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Mini Review

Resistin: An Atypical Adipokine in Metabolic Syndrome

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Abstract

Both obesity and Type 2 Diabetes Mellitus (T2DM) have become a global epidemic. Not only are numbers of adults with obesity and T2DM increasing; the number of children both developing obesity and developing T2DM is also increasing at an alarming rate. A molecular link exists between obesity and T2DM. Adipose tissue, once believed to be just a storage depot for triglycerides, has been classified as an endocrine gland, releasing adipocyte-specific cytokines termed adipokines. These adipokines influence glucose sensitivity and insulin resistance, providing the molecular link between obesity and T2DM. Such is the association between these two that the term Diabesity has been employed to collectively refer to them. One such adipokine, Resistin, has been the center of much debate. Originally identified in mice to be secreted from adipocytes, the adipokine was found to convey insulin resistance, with levels increasing in response to increasing adiposity. However, the human form of Resistin is secreted from Peripheral Blood Mononuclear cells and vascular cells. In humans, Resistin plays mainly an autocrine and paracrine action on the cells comprising the white adipose tissue environment, contributing to the chronic low-grade inflammation seen in obesity-related White Adipose Tissue depots. Resistin also plays an endocrine function, modulating vascular smooth muscle cells, as well as increasing Low Density Lipoprotein uptake. Resistin, an atypical adipokine, therefore plays a significant role in the pathogenesis of certain aspects of obesity-related metabolic syndrome.

Keywords: Adipokine; Diabesity; Metabolic Syndrome; Obesity; Resistin; Type 2 Diabetes Mellitus

Abbreviations:

BMI	:	Body Mass Index
CAM	:	Cell Adhesion Molecule
IL	:	Interleukin
NF-κB	:	Nuclear Factor Kappa-B
PBMC	:	Peripheral Blood Mononuclear Cells
T2DM	:	Type 2 Diabetes Mellitus
TLR4	:	Toll-Like Receptor 4
TNF- α	:	Tumor Necrosis Factor- α
WAT	:	White Adipose Tissue
WHO	:	World Health Organization

Obesity & Metabolic Syndrome

The prevalence of obesity is increasing at an alarming rate worldwide. Such is this rate of increase; the World Health Organization (WHO) has designated obesity as an epidemic, branding it one of the most serious public health challenges of the 21st century [1]. Recent figures show that almost 2 billion people are classified as overweight, with half a billion-people classified as obese. An alarming incidence of childhood obesity is on the increase too, with over 40 million pre-school children classified as obese

Both the condition of being overweight and obesity can be defined as an excessive accumulation of body fat, presenting increased risk to the individual's health. Attributable to obesity are predispositions to Type 2 Diabetes Mellitus (T2DM), ischemic heart disease, and even certain strains of cancer. The standard criteria to determine body composition is Body Mass Index (BMI); a ratio of height and weight. Although a crude estimate of composition, it provides a relative accurate prediction of an

individual's composition. According to the BMI scale, greater than or equal to 25 is classified as overweight, with a BMI of 30 or above obese. The obese category can be further subdivided to morbidly obese; a BMI of 40 and above [1].

For most individuals, the occurrence of overweight can be attributed to an imbalance in calorific values; the intake amount of calories being far greater than calorie expenditure. Surplus calorie intake leads to accumulation of visceral fat, and the development of metabolic syndrome. These are key steps to development of obesity-related T2DM [2]. However, increased calorie consumption is not the only contributor to obesity. A genetic element exists with obesity, with over 300 Single Nucleotide Polymorphisms (SNPs) related to obesity identified to date [3]. Altered thyroid function can also contribute to increased weight gain.

Metabolic syndrome is a multi-factorial condition whose etiology stems from an increase in visceral adipose tissue. Although there are many different criteria for metabolic syndrome, the WHO classically define Metabolic syndrome as having one form of high blood glucose, such as T2DM, impaired glucose tolerance or fasting glucose, or insulin resistance. Two of the following are also required accompanying the above for metabolic syndrome; high blood pressure (≥140/90mmHg), dyslipidemia in the form of low High-density lipoprotein and/or high serum triglycerides, central obesity (BMI ≥30kg/m^2) or microalbuminuria [2].

Adipose Tissue as an Endocrine gland

Adipose tissue exists in two distinct forms; Brown Adipose Tissue and White Adipose Tissue (WAT). Most commonly associated with obesity, WAT was previously considered solely as a passive energy reservoir, providing thermal insulation and thermogenesis [4]. However, WAT is now considered as the largest and most complex endocrine gland within the human body. WAT is now known to comprise of a multi-cellular environment, secreting large quantities of cytokines, lipids, metabolites and adipocyte-specific cytokines termed "Adipokines". These adipokines have been the source of extensive research, and can act on an autocrine, paracrine and endocrine level [5].

WAT consists of a complex plethora of cell types. Embedded with adipocytes are white blood cells such as monocytes/ macrophages, T cells and dendrocytes, endothelial cells, as well as fibroblasts. Each cell type within the complex cellular mixture, the WAT depot has the ability to regulate and be regulated by the cells surrounding it. WAT is also innervated by the sympathetic nervous system; the hypothalamus playing a regulatory role on lipid homeostasis. Taken together, the WAT depot has the ability to influence itself, as well as peripheral actions on glucose homeostasis and central influences on appetite and satiety.

Adipokines, named from their source of secretion, are small signaling molecules regulating numerous biological functions, such as glucose and insulin homeostasis, satiety, synaptic plasticity, adipogenesis, as well as lipid metabolism [6]. Increase in adipocyte size, such as occurs during obesity, causes dysregulation of the WAT depot, altering homeostasis within its structure. This shift in balance plays a key and complex role in the development of obesity-related diseases such as insulin resistance (T2DM), as well as metabolic disease and cardiovascular disorders such as stroke [7].

Resistin as an Adipokine

One of these adipokines, Resistin, has a controversial and contradictory function across species. Originally identified in mice by three different research groups, Resistin, also known as FIZZ3, was first identified as an adipocyte-specific cytokine. It is generally accepted that serum Resistin levels raise in both diabetic and obese mouse models in response to acute hyperglycemiain both genetic and diet-induced obese mouse Models [8]. This increase results in induction of insulin resistance and glucose intolerance, as well as hyperglycemia and increased plasma fatty acid concentrations [9]. This increase in susceptibility to insulin resistance can also be seen in mice expressing a humanized form of Resistin [10].Although several other isoforms of Resistin exist (see Table 1), Resistin remains the most well studied of the RELM family [9].

Name	Species	Location	Function
Resistin	Humans, rodents	Rodents: Adipocytes, Humans: Peripheral Blood Mononuclear cells, vascular Smooth Muscle Cells	Rodents: Insulin resistance, Humans: Immune responses
RELMα	Rodents	Adipocytes	Induction of innate and adaptive immune response
RELMβ	Humans, rodents	Goblet cells	Localized gut immune response
RELMγ	Rodents	Hematopoietic cells	Unknown; Possibly cytokine

Table 1: The Resistin Superfamily**.** Four variants of Resistin are known to date, with only two expressed in humans. All Resistin-Like Molecule (RELM) variants act in an inflammatory mediation capacity, with only Resistin producing insulin-desensitizing effects.

In humans however, there is very little expression of Resistin mRNA in adipose tissue. Resistin is mainly found expressed in Peripheral Blood Mononuclear Cells (PBMCs) [11], with expression of Resistin increasing on differentiation of PBMCs to macrophages. Similarly to mice, it is generally accepted that as obesity increases and infiltration of macrophages occurs in WAT depots, levels of Resistin also increase [9]. Since Resistin is predominantly found in PBMCs rather than adipocytes, Resistin belongs to the WAT depot rather than adipocytes, and is increased therein upon macrophage infiltration. Therefore, based on its origin

in humans, Resistin can be considered an atypical adipokine.

Interestingly, the functional data seen in rodents also does not correlate well in Humans. Although human adipocytes also produce and secrete Resistin, it is not the primary source of the protein [12]. The majority of human Resistin still originates from the WAT depot; however the primary cell type secreting Resistin being PBMCs rather than adipocytes[11]. Resistin levels therefore can still be found within the WAT depot. It is implied that Resistin is involved in a more inflammatory-like response rather than an insulin desensitizing response, a characteristic that is reflected in all RELM isoforms [9]. This inflammatory response, somewhat similar to that of Tumor Necrosis Factor- α (TNF- α) [12], is believed to link human Resistin with atherosclerosis and cardiometabolic disease [13].

The precise receptor for human Resistin has yet to be identified. Currently, it is proposed that Resistin binds to the Toll-Like Receptor 4 (TLR4), stimulating an intracellular signaling cascade resulting in activation of Nuclear Factor Kappa-B (NF-κB) [14]. This in turn upregulates the expression of Cytokines, activating the Innate immune system. In cultured monocytes, activation of adenylyl cyclase-associated protein 1 also leads to NF-κB activation, resulting in the production of inflammatory cytokines such as Interleukin (IL)-6, TNF α, and IL-1β [15]. These cytokines are proposed to induce an autocrine and paracrine effect on the surrounding WAT depot, exacerbating the chronic low-grade inflammation seen in diabesity and obesity-related metabolic disorders [9].

Resistin and Metabolic Syndrome

Metabolic syndrome consists of a group of interrelated clinical disorders. These disorders act as risk factors to increase the risk of the development of T2DM and cardiovascular-related disorders. The role Resistin plays in the progression of metabolic syndrome remains controversial to date.

What makes the role of Resistin in metabolic syndrome controversial is firstly the location and function of Resistin, as well as correlations to serum concentrations. Unlike rodent Resistin, human Resistin is found in PBMCs rather than adipose tissue. The true receptor for Resistin in humans still remains elusive, adding to the supposition of a biological function. Several studies have demonstrated correlations of Resistin with metabolic syndrome risk factors. However, finding associations with a multi-faceted syndrome is difficult. In addition, Resistin is believed to have autocrine and paracrine activities, localizing Resistin's actions to the WAT depot, negating the need for elevated serum levels.

Resistin and Insulin Resistance

In mice, Resistin is expressed in adipose tissue and secreted in response to increased adiposity. Circulating Resistin levels have been demonstrated to decrease sensitivity to insulin. This prompted initial human studies to investigate the role of human Resistin in the pathogenesis of T2DM and insulin resistance. Studies investigating the relationship between circulating Resistin levels and insulin resistance have generated conflicting results, with some studies showing positive correlation [16] while other fail to identify any significant differences [17].

The effects of humanized Resistin in mice produce similar results to those obtained with native murine Resistin. A humanized Resistin transgenic mouse model, expressing PBMC Resistin and lacking adipose-derived Resistin, developed insulin resistance in muscle and in adipose tissue. This was also accompanied by inflammation localized to the WAT Depot [18]. In other studies, using human Resistin, Lipopolysaccharide produced an increase in Resistin release with development of hepatic insulin resistance. Both studies however demonstrated an increase in inflammation [10]. Taken with a lack of correlation in human studies of serum Resistin and insulin resistance, many researchers were deterred from pursuing Resistin as a marker of insulin desensitivity, pursuing its role in inflammation instead [9].

Resistin and Inflammation

It appears more likely that the effect of Resistin on metabolic syndrome is mediated through an inflammatory role. Human Resistin circulates as multimers; the oligomeric form of Resistin having a more potent stimulatory effect on pro-inflammatory cytokine release [19]. Human Resistin is localized to PBMCs, where release of Resistin is increased on monocyte differentiation [11]. Resistin was also found to be present in cell types accumulated within WAT depots, contributing to the chronic sub-clinical low-grade inflammation that accompanies increased adiposity in diabesity [20].

Human Resistin has been shown to be both released from PBMCs, as well as acting on PBMCs. Within the WAT depot, this results in both autocrine and paracrine actions on PBMCs. Activation of PBMCs by Resistin upregulates the expression of pro-inflammatory mediators such as the Interleukins IL-1β and IL-6, as well as increasing its own production through positive feedback mechanisms [21]. Also induced is TNFα, a pro-inflammatory cytokine known to cause insulin Resistance [22]. Therefore, Resistin induction by chronic low-grade inflammation in the WAT depot further enhances and maintains the inflammatory response locally through positive auto-regulatory feedback mechanisms. Based on the autocrine role of Resistin, serum Resistin levels may be the cause of secondary effects of Resistin; the primary effects of inflammation occurring in the WAT depot.

Resistin & Atherosclerosis

It is well known that Resistin is not only a biomarker of atherosclerosis, but also mediates atherosclerotic processes[23]. In addition to PBMCs being a primary target for Resistin, vascular cells have also been identified key to Resistin's function. Expression

and synthesis of Resistin can be found in vascular cells of the WAT depot, as well as in atherosclerotic lesions [24]. Systemically, levels of circulating Resistin can be correlated with inflammatory markers, such as TNF-α and IL-6 [21]. Resistin's effects on vascular dysfunction are caused by decreasing vascular smooth muscle cellNitric Oxide production, as well as increasing Cell Adhesion Molecules (CAMs) such as VCAM1 and ICAM1 [25].

Circulating Resistin levels also correlate with increased endothelial cell activation markers. Serum levels of Endothelin-1 for example are increased in patients with unstable angina [26]. Resistin increases uptake of oxidized Low Density Lipoprotein by macrophages promoting foam cell production, a key step in the development of atherosclerotic plaques [24]. Given that inflammation can promote atherosclerotic progression, Resistin's role in atherosclerosis is likely to gain considerable further investigation.

Conclusion

Resistin, an atypical adipokine exerts its effects mainly on an autocrine and paracrine basis. Contrary to its rodent counterpart, human Resistin appears to be a mediator of inflammation, originating from PBMCs and vascular cells, and exerting its effects within the WAT depot, maintaining chronic low-grade inflammation. Resistin's capabilities as an inflammatory mediator not only accentuates the inflammatory response, but influences vascular-mediated events at an endocrine level. Without a bona fide receptor for Resistin, the exact function of this adipokine remains elusive, while efforts are likely to focus on its role in cardiovascular disease.

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