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Review

An update on the biology and physiology of resistin

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Abstract. Resistin is a newly discovered adipocyte hormone. It is related to resistin-like molecules α, β and γ in structure and function. Resistin is produced by white and brown adipose tissues but has also has been identified in several other tissues, including the hypothalamus, pituitary and adrenal glands, pancreas, gastrointestinal tract, myocytes, spleen, white blood cells and plasma. The tissue level of resistin is decreased by insulin, cytokines such as tumour necrosis factor α, endothelin-1 and increased by growth and gonadal hormones, hyperglycaemia, male gender and some proinflammatory cytokines, such as interleukin-6 and lipopolysaccharide. Resistin antagonizes insulin action, and it is downregulated by rosiglitazone and peroxisome proliferator-activated receptor γ agonists. Since evidence of a direct link between resistin genotype and human diabetes is still weak, more molecular, physiological and clinical studies are needed to determine the role of resistin in the aetiology of type 2 diabetes.

Key words. Resistin; insulin resistance; obesity; diabetes mellitus; glucose metabolism.

Introduction

Diabetes mellitus is a common endocrine disorder affecting almost 6% of the world's population. The prevalence of this chronic metabolic disease is on the increase [1]. Globally, the figure for the people with diabetes is said to have risen from 30 million in 1985 to 143 million in 2000. It is estimated that in the year 2010 it will be 220 million and 300 million in 2025 [2–4]. The majority of these patients will have type 2 diabetes, which is associated with inactive life style and unhealthy or inappropriate diet [4].

The pathogenesis of diabetes mellitus is less than clear. However, it is now widely accepted that the cause of diabetes mellitus is multifactorial and that both genetic and environmental factors are involved. Environmental causes of type 1 and 2 diabetes may include among others immunological factors [5] and viral infections [6]. Although, genetic factors play a very important role in the aetiology of type 2 diabetes compared to type 1, one of the most important environmental factors that has been proved to cause diabetes is obesity. Obesity can develop as a consequence of a combination of inadequate physical activity and inappropriate diet. Type 2 diabetes is considered to be spreading like an epidemic in the developed world and is strongly associated with obesity [7]. Type 2 diabetes has recently been associated with a newly discovered peptide hormone called resistin.

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Structure of resistin

Resistin (also called FIZZ3: found in inflammatory zone; ADSF: adipocyte secreted factor) is a cysteine-rich, 108-amino acid peptide hormone with a molecular weight of 12.5 kDa [7]. Recent reports have now shown that human resistin [7] has 108 amino acids, while rat [8] and mouse [9] resistin has 114 amino acids. Pig resistin has just been cloned [10]. It has 109 amino acids and is located on chromosome 2 at 2q21. (fig. 1, table 1). Resistin was for-

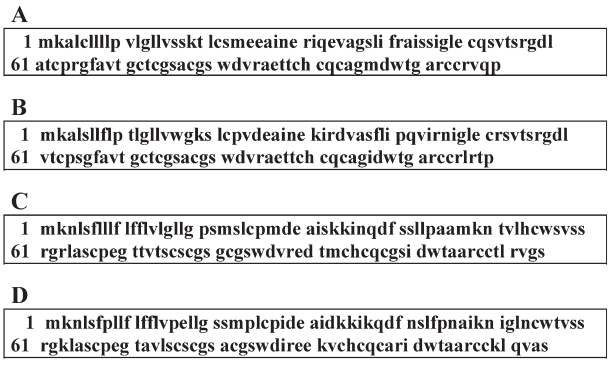

Figure 1. Amino acid sequences of (*A*) human, (*B*) pig, (*C*) rat and (*D*) mouse resistin proteins. Note that human and pig resistins are composed of 108 and 109 amino acids, respectively. Rat and mouse resistins each have 114 amino acids.

Table 1. Types of resistin, their amino acid number, the species in which they have been characterized and their chromosome location.

Type of resistin	Species	Number of amino acids	Chromosome location
Resistin	human	108	19; 19p13.3
	pig	109	2; 2q21
	rat	114	8 A1.1; 8 0.37 cM
	mouse	114	12; 12p12
RELM α	rat	111	11; 11q21
	mouse	111	16; 16 A1
RELM β	human	111	3; 3q13.1
	mouse	105	16; 16 A1
RELM γ	rat	111	11; 11q21
	mouse	111	16;16 A1

RELM, resistin-like molecule.

mally regarded as an adipocyte-derived mediator of hepatic insulin resistance [11]. Other investigators, including Rajala et al. [12], have estimated mouse resistin molecular weight to be around 10 kDa. Resistin is a disulfide-linked homodimer which can be converted easily to a monomer. Cysteine is the most common amino acid in resistin, where it forms approximately 12% of its amino acid sequence [13]. Resistin can also dimerize through a disulphide bond formed by the N-terminal-most cysteine (Cys26) [14]. The proximal 264-bp fragment of the mouse resistin promoter is adequate for its expression in fat cells [15]. The structure of resistin indicates that it may belong to a new family of cytokines [12]. Although Cys-26 is both necessary and adequate for the homodimer formation, resistin, RELM-α and RELM-β can interact with one another regardless of the position of Cys-26 through covalent bonds [14]. However, when the Cys-26 residue is mutated to alanine, it is released as a monomer, indicating the importance of Cys-26 in the dimerization of this hormone [13].

Recombinant resistin

Bioactive recombinant resistin, produced and characterized in *Escherichia coli* is now available for use [16]. This recombinant resistin shows a dose-dependent antagonizing action against insulin, and the formation of a homodimer is not required for its biological activity [16]. However, recombinant resistin can reversibly convert from α-helical to β-sheet structure with a tendency to aggregate by forming intermolecular disulphide bonds [17]. Furthermore a new isoform of the rat resistin gene, named S-resistin (short resistin), has recently been detected in adipose tissue by reverse transcription-polymerase chain reaction (RT-PCR) [18]. Del Arco et al. [18] showed that the complementary DNA (cDNA) variant and genomic sequences of S-resistin lack the second exon containing the secretory consensus signal. This isoform of resistin is non-secretable.

Resistin-like molecules (RELMs)

RELMs are polypeptides of 105–114 amino acids with three domains (N-terminal signal sequence, a variable middle portion and a highly constant C-terminal sequence that forms about half of the molecule). The C-terminal of RELM appears to determine the signature of the molecule [19–21]. Three types of RELMs have been described, RELM-α, RELM-β and RELM-γ.

RELM-α

RELM-α (FIZZ-1) has 63% homology with resistin. The C-terminal is highly related to resistin, especially the last 38 amino acids, in contrast to the N-terminal, which is only slightly related to resistin [22]. RELM-α has been identified in both rat [23] and mouse [24] tissues. RELM-α protein in both rat and mouse contains 111 amino acids. In rat, RELM-α is found on chromosome 11 and located at 11q21. However, it is located at chromosome 16; 16A1 in mouse (fig. 2, table 1). RELM-α messenger RNA (mRNA) is expressed in white adipose tissue of the heart, lung and tongue but not expressed in 3T3-L1 adipocytes nor in pre-adipocytes [18–20]. RELM-α is also present in the inflammatory zone of mice with allergic pulmonary inflammation [21]. However, the degree of expression of RELM-α appears to be higher in adipose tissue of the mammary gland and tongue than in that of the lung. In spite of the similarities with resistin in tissue distribution, RELM-α is monomeric rather than homodimer.

A

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1 mktatcslli cvfllqlmvp vntdgtldii gkkkvkella hqdnypsavr ktlsctnvks
61 mskwascpag mtatgcscgf acgsweiqne nicnclcliv dwayarccql s
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B

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1 mktttcslli cisllqlmvp vntdetieii venkvkella npanypstvt ktlsctsvkt
61 mnrwascpag mtatgcacgf acgsweiqsg dtcnclcllv dwttarccql s
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Figure 2. Amino acid sequences of (*A*) rat and (*B*) mouse RELMα proteins. Rat and mouse RELMα proteins each have 111 amino acids.

RELM-β

RELM-β (FIZZ2), like resistin, is a disulfide-linked homodimer which can be converted to a monomer and is present in the mouse colon. It has a molecular weight of 9 kDa. The conversion to a monomer requires a single cysteine (11^{th} cysteine), which is not present in RELM-α [13]. The 11^{th} cysteine is present in the variable N-terminal domain of the RELMs. RELM-β has 37% homology with resistin [22]. Studies using RT-PCR analysis have demonstrated that RELM-β mRNA is found only in the undifferentiated, proliferating colonic epithelial cells of mouse. It is absent in adipose tissue of mouse [19]. RELM-β was first located within the proliferating cells of the colonic epithelium and disappears as soon as the cell becomes mature. Immunohistochemistry shows that RELM-β is highly expressed in goblet cells located primarily in the distal half of the colon and cecum, with lower levels detectable in the proximal colon of mouse [25]. Moreover, high levels of RELM-β can be detected in the stool of humans [25]. Human RELM-β protein has 111 amino acids [26] and is located on chromosome 3 at 3q13.1. In contrast, mouse RELM-β protein has 105 amino acids and is associated with chromosome 16 at 16 A1 (fig. 3, table 1).

RELM-γ

RELM-γ is the most recently discovered member of the RELM family and was first observed in nasal respiratory epithelium of rats exposed to cigarette smoke [27]. The highest expression of RELM-γ was found in haemopoietic tissues, indicating a cytokine-like function for RELM-γ [27]. RELM-γ is also expressed in white adipose tissue of rat, and is similar to RELM-α [27]. The nasal respiratory epithelium of cigarette smoke-exposed rats shows high expression of RELM-γ mRNA [27]. Rat and mouse RELM-γ protein both have 111 amino acids each. Rat RELM-γ is found on chromosome 11 at 11q21, while mouse RELM-γ is located on chromosome 16 at 16 A1. (fig. 4, table 1).

Tissue distribution of resistin

Adrenal gland

Weak resistin protein immunoreactivity has been observed in the adrenal cortex of rat [28]. Expression of resistin mRNA was also reported in rat adrenal gland [28]. The localization of resistin to the adrenal gland suggests that resistin may play a role in the function of this gland.

Pituitary gland

Investigation of the expression of resistin mRNA by RT-PCR analysis showed that resistin is present in the mouse pituitary gland [29]. Pituitary gland resistin mRNA is localized mainly to the anterior and intermediate lobes, with little staining in the posterior lobe [29]. The authors showed that the peak in pituitary resistin mRNA level was unaffected by early weaning but was abolished by neonatal treatment with monosodium glutamate, suggesting that the basal hypothalamus regulates pituitary resistin. In addition to the localization of resistin in pituitary gland by RT-PCR, immunohistochemistry was also used to demonstrate resistin protein in the pituitary gland of mouse.

Hypothalamus

Immunohistochemical observation confirms the presence of resistin protein in the mouse brain where it is located in the cells of the arcuate nucleus [29]. A few cells in the ventrolateral and ventromedial nuclei of the hypothalamus and in the dorsal periventricular region of the mouse also contain resistin [29]. In addition to the immunohistochemical studies, RT-PCR studies also show

A

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1 mgpsscllli lipllqlinp gstqcsldsv mdkkikdvln sleyspspis kklscasvks
61 qgrpsscpag mavtgcacgy gcgswdvqle ttchcqcsvv dwttarcchl t
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B

```
1 mkptlcflfi lvslfplivp gnaqcsfesl vdqrikeals rqepktisct svtssgrlas
61 cpagmvvtgc acgygcgswd irngntchcq csvmdwasar ccrma
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Figure 3. Amino acid sequence of (*A*) human and (*B*) mouse RELMβ protein. Human and mouse RELMβ proteins each have 111 and 105 amino acids, respectively.

A

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1 mktatcslli cifllqlmvp vstdgtlesi veqkvkella hrdncpstvt ktlsctsvka
61 tgrlascppg mavtgcacgy acgswdirdg ttchcqcavm dwatarccql s
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B

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1 mktttcslli cisllqlmvp vntegtlesi vekkvkella nrddcpstvt ktfsctsita
61 sgrlascpsg mtvtgcacgy gcgswdirdg ntchcqcstm dwatarccql a
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Figure 4. Amino acid sequences of (*A*) Sprague-Dawley rat and (*B*) mouse RELMγ protein. Rat and mouse RELMγ proteins each have 111 amino acids.

that resistin mRNA expression is significantly higher in the arcuate nucleus compared to other parts of the hypothalamus [29]. These observations show that resistin may be produced and secreted by the arcuate nucleus of the hypothalamus. Substances produced by the arcuate nucleus could possibly be detected in the nerves projecting into the posterior pituitary via the hypothalamohypophysial tract. Since pituitary resistin is mainly located in the anterior and intermediate lobes with little staining in the posterior lobe, it is tempting to postulate that the resistin produced by the arcuate nucleus may enter into circulation through the capillary loops formed by the superior hypophyseal vessels. In fact, it has been shown that pituitary resistin mRNA expression is dependent upon an intact hypothalamus [29]. It is worth noting that monosodium glutamate (MSG)-treated mice become obese as adults and show hyperglycaemia and hyperinsulinaemia. It is well known that MSG selectively destroys the arcuate nucleus of the hypothalamus [30].

White adipose tissue

Resistin mRNA expression has been shown in 3T3-L1 adipocytes [7] and in white adipose tissue (WAT) of mouse [7], rat [31] and human [32–33]. Resistin concentration is highest in the adipose tissue of female gonads in mouse [21] and rat [31]. Some investigators [34] observed that resistin was barely detected in mature human adipocytes but was highly expressed in preadipocytes. A more recent study carried out by McTernan et al. [33] showed that resistin mRNA expression is more prominent in the abdominal subcutaneous and omental fat compared to thigh and mammary fats in human. In addition to RT-PCR analysis of resistin mRNA expression, immunohistochemistry has been used to localize resistin protein in white adipose tissue [28].

Brown adipose tissue

Recent investigations show that resistin protein and mRNA are also present in brown adipose tissue (BAT) of rat [28] and in the BAT cell line T37i [35]. Resistin transcripts were not detected in undifferentiated T37i cells, indicating that the resistin gene occurs during the differentiation of adipocytes [35]. Since BAT responds differently to hormones and other agents when compared to WAT [35], the role of resistin in BAT physiology is far from clear. Insulin and thiazolidinediones increase resistin expression in BAT, while dexamethasomne and isoproterenol decrease resistin expression in BAT [35].

White blood cells

Resistin mRNA expression is present in human peripheral blood monocytes [36] and in human macrophages [11]. Resistin mRNA is also abundant in human primary acute leukaemia and myeloid cell line U937 and HL60 but not in *raw*264 mouse myeloid cell line [37]. The significance of the expression of resistin mRNA in blood cells is unknown; however, resistin may play a role in the function of these cells. It is worth noting that neurotransmitters such as serotonin are present in red blood cells [38].

Spleen

Resistin has been identified in splenocytes of lean and obese rats [39]. The question arising now is what would resistin be doing in the spleen? Since the spleen contains a large number of blood cells, it is not surprising that it was detected in the spleen.

Skeletal muscle

Resistin mRNA expression can be induced in L6 myocytes when incubated with C/EBPα [40]. Resistin mRNA expression is also present in the normal skeletal muscle cells of rats [28]. Rat skeletal muscle cells are also rich in resistin protein [28]. The presence of resistin in muscle cells may indicate a regulatory role for resistin in the insulin-induced uptake of glucose by muscle.

Placenta

Resistin mRNA expression has been identified in human placenta where it is localized to trophoblastic cells. Resistin expression was more conspicuous in term placenta compared to placenta of first trimester [41]. Placental resistin may be transported to the fetus in pregnancy.

Gastrointestinal tract

Resistin protein and mRNA have been detected in the cells of the gastrointestinal tract of rat, using immunohistochemistry and RT-PCR, respectively. Both methods have shown that resistin is present in the oxyntic and neuroendocrine cells of the mucosa of the gastric fundus and pylorus of rat. Weak resistin immunostaining is present in the epithelial cells of the duodenum of the rat [28]. The localization of resistin to the neuroendocrine cells of the stomach indicates that resistin may play a role in the regulation of the amine precursor uptake and decarboxylation (APUD) system.

Pancreas

Resistin protein and mRNA are present in human pancreatic islets and also in the Min6 β cell line [42]. Resistin mRNA expression is upregulated in insulin-resistant A-ZIP transgenic compared to wild-type mice [42]. This may imply a role for resistin in the aetiology of insulin resistance.

Synovial fluid

Resistin is present in synovial fluid of patients with both rheumatoid arthritis (RA) and osteoarthritis (OA). In patients with RA, however, synovial resistin levels were approximately 10 times higher than in those with OA. Furthermore, the synovial fluid levels of resistin are positively correlated with systemic markers of inflammation such as erythrocyte sedimentation rate and C-reactive protein. This observation supports the notion that resistin is involved in inflammatory and metabolic pathways in human rheumatological disease [43].

Plasma

Resistin is observed in the mouse blood circulation. The plasma level of resistin is increased in some genetic (ob/ob and db/db) and diet-induced models of diabetic obesity [7]. The plasma level of resistin in human is 14.3 ng/ml (7.3–21.30) [44–45].

The presence of resistin in many tissues, including bodily fluids such as synovial fluid and plasma (table 2) may indicate a ubiquitous nature of resitin and global role in the control of body homeostasis. Resistin has been detected in a greater variety of rodent compared to human tissues because of the availability of rodent tissues (table 3). It is likely that more studies on the pattern of distribution and physiological role of resistin in human tissues will be performed in the near future.

Inductors of resistin expression

Growth hormone

Twenty-four-hour continuous infusion of growth hormone (1 mg/kg/day) caused marked (720–950%) increases the level of resistin mRNA in rat epididymal and subcutaneous WAT when compared to controls [46]. The ability of growth hormone to induce resistin mRNA expression may be due to the growth-promoting action of growth hormone. It is worth noting that excessive growth hormone may contribute to the development of diabetes. It has been shown that patients with acromegaly had a higher prevalence of hypertension and diabetes [47].

Table 2. Tissue distribution of resistin in human, rat and mouse.

Tissue/cell	Type of resistin	Species	Method of localization	Authors
Adrenal gland	resistin protein resistin mRNA	rat	immunohistochemistry, RT-PCR, Southern blot	Nogueiras et al. [28]
Pituitary	resistin protein resistin mRNA	mouse	immunohistochemistry, RT-PCR	Morash et al. [29]
Hypothalamus (arcuate nucleus)	resistin protein resistin mRNA	mouse	immunohistochemistry, RT-PCR	Morash et al. [29]
WAT	resistin protein resistin mRNA	mouse rat human	Immunohistochemistry, RT-PCR	Steppan et al. [7] Kim et al. [31] McTernan et al. [32] Nogueiras et al. [28]
BAT	resistin protein resistin mRNA	T37i cell line rat	immunohistochemistry, RT-PCR	Viengchareun et al. [35] Nogueiras et al. [28]
Monocytes	resistin mRNA	human	RT-PCR	Lu et al. [36]
Macrophages	resistin mRNA	human	RT-PCR	Patel et al. [11]
Myeloid cell	resistin mRNA	human (U937) cell line	RT-PCR	Yang et al. [37]
Primary acute leukaemia cell	resistin mRNA	human (HL60) cell line	RT-PCR	Yang et al. [37]
Spleen	resistin mRNA	rat	RT-PCR	Milan et al. [39]
Muscle	resistin protein resistin mRNA	rat L6 myocytes	immunohistochemistry, RT-PCR	Nogueiras et al. [28] Song et al. [40]
Placenta	resistin mRNA	human	RT-PCR	Yura et al. [41]
GI tract	resistin protein resistin mRNA	rat	immunohistochemistry, RT-PCR	Nogueiras et al. [28]
Pancreas	resistin protein resistin mRNA	rat human	immunohistochemistry, RT-PCR	Minn et al. [42]
Synovial fluid		human	ELISA	Schaffler et al. [43]
Plasma	resistin protein	human	ELISA	Stejskal et al. [44]

GI tract, gastrointestinal tract; BAT, brown adipose tissue; WAT, white adipose tissue; RT-PCR, reverse transcription polymerase chain reaction.

Table 3. Comparison of current distribution of resistin in human and rodent tissues and cells.

Tissue/cell	Rodent	Human
Adrenal gland	+	–
Pituitary	+	–
Hypothalamus (arcuate nucleus)	+	–
WAT	+	+
BAT	+	–
Monocytes	–	+
Macrophages	–	+
Myeloid cell	–	+
Primary acute leukaemia cell	–	+
Spleen	+	–
Muscle	+	–
Placenta	–	+
GI tract	+	–
Pancreas	+	+
Synovial fluid	–	+
Plasma	+	+

(–), has not yet been demonstrated; (+), has been demonstrated; GI tract, gastrointestinal tract; BAT, brown adipose tissue; WAT, white adipose tissue; RT-PCR, reverse transcription polymerase chain reaction.

Hyperglycaemia

Hyperglycaemia increases resistin expression in the 3T3-L1 adipocyte cell line [12, 48]. Hyperglycaemia is a known cause of release of reactive oxygen (ROS) and nitrogen (RNS) species [49]. The release of ROS and RNS induces oxidative stress, leading to abnormal gene expression, faulty signal transduction and apoptosis of cardiomyocytes. Hyperglycaemia also induces apoptosis via p53 [50] and the activation of the cytochrome c-activated caspase-3 pathway, which may be triggered by ROS [51–52].

Steroid hormones

Dexamethasone

Dexamethasone can increase the expression of mRNA resistin and protein 2.5–3.5 fold in the 3T3-L1 adipocyte cell line [48]. Peroxisome proliferator-activated receptor α plays an important role in the constitutive expression of resistin in adipose tissue [53].

Gonadal hormones

There is an increase in resistin mRNA expression in male rats [54]. Moreover, resistin mRNA is increased in mice with elevated androgen levels [55]. This shows that androgen could be a regulator of resistin expression in mouse adipose tissue. Since resistin has been demonstrated to antagonize insulin's action in rodents [7], resistin could be a link between steroid hormones and altered glucose metabolism. Steroid hormones have been implicated in the pathogenesis of obesity and diabetes. For example, the rise of morning cortisol values was positively associated with high body mass index, waist/hip ratio, abdominal sagittal diameter and glucose in men [56]. Moreover, steroid hormones can induce insulin resistance [57].

Neuropeptide Y (NPY)

Intraceberoventricular administration of NPY can stimulate resistin gene expression in mice WAT [58]. These observations indicate that NPY may have a role in regulating resistin gene expression in WAT and thus play a role in the brain-fat axis [59].

Age

Circulating resistin levels increase as a rat ages, probably due to the increase in body fat [60]. This observation correlates well with the pattern of occurrence of obesity and type 2 diabetes because it is well known that the risk of having obesity and diabetes increases with age. There is an age-related increase in total body fat and visceral adiposity until age 65 which may be associated with diabetes and or impaired glucose tolerance. One study shows that the prevalence of type 2 diabetes increases progressively with age, peaking at 16.5% in men and 12.8% in women at age 75–84 [61].

Inhibitors of resistin expression

Insulin

Insulin can significantly suppress resistin expression in mouse and adipocyte cell lines [48]. The downregulation of resistin mRNA by insulin is probably through the synthesis of proteins that may accelerate the degradation of resistin in 3T3-L1 adipocytes. The pathway of this action is through PI3-kinase, ERK or p38 MAP-kinase [62].

Fasting

Fasting decreases resistin mRNA expression in white adipose tissue but not in brown adipose tissue. A recent report showed that mice lacking the adipocyte hormone resistin display low blood glucose levels after fasting. This is said to be due to reduced liver glucose production [63]. Banerjee et al. [63] showed that this reduced mouse hepatic glucose production is partly due to the activation of adenosine monophosphate-activated protein kinase and decreased expression of gluconeogenic enzymes. This study also indicated that lack of resistin reduces the increase in post-fast blood glucose usually associated with increased body weight.

Somatropin

Somatropin can moderately inhibit the expression of both the resistin transcript and protein by 30–50% in the

3T3-L1 adipocyte cell line [48]. However, Silha et al. [64] observed that resisting levels were similar in acromegaly and normal patients. This shows that resistin may not be responsible for the insulin resistance observed in acromegaly patients.

Thyroid hormones

Resistin is decreased in hyperthyroid rats [54, 65]. This is not surprising, because weight loss is a frequent presenting feature of hyperthyroidism [66]. Thyroid hormones may help in the activation of the various pathways involved in the inhibition of resistin expression in adipocytes.

Endothelin-1

Endothelin-1 (ET-1) a 21-amino acid peptide with vasoconstrictor, positive inotropic, mitogenic and metabolic properties inhibits resistin expression in 3T3-L1 adipocytes. ET-1 at 100 nM significantly decreased basal resistin secretion by 59% [67]. Increased levels of plasma ET-1 have been observed in numerous diseases, including human congestive heart failure, obesity and diabetes [68]. In all of these disease conditions, a strong correlation between ET-1 levels and the severity of the disorder has been observed. Interestingly, resistin can induce an increase in ET-1 release and ET-1 mRNA expression in endothelial cells [69].

Neurotransmitters

Epinephrine is able to moderately inhibit resistin expression. In one study, expression of both the transcript and protein forms of resistin was reduced by 30–50% in the 3T3-L1 adipocyte cell line [48].

Isoproterenol inhibits resistin gene expression in the 3T3-L1 adipocyte cell line by 20% when compared to non-treated controls [70]. The inhibition of resistin gene expression by isoproterenol is mediated via a G-protein-coupled pathway and adenylyl cyclase. The β-adrenergic receptor antagonist propranolol reverses the inhibitory effect of isoproterenol, whereas the α-adrenergic receptor antagonist phentolamine has no effect. Moreover, the inhibition of resistin gene expression is decreased by cholera toxin and forskolin [70]. This observation may confirm the role of the sympathetic nervous system in the aetiology of insulin resistance [71].

Peroxisome proliferator-activated receptor γ

Peroxisome proliferator-activated receptor γ (PPARγ) is a nuclear receptor with an important role in the regulation of adipocyte differentiation and lipid metabolism [72]. Although PPARγ is found in several types of tissues, it is most abundant in adipose tissue [72]. PPARγ together with the retinoid X receptor binds to DNA as a heterodimer, acting as a transcription factor to regulate the production of proteins involved in lipid and glucose metabolism. PPARγ plays a key role in adipogenesis because it regulates the differentiation of pre-adipocytes to adipocytes in cooperation with other transcription factors. Moreover, it is involved in the modulation of insulin sensitivity and regulation of the endocrine functions of fat tissue [72]. Overexpression of PPARγ (but not PPARα) reduces resistin expression [40]. The PPARγ-induced reduction in resistin expression reached 80% after exposure to 100 nM rosiglitazone for 96 h [11]. One group of PPARγ agonists, the thiazolidinediones (TZDs), decreases insulin resistance, and because of this effect the three currently available TZDs (troglitazone, rosiglitazone and pioglitazone) have been approved for the treatment of type 2 diabetes [73].

Controversial factors in resistin expression in adipocytes

Proinflammatory cytokines

Lipopolysaccharide

Some studies showed that lipopolysaccharide (LPS) increases resistin gene expression in rat WAT, mouse 3T3-L1 adipocytes and human peripheral blood monocytes [36, 74]. In contrast, Rajala et al. [12] showed that LPS failed to upregulate resistin expression either transcriptionally or translationally in 3T3-L1 adipocytes. The conflicting results reported by these authors could be due to the different doses or periods of LPS treatment applied or the use of a different animal model. In Rajala's [12] study, FVB mice were injected with 100 ng/g body weight LPS, and resistin response was evaluated 24 h post-injection, while in the study of Lu et al. [36] Wistar rats were injected with 3 mg/kg body weight LPS for 1, 2, 4 or 8 h.

Tumour necrosis factor alpha

Proinflammatory cytokines such as tumor necrosis factor alpha (TNFα) significantly increased resistin mRNA expression in human peripheral blood mononuclear cells [74]. Other reports showed that TNF-α can inhibit resistin gene expression by up to 70–90% in the 3T3-L1 mouse cell line [75]. The inhibition of resistin by TNF-α is time and dose dependent and can occur even at very low concentrations of 1 ng/ml. The reason for these contradictory reports may be due to the different types of tissues and cells used and the time of incubation with TNF-α. Studies by Kaser et al. [74] incubated human polymorphonuclear cells with 5–500 ng/ml of TNF-α for a period of 12–24 h, whereas Fasshauer et al. [75] used 3T3-L1 mouse cell

lines with 100 ng/ml of TNF-α for a period of 16 h after prolonged pretreatment of the cells in culture medium.

Interleukin-6

Proinflammatory cytokines such as interleukin (IL)-6 significantly increased resistin mRNA expression in human peripheral blood mononuclear cells [74]. In other studies IL-6 failed to upregulate resistin expression either transcriptionally or translationally in 3T3-L1 adipocytes [12]. The differences between these results may be due to methodological as well as the species of animal used in the experiment as described for the controversy surrounding the role of LPS in resistin expression.

Gender

In both WAT and BAT, resistin mRNA expression is higher in male rats compared to females [28, 54]. In contrast, Yannakoulia et al. [76] observed that resistin concentrations were significantly higher in women compared to men. All of these observations show that the significance of gender on the degree of resistin expression in adipocytes is far from understood.

Effect of cold

Acute cold exposures (18 h at 6 °C) did not have any effect on resistin expression either in rat WAT or BAT [77]. The significance of these findings on the effect of cold on resistin is not clear.

The fact that several factors (fig. 5, table 4) can induce and reduce resistin mRNA expression in rodent and human tissues suggests that resistin can be controlled by therapeutics (insulin, PPARγ agonists) as well as life style (fasting/dieting). This could imply that obesity-induced type 2 diabetes, involving a possible overexpression of resistin, can be managed.

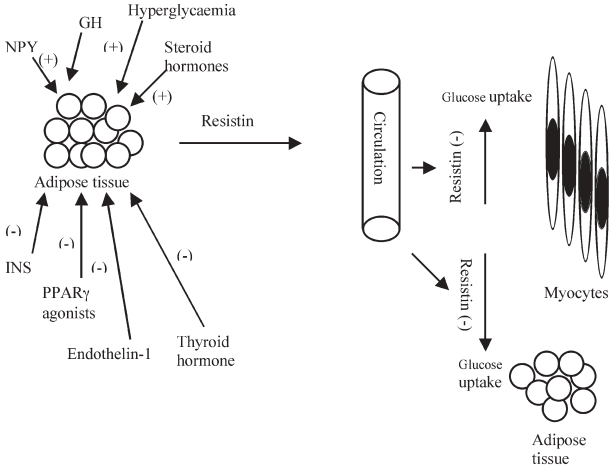

Figure 5. Schematic diagram showing factors that stimulate (+) or inhibit (–) resistin expression in adipocytes. Some physiological effects of resistin are also shown.

Table 4. Factors that induce and reduce resistin expression.

Inducers of resistin expression	Inhibitors of resistin expression	Factors with controversial effect
Growth hormone	insulin	LPS
Hyperglycaemia	fasting	TNF-α
Steroid hormones	somatotropin	IL-6
Neuropeptide Y	thyroid hormone	gender
Ageing	endothelin-1 epinephrine and isoproterenol PPARγ	

IL-6, interleukin-6; LPS, lipopolysaccharide; PPARγ, peroxisome proliferator-activated receptor γ; TNF-α, tumour necrosis factor alpha.

Physiological effects

Resistin antagonizes insulin action, and in the mouse model it is downregulated by antidiabetic drugs [7, 13]. Resistin has been shown to cause impaired glucose metabolism in wild-type mice, and increased levels of resistin mRNA have been detected in genetic and diet-induced forms of obesity [7]. Resistin mRNA expression is regulated by glitazones, a new class of anti-diabetic drugs in the mouse model. These drugs, including rosiglitazone, reduce blood glucose and lipid levels by modulating PPARγ [78]. Recent studies show that infusion of resistin (30–150 µg/kg) rapidly induces severe hepatic but not peripheral insulin resistance in the rat [79].

Injection of anti-resistin antibody into mice with diet-induced obesity and insulin resistance and hyperglycaemia reduces blood glucose levels and improves insulin sensitivity. Moreover, administration of resistin to normal mice causes impaired glucose tolerance. The effect of resistin is similar to that of TNFα in many ways: secretion is enhanced by obesity, and they both act directly on fat cells to antagonize insulin-induced glucose uptake in rodents [7, 80]. Moreover, the effect of TNF-α and resistin are both attenuated by PPARγ agonists such as thiazolidinediones in rodents [7, 81–82].

Resistin is thus a sensor of nutritional activity and has an inhibitory effect in adipocyte differentiation in the rat [31]. Resistin correlates positively with body fat mass and negatively with waist-to-hip ratio in humans [76]. Resistin inhibits glucose uptake in L6 myocytes by decreasing the intrinsic activity of cell surface glucose transporters [83].

Signal transduction and resistin

Resistin expression can be suppressed by overexpression of the PI3-kinase p110α catalytic unit and by Akt, MKK6, MKK7 and MEK1 in 3T3-L1 adipocytes [40].

Resistin expression is also suppressed by C/EBPζ, a negative regulator of C/EBPα [40].

Resistin, obesity and insulin resistance

Although F344 rats developed insulin and leptin resistance, no role was attributable to resistin in the aetiology of insulin resistance in this species [84].

A correlation between obesity and the level of resistin has been reported in rodents [7] and humans [85–86]. They noted that the more severe the obesity, the higher the level of resistin in humans [45]. However, Way et al. [87] observed that resistin expression is significantly reduced in the WAT of several experimental models of obesity, including ob/ob, db/db, tub/tub and KKA^y mice when compared to their lean counterparts.

Le Lay et al. [88] reported decreased resistin expression in mice with different sensitivities to a high-fat diet. They observed that FVB mice, which did not develop obesity after an 8-week high-fat diet, showed no changes in resistin expression. However, transgenic mice which developed high-fat-induced obesity displayed a decrease in the level of adipocyte resistin. In addition, Janke et al. [34] did not find any relationship between body weight, insulin sensitivity and adipocyte resistin gene expression in humans.

In a way that further complicates the link between obesity and resistin, some investigators did not find any difference between the tissue level of resistin in lean patients, obese patients and patients with type 2 diabetes [89]. A possible shortcoming of this study was the relatively small number of short-listed patients.

A possible reason for these discrepancies regarding the degree of resistin expression in the adipocytes of obese subjects may be due to species differences and/or compensatory mechanisms. Way et al. [87] reported an increase in adipose tissue expression of resistin in both ob/ob and Zucker diabetic fatty rats when fed with PPARγ agonists. Way et al. [87] further showed that decreases in the tissue profile of resistin are not required for the hypoglycaemic effects of PPARγ agonists (rosiglitazone, GW1929) in genetic animal models of type 2 diabetes. In contrast, Moore et al. [90] showed that rosiglitazone reduces resistin mRNA expression in WAT of diabetic db/db mice. This reduction in resistin gene expression by thiazolidinedione is mediated in part by downregulating histone acetylation associated with the binding of C/EBPα (a basic leucine zipper-containing transcription factor: enhancer binding protein α) in mature adipocytes [15, 91]. Rosiglitazone treatment does not prevent the LPS-induced increase in resistin expression [36]. The resistin-reducing effect of rosiglitazone in db/db diabetic mice is not absolutely required for lowering the blood glucose level [90].

Resistin gene and diabetes mellitus

The cDNA sequence of human resistin is related to human chromosome 19 with a cytogenetic map of 19p13·3–19p13·2 [92]. The human resistin locus has nine resistin single-nucleotide polymorphisms (SNPs) with no coding variants [93]. The genetic effect of the resistin gene does not appear to contribute to the aetiology of type 2 diabetes [94]. In a similar study, Osawa et al. [95] investigated whether the SNPs in the resistin gene are associated with type 2 diabetes. They did not observe any association of the three identified SNPs with Japanese type 2 diabetes. In contrast, Engert et al. [93] observed that 5′ flanking variants (g.-537 and g.-420) of resistin are associated with obesity. In addition, Ma et al. [96] observed an interaction between obesity and the association of type 2 diabetes and the genotype at SNP6 in Caucasians. In a recent study on 1102 Chinese type 2 patients, Tan et al. [97] showed an association of resistin gene 3′-untranslated region + 62G→A polymorphism with type 2 diabetes and hypertension.

Resistin and hypertension

Circulating resistin levels are not in any way related to insulin resistance in patients with essential hypertension [98] and in normal, obese and diabetic patients [99]. Other investigators have reported a significant correlation between resistin and insulin resistance and hypertension [64].

Future prospectives

Since the incidence and prevalence of obesity and type 2 diabetes will continue to increase, interest in molecules that contribute to the aetiology of these conditions will continue to generate significant interest among researchers. The availability of recombinant resistin will help in the search for a more physiological role of resistin. Greater understanding of how resistin works will also be enhanced if and when receptors of resistin are discovered.

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