Resistin- and Obesity-associated Metabolic Diseases

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Abstract
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The link between obesity and diabetes is strong as well as complex. Fat cells produce many circulating regulators of insulin sensitivity, including pro-inflammatory cytokines. In rodents, resistin is produced by adipose tissue, and is a significant regulator of glucose metabolism and insulin sensitivity. In humans, resistin is derived made mainly from macrophages. Given the emerging interrelationship between inflammation and metabolic disease, hyperresistinemia may be a biomarker, and/or a mediator, of metabolic and inflammatory diseases in humans as well as in rodents.

The problem of obesity-associated metabolic diseases
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Diabetes mellitus (DM) is a chronic disease characterized by hyperglycemia and other metabolic abnormalities. The natural history of DM includes numerous complications including heart disease, stroke, kidney failure, blindness, and neuropathy [1]. Aggressive treatment of hyperglycemia reduces these risks [2]. A minority of patients suffer from type 1 DM, caused by pancreatic β-cell failure leading to an absolute loss of insulin. Type 2 DM stems from failure of the body to respond normally to insulin–called "insulin resistance"–coupled with the inability to produce enough insulin to overcome this resistant state. This common form of diabetes is often associated with obesity, and the current epidemics of these two conditions are seemingly related [3]. This is glaringly evident in children, who are increasingly plagued by obesity, and in whom the prevalence of type 2 DM (formerly termed "adult onset") is approaching that of type 1 diabetes (formerly termed "juvenile onset") [4]. The epidemic of diabetes has a huge associated cost in terms of healthcare dollars as well as human morbidity and mortality [5]. Recent studies predict that one in three Americans born in the year 2000 will develop diabetes in their lifetime [6]; the vast majority of cases will be obesity-associated type 2 DM.

The mechanism underlying insulin resistance in type 2 DM is not well understood. Except for sporadic cases, insulin receptor (IR), glucose transporters, and insulin receptor substrates (IRS) are normal [7]. Obesity is strongly associated with insulin resistance and type 2 DM in humans as well as rodent models and, although the connection between increased adiposity and insulin resistance remains a mystery, two critical concepts have emerged over the past decade. The first is that increased adipose tissue is indeed linked to the insulin resistance in key insulin-sensitive tissues such as liver and muscle [8]. The second is that adipose tissue, where the majority of energy equivalents are stored in the body in the form of triglycerides (TG), is an endocrine organ that communicates with other tissues via a host of secreted factors [9, 10].

Adipose tissue as an endocrine organ
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Adipose tissue has long been known to secrete free fatty acids (FFA), the product of TG hydrolysis, in response to the body's demand for energy in times of reduced nutrient supply. It is now recognized that increased serum levels of FFA is an important factor contributing to insulin resistance in peripheral tissues [11]. In addition, adipocytes also secrete a variety of polypeptides including leptin, adipsin, adiponectin, resistin, tumor necrosis factor-α (TNFα), interleukin-6 (IL-6), plasminogen activator inhibitor-1 (PAI-1), and monocyte chemoattractant protein-1 (MCP-1) [12]. A subset of these adipose-derived proteins

is adipocyte-specific, while others are not. In rodents, the adipocyte-specific proteins leptin, adiponectin, and resistin have all been implicated in the modulation of insulin sensitivity. Leptin is an insulin-sensitizing hormone, and deficiency due to leptin gene mutation [13] or reduced adipose mass causes insulin resistance [14,15]. In obese states other than that due to leptin gene mutation, however, leptin levels are markedly increased but leptin action is reduced by concomitant leptin resistance [16]. Another adipose-specific hormone, adiponectin, has insulin-sensitizing properties, but its levels are decreased in obesity, thereby contributing to insulin resistance [17]. Resistin, which in rodents is an adipocyte-specific circulating hormone whose increased levels in obesity promote insulin resistance [18], is the subject of this review and will be discussed at great length later in this section.

Intriguingly, quite a few adipose-secreted proteins that are also secreted by other tissues also play a role in innate immunity, a relatively primitive defense mechanism against infection [19]. Proteins such as tumor necrosis factor-α and interleukin-6 are cytokines that are mainly produced by macrophages. These cytokines directly promote inflammation, and also act on the liver to produce acute phase proteins that contribute to the inflammatory process, and are also produced by adipocytes. A number of these cytokines induce Suppressor of Cytokine Signaling-3 (SOCS-3), an intracellular signaling molecule that impairs the signaling of both leptin and insulin. SOCS-3 levels are elevated in obesity and may thus represent a final common pathway of obesity-associated resistance to the actions of both leptin and insulin [20]. They may also induce cellular insulin resistance via their effects on NF-κB [21] or Jun-kinase [22], in part via serine phosphorylation of the Insulin Receptor Substrates 1 and 2 [23]. Recently, two more molecules produced by fat have been suggested to play a role in glucoregulation. Retinol binding protein 4 (RBP4), although largely produced in liver, is also made by adipocytes, with increased levels in obesity contributing to impaired insulin action [24]. Although the mechanism by which RBP4 regulates glucose homeostasis is unknown, retinoids are known to be potent regulators of immunity [25]. Another adipocyte secreted protein, visfatin, was initially characterized as pre-B-cell colony-enhancing factor, or PBEF [26], yet appears to mimic insulin action [27].

Inflammation and diabetes
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In recent years, an unexpected relationship between inflammation and type 2 DM has emerged. As noted above, several adipocyte-derived factors implicated in insulin resistance are cytokines which are also produced by macrophages. The similarity between macrophages and adipocytes extends beyond cytokine production. Macrophages store abundant amounts of lipid, particularly in states of nutritional excess such as obesity that predispose to atherosclerosic vascular lesions, characterized by lipid-laden macrophages known as foam cells [28]. It has also become evident that macrophage infiltration of adipose tissue is characteristic of obesity [29,30], although the pathophysiological consequences are unknown. The anatomic blurring of the line between adipocytes and macrophages is paralleled by the tissue expression of the polypeptide hormone resistin, whose levels are increased in insulin resistant mice and humans [31,32]. The close relationship between inflammation and diabetes is supported by the observation that stimulation of the

innate immune response, for example by bacterial endotoxin during sepsis [33], results in insulin resistance that contributes to the high mortality of critical illness [34]. The interaction between inflammation and insulin signaling is also suggested by the ability of aspirin to improve insulin resistance, in part by preventing the antagonistic effects of fatty acids and cytokines [35]. Perhaps the response to infection is more effective when glucose is shunted from muscle to the inflammatory cells involved in the immune response and tissue repair [36].

Peroxisome Proliferator Activated Receptor γ (PPARγ) and insulin sensitivity
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PPARγ, a member of the nuclear hormone receptor superfamily of ligand-regulated transcription factors, is the molecular target of the thiazolidinedione (TZD) class of antidiabetic drugs that improve insulin sensitivity throughout the body [37]. PPARγ expression in adipose tissue is 10–100-fold greater than in muscle and liver [38,39] and mice lacking adipose tissue fail to respond to TZD treatment [40,41] whereas mice lacking PPARγ in skeletal muscle retain normal responsivity to TZDs [42]. These observations strongly suggest that the antidiabetic actions of TZDs are mediated by changes in adipose-secreted products; our laboratory and others have hypothesized that the adipocyte-secreted factors altered by TZD treatment are likely to play a role in the pathophysiology of obesity-associated insulin resistance and diabetes [43]. Indeed, TZDs lower plasma FFA levels, by concerted effects on adipocyte FFA uptake [44], recycling [45,46], and release [47] that, together, lead to increased lipid partitioning from the rest of the body to adipose tissue. TZDs also affect the gene expression of adipocyte-secreted products, inducing adiponectin [48,49], while decreasing leptin [50,51], RBP4 [24], and resistin [18,52]. Of note, PPARγ is also expressed at high levels in macrophages, where its role in lipid storage is analogous to its function in adipose tissue [53,54]. PPARγ ligands also have anti-inflammatory actions in macrophages, largely via downregulation of gene expression [55,56].

Resistin: A mediator of insulin resistance in the rodent
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This review is focused on resistin, which we discovered in 2001 as a TZD downregulated gene in mouse adipocytes [18]. Resistin is expressed exclusively in adipocytes in mice [18], but is found predominantly in macrophages in humans [57]. TZDs inhibit resistin gene expression in human macrophages [57,58] and lower serum resistin levels in humans as well as rodents [59–61]. In rodents, evidence is accumulating that resistin impairs insulin sensitivity. Circulating levels of resistin are increased in obesity [31], and an increase in serum resistin levels has been shown to induce insulin resistance in several rat and mouse models, including acute administration [18,62], adenoviral-mediated hepatic gene delivery [63], and transgenic expression [64,65]. All of these studies suggest that hyperresistinemia causes insulin resistance and predisposes to type 2 DM. Consistent with the conclusions from gain of function studies, loss of resistin signaling improves insulin sensitivity and glucose homeostasis in several rodent models including antibody neutralization [18], germline gene mutation [66], reduced gene expression

using antisense oligonucleotides [67], or transgenic expression of a dominant negative form [68].

The structure of resistin is unique, with the exception of a small family of related proteins called Resistin-Like Molecules (RELMs) or Found in Inflammatory Zone (FIZZ) factors [69,70]. All of these proteins are cysteine-rich, with the cysteines in a signature pattern not found in any other known proteins. Mouse pre-resistin is 114 amino acids, and the secreted form consists of 94 amino acids, of which 11 are cysteine. Resistin migrates as a dimer on nonreducing SDS-PAGE gels, and this is entirely due to a single intermolecular disulfide bond involving the most N-terminal cysteine (C26 of the pre-resistin, C6 in the secreted form) of the molecule [71]. The remaining 10 of cysteines form intramolecular disulfide bonds, giving the C-terminus a compact shape [72]. The dimeric form of resistin is active *in vivo* and in cultured cells [72], and retains biological activity *in vitro* and *in vivo* with a Flag epitope at the C-terminus of each resistin molecule [18,73].

Resistin and vascular disease
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Several studies have demonstrated effects of resistin on vascular cell function that might be expected to contribute to vascular disease. Resistin increases the expression of the adhesion molecules VCAM-1 and ICAM-1, upregulates the monocyte chemoattractant chemokine-1, and promotes endothelial cell activation via ET-1 release [74]. In human saphenous vein endothelial cells, resistin promotes proliferation in part by inducing endothelin-1 [75]. In two additional studies, resistin also increased the proliferation of human aortic smooth muscle cells, as well as the expression of adhesion molecules including VCAM-1 and ICAM-1 [76,77]. Resistin also stimulates the macrophage secretion of pro-inflammatory cytokines [78]. Potentially connected to these findings, studies in Japanese and American patients have observed a correlation between increased serum resistin levels and atherosclerosis [79,80]. Excitingly, a study published recently demonstrated increased resistin expression in mouse atherosclerotic lesions, correlating with increased circulating resistin levels in humans with premature coronary artery disease [81].

Resistin signaling
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The signaling mechanism(s) by which resistin impairs insulin action are just beginning to be unraveled. The receptor for resistin is unknown. We have preliminary evidence for resistin binding to mouse hepatocytes and adipocytes, and are attempting to clone the receptor in studies being performed in parallel to those in this proposal, funded by a Freedom to Discover grant from BMS Research Foundation to the PI that is intended to support high risk projects. We are not requesting funding for these studies in this proposal, both because of their risky nature as well as the high cost of the experiments, which would not be feasible to include in the modest budget of the present project. However, the present studies, particularly those in Aim 2, will inform the receptor studies and, likewise, the present studies will benefit from any new information on the receptor (from this lab or elsewhere). Downstream of its putative receptor, resistin appears to inhibit the AMP-activated kinase (AMPK) in liver and, in some reports, muscle [63,66,67]. AMPK serves as a fuel gauge and is known to inhibit hepatic gluconeogenesis and stimulate muscle

glucose uptake [82]. In addition, we have recently observed that resistin activates SOCS-3 in mouse adipose tissue [73]. As noted earlier, SOCS-3 is known to suppress insulin signaling in several tissues [83–86], including adipose tissue [20]. Thus at least two intracellular signaling pathways are likely to be downstream of the resistin and insulin receptors, and contribute to the antagonism of insulin action by resistin.

Critical questions regarding resistin physiology and pathophysiology in the mouse
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Several important questions about these effects of resistin in the rodent remain unanswered. First, what is the relationship between resistin and leptin? The gene expression and serum levels of leptin and resistin are remarkably similar; both have diurnal variation and are higher in fed than in fasted animals. Second, what insulin-responsive tissues are most affected by resistin? This appears to be highly dependent on the model being studied. In the hyperresistinemic rat, insulin action in muscle was affected more than liver [63,64], whereas in the mouse the effects on liver have been pronounced without major changes in insulin signaling observed in muscle [66,67]. The first and second specific aims of this proposal address these important issues. Furthermore, questions have been raised about the physiological role of disulfide linked/dimeric versus reduced/monomeric forms of resistin. A resistin missense mutant without the N-terminal cysteine residue and therefore lacking the intermolecular disulfide bridge was shown to have increased stimulatory activity on hepatic glucose production in euglycemic hyperinsulinemic clamp studies *in vivo* [72]. However, a similar monomeric mutant had little or no activity in cardiac myocytes where wild type dimeric resistin impaired insulin stimulated glucose uptake [87]. These data suggest that the monomeric form may have different activities in different cell types, perhaps under different conditions. Similar tissue specific effects have been demonstrated for different molecular forms of adiponectin [88].

Human resistin
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While many important questions remain, it is clear that adipocyte-derived resistin plays major roles in normal glucose homeostasis as well as in the pathophysiology of insulin resistance in rodents. As with all rodent models, a major question is whether these conclusions translate to the human situation. Two aspects of resistin biology are particularly relevant to this issue. First, although the human and mouse protein sequences are highly related, their identity of ~ 60% is less than usual for hormones with conserved functions across species, although there are precedents such as parathyroid hormone (PTH) which is 70% (59/84 amino acids) identical between mouse and human (BLAST comparison, data not shown); indeed, both mouse and human PTH and PTH-related polypeptide bind to the same receptor despite less than 30% overall amino acid identity (BLAST comparison, data not shown). In the case of resistin, the human and mouse genes are syntenic (on human chromosome 19 and mouse chromosome 8), and exhaustive attempts to find another human resistin gene have been unsuccessful [18,89]. Hence, the gene identified as human resistin is highly likely to be the mouse ortholog. The human and mouse promoter

sequences are also quite divergent [89–91], and in this context it is not surprising that the adipose-specific gene expression of rodent is not recapitulated in humans. Indeed, although resistin mRNA is detectable in human adipose tissue [92], it is expressed at much higher levels in mononuclear cells including macrophages [57,93]. Inflammatory stimuli also induce resistin in human monouclear cells as well as in human serum [58,94].

Given the tremendous potential value of translating the mouse data to the human, it is critical to determine whether levels of resistin are increased in human obesity, insulin resistance, and/ or type 2 diabetes, and whether hyperresistinemia is a contributing factor to these pathophysiological states in humans. Several groups have failed to identify changes in resistin levels in obesity, insulin resistance, or type 2 DM [95–99]. Yet quite a few others, studying diverse populations using different assays, have found significant relationships with one or more of these conditions [32,100–115]. In interpreting the opposing conclusions of some studies, it must be recognized that the resistin assays being used are often quite different from one another, and all are new and not well-validated. Moreover, they are being applied to very diverse populations. In addition, there may be multiple molecular weight forms of circulating resistin. The crystal structure of resistin suggests that it too may form higher molecular weight oligomers that represent noncovalent trimers of the disulfide linked dimeric unit [72]. Indeed, a recent report has documented very high molecular weight forms of resistin in the circulation of children and adults [95]. This is intriguing in light of recent observations that high molecular weight oligomeric forms of adiponectins may be more predictive of insulin sensitivity than the total adipoectin level [116]. This may be another reason why different studies have come to different conclusions about the relationship between hyperresistinemia and disease in humans.

Resistin levels have also been reported to correlate with atherosclerotic cardiovascular disease [79,80,117] as well as C-reactive peptide and other inflammatory factors [79,100,118,119]. The correlation with inflammation is particularly noteworthy given the observation that resistin is produced by macrophages in response to inflammatory signals, and the increasing recognition that obesity, type 2 diabetes, and atherosclerosis are inflammatory diseases. Indeed, proinflammatory cytokines whose levels are increased in obesity and diabetes, such as TNFα and IL-6, dramatically induce resistin in human macrophages [58,120]. Moreover, resistin itself markedly stimulates the expression of proinflammatory cytokines in human mononuclear cells [91]. Thus, the communication between adipocytes and macrophages may lead to hyperresistinemia even if human resistin is mainly expressed in macrophages.

There is also genetic evidence that resistin may play a role in obesity, insulin resistance, and/or type 2 DM in humans. A single nucleotide polymorphism at the promoter region (− 420 C→G) has been significantly linked to obesity and/or insulin resistance in several populations in Europe, Japan, and the United States [32,103,105,121–126]. Intriguingly, this polymorphism introduces an Sp1 site that increases resistin gene promoter activity in transient transfection transcription assays [32,124,127]. This correlates with increased circulating resistin levels in other studies [32,105,128], including one that showed a gene dosage effect of the single nucleotide substitution on serum resistin levels [32]. Meta-analysis of several studies involving over 4000 patients confirmed the relationship between this resistin gene polymorphism and type 2 DM [32]. The large number of cross-sectional and genetic studies in support of a role of resistin in human disease is promising.

Conclusion

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The link between obesity and diabetes is strong, and inexorably increasing as a public health menace. Over the past 10 years, there have been major changes in how scientists view this problem. The fat cell is an endocrine organ, producing many potential mediators of insulin resistance including pro-inflammatory cytokines. At the same time, obesity, type 2 diabetes, and cardiovascular disease are increasingly recognized as having inflammatory components. Resistin is a potential mediator of the obesity-diabetes link. In rodents, resistin expression is limited to adipose tissue, and resistin deleteriously affects glucose metabolism and insulin sensitivity in at least some models. Much still needs to be learned about the scope of resistin functions, and its mechanism of action. In humans, resistin appears to be an inflammatory molecule made mainly in macrophages, but given the interrelationship between inflammation and metabolic disease, and between adipocytes and macrophages, a conserved role of hyperresistinemia in the modulation of glucose metabolism and in the pathogenesis of insulin resistance is quite plausible. Resistin may thus be a biomarker and, potentially, a mediator of metabolic and inflammatory disease that could be targeted by novel therapies aimed at stemming the tide of the epidemic of insulin resistance and its metabolic and cardiovascular complications.

Acknowledgments

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