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Invited critical review

Resistin: Insulin resistance to malignancy

Pilar Codoñer-Franch [a,b,*], Eulalia Alonso-Iglesias [c]

[a] Department of Pediatrics, Dr. Peset University Hospital, Valencia 46017, Spain
[b] Department of Pediatrics, Obstetrics and Gynecology, University of Valencia, Valencia 46010, Spain
[c] Department of Biochemistry and Molecular Biology, University of Valencia, Valencia 46010, Spain

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ABSTRACT

Adipose tissue is recognized as an endocrine organ that secretes bioactive substances known as adipokines. Excess adipose tissue and adipose tissue dysfunction lead to dysregulated adipokine production that can contribute to the development of obesity-related co-morbidities. Among the various adipokines, resistin, which was initially considered as a determinant of the emergence of insulin resistance in obesity, has appeared as an important link between obesity and inflammatory processes. Several experimental and clinical studies have suggested an association between increased resistin levels and severe conditions associated with obesity such as cardiovascular disease and malignancies. In this review, we present the growing body of evidence that human resistin is an inflammatory biomarker and potential mediator of obesity-associated diseases. A common pathway seems to involve the combined alteration of immune and inflammatory processes that favor metabolic disturbances, atherosclerosis and carcinogenesis. The mode of action and the signaling pathways utilized by resistin in its interactions with target cells could involve oxidative and nitrosative stress. Therefore, resistin could function as a key molecule in the complications of obesity development and could potentially be used as a diagnostic and prognostic marker.

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1. Introduction

Obesity is associated with significant adverse health effects, known as "co-morbidities," such as hypertension, dyslipidemia, insulin resistance (IR), diabetes and fatty liver disease that lead to an increased risk of cardiovascular disease. Obesity also predisposes our body to several other apparently unrelated diseases such as asthma or cancer [1]. Although these associations have been unquestionably proven in clinical studies, the mechanisms behind these facts remain unexplained.

Adipokines are cytokines produced mainly by adipose tissue (the basis of the name is "adipose tissue cytokines") that play an important

Abbreviations: ER, endoplasmic reticulum; HDL, high density lipoprotein; IL, interleukin; IR, insulin resistance; JAK/STAT, Janus kinase/signal transducer and activator of transcription; LDL, low density lipoprotein; MAPK, mitogen-activated protein kinase; MetS, metabolic syndrome; NASH, non-alcoholic steatohepatitis; NF-κB, nuclear factor kappa B; NO, nitric oxide; *Retn*, gene coding for resistin; ROS, reactive oxygen species; T2DM, type 2 diabetes mellitus; TNFα, tumor necrosis factor α; TLR4, toll-like receptor 4; UPR, unfolded protein response.

* Corresponding author at: Department of Pediatrics, Dr. Peset University Hospital, Avenida Gaspar Aguilar, n° 90, 46017 Valencia, Spain. Tel.: +34 961622389; fax: +34 963864815.
E-mail address: pilar.codoner@uv.es (P. Codoñer-Franch).

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role in short and long term energy balance, metabolism and inflammatory responses, and therefore they are thought to play a role in the diverse consequences of obesity [2]. Adipokines are produced by several cell types in adipose tissue. In addition to adipocytes that represent one-third of adipose tissue cells, infiltrating leukocytes, and vascular endothelial and stromal cells including macrophages and fibroblasts are also involved in this function [3]. The amount and proportion of the various types of cells in fat masses in different areas of the body area were found to be quite different. Compared to subcutaneous adipose tissue, ectopic fat located in the omentum (visceral fat) or around the heart (epicardial or mediastinal fat) contains a larger number of inflammatory and immune cells. Indeed, this ectopic fat mainly contributes to chronic low-grade inflammation accompanying the obesity [4].

Among the adipokines, resistin has raised considerable research interest in recent years [5]. Although adipocyte-specific in rodents, in humans this circulating hormone is predominantly expressed as an inflammatory molecule in macrophages [6]. It is now clear that the physiological role of resistin is more complex than originally described. The focus has switched from resistin being a molecular link between obesity and IR to its putative role as a biomarker of cancer promotion and progression in obese subjects. Interestingly, the common pathway between these two conditions involves metabolic diseases and inflammation.

This review summarizes the recent knowledge in this field of research. We have highlighted current evidence and discussed actual controversies surrounding the relationship between resistin and IR and other obesity-related metabolic changes. Moreover, the possible mechanisms underlying atherosclerosis and resistin are reviewed linking to chronic low-inflammatory state. Finally, its potential role in the development of malignancies has been explored. This review also discusses potential mechanisms of resistin action based on data from animal and human clinical studies.

2. Resistin: the molecule

Initially reported as an "adipose-tissue-specific secretory factor" [7] and "found in inflammatory zone 3" [8], the name resistin ("resistance to insulin") was introduced in 2001 by Steppan et al. [9] to describe a small circulating mouse protein that was specifically expressed and secreted by adipocytes and the serum levels of which increased markedly in mouse models of genetic and diet-induced obesity. Interestingly, two crucial observations from this pioneer work suggested the role of this protein in glucose metabolism and IR. First, the circulating levels of resistin "in vivo" and its expression in adipocytes "in vitro" were downregulated by rosiglitazone, an anti-diabetic drug of the thiazolidinedione family that enhances sensitivity to insulin. Second, experimental manipulation of circulating levels of resistin in mice was shown to affect blood glucose and insulin function. For example, resistin immunoneutralization improved IR in diet-induced obese mice, whereas the opposite was observed in normal mice treated with recombinant resistin. These results were reproducible in insulin-stimulated glucose uptake experiments in cultured adipocytes [9]. The potential pathophysiological and clinical significance of this discovery has triggered several efforts to clarify the specific role of resistin in obesity-induced IR and diabetes in humans. However, in contrast to mice, the primary source of circulating resistin in humans are cells other than adipocytes including peripheral blood mononuclear cells, macrophages and bone marrow cells [10], and inflammatory conditions appear to be the main determinants of circulating levels of resistin [11]. The biology of resistin has turned out to be much more complex than expected, and therefore, the differences in the function and mechanisms of action of resistin between rodents and humans and the implications of resistin in a broader spectrum of pathologies should be considered in current and ongoing investigations.

Resistin is the founding member of resistin-like molecules, a small family of secreted proteins associated with the activation of inflammatory processes [8]. The hallmark of these proteins is a 10–11-cysteine-rich motif at the carboxyl terminus that sustains the globular domain of the resistin monomer through the formation of 5 disulfide bridges [12]. This carboxy-terminal globular domain has been proposed to constitute the receptor-binding site of resistin [13]. Disulfide and non-disulfide bonds were also shown to be important in the formation of higher assembly states (dimers, trimmers and hexamers) for circulating resistin [12,14]. The factors and mechanisms involved in the interconversion between the low and high molecular weight forms of circulating resistin have not been established yet but seem to be relevant to its biological activity and tissue-selectivity. Resistin activity might also be modified by interacting with other members of the resistin-like molecule family and other proteins such as heparanase [15]. Although they have opposite functions, resistin and adiponectin have similar structure and behavior, suggesting a potential avenue for exploring the mechanisms of resistin action.

Despite their suggested common three-dimensional structures, the differences between mouse and human resistin have been demonstrated at the protein and genomic levels [16,17]. Mouse resistin is an 11 kDa polypeptide consisting of 94 amino acids that is synthesized as a longer precursor containing a 20 amino acid signal sequence. The human resistin pre-polypeptide precursor gives rise to a mature molecule of 12.5 kDa (108 amino acids) and shares only a 59% sequence identity with its murine counterpart. At the genomic level, the gene coding for resistin (*Retn*) is located in syntenic regions of the mouse chromosome 8A1 and human chromosome 19p13.3 at a similar distance from the insulin receptor gene. Analysis of their genomic organization reveals major differences including low sequence identity (46.7% and 64.4% at DNA and mRNA levels, respectively), disparity in size with the mouse gene being about three times larger than the human gene and most interestingly, markedly divergent promoter regions and the deletion in the human gene of a very large intron at the 3′UTR region where several regulatory sequences are located [18]. The relevance of these differences in driving the changes in resistin expression and regulation in mouse adipocytes and human immune cells remains to be clearly established. By this way, the loss in the human gene of a peroxisome proliferator-activated receptor gamma binding site implicated in the adipocyte-specific expression of the resistin gene in mice has been considered [17,19]. Recently, the expression of several miRNAs, which are short non-coding RNAs that generally bind to the 3′UTR regions of target genes and inhibit mRNA translation, has been related to glucose homeostasis, adipogenesis and white adipose tissue inflammation [20,21]. Among these miRNAs, miR-492, has been specifically linked to resistin expression [22]. The presence of different 3′UTR regions in the mouse and the human genes might represent a potential target for miRNA-mediated differential regulation of resistin expression.

After more than twelve years of intensive research in the field, it has been clearly established that secreted circulating resistin can exert pleiotropic biological effects through endocrine, paracrine and autocrine mechanisms. An increasing number of cells and tissues are being reported as being responsive to resistin, thus potentially implicating resistin in a wide range of physiological and pathological processes. Of particular clinical interest is the implication of resistin in cardiovascular system function, cancer development and metastasis, and elucidating such interactions requires a detailed knowledge of the mechanisms of resistin action. Unfortunately, these mechanisms, as well as the resistin receptor, are poorly understood. Scattered results have been reported over the past few years using different experimental approaches. For example, it was suggested that, in human myeloid, epithelial and endothelial cells, resistin binds to toll-like receptor 4 (TLR4) to affect nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) downstream signaling mechanisms [23]. TLRs are innate immune receptors that recognize a variety of ligands and mediate the expression of several inflammatory proteins [24,25]. Benomar et al. [26] have also proposed that TLR4 is the "in vivo" receptor for resistin in the hypothalamus and mediates the activation of pro-inflammatory pathways and IR