Juniper Online Journal of Case Studies
ISSN: 2476-1370

Juniper Publishers
key to the Researchers

Review Article
Volume 6 Issue 3 - March 2018
DOI: 10.19080/JOJCS.2018.06.555686

JOJ Case Stud

Resistin, Is There any Role in the Mediation of Obesity, Insulin Resistance and Type-II Diabetes Mellitus?

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Submission: February 21, 2018; **Published:** March 05, 2018

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Abstract

Resistin is a member of a class of cystein-rich proteins collectively termed as resistin-like molecules. Resistin has been implicated in the pathogenesis of obesity-mediated insulin resistance and T2DM (Type II diabetes mellitus). In addition, resistin also appears to be a pro-inflammatory cytokine. Taken together, resistin, like many other adipocytokines, may possess a dual role in contributing to disease risk. However, to date there has been considerable controversy surrounding this 12.5kDa polypeptide in understanding its physiological relevance in both human and rodent systems. Furthermore, this has led question, whether resistin represents an important pathogenic factor in the etiology of T2DM or not. In this review, authors have made an attempt to discuss the key controversies and developments made so far towards the involvement of resistin molecule in the causation and progression of obesity and type II diabetes mellitus and factors associated with alteration in the expression of this magic molecule at physiological and genetic levels.

Keywords: Resistin; Obesity; T2DM; Insulin resistance

Introduction

Adipose tissue is known to produce a vast array of adipocyte-derived factors, known as adipocytokines. Under normal physiological conditions adipocytokines may play an influential role in energy homoeostasis, triacylglycerol (triglyceride) storage and mobilization of fat, with increased adiposity, specifically central adiposity. These processes can be substantially dysregulated [1]. Furthermore, apparently the pathogenesis of T2DM (Type II diabetes mellitus) is mediated through the concurrent progression of insulin resistance and subclinical inflammation, although the molecular mechanisms for this are less understood. It is, however, apparent that obesity represents one of the foremost contributory factors leading to diabetes, as such; the expression and functional properties of adipocytokines and their effects on metabolism have been the subject of intense research. Indeed, studies on adipocytokines and their potential effects in human obesity and T2DM have implicated them in the pathogenesis of the metabolic syndrome. Such factors include TNF-α (tumour necrosis factor-α), IL (interleukin)-6, angiotensinogen, leptin, PAI-1 (plasminogen activator inhibitor-1) and resistin. This review will address our current understanding of the pathophysiological role of resistin, and evaluate resistin as a pathogenic factor implicated in metabolic mechanisms leading to the development of T2DM. In addition, we will highlight the continuing complexity of the biology of resistin and its role in the progression of disease and the potential interplay between several mechanisms associated in the pathogenesis of T2DM.

Since the discovery of resistin in 2001, there have been over 260 publications that have informed our present understanding of its function. This has paradoxically created a maelstrom of controversy and ambiguity surrounding the functional significance of resistin. Indeed, researchers outside the field of resistin over the last few years have been unclear as to whether this molecule may deserve much attention as an important pathogenic factor in the progression of obesity-mediated diabetes. Nevertheless, although several questions remain unanswered to date regarding resistin, one question remains pertinent to all others, what is the precise physiological function of resistin? Although this is not necessarily an easy question to answer and this review may only highlight some aspects of resistin in disease, it is clear that the physiological role of resistin is more complex than originally envisioned. Despite an incomplete current understanding of the role of resistin, this review will assemble and discuss some of the existing literature

on resistin evaluating the current metabolic effects of this protein, with the intent of providing an insight as to where the role of resistin may lie.

The Discovery of Resistin

Resistin, a putative adipocyte-derived signaling polypeptide, was originally identified by three independent groups using a variety of techniques [2,3]. Initial studies showed that resistin was up-regulated in rodent models of obesity and insulin resistance and down-regulated by an insulin-sensitizer, RSG (rosiglitazone) [3]; however, immunoneutralization of resistin reduced hyperglycemia and improved insulin sensitivity [3]. These observations not only brought resistin to much scientific attention, but characterized it as a potential etiological link between obesity and diabetes, with a clear functional role as a pathogenic factor contributing to insulin resistance. Additionally, this revealed possibilities of the mechanistic action for TZDs (thiozolidinediones) and their subsequent therapeutic applications.

The Metabolic Role for Resistin: An Ongoing Debate

Resistin and obesity

Since the initial investigation of resistin in numerous rodent models of obesity and insulin resistance [3,4], ongoing experimental data has generated further inconsistency. Human studies have highlighted increased resistin expression in adipose tissue [5], particularly abdominal depots [6,7]; furthermore, positive correlations between serum resistin and body fat content have also been reported [8]. On the contrary, several studies have failed to demonstrate such correlations in rodents, with groups also reporting either reduced [9-11] or no alteration [12] of resistin levels in various models of obesity. Although it is difficult to address such diverse findings using similar, and in some instances the same, rodent models, inconsistencies may depend upon methodological differences [13].

Studies by [14] showed that various murine models of obesity had higher circulating resistin levels compared with their lean counterparts. These observations coincided with rodent studies by Rajala and coworkers [15], showing circulating resistin levels significantly elevated and concordant with increasing levels of insulin, glucose and lipids; thus substantiating the initial evidence that addressed the etiology of resistin with increasing adiposity [3]. Recently, [16] 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, in view of this and previous studies [17], it was suggested that elevated resistin expression was a result of adipocyte differentiation [16]. 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 [16]. Therefore, at least in rodents, a regulatory feedback mechanism for resistin in adipogenesis may occur, acting as an adipose sensor for nutritional status. In accordance with these observations, [18] generated transgenic mice over expressing a dominant inhibitory form of resistin which functioned to block the inhibition of resistin mediated adipocyte differentiation. These transgenic mice developed obesity, possibly owing to enhanced adipocyte differentiation and adipocyte hypertrophy, as indicated by increased circulating levels of adiponectin and leptin [18].

Recent investigations of human resistin in relation to obesity have shown higher serum resistin levels in obese subjects compared with lean subjects [19-21], which positively correlated with the changes in BMI (body mass index) and visceral fat area [21-23]. The implication that resistin is important in human adipose tissue has been corroborated by studies showing increased protein expression with obesity [23], as well as protein secretion from isolated adipocytes [24]. These recent observations are concomitant with initial studies that showed increased serum resistin levels [8] and gene expression levels in abdominal depots [6,7] in states of increased adiposity. A further study has shown significant reduction in circulating resistin levels following moderate weight loss and post-gastric bypass [19]. Collectively, these observations suggest resistin could indirectly be subjected to nutritional regulation in humans.

Resistin, insulin resistance and T2DM

It is currently established that central obesity is a contributing factor to the pathogenesis of insulin resistance and consequently to T2DM. Although, it is apparent that inconsistencies remain in the data for a role of resistin in obesity, there is a growing body of evidence suggesting a role for resistin in the etiology of insulin resistance and T2DM.

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* [25] and *in vitro* [26]. Additionally, serum resistin levels were increased by approx. 20% in T2DM subjects [24], such findings have been re-affirmed by [27]. In contrast, other studies have reported no associations between serum resistin levels and markers of insulin resistance in T2DM patients [28-30] or insulin-resistant patients [31]. Moreover, serum and plasma resistin levels were either reduced or increased in T2DM patients with no significant correlation with HOMA-IR (homoeostasis model assessment for insulin resistance), waist circumference, BMI or total cholesterol [32,33]. Consequently, these studies suggest resistin is unlikely to play a critical endocrine role in insulin resistance or energy homoeostasis in humans. Nevertheless, a paracrine or autocrine manner of resistin to moderately affect metabolism cannot be ruled out.

Human genetic studies of resistin

Several SNPs (single nucleotide polymorphisms) have been identified in the *Retn* gene, but only few have minor allele

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frequencies over 5% and are associated with disease risk [34-36]. Therefore further confusion ensues when reviewing genetic studies examining associations between resistin and disease. In a study of non-diabetic French Canadians in Quebec [34], two *Retn* 5'-flanking SNPs (−537 and −420) were associated with increased BMI. 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.) [37]. Additionally, the −420C→G SNP (−180 relative to putative transcription start site) was associated with higher resistin mRNA levels in abdominal fat of obese subjects [26]. Conversely, [35] 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), an ATG triplet repeat in the 3' -untranslated region of the resistin gene was associated with a decreased risk of insulin resistance [38].

Genetic analysis of resistin using a Japanese population demonstrated that a −420G/G genotype was associated with T2DM and could accelerate the onset of disease by 4.9 years [35]; moreover, the genotype itself was a primary variant determining T2DM susceptibility [36]. Consistent with these findings, elevated levels of serum resistin were reported in T2DM subjects carrying the −420G/G genotype [39]. In contrast, studies in a Japanese obese population reported −638G→A, −420C→G, and −358G→A SNPs, which although associated with serum resistin, did not confer any association with obesity or insulin resistance [40,41]. These genetic studies highlight the discrepancies in resistin SNP analysis examining the association with obesity related insulin resistance; these may partly be explained by different genetic backgrounds or environmental conditions of the populations studied. So, further studies on the physiology of resistin and genetic implications for the development of this disease are therefore crucial.

Conclusion

Though, literature is full of studies supporting the correlation of resistin with obesity and insulin resistance in both clinical and experimental laboratory models, but at the same time, handful contradictory reports again forced to the scientists to look into the genetics and other triggering factors involved in the expression of resistin. So, these can be accounted prior to make any final recommendations on this magic molecule as an investigative/diagnostic tool for early detection of risk of two of the major health problems of the day i.e., obesity and type II diabetes mellitus.

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DOI: 10.19080/JOJCS.2018.06.555686

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