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Is resistin the master link between inflammation and inflammation-related chronic diseases?

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Abstract:

Resistin has been firstly discovered in mice and was identified as an adipose tissue-secreted hormone or adipokine linking obesity and insulin resistance. In humans, resistin has been characterized as a hormone expressed and secreted by Immune cells especially by macrophages, and was linked to many inflammatory responses including inflammation of adipose tissue due to macrophages' infiltration. Human and mouse resistin display sequence and structural similarities and also dissimilarities that could explain their different expression pattern. In mice, strong pieces of evidence clearly associated high resistin plasma levels to obesity and insulin resistance suggesting that resistin could play an important role in the onset and progression of obesity and insulin resistance via resistin-induced inflammation. In humans, the link between resistin and obesity/insulin resistance is still a matter of debate and needs more epidemiological studies. Also, resistin has been linked to other chronic diseases such as cardiovascular diseases and cancers where resistin has been proposed in many studies as a biological marker.

1. Introduction

Adipose tissue and especially white adipose tissue (WAT) plays a crucial role in the regulation of whole-body energy homeostasis by buffering circulating glucose as well as free fatty acids. Indeed, in the fasting state adipose tissue provides energy to the whole body whereas in over-nutrition it has an energy storage role due to its plasticity and its ability to store lipids and carbohydrates once transformed into triglycerides. Furthermore, WAT especially visceral adipose tissue presents a high secretory activity as evidenced by the fact that about 30% of WAT genes express secretory proteins named adipokines including hormones and adipocytokines¹. Thus, WAT fully plays the role of an endocrine tissue that secretes a variety of adipokines acting through endocrine, autocrine, or paracrine mechanisms. The WAT secretome is highly complex and secreted adipokines could be subdivided into four groups: metabolic, pro-inflammatory, extracellular matrix, and pro-mitogenic/pro-angiogenic adipokines². The secretion of most of these adipokines is modulated by metabolic environment conditions. Indeed, selected adipokines are secreted in response to acute or chronic over-feeding and others to energy restriction. Consequently, adipokines' secretion is modulated depending upon adipose tissue size either in physiological or pathophysiological states. Besides, increased adipose tissue size as in obesity is known to promote insulin resistance and type 2 diabetes, additionally both obesity and type 2 diabetes are associated to low grade inflammation. Despite numerous epidemiological studies linking obesity to type 2 diabetes, the underlying molecular mechanisms are not fully deciphered. In the present review we will focus on resistin, an adipokine, which has been described as a hormone linking obesity to insulin resistance mainly through inflammatory mechanisms.. Resistin, previously known as FIZZ3 or adipose tissue-specific secretory factor (ADSF), is a cysteine-rich polypeptide encoded by the *RETN* gene that has been first described by Steppan and collaborators³ through the screen for targets of thiazolidinediones (TZD) (insulin sensitizer drug used to treat type 2 diabetes) in WAT of mice. According to several studies in mice, high resistin plasma levels are linked to many dysfunctions such as the alteration of lipid and carbohydrate metabolisms, inflammation, and insulin resistance. In contrast, in humans the direct relationship between resistin circulating levels and insulin resistance is still a matter of debate. Besides, resistin-induced inflammation is also implicated in many other chronic diseases including cardiovascular diseases and cancers. The differences between human and mouse resistin could be attributed to molecular structure, localization, and signaling. Here we will review these issues and highlight resistin implication in chronic diseases: metabolic disorders, cardiovascular diseases, and cancers.

2. Human and mouse resistin: sequences and distributions

2.1 Mouse resistin structure

Three groups have described and functionally characterized mouse resistin. Firstly, resistin has been identified as Found in Inflammatory Zone (FIZZ)3 which was linked to pulmonary inflammation⁴. Then a group reported the discovery of a target of the insulin sensitizers' thiazolidinediones (TZDs) that contributes to insulin resistance³, and concomitantly Kim and collaborators reported the characterization of a serine/cysteine rich secretory protein, which they named Adipose tissue-specific Secretory Factor (ADSF)^{3,5}.

Mouse resistin is a 11-kiloDalton protein encoded by a gene named *RETN* located in chromosome 8A1. The polypeptide is produced as a precursor, which undergoes post-translational cleavage to form a 94 amino acid mature protein before the elimination of a 20-amino-acid signal sequence. Importantly, resistin exhibits five intra-chain disulfide bridges involving several cysteine (Cys) residues at 51-104, 63-103, 72-89, 74-91, and 78-93 positions. Thus, resistin contains 11 cysteine residues structured in a unique motif also found in other secreted growth factors⁶. The presence of these cysteine residues especially at the carboxyterminal of resistin permits the assembly of the globular domain of resistin monomer through the formation of these five disulfide bridges⁷, the globular domain is thought to be the binding domain of resistin⁸. The secondary structure of resistin is organized as one α -helix and six β -sheets⁷. The secondary structure of resistin driven by these cysteine residues appeared to be critical for the biological activity as well as tissue selectivity⁹. The structure of resistin allows the formation of oligomers through the disulfide-dependent multimeric assembly. Indeed, trimers and hexamers are the most predominant at the plasma levels, where trimers are thought to be the more biologically active form⁷. However, the mechanisms involved in the oligomerization of resistin monomers are still unknown. Furthermore, resistin action could be also more complex than thought due to its potential interaction with other members of the resistin-like molecule (RELM) family that includes mouse RELM α and RELM β as well as other proteins such as heparanase¹⁰.

2.2 Human resistin structure

The human resistin is a 12.5 –kilodalton protein is encoded by the *RETN* gene located on chromosome 19q13.3 that shares 59% identity with murine resistin^{11,12}. Human resistin possesses a cysteine signature as its mouse counterpart. These cysteine residues allow as for mouse resistin the formation of oligomers with a molecular mass of 660 kDa and a trimer of 45 kDa that are found in human sera¹³. It has been also reported that human resistin tends to form dimers and trimers involving most likely Cys22¹⁴. Similar to mouse resistin, human resistin mainly consists of a α -helical coiled-coil domain and possesses a cysteine residue at

position 6, which is crucial for the oligomerization. Furthermore, it has been also reported that human resistin can form oligomers through covalent and non-covalent linkages¹⁴. In contrast to mouse resistin, the predicted secondary structures of human resistin lack a β -sheet jelly roll folding pattern and instead, it exhibits two β -sheets surrounded by α -helical domains¹⁴. In humans, the trimers and the oligomers of resistin exhibit higher pro-inflammatory effects evidenced by increased secretion of inflammatory cytokines such TNF α , IL-1 β IL-6, and IL-8 in human immune cells¹⁵.

2.3 Resistin expression locations

The human and mouse resistin gene (*RETN*) expression patterns show clear distinctions; indeed, mouse *RETN* is mainly expressed by adipose tissue and exactly by adipocytes as evidenced by Northern blot analysis revealing resistin mRNA in white adipose tissue and adipocytes (Steppan) even though, using PCR, more recent findings reported *RETN* expression in other locations such as the hypothalamus¹⁶ (change the reference). In contrast, human *RETN* is expressed in immune cells: macrophages, monocytes, and neutrophils¹⁷. Indeed, in human the expression pattern of *RETN* expression established by Taqman analysis revealed bone marrow and spleen as major site of expression⁷. In addition during human monocyte-macrophage differentiation *RETN* expression was increased as evidenced Taqman analysis⁷. Thus, according to these expression patterns both mouse and human resistins have been associated and linked to specific functions and roles that we will discuss in this review. Several studies reported that mouse resistin is produced during adipocyte differentiation and its circulating levels are high in mouse models of obesity and insulin-resistance¹⁸, and considered as the potential link between obesity and type 2 diabetes³. Furthermore, mice fed high-fat diet exhibited higher resistin levels, and leptin treatment reduced the resistin expression levels of genetically obese mice (*ob/ob*) due most likely to the decrease in body weight and the restoration of insulin responsiveness¹⁹. In humans, resistin has been linked to obesity and type 2 diabetes diseases characterized by chronic low-grade inflammation resulting from macrophage infiltration of adipose tissue^{20,21}.

The difference between human and mouse *RETN* expression patterns could be attributed to dissimilarities in gene sequences. At the amino acids and mRNA levels, mouse and human resistins respectively exhibit 59% and 64.4% identity¹². At the genomic level, the mouse resistin genomic sequence only shares 46.7% identity with its human counterpart and also shows a longer sequence reaching nearly three times the human resistin genomic sequence. Most importantly, mouse resistin genomic sequence carries at its 3' UTR region just after the stop codon an extra intron called intron X consisting of 2279 nucleotides in length, which is missing in human¹². Intron X could be of importance regarding the resistin expression

pattern; indeed, this intron carries putative transcription factor binding sites such as PPAR/RXR heterodimer binding sites also called IntX-PPRE that binds PPAR/RXR-like protein factors present in differentiated adipocytes¹², contributing most likely the down-regulation of mouse resistin in response to TZDs known as PPAR γ agonists³. The presence of regulatory sequences in introns has been previously reported for various genes such as mouse major histocompatibility gene, human neuropeptide YY1 receptor gene, human S6 ribosomal protein gene, mouse α 2u-globulins gene²²⁻²⁵.

The human *RETN* gene contains adipogenic transcription factor C/EBP α binding sites similar to the mouse *RETN* gene¹². Differences have been reported such as the presence of the Arg-Gly-Asp (RGD) motif in human resistin but not in its mouse counterpart. The RGD motif is known to mediate cell attachment and is found in other proteins as fibronectin²⁶ and integrins²⁷.

Besides the primary expressing tissues of *RETN* gene, peripheral blood mononuclear cells, macrophages, and bone marrow in humans; ²⁸, human *RETN* gene expression is also expressed to a less extent in the hypothalamus, the pituitary gland, gut epithelial cells, adrenal cells, skeletal muscle, pancreas, spleen, goblet cells, and synovial tissue²⁸. Importantly, whether human adipocytes have been described as non-resistin secreting cells, human adipose tissue produces resistin originated from resident non-adipocyte inflammatory cells²⁹.

The disparity between mouse and human resistin is also evidenced by differential regulation in response for example to TNF α where *RETN* expression is decreased in mouse adipocytes and increased in human monocytes^{30,31}.

3. Resistin mechanisms of actions and targeted tissues

Here, we will discuss the signaling pathways activated by resistin with a special focus on the potential binding sites of resistin.

3.1 Resistin receptor (s)

The search for resistin receptors was based on the pro-inflammatory action of resistin, and in this context, several groups had described different potential resistin receptors.

3.1.1 Resistin binds to Toll-like receptor 4

Toll-like receptor 4 (TLR-4) belongs to the TLRs family that is activated by recognition of pathogen-associated molecular sequences such as lipopolysaccharides (LPS). Thus, TLRs are implicated in numerous intracellular mechanisms aiming to resist and reduce invading microorganisms in host cells. It is well established that LPS binds to TLR-4 at the cell surface to initiate TLR-4 signaling pathways through the interaction of TLR-4 with myeloid differentiation factor 2 (MD2) and the activation of human myeloid differentiation factor 88

(MyD88). This leads to the cytonuclear translocation of nuclear factor-kB (NF-kB). The activation of the TLR-4 signaling pathway initiates the overexpression and/or secretion of pro-inflammatory cytokines, proteolytic enzymes, and adhesion molecules^{32,33}. Tarkowski and collaborators showed that resistin was able to compete with LPS for TLR-4 and they show that resistin action on human leucocytes and cytokine production was completely abolished in the presence of TLR-4 antibodies³⁴. The binding of resistin to TLR-4 has been functionally validated in HEK cells expressing TLR-4 where resistin was able to activate TLR-4 signaling pathways promoting NF-kb activation. Furthermore, resistin selectively binds to TLR-4 and, was unable to bind and activate TLR-2³⁴. More recently, we reported that resistin when chronically administered intracerebroventricularly (ICV) induces both inflammation and insulin resistance of the hypothalamus and peripheral tissues in a TLR-4 dependent manner, since resistin effects were abrogated in TLR-4^{-/-} mice³⁵. The binding of resistin to TLR-4 has been evidenced by cross-linking experiments in neurons³⁵.

3.1.2 Resistin binds to decorin

Decorin is a member of the small leucine-rich proteoglycan gene family that binds to many cellular components including matrix structural molecules and complexes. For example, decorin binds to collagens and growth factors especially those belonging to the transforming factor- β ligand superfamily³⁶. Furthermore, decorin also induced an anti-tumorigenic signal leading to the repression of tumor cell proliferation, survival, migration, and angiogenesis³⁶. Decorin has been also found in adipose stromal cells (ASCs), these cells are considered mesenchymal progenitors in white adipose tissue. Interestingly, cleaved decorin (delta-decorin) has been identified in ASCs and the screen for delta-decorin-binding proteins identifies resistin as a potential ligand³⁷. Indeed, the exposure of 3T3-L1 cells expressing delta-decorin to resistin increased cell proliferation and reduced lipid accumulation³⁷. Thus, these authors attributed to resistin a role in adipocyte progenitors through the binding to delta-decorin³⁷.

3.1.3 Resistin promotes Insulin-like growth factor 1 receptor (IGF-1R) activation.

Rheumatoid arthritis (RA) is characterized by leukocyte infiltration of synovial tissue leading to inflammation that promotes hyperplasia and pannus formation (abnormal layer of fibrovascular tissue). A special focus on different growth factors was assessed to understand the onset of the pathogenesis of RA. In this context, Bostrom and collaborators have described crosstalk between resistin and IGF-1 signaling pathways in RA³⁸. These authors showed that low levels of IGF-1 and increased levels of resistin characterize RA synovia. Furthermore, the stimulation of human synovial fibroblasts with resistin in the absence of

exogenous IGF-1 increased the phosphorylation of IGF-1 receptors (IGF1-R) activating then downstream pathways including the phosphorylation of Akt. However, authors did not mention whether human synovial fibroblasts secrete IGF-1 that could contribute to IGF-1R phosphorylation. Authors concluded that resistin uses IGF1-R pathway at least in RA synovia without showing direct binding of resistin to IGF1-R³⁸.

3.1.4 Resistin binds to mouse receptor tyrosine kinase-like orphan receptor (ROR)1.

ROR1 belongs to the tyrosine-kinase family of receptors³⁹ and possesses at the its extracellular domains three well-identified structures: an Ig-like domain located near the N-terminal end, a Frizzled (FZZ)I-like domain (rich in cysteine), and a Kringle (KR) domain (rich in cysteine). The intracellular region of ROR1 contains a conserved tyrosine kinase catalytic domain. ROR1 is implicated in osteogenesis as a co-receptor for WNT proteins³⁹. Sanchez-Solana and collaborators showed that the effect of resistin on adipose tissue expansion could be mediated by ROR1. They showed that resistin interacts with specific domains of the extracellular region of the ROR1 receptor leading to the inhibition of ROR1 tyrosine phosphorylation modulating then MAP kinase pathway as well as Glut4 and Glut1 expression in 3T3-L1 cells³⁹.

3.1.5 Resistin binds to adenylyl cyclase-associated protein 1.

ROR1 and decorin have been described as putative receptors for resistin, and no evidence concerning their implication in resistin-induced inflammation in human. More recently, the inflammatory actions of resistin in human monocytes were attributed to the binding of resistin to adenylyl cyclase-associated protein 1 (CAP1)⁸. CAP-1 has been described to be mainly associated with plasma membrane of human monocytes and involved in many cellular functions such as binding to actin, activation of adenylate cyclase activity, cytoskeleton organization and biogenesis, signal transduction, and the establishment and/or maintenance of cell polarity⁴⁰. Lee and collaborators reported that resistin binds to human monocyte CAP-1 initiating signaling cascade involving the up-regulation of cyclic AMP, protein kinase A leading to the activation of the pro-inflammatory NF-kB transcription factor⁸.

3.2 Resistin mechanisms of action

According to the previous reports concerning resistin binding sites, TLR-4 and CAP-1 are the only receptors that have been demonstrated to directly bind resistin to initiate proinflammatory responses both in humans and mouse^{34,35}. Importantly, resistin interaction with CAP-1 seems to be specific to human monocytes, whereas resistin binding to TLR-4

seems to have a larger specter since this interaction has been reported in both human and mouse tissues (figure 1).

Furthermore, most studies brought strong shreds of evidence that link resistin to inflammation both in humans and mice. In human macrophages, resistin induces the expression of pro-inflammatory cytokines as well as intracellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1). Also, human resistin promotes chemotaxis and the recruitment of leukocytes to inflamed tissues through the induction of chemokine (CCL2) and MCP-1 expression^{15,41,42}. Thus, the pro-inflammatory action of resistin in humans is mostly attributed to its release by monocytes and macrophages that infiltrated a variety of tissues and organs such as adipose tissue in obese patients. It has been also reported that resistin secretion by immune cells is activated by pro-inflammatory cytokines such as C-Reactive Protein (CRP), IL-6, IL-1, IL-12, and TNF α ^{15,28}. Furthermore, human resistin is predominantly expressed by peripheral blood mononuclear cells (PBMCs) and this expression augments when these cells differentiate to macrophages⁴³. Interestingly, as in mice, human resistin expression in macrophages is diminished in response to thiazolidinedione (TZD) drugs (antidiabetic drug improving insulin sensitivity through most likely the reduction of resistin-induced inflammation) associated to reduce resistin plasma levels^{7,41}. Resistin has been also suggested to contribute to vascular smooth muscle proliferation in humans and mouse promoting the monocyte adhesion and infiltration into endothelial tissues⁴⁴⁻⁴⁸. Besides, its expression by PBMCs in humans, resistin is also found in non-adipocyte stromal vascular fraction of WAT, atherosclerotic lesions, and fibrotic liver, evidencing that the primary sources of human resistin are macrophages that invade these inflamed tissues⁴⁹⁻⁵¹.

In mice, resistin is mainly expressed in white adipose tissue and also in blood cells³. Furthermore, it has been reported that mouse resistin is produced during adipocyte differentiation and its circulating levels are high in mouse models of obesity and insulin-resistance¹⁸. Indeed, mouse resistin is considered as the potential link between obesity and type 2 diabetes³.

Resistin initiates pro-inflammatory responses through different signaling pathways depending upon the targeted tissue. Indeed, in vascular smooth muscle cells (VSMCs), resistin induces the expression of cytokines and chemokines via the transcription factor NF- κ B leading to the alteration of VSMCs functions²⁸. In PBMCs, resistin activates the cytoplasm-nuclear translocation of p65 and p50 NF- κ B subunits activating the production of pro-inflammatory cytokines⁵². Resistin is also involved in the regulation of bone remodeling through the activation of Nf- κ B pathway known as a key regulator of osteoclastogenesis⁵³. Resistin also induces inflammation through the activation of several MAP kinase pathways including p38, JNK, and ERK1/2 known to increase the expression of pro-inflammatory cytokines'

expression⁵⁴. Resistin/MAP kinase signaling pathway inhibits eNOS gene expression in VSMCs reducing then NO-dependent vasodilation leading to vascular dysfunctions increasing then the predisposition to thrombosis, angiogenesis, and cell adhesion⁵⁵. Furthermore, resistin/MAP kinase pathways have been associated with the augmentation of VSMCs proliferation in human coronary artery promoting vascular diseases⁵⁵. Furthermore, the resistin-induced insulin resistance has been largely documented implicating the alteration of insulin signaling pathways, this will be discussed later in the review.

4. Resistin and chronic diseases

4.1 Resistin in metabolic disorders (obesity and type 2 diabetes):

A class of anti-diabetic drugs called thiazolidinediones (TZDs) known to increase target-tissues insulin sensitivity selectively bind to a nuclear receptor, abundant in adipocytes, called peroxisome proliferator activated receptor- γ (PPAR γ). Indeed, patients carrying a dominant-negative PPAR γ allele have severe insulin resistance. Besides, resistin has been identified as a target gene of TZD-bound PPAR γ ³ as evidenced by its down-regulation in human macrophages following TZDs treatment²⁰. Furthermore, in mice, resistin plasma levels are positively correlated to obesity and insulin resistance, and resistin-treated mice or transgenic mice overexpressing resistin exhibit glucose intolerance and impaired hepatic insulin responsiveness^{3,19,56}. Resistin-induced insulin resistance has been also evidenced by the almost total recovery of insulin responsiveness of diet-induced obese mice following the treatment with resistin antibodies³, and the knockdown or deletion of resistin in genetically obese mice *ob/ob* (lacking leptin gene) restored muscle and WAT insulin sensitivity, and increased hepatic insulin sensitivity of high fat diet mice^{3,6,57}. The implicated signaling pathways have been investigated, indeed, the resistin knock out mice exhibit a higher glucose tolerance with lower fasting glycaemia due in part to the activation of AMP kinase and reduced gluconeogenic enzymes in the liver⁶, associated to lower expression of the pro-inflammatory cytokine TNF α as well as lower phosphorylation level of JNK (cJun N-terminal kinase, a key MAP kinase involved in inflammatory response) in adipocytes⁵⁸. To further decipher implicated signaling pathways different cell models have been used, for instance resistin impaired insulin responsiveness and signaling in murine 3T3-L1 adipocytes, cardiomyocytes, and skeletal muscle cells⁴³; and abolished insulin-induced IRS1/PI3kinase/Akt signaling pathways through increased phosphorylation of p38 and JNK that phosphorylate IRS1/2 on serine residues altering then insulin signaling³⁵. Besides its peripheral effects, different authors have suggested that resistin could also act directly within the brain, since resistin have been found in human cerebrospinal fluid indicating that it crosses the brain blood barrie⁵⁹. In the same line of evidence in mice

intracerebroventricular (ICV) infusion of resistin abolished insulin-dependent phosphorylation of insulin receptor, IRS-1/2, and Akt in the hypothalamus and peripheral tissues such as liver, muscle and WAT, concomitantly with the downregulation of adiponectin receptors in these tissues^{35,60}. All these resistin effects were abolished in mice lacking TLR-4³⁵ revealing that resistin mediates its effects through binding to TLR-4. Furthermore, central resistin impaired adiponectin signaling, an insulin-sensitizing hormone. Indeed, resistin ICV infusion downregulated APPL1, a key protein in adiponectin signaling, in the hypothalamus and liver contributing to insulin resistance⁶⁰. Indeed, APPL1 interacts with Akt and blocks Akt association with its inhibitor TRB3, promoting insulin-dependent Akt activation evidencing the insulin sensitizer role of adiponectin⁶¹. Central resistin also increased plasma FGF-21 levels and down-regulated FGF-1 receptors in the hypothalamus and peripheral tissues leading to FGF-21 resistance amplifying then insulin resistance⁶⁰. FGF-21 has several beneficial effects on insulin sensitivity and glucose and lipid metabolism. Indeed, FGF-21 is mainly produced by liver and promotes the expression of adiponectin by adipose tissue promoting then overall insulin responsiveness^{60,62}. The effects of resistin on adiponectin and FGF-21 signaling pathways are TLR-4 dependent as evidenced by the abrogation of resistin effects in TLR-4 knock out mice⁶⁰.

In humans, obese patients exhibit a higher infiltration of macrophages into adipose tissue leading to increased resistin expression in adipose tissue associated with higher resistin plasma levels as compared to lean individuals^{29,43,63}. However, in humans, the relationship between resistin plasma levels and insulin resistance is still matter of debate. Indeed, it has been reported that resistin plasma levels were positively correlated with insulin resistance in diabetic women and obese or overweight non-diabetic women⁶⁴. Other studies reported higher circulating resistin in diabetic and obese non-diabetic patients⁶⁵. A positive correlation between resistin plasma levels in obese diabetic Egyptian patients has been found but no correlation in obese non-diabetic groups⁶⁶. Furthermore, other reports positively correlated plasma resistin levels to visceral, intrathoracic, and pericardial fat as reported in a cross-sectional study⁶⁷. In contrast, other studies revealed no correlation between resistin and insulin resistance in obese individuals^{68,69,70,71,72}, and obese subjects submitted to diet or bariatric surgery exhibited either reduced or not changed resistin plasma levels^{70,73,74}. More recently, to address these discrepancies a systematic review and meta-analysis concluded that in type-2 diabetes and obese individuals, the resistin plasma levels were positively correlated with insulin resistance in patients exhibiting hyper-resistinemia, and no correlation was found in patients with normal resistin plasma levels⁷². Besides, it has been also reported that high resistin plasma levels combined with low adiponectin plasma levels promote T2D in obese individuals⁷⁶. Furthermore, in pathologies known to contribute to T2D

and to aggravate it such as non-alcoholic fatty liver disease (NAFLD), the liver resistin expression is higher as compared to the control group suggesting its potential Implication in the hepatic insulin resistance of patients with NAFLD⁷⁷.

Besides, epidemiological studies reported that variation of resistin plasma levels could be attributed to genetic factors⁷⁸, a part of this variance is attributed to a single nucleotide polymorphism of the *RETN* gene -420C>G⁷⁸. Other polymorphisms have been described in the promoter region of the human *RETN* gene, indeed the -638G>A, -420C>G, and -358G>A polymorphisms were associated with resistin plasma levels in Japanese obese patients⁷³. Interestingly, in the Japanese population, SNP -420 in the *RETN* gene was correlated to high resistin plasma levels associated with higher monocyte resistin expression and increased predisposition to T2D^{79,80}. However, in Caucasian populations such as in an Italian or American Caucasian cohorts -420 C/G SNP in *RETN* is not associated with changes with resistin plasma levels despite its association with obesity and metabolic disorders^{81,82}. Besides, in an Egyptian obese cohort, two SNPs of *RETN* (-420C/G and +299G/A) are significantly associated with high resistin plasma levels⁸³.

These discrepancies in these data generated from different cohorts might be attributed to ethnic differences and this increases the difficulties to establish a strong link between resistin and obesity/insulin resistance in humans.

4.2 Resistin and inflammation

Resistin plasma levels had been associated with many human diseases induced or aggravated by the inflammatory state. Indeed, elevated resistin levels have been associated with a high inflammatory state in patients with sepsis and acute pancreatitis⁸⁵⁻⁸⁸. Also, elevated plasma resistin levels have been found in diseases characterized by low-grade inflammation such as T2D, coronary atherosclerosis, chronic kidney diseases, or rheumatologic disorders^{41,69,72,86,89}. Increasing pieces of evidence are linking inflammation to cancer^{90,91}, in this context many reports indicate that resistin-induced inflammation is a critical hallmark of cancer and its progression⁹²⁻⁹⁴. Importantly, experimental and epidemiological studies revealed the potential association between elevated resistin plasma levels and obesity-associated cancers^{92,95}.

Despite the many pieces of evidence linking resistin to inflammation, it is still unclear whether an inflammatory environment is necessary for resistin secretion or whether resistin is necessary for inflammation onset. Thus, hyper-resistinemia could be a consequence of an initial inflammation, which in turn will be amplified by resistin. Further investigations are needed to establish the kinetic of resistin-induced inflammation to understand resistin and pro-inflammatory cytokines cross-talk.

4.3 Resistin and cardiovascular diseases (CVD)

Several studies reported that elevated resistin was causally linked to atherosclerosis, heart failure, and cardiac ischemic events^{51,72,96–99}. Furthermore, elevated resistin was considered as a predictive marker of coronary atherosclerosis^{98,100–104} and with myocardial infarction risk as well as cardiovascular diseases and all-cause mortality in T2D patients¹⁰⁵. High resistin levels were also associated with hypertension in women without T2D¹⁰⁶, and with the risk of cardiovascular diseases through resistin-induced inflammation^{107,108}. Other studies suggested that resistin-induced cardiovascular disease could be independent of inflammation⁵⁶. Thus, further clinical investigations are needed to establish the mechanism by which resistin induces directly or indirectly cardiovascular diseases.

Besides, many animal or cell studies aiming to decipher the molecular mechanisms underlying resistin-induced cardiovascular diseases link cardiovascular diseases to elevated resistin. In this line of evidence, resistin overexpression in rat cardiomyocytes reduced cell contractility affecting then contraction/relaxation velocities⁵¹, which promoted cardiac hypertrophy^{109,110}. It has been also reported that human resistin impaired glucose uptake in isolated mouse cardiomyocytes¹¹¹ that could increase the severity of heart failure¹¹².

Importantly, the deleterious effects of elevated resistin could be also secondary to the alteration of metabolic markers known to promote cardiovascular diseases. Elevated resistin levels have been positively correlated to plasma levels of triglycerides and apolipoprotein B, and negatively correlated to high-density lipoprotein (HDL)¹¹³, but other studies reported a positive correlation between resistin and HDL cholesterol known to be anti-atherosclerotic¹¹⁴. However, major studies reported negative impact of resistin on cardiovascular functions as also evidenced by resistin-induced atherosclerotic plaques known to damage blood vessels increasing thrombosis risk^{15,116}.

At the mechanistic levels, resistin promotes the down-regulation of LDL receptors through the activation of PCSK9 (Pro-protein Convertase Subtilisin/Kexin type 9) leading to hypercholesterolemia¹¹⁷; and in the intima of vessels, increases ROS production and LDL accumulation and, also increases monocyte recruitment in the vessels.^{9,118} Resistin also augments the lipid accumulation in macrophages leading to foam cells^{116,119}. Besides, resistin increases endothelin-1 (ET-1) secretion as well as VCAM1 and MCP-1, and on the other hand reduces the nitric oxide synthase; these events promote endothelial dysfunctions with a defect in vascular vessels contractility^{116,118}. Elevated resistin plasma levels aggravated coronary artery diseases^{120–122} suggesting that resistin plasma levels could be used as a marker of coronary artery disease as well as myocardial ischemia¹²³.

4.4 Resistin and cancers

It is well established that cancer development and progression are associated with elevated systemic inflammation as well as organ inflammation¹²⁴. It has been reported that in cancer

patients, the resistin plasma levels are high¹²⁴. Resistin promotes cancer cells' growth as it promotes prostate cancer cell proliferation via the activation of PI3K/Akt signaling pathway^{94,125-127}. Resistin also activates anti-apoptotic signaling pathways promoting tumor cell survival through the activation of Nf-kb and PI3k/Akt signaling pathways^{95,128}. Other studies reported that resistin exerts its anti-apoptosis effects through the inhibition of caspase-3 and caspase-7 expression¹²⁹. Also, resistin has been described as a promoter of cell invasion and metastasis of lung adenocarcinoma and interestingly this implicated the activation of TLR-4/Src/EGFR/PI3K/Nf-kb signaling pathway¹³⁰. In breast cancer (BC) cells resistin through Src/PP2A/PKCa pathway activates ezrin, radixin, and moesin proteins known to promote migration and invasion¹³¹. Resistin-induced NF-kb, Akt, and ERK signaling pathways promote metastasis by facilitating the cell adhesion of hepatic carcinoma cells to endothelium and to increase invasion in various liver cancer lines^{132,133}. Besides, resistin promotes pancreatic cancer progression through both CAP1 and TLR-4 by activating the STAT-3 signaling pathway¹³⁴. Furthermore, many other studies reported that resistin promotes angiogenesis in various cancer cells through the expression of VEGF, MMP2 implicating different regulatory pathways including miR-186, miR-16-5p/PI3kinase/Akt, Erk1/2 pathways^{91,135,136}. Interestingly, resistin induces many factors involved in cancer therapeutic resistance such as KLF4 and Nanog promoting doxorubicin resistance, fatty acid synthase, and caveolin in myeloma promoting resistance to dacarbazine treatment. In the same line, resistin by down-regulating specific microRNAs such as let-7a, miR-200c, and miR-186 conferred resistance towards cisplatin-treatment in ovarian cancer cells¹³⁷. Taken together these data attribute to resistin an important role in the progression of several cancers through different mechanisms.

5. Conclusion

Resistin has emerged in recent years as a key inflammatory cytokine involved in many chronic diseases. In mice, resistin was initially identified as a link between obesity and insulin resistance as it is expressed by adipose tissue proportionally to fat size. This has been supported by many reports in mice using diet or genetic models. This role is still a matter of debate in humans. Indeed, several studies reported an association between resistin levels and obesity or insulin resistance and in other studies, no correlation was found. Furthermore, the epidemiological studies were performed in different countries and including different populations (different conditions of inclusion to the studies, lifestyle, ethnic origin, etc...). Recent systemic review and meta-analysis revealed that in type 2 diabetes and obese individuals, resistin plasma levels were positively correlated to insulin resistance when subjects exhibited high resistin but not in subjects with normal resistinemia. The discrepancies between human and mouse resistin could be attributed to differences in

genomic sequences as well as expression sites. Whether mouse resistin is mostly expressed by adipose tissue, human resistin is predominantly expressed in peripheral blood mononuclear cells with higher expression in macrophages. Despite these differences between human and mouse, there is a strong body of evidence demonstrating the potential role of resistin as a mediator between inflammations and many chronic diseases such as metabolic disorders, cardiovascular diseases, and cancers (figure 2). However, further studies are needed to decipher the complex underlying mechanisms by which resistin is implicated in the onset of these chronic diseases with a special focus on resistin signaling. Indeed, whether TLR-4 and CAP-1 receptors appear to be the most plausible initiators of resistin signaling cascade, however, more investigations are needed to understand where, when, and how these two receptors are implicated in resistin actions.

6. References

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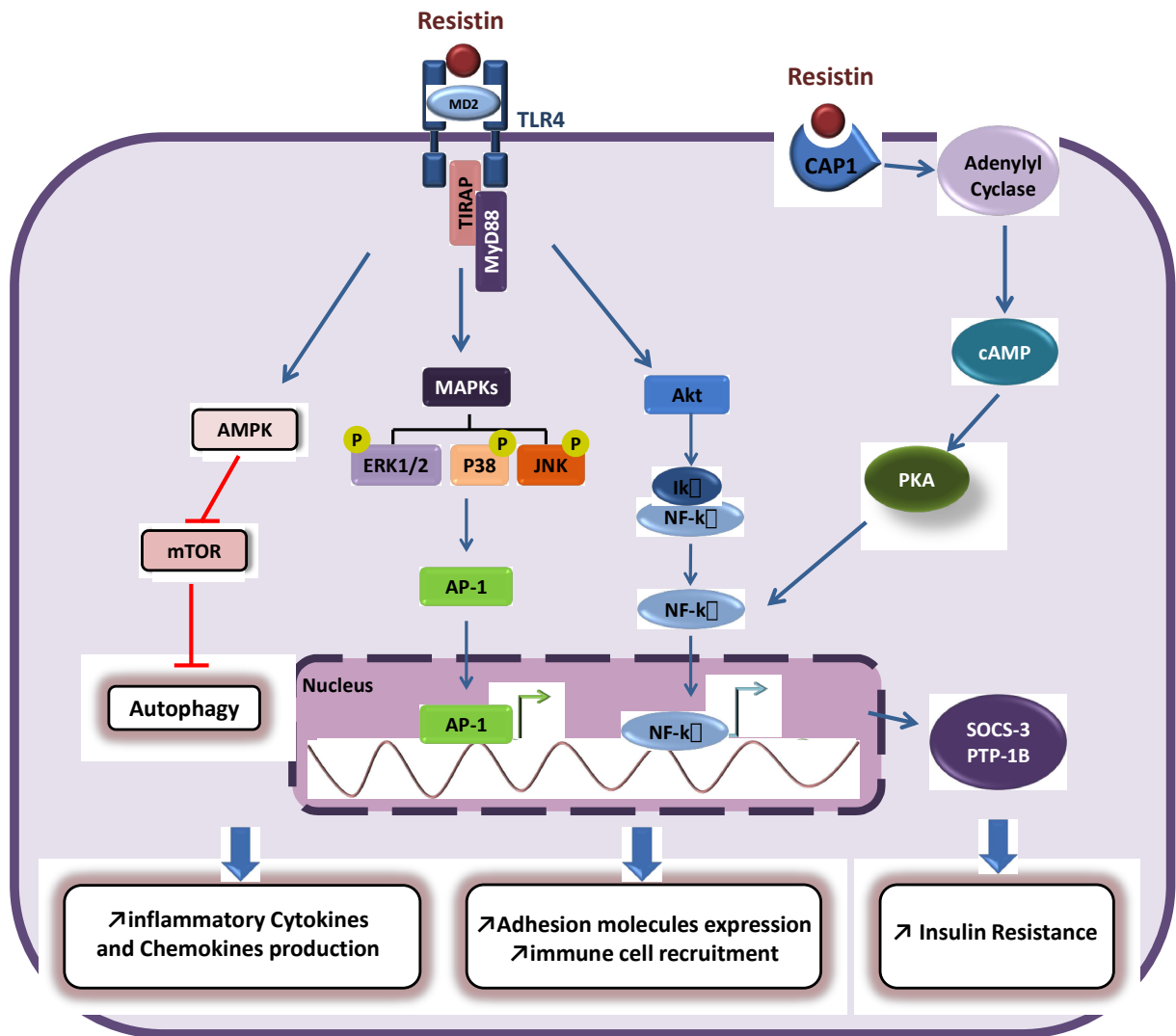


Figure 1: Comparison of resistin signaling pathways involving TLR-4 or CAP1.

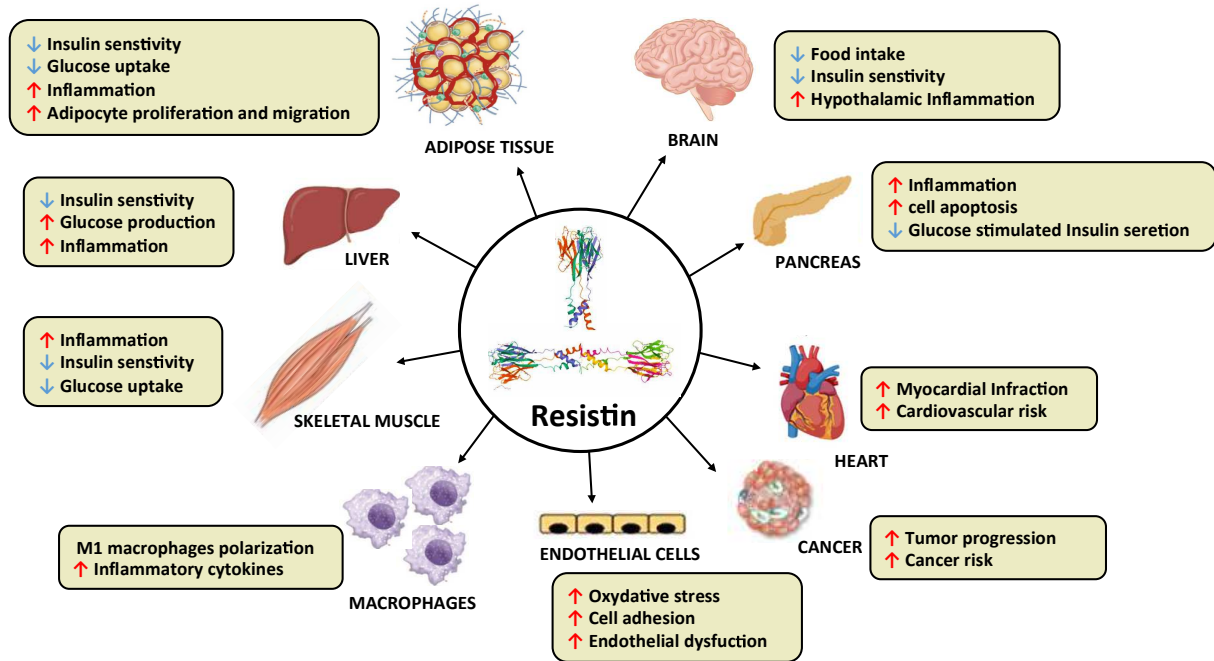


Figure 2: Schematic representation of key pathophysiological effects of resistin.