounding variable of age, as non-obese subjects were significantly younger than obese subjects (47).

Resistin insulin resistance and T2DM

Early rodent studies determined that reduced serum resistin levels in mice were associated with decreased adiposity and improved insulin sensitivity (47). Rajala *et al*., (36) recently demonstrated that circulating resistin levels were significantly elevated and positively concordant with rising levels of insulin, glucose and lipids in *Lep*ob/ob mice. Furthermore, Asensio *et al*.,(38) highlighted that leptin administration in *ob/ob* mice improved insulin sensitivity, which was affiliated with a decrease in resistin gene expression. Collectively, these studies suggest leptin may exert insulin resistance- ameliorating effects via counter-regulatory interactions and potentially suppressive mechanisms towards resistin. In contrast, Lee and co-workers (46) reported that neither transcriptional regulation of resistin nor circulating resistin levels correlated with serum insulin or glucose levels. Furthermore, although resistin mRNA levels were increased in insulin-resistant rats, no apparent change in insulin sensitivity was observed (3). In evaluating resistin and its association with insulin sensitivity in humans, several studies have identified positive correlations between resistin levels and insulin resistance *in vivo* (46) and *in vitro* (48). Additionally, serum resistin levels were increased by approx. 20% in T2DM subjects (4), such findings have been re-affirmed by Fujinami *et al*., (50). In contrast, other studies have reported no associations between serum resistin levels and markers of insulin resistance in T2DM patients (50,51) or insulin-resistant patients.

Effect of resistin on glucose homoeostasis

Recently, it has been reported that transgenic mice over expressing resistin exhibited impaired insulin-mediated glucose transport (23). This altered glucose metabolism appeared to occur without affecting insulin receptor signalling, therefore acting by reducing the intrinsic activity of cell-surface glucose transporters (23). Lazar and co-workers (10) have recently shown resistin induced the expression of SOCS (suppressor of cytokine signalling)-3, a known inhibitor of insulin signalling. Moreover, the loss of SOCS function was shown to impair resistin from antagonizing insulin action in adipocytes (10). This suggested that the insulin-independent action of resistin on adipocytes could partly be mediated by SOCS-3, which could have an impact on normal glucose homoeostasis (10). This worsening of glucose homoeostasis was shown to be entirely attributable to the severely impaired insulin-mediated suppression of hepatic gluconeogenesis, rather than peripheral insulin resistance (36). The study consequently suggested that fat and gut-derived resistin and RELM-β may have clear and rapid effects on stimulating the rate of hepatic glucose production, as opposed to increasing glucose uptake or influencing peripheral insulin sensitivity (36). Furthermore, this supported the notion of the existence of a feedback mechanism between adipose tissue and insulin-target organs, such as the liver. These findings have been reinforced by studies showing that the ablation of the resistin gene in mice lowering fasting glucose levels through reducing hepatic glucose production without significantly altering whole-body glucose disposal (59). This study showed that improvement in glucose homoeostasis was partly mediated via increased activation of hepatic AMPK (AMP-activated protein kinase) with reduced gene expression of the gluconeogenic enzymesG6Pase (glucose 6-phosphatase) and PEPCK (phosphoenolypyruvate carboxykinase) (60). Rangwala *et al.,* (60) documented that mice with chronic hyper-resistinaemia exhibited higher blood glucose levels and impaired glucose tolerance; this was associated with increased hepatic glucose production, partially due to increased hepatic expression of gluconeogenic enzymes. Nonetheless, impairment of normal glucose homoeostasis caused by chronic hyper-resistinaemia may require more severe measures to counter regulate these effects. Studies in Pima Indians have reported serum resistin levels were not associated with fasting glucose and insulin levels, although they were proportional to the degree of adiposity (41). Additionally, one study indicated serum resistin levels were inversely correlated with glucose disposal rates, whereas others indicate a modest effect of resistin on glucose uptake *in vitro* (43). Collectively, resistin transgenic and gene-deletion studies in rodents have provided evidence that resistin may have a predominant physiological role in the liver by contributing to the regulation of fasting blood glucose levels.

Human Genetic Studies of Resistin

Several groups have investigated whether the human resistin locus is associated with increased susceptibility to diabetes or obesity. Two studies have found an association with obesity but not with type 2 diabetes. In a study of nondiabetic population of Quebec, Canada, two single-nucleotide polymorphisms (SNPs) associated with the 5′ flanking (promoter) variants were associated with body mass index (53). Examination of the same variants in a Scandinavian population did not show this association, and neither population had any association with diabetes (53). Another study conducted among whites in Boston, Mass., USA, found eight SNPs in the 5′ flanking and intronic regions of the resistin gene (54). This study failed to identify association with type 2 diabetes but did identify a SNP associated with obesity (53). Two studies found associations of the resistin gene with changes in insulin sensitivity but not obesity. Pizzuti *et al.,* (54) examined an Italian population of nondiabetics and found that an allele of an ATG triplet repeat in the 3′ untranslated region is associated

with lower fasting insulin, insulin resistance index, and serum triglycerides, suggesting a higher insulin sensitivity. Wang *et al*., (55)identified additional resistin SNPs which also were not associated with type 2 diabetes, but the SNP in the promoter region was a determinant of insulin sensitivity index. Several studies did not find an association of resistin with either diabetes or obesity. Sentinelli *et al*., (56) discovered no sequence variants in the coding sequence, and a mutation in the 3′untranslated region was not associated with either diabetes or obesity. In a study of a Japanese population the identification of three intronic SNPs in 24 patients failed to identify any association with type 2 diabetes compared to controls (57).

Furthermore, a resistin genotype at nucleotide +299 (IVS2+181G→A) and obesity was a significant determinant of T2DM risk among Type II diabetic Caucasians in Boston (MA, U.S.A.) [Ma, X.,] the −420C→G SNP (−180 relative to putative transcription start site) was associated with higher resistin mRNA levels in abdominal fat of obese subjects (53). Mattevi et al. (58)showed an association between the −420C→G polymorphism with lower BMI in non-diabetic individuals from a Brazilian population of European descent, although, among non-diabetic Caucasians in Sicily and Gargano (Italy), anATGtriplet repeat in the 3_-untranslated region of the resistin gene was associated with a decreased risk of insulin resistance (54). Elevated levels of serum resistin were reported in T2DM subjects carrying the −420G/G genotype (2). In contrast, studies in a Japanese obese population reported the −638G→A, −420C→G, and −358G→A SNPs, which although associated with serum resistin, did not confer any association with obesity or insulin resistance (57).

Conclusion

This review conclude that upregulation of resistin expression in cases of obesity and insulin resistance indicates that resistin may play a part in the development of insulin resistance. Resistin appears to play a much larger role in inflammation than obesity or insulin resistance. Yet,inflammation can play a major role in the development of obesity and insulin resistance. Some genetic studies have demonstrated an association between resistin and insulin resistance and obesity.

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