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Abstract

Resistin is a peptide hormone belonging to the class of cysteine-rich secreted proteins involved in the modulation of inflammation and immunity, particularly in insulin-resistant states. Circulating levels of resistin are elevated in obesity, diabetes and other chronic inflammatory conditions such as Inflammatory Bowel Disease. However, the pathogenic role of resistin in the onset and progression of these diseases is not completely understood and the partial homology of resistin in animal models compared to humans limits our understanding of its physiological role. This review aims to summarize the main mechanisms linking resistin to inflammation as well as its clinical significance in different chronic liver and gastrointestinal diseases.

Keywords: Resistin, Adipokines, Inflammation

Introduction

Resistin was first identified in 2001 and for its ability to induce insulin resistance was considered the missing link between obesity and type 2 diabetes mellitus (DM2).[1] Steppan et al. discovered a new messenger RNA (mRNA), then named resistin, during an experiment performed on 3T3-L1 adipocytes, aimed to find the genes regulated by thiazolidinedione (TZD), involved in the antidiabetic and insulin-sensitizing effects of the drug.[1] In the same years, another group independently confirmed these data during a microarray analysis of WAT.[6] Both human and mouse resistin are encoded by *Retn* gene but the different genomic organization (human resistin is located on chromosome 19 while rodent resistin is located on chromosome 8) and the different promoter regions, indicate different mechanisms of regulation, hence different functions.[2] In mice, resistin in highly expressed by white adipose tissue (WAT) and higher plasma levels were found in genetic obesity models (Ob/Ob).[1] In humans, resistin is mainly secreted by peripheral blood mononuclear cells (PBMCs) but it can also be expressed and upregulated in the liver during chronic injury, promoting the activation of hepatic stellate cells (HSCs) and release of pro-inflammatory cytokines *via* activation of the nuclear factor (NF)-kB signaling pathway.[4] Specifically, resistin is able to upregulate pro-inflammatory mediators such as tumor necrosis factor alpha (TNF-a), interleukin-12 (IL-12), interleukin-6 (IL-6) and the chemokine (C-C motif) ligand 2 (CCL2) or monocyte chemoattractant protein 1 (MCP-1) in macrophages.[5-6]

Resistin: biochemistry and biology

Resistin belongs to the family of FIZZ (found in inflammatory zone) or resistin-like molecules (RELM) reach in cysteine. [1,3] Human resistin is a 108 aminoacids (aa) peptide and is characterized by a signal sequence of 18 aa and by a mature region of 90 aa. The murine counterpart is a 114 peptide including 20 aa signal sequence.[7] Human and murine sequence share about 60% homology and are syntenic. The gene encoding for mouse resistin is located on chromosome 8 while the gene encoding for human resistin is located on chromosome 19. Both murine and human *Retn* are at

similar distance from the insulin receptor gene.[2] In rodents, resistin is up-regulated during adipocytes differentiation, it is primarily released by mature WAT and it can be detected in serum as a high molecular weight hexamer (two trimers linked by disulfide bonds) or as a low molecular weight trimer.[8-9] While most resistin circulates as hexamer, its trimeric form is more bioactive. A mutation in a single cysteine at position 26 determining the aa change from cysteine to alanine (C26A) impairs the ability to form disulfide bonds preventing hexamers formation. The infusion of a mutated protein significantly ameliorates insulin sensitivity during clamp studies.[10]

In humans, resistin is predominantly released by monocytes and macrophages and resistin mRNA increases along with macrophages differentiation.[11] The very low resistin mRNA expression in the adipocytes may be due to the loss of the genomic binding site for peroxisome proliferator-activated receptor γ (PPARγ) which controls the *Retn* gene in mice. Nevertheless, treatment of activated macrophages with rosiglitazone down-regulates by 80% resistin mRNA suggesting that despite the differences in tissue expression, the mechanisms of TZD in the regulation of human and mouse resistin is conserved.[11]

Signaling pathways: in vitro experiments and mouse models

As a secreted peptide, resistin can act both in an endocrine and paracrine manner through specific receptors located on the surface of target organs such as adipose tissue, liver and muscle. To date, two receptors have been found in mice: decorin (a fragment of proteoglycan) and tyrosine kinase-like orphan receptor 1 (ROR1).[12-13]

In vitro experments in HepG2 cells show that resistin is able to modulate glucose metabolism contributing to the development of insulin resistance (IR) through the AMP-activated protein kinase (AMPK)-dependent and -independent suppressor of cytokine signaling-3 (SOCS-3) pathways.[14]

The AMPK pathways are activated by the decrease in the ATP:AMP ratio acting as a sensor of cellular energy status. When AMP levels increase, AMPK activation inhibits energy-consuming pathways, such as protein, fatty acid and glycogen synthesis, and activates ATP-producing

pathways, such as fatty acid oxidation and glycolysis.[15] Luo and colleagues demonstrated that resistin is able to induce IR in HepG2 cells through the induction of SOCS3 expression and through the reduction of the insulin receptor substrate-2 (IRS-2) and the protein kinase B (Akt) phosphorylation, thus leading to the increase of glucose 6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK) and to the decrease of glucose transporter 2 (GLUT2) expression promoting IR.[13] Furthermore, resistin can act as a glucose-dependent insulinotropic polypeptide (GIP) receptor agonist, thus on one hand increasing Akt phosphorylation and the activity of the adipocyte lipoprotein lipase (LPL) and on the other decreasing the liver kinase B1 (LKB1) and AMPK phosphorylation.[16] Resistin can also have a potential role in vascular disorders. In fact, in vitro resistin is able to induce both proliferation and migration of endothelial cells, favoring the release of endothelin-1, to increase the expression of vascular endothelial growth factor receptors (VEGFRs) and of matrix metalloproteases (MMPs) and to activate both the extracellular signal-regulated kinases (ERKs) 1 and 2 and p38 pathways. [17]

In mouse models, resistin levels were found significantly higher in both diet- and genetic-induced obesity and diabetic mice.[1,18-19] The administration of recombinant resistin in wild type mice impaired glucose metabolism promoting IR through the inhibition of AMPK activity in different target organs and tissues, such as liver, skeletal muscle and WAT.[18,20] Oliveira and colleagues, showed a rapid increase of resistin levels in mice fed a high-refined carbohydrate-diet, suggesting a possible impact on the development of acute metabolic dysfunctions.[20] In a mouse model fed with a high fat diet, Castañeda et al., showed a low adiponectin:resistin ratio after exposure to chronic stress, hypothesizing that diet alone was not sufficient to change serum adipokines levels and impair glucose metabolism .[21]

Clinical aspects of resistin

Resistin in obesity, insulin resistance and diabetes

Several studies linking resistin to obesity suggested that this adipokine could have a role in the pathogenesis of IR and type 2 diabetes (T2D). Obesity is a condition characterized by a low-grade chronic inflammation state in which an expanded and inflamed adipose tissue releases several inflammatory mediators that contribute to the worsening of inflammation and to the development of IR and eventually T2D. Particularly, visceral adipose tissue is considered the main source of resistin and the known association between central adiposity and IR strengthen the hypothesis that resistin could be linked to T2D. Most studies reported that serum resistin levels were significantly higher in obese subjects than in lean controls, [22-23] but a few failed to find a significant difference among these two groups. [24-26] However, serum resistin levels were positively correlated both with anthropometric and metabolic parameters, in cluding BMI, waist circumference, HOMA index, insulin and glucose levels and glycosylated hemoglobin. [23,24,27-31]

The effective role of resistin in the pathogenesis of T2D is still a matter of debate, since available studies have shown conflicting results [23,32-35] [26,27,36-40]. Some evidence show that serum resistin levels are significantly higher in diabetic subjects compared to healthy controls [37, 40] although no correlation was found between serum resistin levels and obesity or markers of IR.[40] Possible explanations for these different results may be the different demographic, the low number of cases enrolled in the studies and the use of different assay methods, probably leading to conflicting results. Nevertheless, overall there is substantial evidence supporting a role of resistin in the pathogenesis of obesity, IR and T2D.

Resistin and chronic hepatitis

1. Chronic Viral Hepatitis

The natural history of chronic hepatitis is characterized by long-lasting inflammation and hepatocellular necrosis that lead to fibrogenesis, which overtime can progress to cirrhosis and liver failure. Prognosis and clinical management of patients with chronic hepatitis are strongly affected

by the degree of liver fibrosis. Hence, the accurate staging of fibrosis is crucial.[67] Beyond liver biopsy and non-invasive imaging approaches, several biomarkers are under investigation.

Most of the studies investigated the usefulness of serum resistin as biomarker of disease severity in patients with chronic viral hepatitis. In a recent work, Zhongji and colleagues tested serum resistin as a biomarker of inflammation in patients with Chronic Hepatitis B (CHB).[68] They analyzed 85 CHB patients, 70 CHB-related cirrhosis and 79 CHB-related liver failure and found that in cirrhotic patients and in those with liver failure, circulating resistin was significantly higher compared to CHB, suggesting that resistin could play a role as indicator of disease severity.[68] Similar results were previously observed by Tsochatzis et al..[69] In a group of 64 Chronic Hepatitis C (CHC) patients, Durazzo and colleagues showed that serum resistin levels significantly decreased after the antiviral treatment but their data are in contrast to what reported by Lo Iacono et al, who found no changes of circulating resistin after therapy in a group of CHC patients.[70-71] Tiftikci and colleagues measured serum resistin level in a group of 51 CHC patients to assess its association with histological features.[72] The authors found that serum resistin was not correlated with hepatic fat but significantly decreased with the severity of hepatic fibrosis hypothesizing an effect of this adipokine on liver fibrogenesis through the activation of HSCs as previously documented.[73]

2. Non Alcoholic Fatty Liver Disease

In the last decade the epidemiology of chronic liver diseases is changing due to the emerging epidemic of chronic hepatitis linked to metabolic disorders, namely non-alcoholic fatty liver disease (NAFLD), ranging from simple fatty liver (NAFL) to steatohepatitis (NASH) and cirrhosis.[41] This shift in epidemiology is mainly due to the rapid change in eating habits, with a diet richer in sugar and lipids compared to the past healthy regimens. Of note, overweight and obesity in children and adults have reached prevalence rate of 10-15% thus forecasting the progressive and future risk in adulthood.[42]

Non-Alcoholic Fatty Liver is a benign and reversible clinical condition characterized by the accumulation of triglycerides in the hepatocytes. In some cases, NAFL may progress to a more severe form, namely Non-Alcoholic SteatoHepatitis (NASH), characterized by the joint presence of steatosis, ballooning degeneration and lobular inflammation with or without fibrosis. Originally, it has been hypothesized that NASH could be the result of "two hits", where the first hit the accumulation of the fat in the hepatocytes that makes the liver more susceptible to a second hit (oxidative stress, pro-inflammatory cytokines, mitochondrial damage, etc.) leaing to worsening of liver damage.[43] To date, the diagnosis of NASH is based on liver biopsy, an invasive and risky procedure. For this reason, the need of non-invasive biomarkers able to discriminate subjects with simple steatosis from those with NASH or with a higher risk to develop it, is one of the primary aims to reach.

Several studies showed higher resistin levels in NAFL subjects compared to lean controls [44] and in the setting of NASH, a significant correlation between serum resistin and inflammation has been reported.[45] However, some studies failed to confirm these associations. Recently, Gierej and colleagues showed that resistin plays a role in the pathogenesis of IR, that in turn contributes to the pathogenesis of NASH.[46] In their study the authors analyzed 214 liver biopsies from a cohort of bariatric patients confirming that resistin is expressed by Kuppfer cells and histiocytes and that its expression is associated with NASH in terms of steatosis, ballooning and inflammation. More studies are needed to better understand the role of resistin in the pathogenesis of this complex disease. The putative role of resistin in the onset and progression of NASH is depicted in Figure 1A.

Resistin and cardiovascular disorders

Some evidence suggests that resistin can be linked to the pathogenesis of atherosclerosis because of its role in the inflammatory process. Resistin is able to promote endothelial cells activation favoring the expression of the Vascular Cell Adhesion protein 1 (VCAM-1), the Intercellular Adhesion Molecule 1 (ICAM-1) and the chemokine (C-C motif) ligand 2 (CCL2).[47] Furthermore, resistin up-

regulates the P-selectin gene in endothelial cells promoting monocytes adhesion through the activation of both Nuclear factor kappa B (NF-kB) and activator protein 1 (AP-1) pathways.[48-49] In the study by Langheimet et al., higher levels of resistin were found in patients with acute coronary syndrome compared to those with stable coronary artery disease (CAD) or with normal coronary arteries at angiography.[50] An association between resistin levels and ischemic stroke has been identified in several studies.[51-53] In addition, serum resistin has been shown as independent marker of aortic stiffness in 104 patients with CAD.[54] To better understand the pathophysiology of atherosclerosis, Calabrò and colleagues tried to clarify the association between resistin and pro-thrombotic characteristics in human coronary artery endothelial cells (HCAECs). They found that the incubation of HCAECs with resistin upregulated the expression of tissue factor through the activation of NF-kB pathway and concluded that resistin may favor a pro-thrombotic phenotype in endothelial cells.[55] Finally, an association between resistin levels and arterial hypertension has been also reported. In a recent meta-analysis including 718 hypertensive patients and 645 normotensive controls, serum resistin levels were found significantly higher in the first group compared to the second one, indicating that this adipokine may be considered a risk factor for hypertension.[56]

Resistin and autoimmune disorders

Autoimmune diseases embrace an heterogeneous spectrum of disorders characterized by an imbalance between an anti-inflammatory condition and an inflammatory state. It is known that adipose tissue, in addition to adipocytes, comprises a certain number of T cells and myeloid cells.[57] In the WAT of lean subjects, T helper 2 cells together with T/B regulatory cells and natural killer cells cooperate to suppress inflammation.[57] Conversely, in obese subjects, the expanded and inflamed WAT create a susceptible environment characterized by a large amount of immune cells (mainly T helper 17) associated with a pro-inflammatory phenotype that predispose to the development of autoimmune disorders.[58-59] In keeping with this, obesity has been often associated with the degree of inflammation in different autoimmune diseases such as rheumatoid arthritis,

systemic lupus erythematosus, psoriasis and multiple sclerosis.[60-62] In some studies, circulating resistin was found significantly higher than controls in patients with relapsing-remitting multiple sclerosis, ankylosing spondylitis and psoriasis.[63-66] However, the specific role of this adipokine in mediating autoimmune inflammation deserve further investigations.

Resistin and Inflammatory Bowel Diseases

Inflammatory bowel diseases (IBD) are characterized by a state of chronic inflammation due to an impairment of both gut epithelial barrier and immune response to the intestinal microflora in susceptible individuals.[74] Despite the etiopathogenesis of IBD is not clear, it is known that inflammatory reactions occurring in the bowel can penetrate in the surrounding visceral adipose tissue as demonstrated by imaging techniques.[75] Thus, the so called creeping fat (ranging from mesentery to the inflamed intestine) is a characteristic feature of IBD, mainly of Crohn's disease (CD) as depicted in Figure 1B. However, the role of adipocytokines in the pathophysiology of IBD is far from clear. Several studies showed significantly higher levels in patients with CD and ulcerative colitis (UC) compared to healthy controls[76-78] but overall a clear correlation between circulating resistin and disease severity has not been found.[79]

Interestingly, a recent meta-analysis suggests that resistin could be a risk factor for the development of colorectal cancer, despite the heterogeneity of the studies considered.[80] This association has laid the basis for the investigation of the relation between resistin and colon cancer. Recently, Singh and colleagues found that in p53 cells resistin is able to induce G1 phase arrest through its binding with Tall Like Receptor 4 (TLR4) on colon cancer cells that activates TLR4-MyD88 and MAPK pathways. Activated MAPK up-regulate SOCS3, in turn acting as a negative regulator, shutting down JAK2/STAT3 signaling and blocking tumor growth.[81]

Conclusions

Most evidences suggest that adipose tissue in all its forms and depots (visceral fat, mesenteric fat, creeping fat) can be involved in the etiopathogenesis of different chronic inflammatory diseases ranging from NAFLD to IBD through the release of different adipocytokines. Resistin is a signaling molecules expressed in macrophages that seems to play a role in inflammation throughout different pathways, but the exact mechanism by which it affects multiple organs and tissues is not yet understood. In the setting of NAFLD there is an urgent need to find new biomarkers able to discriminate simple steatosis from NASH to avoid liver biopsy. Furthermore, the non-invasive identification of patients at high risk for advanced liver disease (cirrhosis or hepatocellular carcinoma) is the most important unmet need in clinical practice also in other chronic liver diseases.[82-83] Major efforts are being made to deepen the biological role of resistin and its usefulness as a non-invasive biomarker of disease activity.

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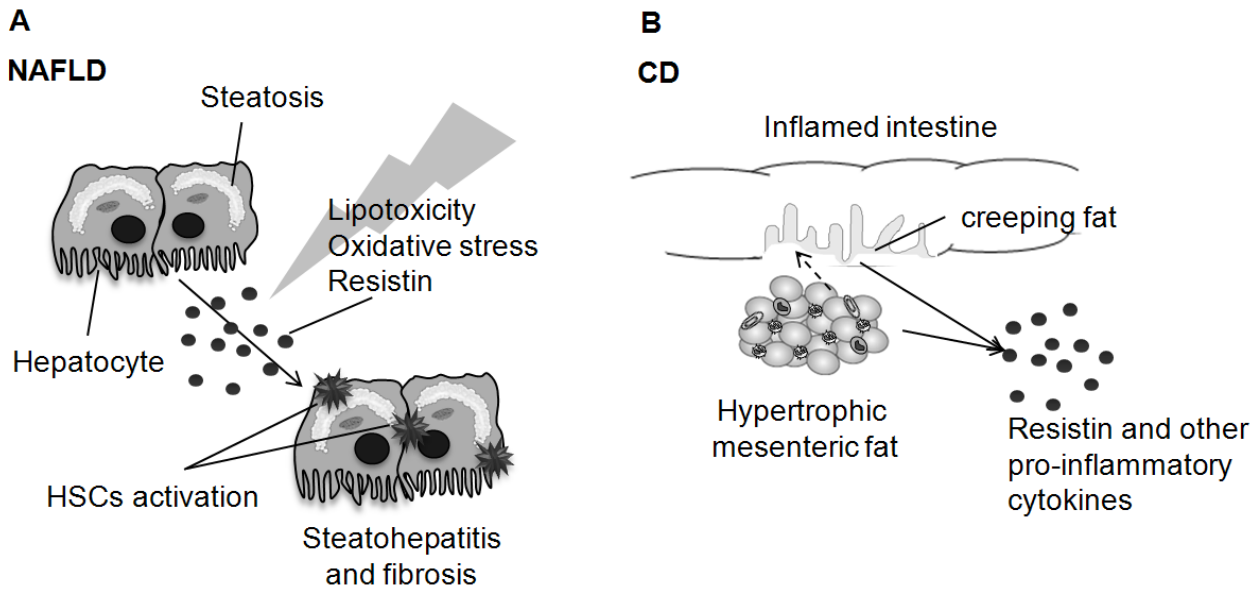
Figure legend

Figure 1. Putative role of resistin in the onset and progression of Non-Alcoholic Fatty Liver Disease (A) and in the worsening of inflammation in Crohn's disease (B).

Footnote. In the setting of NAFLD, resistin could be involved in the progression from simple steatosis to NASH in turn promoting the activation of HSCs through the activation of pro-inflammatory pathways (A). Concerning inflammatory bowel disease, mainly CD, resistin and other pro-inflammatory mediators can be released from both mesenteric and creeping fat contributing to the worsening of inflammation (B).

CD, Crohn's Disease; HSCs, hepatic stellate cells; NAFLD, Non-Alcoholic Fatty Liver Disease.



Tables

Table 1. Resistin-mediated molecular pathways in different clinical conditions and diseases.

Clinical condition/disease	Molecular pathway	References
IR/T2D	↑G6Pase/ ↑PEPCK/ ↓GLUT2 ↑TNFa/ ↑IL-6 ↑AMPK-SOCS-3 ↓IRS-2/Akt	13,14
NAFLD	↑AMPK-SOCS-3 ↓IRS-2/Akt GIP/Akt → ↑LPL/ ↑LKB1	14,15,16
Cardiovascular disease	Endothelin-1/VEGFRs → ↑MMPs ↑VCAM-1/ ↑ICAM-1/ ↑CCL2 ↑P-selectin →NF-kB/AP-1	17,47,48,49
IBD	TLR4/NF-kB → ↑TNFa	74,75
Colon cancer	TLR4-MyD88/MAPK → ↑SOCS3	81

Footnote. AMPK, AMP-activated protein kinase; Akt, protein kinase B; AP-1, activator protein 1; CCL2, chemokine (C-C motif) ligand 2; G6Pase, glucose-6-phosphatase; GLUT2, glucose transporter 2; IBD, inflammatory bowel disease; ICAM-1, intercellular adhesion molecule 1; IL-6, interleukin-6; IR, insulin resistance; IRS-2, insulin receptor substrate-2; MMPs, matrix metalloproteases; NAFLD, non-alcoholic fatty liver disease; NF-kB, Nuclear factor kappa B; PEPCK, phosphoenolpyruvate carboxykinase; SOCS-3, suppressor of cytokine signaling-3 ; T2D, type 2 diabetes; TLR4, tall like receptor 4; TNFa, tumor necrosis factor alpha; VCAM-1, Vascular Cell Adhesion protein 1; VEGFR, vascular endothelial growth factor receptors.