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Resistin: A reappraisal

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ABSTRACT

From a biological point of view, aging can be considered a progressive inability of an organism to react to stress, maintain homeostasis, and survive unfavourable changes during post-maturational life. The expression of several adipokines changes during aging and for some changes, a role in the onset of chronic disease and frailty has been proposed. Among adipokines, resistin was shown in recent studies to play a key role in aging.

Resistin is a small secreted protein that regulates glucose metabolism in mammalians. High resistin levels induce insulin resistance and exert proinflammatory effects. Consistently, resistin has been shown to play a pivotal role in various metabolic, inflammatory, and autoimmune diseases.

Herein, the role of resistin as a molecular link between aging and age-related conditions was reviewed and the clinical implications of this knowledge discussed.

1. Introduction

1.1. Resistin identification

Resistin was first described in 2001 by Steppan et al. as a small circulating mouse protein that was specifically expressed and secreted by adipocytes (adipose-tissue-specific secretory factor, ADSF) (Steppan et al., 2001b; Steppan and Lazar, 2002; Kim et al., 2001). Serum resistin levels were found to be markedly increased in mouse models of genetic and diet-induced obesity. Subsequently, resistin was then proposed as a potential link between obesity and diabetes and implicated in the development of insulin resistance (Steppan et al., 2001a). Resistin was initially studied only in rodent models. In the mouse, the resistin gene (*Retn*) is almost exclusively expressed in white adipocytes and blood cells (Steppan et al., 2001b). This observation indicated that resistin may act *via* a paracrine mechanism. Resistin is produced during adipocyte differentiation and antagonizes the effects of insulin, decreasing glucose intake in adipocytes, muscle cells, and other tissues. Serum resistin levels were found elevated in rodent models of obesity and diabetes, indicating a deregulation of resistin in these chronic diseases (Steppan and Lazar, 2004). In several studies using a mouse model of asthma, resistin was identified as a protein associated with lung inflammation and named the protein found in inflammatory zone 3 (FIZZ3) (Holcomb et al., 2000; Steppan et al., 2001b; Kim et al., 2001). In addition, resistin is predominantly found in an α-helical form in mice, and circulating resistin can be found both as a high-molecular weight (HMW) and as a low-molecular weight (LMW) protein (Patel et al., 2004).

Abbreviations: ACS, acute coronary syndrome; AD, Alzheimer's disease; ADSF, adipose-tissue-specific secretory factor; APO B, apoliprotein B; APO A1, apoliprotein A1; AS, aortic stenosis; AT, aerobic training; ATS, atherosclerosis; BMI, body mass index; CAD, coronary artery disease; cAMP, cyclic adenosine monophosphate; CAP-1, adenylyl cyclase-associated protein 1; CHD, coronary heart disease; CNS, central nervous system; CRP, C-reactive protein; CSF, cerebrospinal fluid; CVD, cardiovascular disease CRF chronic renal failure; DNC, decorin; DM2, diabetes mellitus 2; eNOS, endothelial nitric oxide synthase; ERK, extracellular signal-regulated kinase; ET-1, endothelin-1; FIZZ3, found in inflammatory zone 3; HCAECLs, human coronary artery endothelial cell lines; HDL, high-density lipoprotein; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; HMW, high-molecular weight; HF, heart failure; IGF-1R, insulin growth factor 1 receptor; IL-1, interleukin-1; ICAM-1, intercellular adhesion molecule-1; IR, insufficient renal; IRC, insufficient respiratory chronic; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; LMW, low molecular weight; MAPK, mitogen-activated protein kinase; MetS, metabolic syndrome; MMPs, matrix metalloproteinases; MPC-1, monocyte chemotactic protein-1; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NF-kB, nuclear factor kappa-light-chain-enhancer of activated β cells; OA, osteoarthritis; PAI-1, plasminogen activator inhibitor-1; PBMC, peripheral blood mononuclear cells; PI3K/AKT, phosphatidylinositol 3-kinase/protein kinase B; PLC, phospholipase C; PPAR, peroxisome proliferator-activated receptor; PSCK9, proprotein convertase subtilisin/kexin type 9; RELM, resistin-like molecule; ROS, reactive oxygen species; RT, resistance training; SREBP2, sterol regulatory element-binding protein 2; TNF-α, tumor necrosis factor-alpha; TLR4, toll-like receptor 4; TRAF3, TNF receptor-associated factor 3; VCAM-1, vascular cell adhesion protein 1; VEGFR, vascular endothelial growth factor; VSMCs, vascular smooth muscle cells; JNKs, c-Jun N-terminal kinases

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Notably, several differences have been shown between rodent and human resistin at the level of gene, gene expression regulation, protein, tissue-specific distribution, and insulin resistance induction (Yang et al., 2003; Huang and Yang, 2016).

In humans, peripheral blood mononuclear cells (PBMCs), macrophages, and bone marrow cells are the primary source of circulating resistin (Codoñer-Franch and Alonso-Iglesias, 2015). To a less extent, circulating resistin was also observed in the pituitary gland, hypothalamus, epithelial cells from the gastrointestinal tract (primarily the colonic epithelium), goblet cells, adrenal glands, skeletal muscle, pancreas, spleen, placenta trophoblastic cells, and synovial tissue (Steppan and Lazar, 2002; Filková et al., 2009; Jamaluddin et al., 2012; Codoñer-Franch and Alonso-Iglesias, 2015; Rajala et al., 2003; Satoh et al., 2004; Rangwala et al., 2004; Graveleau et al., 2005). Inflammatory conditions are associated with increased levels of circulating resistin (Lehrke et al., 2004), and resistin production within human adipose tissue appears to predominantly reflect secretion by resident non-adipocyte inflammatory cells (Savage et al., 2001; Patel et al., 2003; Jung et al., 2006; McTernan et al., 2002; Fain et al., 2003; Kaser et al., 2003; Bokarewa et al., 2005; Lehrke et al., 2004; Anderson et al., 2007).

Resistin has been shown to exert several pleiotropic biological effects *via* endocrine, paracrine, and autocrine mechanisms. Increasing number of cell types and tissues are reported responsive to resistin, thus potentially implicating resistin in a wide range of physiological and pathological processes. The implication of resistin in cardiovascular system function and in cancer, particularly in metastatic dissemination, are of special clinical interest. Unfortunately, such roles for resistin, as well as the resistin receptor, remain poorly understood (Hsieh et al., 2014). Resistin was shown involved in the control of blood glucose levels, lipid metabolism, regulation of pituitary somatotropin cells and the hypothalamic centre of satiety, modulation of central nervous system (CNS) cells, and contributes to the synthesis and secretion of pro-inflammatory cytokines and differentiation of monocytes into macrophages. Finally, resistin affects heart contractility, smooth muscle cell activity, angiogenesis, endothelium permeability, renal function, and bone remodelling (Filková et al., 2009; Jamaluddin et al., 2013).

1.2. Resistin: difference between animals and humans

1.2.1. Human resistin

The human resistin pre-polypeptide precursor forms a mature molecule of 12.5 kDa (108 amino acids) and only shares 59% sequence identity with its murine counterpart (Ghosh et al., 2003; Koerner et al., 2005). Resistin is the founding member of resistin-like molecules (RELMs), a family of small secreted cysteine-rich proteins with hormone-like activity (Patel et al., 2004) that initiate inflammatory processes (Holcomb et al., 2000).

In humans, resistin shows a concentration-dependent reversible conformational change (Patel et al., 2004; Aruna et al., 2008) which is considered responsible for its physiological and pathological activities (Filková et al., 2009; Jamaluddin et al., 2012; Codoñer-Franch and Alonso-Iglesias, 2015; Patel et al., 2004). Normally, the serum concentration of resistin in humans ranges from 7 to 22 ng/mL. Apparently, resistin has different sources and different roles/effects in animals compared with humans. In addition, several resistin isoforms resulting from alternative splicing have been reported (Patel et al., 2004; Aruna et al., 2003; Aruna et al., 2008). Human resistin is mostly found in two different conformations: an oligomer with a molecular weight of 660 kDa and a trimer with a molecular weight of 45 kDa. To date, the differences between the two forms of resistin, as well as their biological activities, have not yet been clarified (Codoñer-Franch and Alonso-Iglesias, 2015). However, resistin trimers and oligomers are reportedly more biologically active in humans than in mice (Aruna et al., 2003; Gerber et al., 2005; Aruna et al., 2008), and their assembly appears crucial for the pro-inflammatory properties of resistin (*e.g.* promoting the secretion of tumor necrosis factor (TNF)-α and interleukin (IL)-1β, -6, -8, and -12, generation of reactive oxygen species (ROS), and inhibition of eNOS in response to resistin). Notably, resistin also stimulates the release of monocyte chemotactic protein-1 (MCP-1) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation (Filková et al., 2009; Codoñer-Franch and Alonso-Iglesias, 2015; Silswal et al., 2005)

1.2.2. Mouse resistin

In mouse and rat adipose cells, resistin expression is upregulated by glucocorticoids, growth hormones, prolactin, testosterone, and suppressed by insulin, epinephrine, and somatotropin. Many of these hormones interact with the nuclear hormone receptor family. Mouse resistin is an 11 kDa polypeptide consisting of 94 amino acids produced from a longer precursor containing a 20-amino acid signal sequence. At the genomic level, the gene coding for resistin (*RETN*) is in syntenic regions of the mouse chromosome 8A1 and human chromosome 19p13.3 at a similar distance from the insulin receptor gene (Schwartz and Lazar, 2011). Resistin shows five intra-chain disulphide bridges among cysteine (Cys) residues at the 51–104, 63–103, 72–89, 74–91, and 78–93 positions, and an intra-chain disulphide bridge with the Cys 6 residue. The hallmark of these proteins is a 10–11-Cys-rich motif at the carboxyl terminus that promotes the assemble of the globular domain of the resistin monomer through the formation of five disulphide bridges (Patel et al., 2004). This carboxyl-terminal globular domain has been proposed as the receptor-binding site of resistin (Lee et al., 2009b). Disulfide and non-disulfide bonds were also shown important in the formation of higher-degree assembly states (dimers, trimmers, and hexamers) for circulating resistin (Patel et al., 2004; Banerjee and Lazar, 2001). These bonds have the ability to stabilize resistin structure, making it resistant in strongly denaturing environments (Ghosh et al., 2003). The secondary structure of resistin has an α-helix and six β-sheets per chain (Patel et al., 2004). The mechanisms involved in the conversion between the low and high molecular weight forms have not yet been established. The secondary structure of resistin appears relevant for the biological activity and tissue selectivity (Codoñer-Franch and Alonso-Iglesias, 2015). In addition, the activity of resistin may be modified by the interaction with other resistin-like family members and proteins such as heparanase (Novick et al., 2014).

1.3. Resistin action mechanisms and targets

The mechanisms by which resistin exerts its biological effects in humans are only partially understood. The main physiological role of resistin may be to modulate the inflammatory, immune, and auto-immune responses (Filková et al., 2009). Recent data show a positive correlation between chronic inflammation and clusters of metabolic syndrome (MetS) (Codoñer-Franch and Alonso-Iglesias, 2015), as well as between chronic inflammation and single diseases that are part of the MetS cluster (Park and Ahima, 2013; Ghosh et al., 2003).

In human macrophages, resistin induces inflammatory cytokines and promotes the expression of cell adhesion molecules, including vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and MCP-1 as well as chemokine (C-C motif) ligand 2 (CCL2) expression, contributing to chemotaxis and the recruitment of leukocytes to inflammation sites (Filková et al., 2009; Lehrke et al., 2004; Burnett et al., 2005). During pathological inflammation, the release of resistin by infiltrated monocytes/macrophages is incited by pro-inflammatory cytokines such as C-reactive protein (CRP), IL-1, IL-6, IL-12, and TNF-α (through the activation of NF-kB) (Filková et al., 2009) or by other pro-inflammatory stimuli, such as peptidoglycans and endotoxins. Resistin affects a wide range of cells and tissues *via* autocrine, paracrine, and endocrine mechanisms, enhancing the Th1 immune response as well (Won et al., 2009; Shetty et al., 2004; Qi et al., 2008).

In both human and animal blood vessels, resistin triggers vascular smooth muscle proliferation (Calabro et al., 2004) and endothelial

dysfunction (Verma et al., 2003; Kougias et al., 2005), promoting endothelial-monocyte adhesion and infiltration (Cho et al., 2011; Hsu et al., 2011). Furthermore, resistin can directly activate the complement system (Jamaluddin et al., 2012; Qiu et al., 2014).

The resistin receptor remains unknown, however, Tarkowski et al. suggested the pro-inflammatory effects of resistin may be mediated by its binding to the endotoxin receptor toll-like receptor 4 (TLR4) (Tarkowski et al., 2010). According to Daquinag and colleagues, decorin (DCN) could also act as a resistin receptor in the mouse (Daquinag et al., 2011). Other potential candidate receptors are the tyrosine kinase-like orphan receptor-1 (ROR-1), the insulin growth factor-1 receptor (IGF-1R), and the adenylyl cyclase-associated protein 1 (CAP1). Specifically, resistin binding to CAP1 could lead to increased cyclic AMP levels inside the cell, enhanced protein kinase A and NF-κB activity, and ultimately, promote the production of inflammatory cytokines (Boström et al., 2011; Sánchez-Solana et al., 2012; Lee et al., 2014). Several intracellular signalling cascades are triggered by resistin: NF-kB signalling *via* activation of PI3K/AKT (Rodriguez-Pacheco et al., 2007); the adenylate cyclase, cAMP, protein kinase A cascade; the MAP kinase system; the L-type voltage sensitive calcium channel (Rodríguez-Pacheco et al., 2009) with calcium influx and phospholipase C (PLC) activation, which subsequently leads to the release of calcium from intracellular compartments such as the endoplasmic reticulum (Fig. 1) (Bertolani et al., 2006).

Resistin activates the transcription of pro-inflammatory genes, cytokines, and chemokines *via* NF-κB, contributing to the proliferation of VSMCs and causing endothelial dysfunction. Stimulation of peripheral blood mononuclear cells (PBMCs) with resistin was shown to result in a dose-dependent translocation of p65 and p50 NF-κB subunits from the cytoplasm to the nucleus (Bokarewa et al., 2005). The NF-κB pathway plays a key role in osteoclastogenesis and is considered an especially important pathway for resistin-induced bone remodelling (Thommesen et al., 2006), increased hyperglycaemia-induced resistin expression (Stan et al., 2011), development of insulin resistance *in vivo* (Qatanani et al., 2009), stimulation of pro-inflammatory cytokines in macrophages and PBMCs (Nagaev et al., 2006; Silswal et al., 2005), and endothelial dysfunction (Calabrò et al., 2011; Kralisch et al., 2008). Another mechanism whereby resistin stimulates the production of pro-inflammatory cytokines is the phosphorylation and the consequent activation of the signal transduction proteins, p38, JNK, and ERK (Hsieh et al., 2014). By activating ERK1 and ERK2, resistin induces the proliferation of smooth muscle cells of the human coronary artery, thus impacting the events of vascular restenosis. Resistin also generates oxidative stress, which is another key mechanism for activating MAPK signalling and inhibiting *eNOS* gene expression (Chen et al., 2010). Resistin further reduces the bioavailability of NO by inducing the proliferation of VSMCs and causing endothelial dysfunction. In turn, reduced NO availability leads to impaired vasodilation, but also to increased incidence of thrombosis, vascular permeability, angiogenesis, and cell adhesion. Collectively, these events contribute to atherosclerosis, inflammation of blood vessels and perivascular tissues, and promote endothelial damage, thus accelerating the onset of

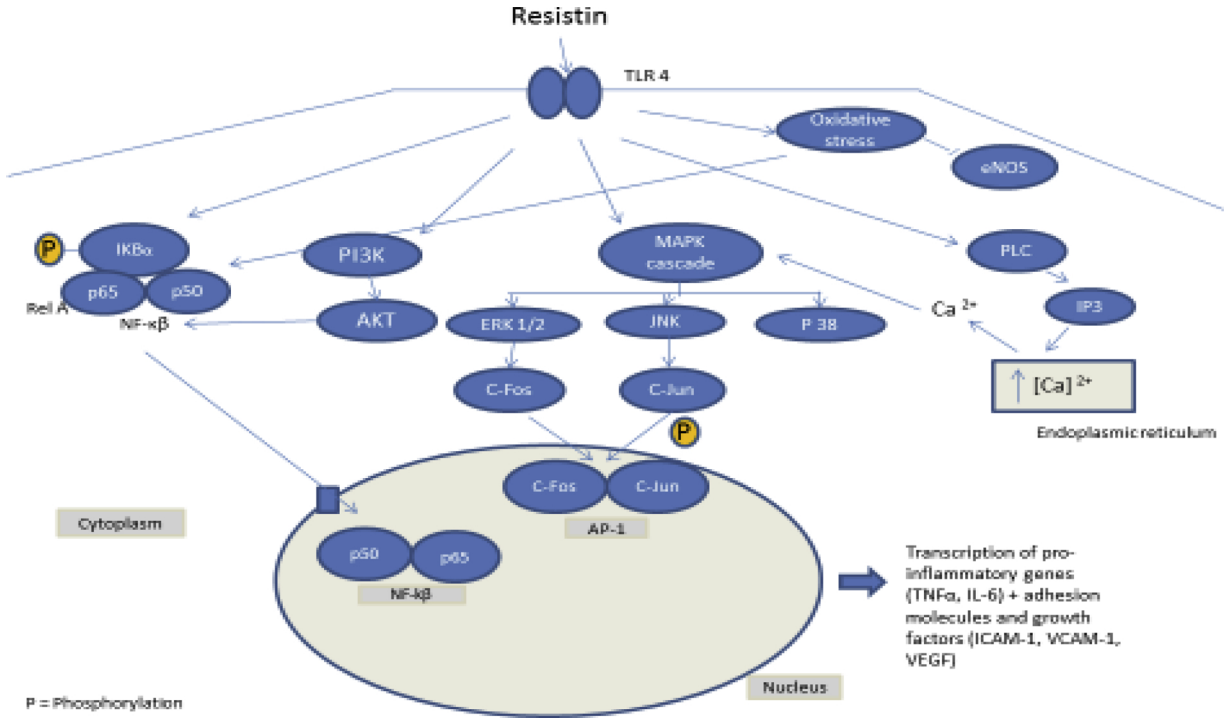

Fig. 1. Resistin Pathway.
Resistin contributes to the vicious circle of inflammation. The association between toll like receptors 4 (TLR4) and resistin and several intertwined action mechanisms of resistin have been proposed.
MAPK: mitogen-activated protein kinase, MCP-1: monocyte chemotactic protein,
PI3K/AKT: phosphatidylinositol 3-kinase/protein-kinase B,
IKBalpha: nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor
E NOS: endothelial nitric oxide synthase
ERK: extracellular signal-regulated kinase,
JNKs: c-Jun N-terminal kinases
PI3K/AKT: phosphatidylinositol 3-kinase/protein kinase B,
NF-k: nuclear factor kappa light-chain-enhancer of activated β cells,
TNF-α: tumour necrosis factor-α, IL-6: interleukin-6, TRAF3: TNF receptor-associated factor 3, VCAM-1: vascular cell adhesion protein 1, ICAM-1: intercellular adhesion molecule-1

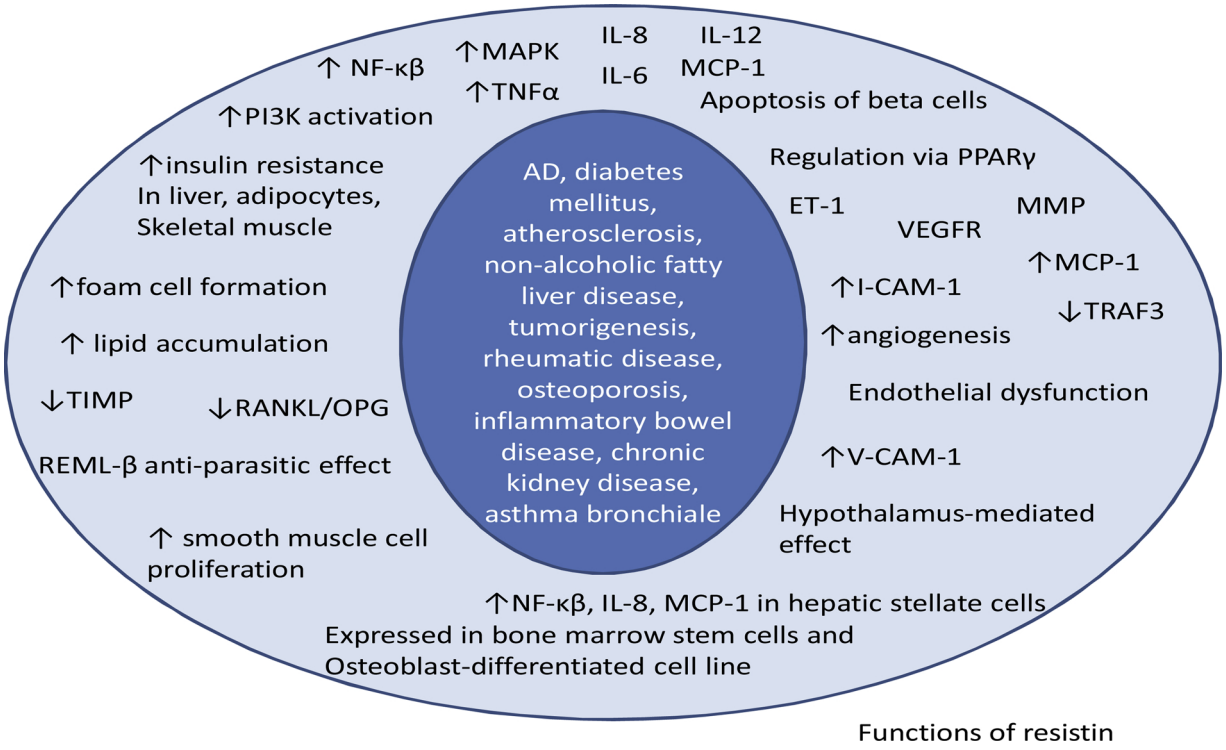

Fig. 2. Role of resistin in different diseases. Resistin affects several cell structures and the function of different tissues. The effects of resistin are similar to the conditions observed in many diseases. ET-1: endothelin-1, IL-8: interleukin-8, IL-6: interleukin-6, IL-12: interleukin-12, ICAM-1: intercellular adhesion molecule-1, MAPK: mitogen-activated protein kinase, MMPs: matrix metalloproteinases, MCP-1: monocyte chemotactic protein, NF-kβ: nuclear factor kappa light-chain-enhancer of activated β cells, PI3K/AKT: phosphatidylinositol 3-kinase/protein-kinase B, PPARγ: peroxisome proliferator-activated receptor gamma, RANKL/OPG: receptor activator of NF-κB ligand/osteoprotegerin, TIMP1: tissue inhibitor of metallopeptidase 1, TNF-α: tumor necrosis factor-α, TRAF3: TNF receptor-associated factor 3, VCAM-1: vascular cell adhesion protein 1.

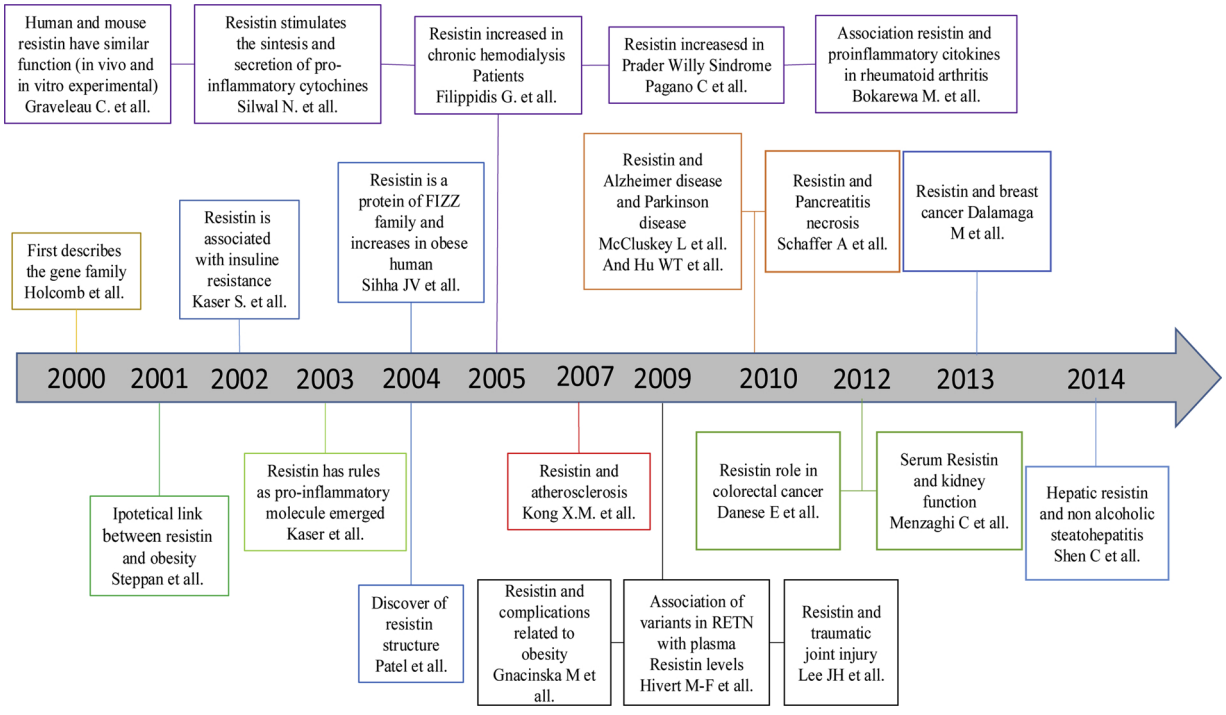

Fig. 3. Historical timeline of resistin.

cardiovascular diseases (CVDs) (Jamaluddin et al., 2012; Jamaluddin et al., 2013; Chen et al., 2010) (Figs. 2 and 3).

2. Resistin and chronic diseases

2.1. Resistin and age-related disease

Studies show that secreted circulating resistin exerts pleiotropic biological effects *via* endocrine, paracrine, and autocrine mechanisms. Resistin is involved in pathological processes other than inflammation, such as endothelial dysfunction, thrombosis, angiogenesis, and dysfunction of smooth muscle cells (Brown et al., 2008; Holcomb et al., 2000; Kusminski et al., 2007; Danese et al., 2012; Schindler et al., 2012; McTernan et al., 2006; Malyszko et al., 2006; Nagaev et al., 2006). As previously mentioned, the expression and secretion of resistin in mononuclear cells are induced by inflammatory stimuli (Lu et al., 2002; Kaser et al., 2003; Kunnari et al., 2006), which increase circulating resistin levels, creating a vicious circle, whereby resistin further enhances the inflammation (Lehrke et al., 2004; Reilly et al., 2005). Resistin is implicated in a wide range of physiological and pathological processes such as atherosclerosis and CVD (Jamaluddin et al., 2013; Libby et al., 2009), non-alcoholic fatty liver disease, osteoporosis, cancer, asthma, Crohn's disease, chronic kidney disease, metabolic diseases, diabetes mellitus 2 (DM2), and autoimmune diseases (lupus erythematosus) (Filková et al., 2009). Resistin expression in cancer cells is associated with an aggressive behaviour (Dalamaga et al., 2013). Moreover, recent data show that high resistin levels may lead to renal failure (Axelsson et al., 2006).

2.2. Correlation among resistin and obesity, MetS, and DM2

Mounting evidence indicates a role of resistin in obesity, MetS, and DM2, although resistin could have opposite effects compared with other adipokines. For instance, adiponectin, another adipokine that is primarily secreted by white adipose tissue, facilitated the effects of insulin on hepatocytes in *in vitro* studies; *in vivo*, adiponectin improved the metabolism of glucose and fatty acids. Adiponectin is apparently primarily involved in the promotion of the metabolism of sugars and fats and in the regulation of insulin sensitivity. Thus, adiponectin may have a protective role against age-related diseases, proving to be an excellent candidate gene for longevity (Fietta and Delsante, 2013). High levels of resistin are associated with low levels of adipokines, which antagonize the protective role of adiponectin, promoting inflammation and disease conditions such as MetS.

2.2.1. Obesity

As previously mentioned, resistin is described as a potential factor in obesity-mediated insulin resistance and DM2. In studies of obese non-diabetic subjects, high serum resistin levels as well as direct correlations between resistin level and adiposity, as measured by body mass index (BMI), were frequently reported (Lazar, 2007; Owecki et al., 2011). Using computed tomography (CT) imaging, resistin levels were associated with quantitative visceral, subcutaneous, abdominal, and intrathoracic fat (Utzschneider et al., 2005; Jain et al., 2009; Won et al., 2009). The association between resistin and obesity is stronger in women than in men (Juan et al., 2003; Chu et al., 2006), although opposite results were reported in other studies (Hansen et al., 2010). Diet and physical exercise decrease resistin levels, which is typically accompanied by a reduction in BMI and fat mass (Azuma et al., 2003). In general, resistin levels appear adjustable and responsive to treatments designed to improve the metabolic profile. Thus, although human resistin is not fat-cell derived, the protein appears associated with obesity and responsive to changes in adipose tissue mass. In a study of obese patients undergoing bariatric surgery, researchers found a reduction in serum resistin levels as early as 3–6 months post-operatively (Edwards et al., 2011; Moschen et al., 2009). Conversely, in a previous study, a small increase in resistin levels correlated with weight loss after a short follow-up (Koebnick et al., 2006), and in another study, serum resistin levels were unchanged following bariatric surgery, despite significant weight loss (de Luis et al., 2011). These studies were small and the studied population underwent different approaches to promote weight loss.

2.2.2. MetS and DM2

In 2003, Moon B. et al. showed that administration of recombinant resistin to diet-induced and genetically obese mice led to impaired glucose tolerance. Additionally, blocking resistin improved blood sugar concentration in obese mice and glucose tolerance in the healthy mice. Resistin decreased glucose uptake in skeletal muscle cells independently of insulin-activated signalling pathways (Moon et al., 2003). In rats with severe hepatic insulin resistance, an increase in serum resistin was observed (Rajala et al., 2003). Furthermore, resistin was shown to induce β-cell apoptosis in rat insulinoma (Gao et al., 2009).

Resistin exerts its glucoregulatory effects by stimulating hepatic glucose production (Banerjee et al., 2004; Muse et al., 2004; Yang et al., 2009). Resistin decreases insulin receptor and glycogen synthase activity and increases the activity of glycogen phosphorylase at the protein level but not the mRNA level (Yang et al., 2009). The result is a lower glycogen content in the liver due to attenuated glycogenesis and enhanced glycogenolysis (Yang et al., 2009). MetS is a cluster of metabolic disturbances that includes obesity, dyslipidaemia, hypertension, and glucose intolerance or diabetes. The components of MetS appear interrelated by underlying hyperinsulinemia (insufficient renal, IR) and inflammation, in which resistin was suggested to play a pivotal role (Meshkani and Adeli, 2009). Specific nucleotide polymorphisms in the *RETN* gene have been shown associated with obesity, IR, and DM2 (Aruna et al., 2008; Cho et al., 2004; Mattevi et al., 2004; Hivert et al., 2009). The initial stages of MetS development (Jialal et al., 2012) may be associated with higher resistin levels but not established MetS (de Luis et al., 2008). Consequently, this may be due to the higher inflammatory burst found in the first stages of metabolic disorder (De Nardo and Latz, 2011). Resistin has been shown to strongly contribute to the onset of DM2, which is an additional risk factor for higher morbidity and mortality in obese subjects due to metabolic derangement (Malo et al., 2011). Therefore, resistin has emerged as a potentially therapeutic target in MetS (Codoñer-Franch and Alonso-Iglesias, 2015; Abate et al., 2014).

Hyper-resistinemia was found in hypertensive patients both with and without DM2 (Takata et al., 2008; Zhang et al., 2010a). Hyper-resistinemia increases the incidence of hypertension in women without DM2 (Zhang et al., 2010a) and is related to myocardial infarction (Jamaluddin et al., 2012) and recurrent ischemic events (Filková et al., 2009; Jamaluddin et al., 2012). Higher resistin levels are found in patients with DM and are positively correlated with gestational diabetes-related complications (Filková et al., 2009; Codoñer-Franch and Alonso-Iglesias, 2015) and complications of CVD (Jamaluddin et al., 2012). These data reinforce the following correlation: resistin/DM2/CVD/inflammation. Regardless of the previous observations, whether hyper-resistinemia is associated to IR in humans remains controversial. Although in several initial studies, a positive correlation between resistin levels and obesity or IR was reported (Degawa-Yamauchi et al., 2003; Azuma et al., 2003), other groups failed to identify changes in resistin levels either in obesity, IR, or DM2 (Lee et al., 2003; Amirhakimi et al., 2011).

2.3. Correlation between resistin and atherosclerosis (ATS), CVD, coronary heart disease (CHD), heart failure (HF), aortic stenosis (AS), and thrombosis

2.3.1. CVD

Clinical studies investigating whether plasma resistin is a predictor

for coronary heart disease (CHD) and cardiovascular mortality yielded conflicting results (Yaturu et al., 2006a; Burnett et al., 2005; Ohmori et al., 2005; Pischon et al., 2005; Efstathiou et al., 2007; Lubos et al., 2007; Pilz et al., 2007; Lee et al., 2009b; Zhang et al., 2011; Menzaghi et al., 2014; Spoto et al., 2013).

In several studies, resistin was shown a major cause of atherosclerosis (ATS) and related CVD (Burnett et al., 2005; Reilly et al., 2005; Langheim et al., 2010; Pischon et al., 2005; Ohmori et al., 2005; Tsukahara et al., 2009), including heart failure (HF) (Cheng et al., 2013) and cardiac ischemic events (Filková et al., 2009; Jamaluddin et al., 2012). Furthermore, resistin is apparently involved in the molecular pathways of angiogenesis, thrombosis migration, and proliferation of the vascular smooth muscle cells as well as increasing MCP-1 and sVCAM-1 expression in murine vascular endothelial cells, indicating a possible mechanism by which resistin may contribute to atherogenesis (Codoñer-Franch and Alonso-Iglesias, 2015; Cheng et al., 2013; Burnett et al., 2005).

A hyper-resistinemia state increases the incidence of hypertension in women without DM2 (Zhang et al., 2010a). In older adults, the correlation between higher serum resistin concentrations and CHD and CVD events was recently confirmed with strong evidence for the role of inflammation (Gencer et al., 2016; Yaturu et al., 2006b; Yaturu et al., 2006a). Conversely, recent data indicate resistin levels were associated with incident CVD events independent of inflammatory markers (Muse et al., 2015) as previously reported for CRP. The Health ABC Study also showed an association between resistin concentration levels and CVD events such as HF in the elderly population (Butler et al., 2009). In adult rat cardiomyocytes, overexpression of resistin reduced cell contractility as well as contraction and relaxation velocities. As theorized by Burnett et al., resistin could confer increased risk for HF *via* direct and indirect mechanisms (Burnett et al., 2005). The overexpression of resistin in cardiomyocytes was associated with an altered response to ischemia-reperfusion injury, reduced contractility, and hypertrophy (Rothwell et al., 2006; Kim et al., 2008).

2.3.1.1. CVD and aging. Researchers from the Department of Surgery of Canada (Mohty et al., 2010) compared middle-aged patients and elderly patients with calcific aortic stenosis (AS). Similar to ATS, AS is a multifactorial disease involving many risk factors, including the aging process. The authors hypothesized the metabolic risk profile associated with valvular calcifying process may be different between elderly and younger patients. The researchers examined a cohort of patients surgically treated for AS. The patients were divided into two groups based on age: 50 patients were < 70 years of age (middle-aged group) and 64 were > 70 years of age (elderly group). Among the different metabolic factors evaluated in the study, only plasma resistin was found significantly associated with the calcifying and inflammatory processes in the elderly group (Sverdlov et al., 2011; Mohty et al., 2010). In *in vitro* experiments, macrophages were found to promote aortic valve calcification *via* the production of cytokines with direct pro-calcifying effects on valvular interstitial cells (Tintut et al., 2002). Elderly patients with higher resistin levels had increased valvular calcium content and greater density of macrophages. Moreover, the elderly patients tended to have an increased valvular T cell density (Verma et al., 2003; Jung et al., 2006).

2.3.2. ATS

In animals, a detailed understanding how resistin affects hypothalamic centers is lacking. However, resistin has an anorexic effect leading to a decrease of body mass and an increase of lipogenic enzymes and inflammatory cytokines in the liver (Vázquez et al., 2008). In several studies, plasma resistin levels were positively correlated with triglycerides and serum apolipoprotein B (APO B) levels (Singh et al., 2015) and inversely correlated with high-density lipoprotein (HDL) cholesterol and apolipoprotein A1 (APO A1) levels. In other studies, resistin and the protective anti-atherosclerotic HDL cholesterol levels showed a positive correlation and atherogenic low-density lipoprotein (LDL) cholesterol showed an inverse correlation with resistin (Owecki and Sowiński, 2006). Recently, an inverse association was also shown between resistin and both HDL and LDL. The quantity as well as quality of plasma lipids and lipoproteins influence cardiovascular risk. Reportedly, resistin is directly associated with the atherogenic small, dense LDL (LDL-III and -IV subclasses) and inversely associated with the larger LDL-I (Abate et al., 2014).

Overall, mounting evidence indicates that resistin plays an active role in the genesis of atherosclerotic plaques, leading to focal damage in the blood vessels, promoting ischemic insults, and increasing the risk of thrombosis (Filková et al., 2009; Jamaluddin et al., 2012). Hyper-resistinemia increases the production of ROS, LDL accumulation in the intima of the vessel, and recruitment of monocytes, which produce resistin and become macrophages that subsequently, by taking up oxidized LDL, become foam cells. Endothelial dysfunction in ATS is mediated by the expression of adhesion molecules on the cell surface, secretion of inflammatory and non-inflammatory cytokines, growth factors, and free radicals that are responsible for altered leukocyte adhesion, endothelium permeability, and vascular tone control, leading to an atherogenesis-promoting microenvironment (Jamaluddin et al., 2012; Codoñer-Franch and Alonso-Iglesias, 2015). Resistin mediates endothelial dysfunction by the release of endothelin-1 (ET-1), expression of VCAM-1, ICAM-1, vascular endothelial growth factor receptors (VEGFRs), matrix metalloproteinases (MMPs), and MCP-1; resistin also reduced TNF receptor-associated factor 3 (TRAF3), a key inhibitor of CD40 signalling in endothelial cells (Anderson et al., 2007; Verma et al., 2003; Kawanami et al., 2004). Subsequently, endothelial dysfunction increases the expression and production of resistin, resulting in increased release (Lefterova et al., 2009). According to different studies, resistin decreases the expression of nitric oxide synthase in human coronary artery endothelial cell lines (HCAECLs) (Jamaluddin et al., 2012), increases permeability of HCAECLs, (Jamaluddin et al., 2013), accelerates plaque progression by stimulating monocyte infiltration (Cho et al., 2011; Cho et al., 2004) and upregulates T-1 (Jamaluddin et al., 2012). Resistin also increases lipid accumulation in macrophages, contributing to foam cell formation (Jamaluddin et al., 2012; Rae and Graham, 2006). *In vivo*, resistin increases atherosclerotic plaque size and progression as well as plaque destabilization and vulnerability (Cho et al., 2004). Clinical study results have indicated a link between circulating plasma resistin and both the presence and the severity of coronary artery disease (CAD) (Burnett et al., 2005; Ohmori et al., 2005).

In CVD, resistin levels increase the symptomatic severity of CAD (Hu et al., 2007; Qiao et al., 2007; Lubos et al., 2007), indicating that increased resistin levels may be a marker of myocardial ischemia and injury in acute coronary syndrome (ACS) (Chu et al., 2008).

In MetS, recent studies focused on the role of resistin in reducing LDL receptor (LDLR) in human hepatocytes (Melone et al., 2012) with important implications for therapeutic approaches to lowering LDL levels and cardiovascular risk.

Resistin could stimulate proprotein convertase subtilisin/kexin type 9 (PCSK9; zymogen enzyme) by enhancing gene expression and stability of the protein, leading to downregulation of the LDLR, as shown in experimental studies (Melone et al., 2012). PCSK9 plays a central role in the regulation of cholesterol homeostasis by increasing the degradation of hepatic LDLR, resulting in hypercholesterolemia, a major cardiovascular risk factor for ATS. The enhancement of resistin-inhibited PCSK9 expression is mediated by sterol regulatory element-binding protein 2 (SREBP2), and the stimulating effect of resistin on LDLR reduction is, at least, in part *via* the PCSK9 pathway (Melone et al., 2012). Potential interactions may occur between PCSK9 and resistin in a variety of biological processes including lipid metabolism, inflammation, and ATS. Resistin-stimulated PCSK9 upregulation is paralleled by increased 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) activity. This effect strengthens the hypothesis that resistin

Table 1
Human and animal studies showing evidence for the role of resistin in chronic diseases.

MODEL	ANALYSIS	EVIDENCE	REFERENCES
Human	Plasma resistin levels and blood parameters	Resistin is weakly associated with body fat in insulin resistance or MetS	(Utzschneider et al., 2005)
Human	CT	Resistin is correlated cross-sectionally with fat depots	(Jain et al., 2009)
Human	Plasma resistin levels and blood parameters	Plasma resistin levels are not associated with insulin resistance and MetS	(Won et al., 2009)
Human	Blood parameters	Overweight after menopause worsens IR and the adipocytokine levels	(Chu et al., 2006)
Human	Plasma resistin levels and blood parameters	Resistin is related to human adiposity and could be a marker for insulin resistance	(Azuma et al., 2003)
Human	Blood parameters	The regulation of resistin may play a role in normalizing obesity-associated insulin resistance	(Edwards et al., 2011)
Human	Serum resistin and blood parameters	Serum resistin is correlated to abdominal fat distribution	(Koebnick et al., 2006)
Human	Measurement of HOMA-IR and adipocytokines in blood levels	Metabolic parameters are associated with elevated ALT	(de Luis et al., 2008)
In vitro rat cells	Recombinant resistin and transfection clones	Resistin does not alter IR signalling	(Moon et al., 2003)
Rat	Infusion of purified recombinant resistin	Novel family of fat- and gut-derived circulating proteins modulates hepatic insulin action	(Rajala et al., 2003)
Rat RINm5F	Treatment of RINm5F with resistin	Resistin can induce β-cell apoptosis	(Gao et al., 2009)
Mouse	Measurement of hepatic glucose production	Resistin diminishes the increase in post-fast blood glucose	(Banerjee et al., 2004)
Mouse	Insulin-clamp technique	Resistin has a role in hepatic insulin resistance	(Muse et al., 2004)
In vitro rat cells	Resistin and insulin treatment	Novel strategies for the treatment of DM2	(Yang et al., 2009)
Human	Polymorphism and BMI	RETN gene variation has gender-specific effects on BMI	(Mattevi et al., 2004)
Human	Resistin level measurements	SNPs in the 3' region of RETN are associated with resistin levels	(Hivert et al., 2009)
Human	Association of resistin with MetS	Controversial association of resistin with obesity and MetS	(Malo et al., 2011)
Human	Serum resistin levels	Hyper-resistinemia contributes to hypertension	(Takata et al., 2008)
Human.	Serum resistin quantification using ELISA	Resistin is increased in obese subjects	(Degawa-Yamauchi et al., 2003)
Human	Cross-sectional studies	Resistin plays a role in insulin resistance and energy homeostasis	(Lee et al., 2003)
Human	Analysis of serum resistin levels	No correlation between obesity and resistin level	(Amirhakimi et al., 2011)

might directly interact with and promote lysosomal degradation of the LDLR, because resistin and PCSK9 have a notable structural similarity in the Cys-rich C-terminal domain (Hampton et al., 2007). Resistin treatment has been proposed to blunt the response to statin therapy by dramatically reversing statin-mediated upregulation of hepatocyte LDLRs (Melone et al., 2012).

2.4. Correlation between resistin and organ injury

2.4.1. Kidney failure

The kidney is an organ capable of producing hormones, active molecules, and substances useful to degrade toxic metabolites, including several amino acids. Resistin emerges as a factor also capable of modulating renal function. First, a reduction in renal function was found to correlate positively with hyper-resistinemia (Filková et al., 2009; Jamaluddin et al., 2012). High levels of resistin were found in patients with chronic renal failure (CRF) and/or associated clinical complications (Filková et al., 2009; Menzaghi et al., 2012). In more recent studies, modulating effects of resistin on renal function were observed (Menzaghi et al., 2012); based on this evidence, hyper-resistinemia could lead to insufficient respiratory chronic (IRC) regardless of the presence of diabetes and/or obesity (Menzaghi et al., 2012). Subsequently, IRC increases the serum levels and the concentrations of metabolites and/or toxic substances due to decreased renal clearance and/or to altered metabolism, particularly in the presence of metabolic acidosis. In several studies, serum resistin levels were shown to be higher in elderly patients with advanced chronic kidney disease (CKD), particularly in patients on haemodialysis (Marouga et al., 2013;Marouga et al., 2016).

2.4.2. Liver failure

Resistin appears to mediate several aspects of liver disease. Resistin plays a role in the pathogenesis of both non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) (Filková et al., 2009; Shen et al., 2014). Resistin reportedly plays an active role in liver necro-inflammation and in the induction of steatotic states (Shen et al., 2014). In addition, resistin is apparently a good predictive marker of NAFLD and NASH due to its association with the severity of inflammation and fibrosis (Shen et al., 2014). Nevertheless, the specific role of resistin in liver failure remains to be determined.

In several studies, serum resistin was found to have a positive correlation with the grades of hepatic steatosis in liver biopsy (Aller et al., 2008) and with the presence and severity of inflammation and fibrosis (Tsochatzis et al., 2008;Pagano et al., 2006).

However, based on other study results, serum resistin shows no difference between simple liver steatosis and NASH (Wong et al., 2006;Jarrar et al., 2008). Conversely, in another study, resistin levels in liver tissue of patients with NASH were significantly higher than in the liver tissue of patients with simple steatosis (Shen et al., 2014), contributing to liver fibrosis by its direct and indirect profibrogenic effects on hepatic stellate cells (Dong et al., 2013). Resistin may also be associated with cirrhosis (Yagmur et al., 2006;Kakizaki et al., 2008); resistin was found to increase with advancing stages of liver cirrhosis and was significantly positively correlated with fasting plasma insulin and HOMA-IR index. Specifically, the binding of adiponectin to its receptors stimulates peroxisome proliferator-activated receptor activity (PPAR) and fatty acid oxidation in the liver and reduces fatty acid synthesis by inhibition of acyl-CoA carboxylase (ACC) and fatty acid synthase (FAS) expression and activity. This entire mechanism is apparently inhibited by resistin (Yagmur et al., 2006;Kakizaki et al., 2008).

2.4.3. Septic shock

Inflammation associated with elevated resistin levels was observed in human subjects with sepsis and septic shock (Anderson et al., 2007; Sundén-Cullberg et al., 2007; Koch et al., 2009). Due to the limited evidence in this field, further in-depth studies of the association between sepsis and resistin are necessary.

2.4.4. Acute pancreatitis

In patients admitted to the hospital with acute pancreatitis, resistin levels were shown to correlate with disease severity, tissue necrosis, and clinical outcome, whereas CRP showed no correlation (Schäffler et al., 2010) (Tables 1–5).

Table 2
Human and animal studies showing evidence for the role of resistin in CVD.

MODEL	ANALYSIS	EVIDENCE	REFERENCES
Human	Adiponectin levels and blood parameters	Low plasma adiponectin and insulin resistance coexist in prediabetes, diabetes, and ATS subjects	(Yaturu et al., 2006a)
Mouse	TaqMan PCR and immunohistochemistry	Role of resistin in CVD	(Burnett et al., 2005)
Human	Plasma resistin levels	Resistin level is associated CHD	(Pischon et al., 2005)
Human	Plasma resistin	High plasma resistin is increased after atherothrombotic ischemic stroke	(Efstathiou et al., 2007)
Human	Analysis of resistin levels	High resistin levels are associated with unstable angina, NSTEMI, and STEMI	(Lubos et al., 2007)
Human	Resistin levels and blood parameters	Resistin is a cardiovascular risk factor	(Pilz et al., 2007)
Human	Measurement of baseline serum resistin	Elevated serum resistin is associated with higher rates of mortality and hospitalization for HF	(Zhang et al., 2011)
Human	Circulating plasma resistin levels	High serum resistin is a marker for CVD	(Menzaghi et al., 2014)
Human	Plasma ADPN levels	Resistin predicts death and fatal CVD events	(Spoto et al., 2013)
Human	Plasma resistin levels and inflammatory markers	Resistin level is correlated with inflammation and coronary ATS in humans	(Reilly et al., 2005)
Human	Expression of EAT adipokines	Resistin is associated with increased endothelial cell permeability	(Langheim et al., 2010)
Human	Serum resistin levels	Resistin polymorphism can be a risk marker for stroke	Tsukahara et al., 2009)
Human	Serum resistin concentrations	High resistin level is associated with poor exercise capacity	(Zhang et al., 2010b)
Human	Serum resistin concentrations	Higher resistin levels are associated with CVD events	(Gencer et al., 2016)
Human	Measurement of adiponectin	Low plasma adiponectin level coexists in diabetes and ATS subjects	(Yaturu et al., 2006b)
Human	Measurement of plasma resistin levels	Association between higher resistin levels and incident CVD, CHD, and HF	(Muse et al., 2015)
Human	Serum resistin and clinical variables	Serum resistin level is not associated with risk of HF	(Butler et al., 2009)
In vitro rat cells	Recombinant human resistin	Resistin stimulates cardiac TNF-α secretion	(Rothwell et al., 2006)
In vitro rat cells	Microarray analysis of adenovirus-mediated overexpression of resistin	Resistin overexpression alters cardiac contractility and promotes cardiac hypertrophy	(Kim et al., 2008)
Human	Plasma lipid blood profile and adipokine levels	Resistin blood level is involved in AS	(Mohty et al., 2010)
In vitro rat cells	Plasma resistin levels	Resistin contributes to atherogenesis	(Jung et al., 2006)
Rabbit	Cloned rabbit resistin and its expression	Resistin aggravates ATS	(Cho et al., 2011)
Human	Plasma resistin concentration.	Polymorphisms in the resistin gene determines the plasma resistin concentration	(Cho et al., 2004)
Human	Plasma resistin	Resistin is involved in CAD	(Hu et al., 2007)
Human	Serum resistin levels	Resistin levels are increased with inflammatory factors	(Qiao et al., 2007)

2.5. Correlation between resistin, bone, and rheumatologic disorders

In the bone, resistin is primarily expressed by mature osteoblasts. *In vitro* study results showed recombinant resistin increases osteoclastogenesis while inducing a weak differentiation of pre-osteoblasts into osteoblasts (Filková et al., 2009). The condition of hyper-resistinemia was detected in patients with rheumatoid arthritis, osteoarthritis (OA), and psoriasis arthritis (Filková et al., 2009) and was found inversely correlated with bone mineralization in patients with hip fractures (Fisher et al., 2011) lumbar spine, or radio fractures (Fisher et al., 2012). Researchers speculated on a mutual interaction between resistin and osteocalcin (Fisher et al., 2011). In a previous study, adipokine levels were correlated with serum levels of osteocalcin, indicating a complex interaction between adipocytes/monocytes/macrophages and osteoblasts. In that study, leptin increased and resistin decreased the secretion of osteocalcin by osteoblasts, and circulating osteocalcin affected leptin (positive feedback) and resistin (negative feedback) (Fisher et al., 2012). This counterbalancing appears an important component of a complex homeostatic framework for effective maintenance of the metabolic homeostasis that depends on the interaction between fat/energy metabolism and skeletal tissue (Fisher et al., 2012). Based on these results, a decrease of bone mineralization can be expected in subjects with MetS.

Resistin levels were reported elevated in OA patients, indicating the

Table 3
Human and animal studies showing evidence for the role of the resistin in organ injury.

MODEL	ANALYSIS	EVIDENCE	REFERENCES
Human	Plasma resistin levels	Resistin plays a role in kidney disfunction	(Menzaghi et al., 2012)
Human	Metabolic and inflammatory markers	Resistin is involved in the malnutrition-inflammation state	(Marouga et al., 2013)
Human	Analysis of circulating resistin	Resistin is a predictor of CVD	(Marouga et al., 2016)
Human	Analysis of resistin, liver chemistry, fasting insulin, and several metabolic parameters	Hepatic resistin overexpression in NASH patients is associated with the severity of liver inflammation and fibrosis	(Shen et al., 2014)
Human	Adipokine blood levels	Insulin resistance is associated with steatosis	(Aller et al., 2008)
Human	Leptin levels, adiponectin, and resistin levels	Resistin levels are independently associated with fibrosis severity	(Tsochatzis et al., 2008)
Human	Plasma resistin levels	Increased resistin is associated with histological disease severity	(Pagano et al., 2006)
Human	Metabolic parameters in blood	Hypoadiponectinemia is associated with NAFLD and NASH	(Wong et al., 2006)
Human	Fasting serum insulin	Interaction between adipocytokines and the pathogenesis of NAFLD	(Jarrar et al., 2008)
Rat	Use of recombinant resistin	Resistin modulates HSC behaviour	(Dong et al., 2013)
Human	Clinical value of resistin	Resistin serum levels are associated with insulin resistance and disease severity	(Yagmur et al., 2006)
Human	Evaluation of the clinical value of resistin	The plasma resistin levels increased in LC	(Kakizaki et al., 2008)
Human	Resistin and cytokine levels	Resistin is a marker of disease severity	(Sundén-Cullberg et al., 2007)
Human	Clinical data	Serum resistin level is elevated in acute inflammation	(Koch et al., 2009)
Human	Blood and plasma	Resistin is a predictive marker of peripancreatic necrosis	(Schäffler et al., 2010)

Table 4
Human and animal studies showing evidence for the role of the resistin in OA.

MODEL	ANALYSIS	EVIDENCE	REFERENCES
Human	Serum resistin levels	High resistin levels are associated with cervical fractures, DM2, and history of stroke	(Fisher et al., 2011)
Human	Cross-sectional study	Serum osteocalcin is positively associated with leptin and inversely with resistin	(Fisher et al., 2012)
Human	Serum resistin levels	Adipokines serum levels are not predictive values for SF	(Presle et al., 2006)
Human	Serum resistin levels	Resistin is a marker in the pathogenesis of RA	(Senolt et al., 2007)
Mouse and Human	Mouse and human cartilage cultures	Resistin represents a new therapeutic target in OA	(Lee et al., 2009a)
Mouse and Human	Serum resistin levels	Resistin may play a role in bone remodelling	(Thommesen et al., 2006)
Human	Serum adiponectin, leptin, and resistin levels	Involvement of adipokines in OA patients compared with serum levels in controls	(de Boer et al., 2012)
Human	Multivariable analysis	The prevalence, demographic distributions, and functional impact of symptomatic knee OA	(Dillon et al., 2006)
Human	Measurement of serum adiponectin and resistin concentrations	Resistin is involved in radiographic changes in hand OA	(Choe et al., 2012)

catabolic role of resistin and other adipokines (Poonpet and Honsawek, 2014). In addition, resistin can be detected in inflamed synovium joints, as observed in rheumatoid arthritis (RA) and OA patients (Presle et al., 2006; Senolt et al., 2007). In both plasma and synovial fluid, the resistin levels are elevated after traumatic joint injuries (Conde et al., 2011). In the weeks immediately after joint injury, both plasma and synovial fluid levels of resistin are elevated. Resistin increases expression of MMP-1, MMP-13, and ADAMTS-4 in human articular chondrocytes. In addition, resistin can stimulate inflammatory cytokines, such as IL-6 and TNF-α, as well as PGE2 synthesis. Resistin stimulates proteoglycan degradation and inhibits the production of proteoglycan and type II collagen in mouse and human cartilage explants (Lee et al., 2009a). Recombinant mouse resistin stimulates osteoblast proliferation and osteoclast differentiation, indicating a role of resistin in osteophyte formation (Thommesen et al., 2006). Plasma resistin concentrations were positively associated with sPIIINP and hs-CRP levels (de Boer et al., 2012). In addition, a positive correlation was observed between synovial resistin levels and systemic markers of inflammation (Schäffler et al., 2003).

Gene expression of both resistin (Steppan and Lazar, 2004; Patel et al., 2003) and osteocalcin is suppressed by PPARγ, a key regulator of mesenchymal stem cell differentiation. Treatment with thiazolidinediones, which are PPARγ agonists, in patients with DM2 caused reduction in circulating resistin (Barac et al., 2008); however, this was associated with reduced bone formation, bone loss, and increased risk of fractures (Schwartz and Sellmeyer, 2008; Solomon et al., 2009). The bidirectional link between resistin and osteocalcin (and in a broader perspective, the bone-vascular axis) should be considered when pharmacological intervention is planned.

Resistin appeared responsive to anti-inflammatory treatment with the anti-TNF-α agent infliximab in both RA and inflammatory bowel disease (IBD) patients.

2.5.1. Age and OA

In the elderly, OA is the most common degenerative joint disease (Dillon et al., 2006) and worldwide, the percentage of OA increases steadily.

Poonpet and colleagues (Poonpet and Honsawek, 2014) focused on the role of adipokines in OA in people 60 years of age or older. Adipokines modulate the energetic balance of the organism, lipid and glucose metabolism, immune response, and reproductive function (Chaldakov et al., 2003; Rajala et al., 2003; Gnacińska et al., 2009). Obesity is considered a risk factor for the initiation and progression of OA. In obese patients, the production of adipokines is increased, indicating a correlation between adipokines and OA. In addition, adipokines play an important role in cartilage and bone homeostasis. Adipokines are produced in knee joints by infrapatellar fat pads (IPFPs), synovium chondrocytes, osteoblasts, and osteoclasts (Presle et al., 2006). Accordingly, adipokine levels correlate with cartilage degeneration and synovial inflammation (de Boer et al., 2012). Regarding resistin, plasma resistin levels were significantly higher than matched synovial levels and increased in obese individuals without direct association with BMI (Degawa-Yamauchi et al., 2003). Resistin levels were significantly higher in females than in males. As previously mentioned, resistin can be detected in inflamed synovium joints as observed in RA and OA patients (Presle et al., 2006; Senolt et al., 2007). In radiographic hand OA patients, plasma resistin levels were higher than in non-radiographic hand OA and controls (Choe et al., 2012).

2.6. Correlation between resistin and the CNS

2.6.1. Alzheimer's disease (AD)

The inflammatory process is a key pathophysiological aspect of DM2, obesity, CVD (Jamaluddin et al., 2012), and neurodegeneration (Sardi et al., 2011). Similarly, resistin was also implicated in neurodegeneration and disorders affecting the CNS, although studies show different effects of resistin depending on the disease.

Alzheimer disease (AD), the most common type of dementia, is a major health problem worldwide, affecting approximately one in eight people over 65 years of age. To date, the connection between resistin and CNS physiology and disease has been addressed in only a few studies. Currently, inflammation is considered to play a role in AD,

Table 5
Human and animal studies showing evidence for the role of resistin in the CNS.

MODEL	ANALYSIS	EVIDENCE	REFERENCES
Human	Analyses of antemortem AD and normal CSF samples	Targeted proteomic screen revealed novel CSF biomarkers that can improve the distinction between AD and non-AD cases compared to using established biomarkers alone	(Hu et al., 2010b)
Human	Analyses of plasma biomarkers	Plasma analytes are associated with the diagnosis of mild dementia/MCI/AD	(Hu et al., 2012)
Mouse	Primary murine neuronal cells with amyloid peptide-stimulated microglia	TLR4 has a role in neuroinflammation in AD	(Walter et al., 2007)
Human	Cross-sectional study	Resistin levels may be considered a predictor of AD	(Kizilarslanoğlu et al., 2015)
Human	Serum resistin levels	Resistin is related to decline in remitters to antidepressive treatment	(Weber-Hamann et al., 2006)

primarily through the acute phase response to damaged tissue, expression of amyloid precursor protein, and several different inflammatory mediators (Lee et al., 2009b). Resistin production was observed in the hypothalamus, where resistin appears to modulate feeding behaviour and energy intake (Vázquez et al., 2008) and inhibit the release of hypothalamic neuropeptides (Brunetti et al., 2004). The resistin levels were altered in the cerebrospinal fluid (CSF) of patients with mild cognitive impairment (Hu et al., 2010a) and AD (Fagan and Perrin, 2012; Hu et al., 2010b). High resistin levels were detected in the plasma of patients after traumatic brain injury (Dong et al., 2010) and more recently, in the plasma of patients with AD (Hu et al., 2012). Increased activity of TLR4, a putative resistin receptor, was observed both in the initial neurodegenerative processes in AD and during disease progression (Walter et al., 2007), thus, confirming the potential role of resistin in AD (Gambuzza et al., 2014). Resistin can also lead to mitochondrial dysfunction. Physiologically, resistin stimulates mitochondrial metabolism. Hyper-resistinemia appears to reduce mitochondrial transmembrane potential, leading to irreversible mitochondrial damage. Mitochondrial dysfunction is also associated with the AD processes (Trifunovic and Larsson, 2008; García-Escudero et al., 2013). In addition, resistin was shown to inhibit p53, and decreased p53 levels predispose individuals to different types of disorders.

A recent *in vitro* study of the neuroblastoma cell line, SH-SY5Y, showed that resistin induces insulin resistance through TLR4 engagement (Benomar et al., 2013) and an increased insulin signalling contributes to AD (Candeias et al., 2012). Furthermore, by enhancing inflammation, resistin promotes the development of MetS and cardiovascular disorders, which are risk factors for AD.

Monocytes and immunocompetent cells, which are typically well represented in AD plaques, increase the concentration of resistin.

Hyper-resistinemia is correlated with high levels of CRP, IL-6, and TNF-α. In the Health, Aging, and Body Composition Study, increased levels of CRP and IL-6, but not TNF-α, were associated with cognitive decline (Palta et al., 2015; Butler et al., 2009). Dik MG et al. showed no association between CRP, IL-6, and cognitive decline in older people (Dik et al., 2005). Conversely, Bruunsgaard et al. found an association between high concentrations of TNF-α and AD (Bruunsgaard et al., 1999). Overall, the association between resistin and AD remains unclear. (Kizilarslanoğlu et al., 2015). The neuroprotective effects of resistin in AD, and more specifically, on the patterns of oxidative stress, mitochondrial dysfunction, and cell vulnerability to stress were also observed (Kizilarslanoğlu et al., 2015). To date, that study is the first report on the protective effects of resistin against neurotoxicity in AD, and resistin was shown to reduce oxidative stress, mitochondrial dysfunction, and increased vulnerability to H_2O_2 in cultured neuronal cells. In different studies endogenous peptides such as leptin (Weng et al., 2007), ghrelin (Andrews et al., 2009), and adiponectin (Qiu et al., 2011) were shown to exert protective effects against neurotoxin-induced cell death. Based on the available data, the protective effects of resistin in cultured cells may be partially attributed to its anti-oxidant property. Moreover, in certain contexts, resistin may also improve mitochondrial function and prevent apoptosis.

Turkish researchers addressed how resistin levels were altered in clinically diagnosed AD patients and the correlation of resistin with other inflammatory markers.

In that study, AD patients (79.86 ± 5.55 years of age) and control subjects (74.22 ± 7.21 years of age) with normal cognitive function were recruited and enrolled. The median resistin levels of patients with AD were significantly higher than in the control group. Elevated resistin levels in the plasma of AD patients support the hypothesis that resistin may play a role in the inflammatory process that contributes to AD.

Inflammation is considered crucial in the pathogenesis of AD. Inflammatory molecules and processes occur in the brain of AD patients (Akiyama et al., 2000; Solfrizzi et al., 2006). Systemic inflammatory response results in the production of cytokines such as IL-1, IL-6, and TNF-α, as well as acute phase reactants, such as CRP and α1-antichymotrypsin (ACT) that circulate in the blood and can affect CNS function (Akiyama et al., 2000; Yasojima et al., 2000; Richartz et al., 2005). Cytokines and acute phase proteins synthesized in the periphery activate microglia and astrocytes and lead to the production of proinflammatory cytokines in the CNS.

The released cytokines lead to neuronal damage through various mechanisms, including neurotransmission alteration, apoptosis, and the production of free radicals, glutamate and nitric oxide. In addition, cytokines increase the expression of amyloid precursor protein (APP) and alter the processing of APP, thus generating larger amounts of amyloidogenic α-amyloid (Brugg et al., 1995; Sheng et al., 2003).

Data obtained from post-mortem AD brains showed high concentrations of acute phase inflammatory reactants, such as CRP and proinflammatory cytokines, in senile plaques and neurofibrillary tangles (Duong et al., 1997; Iwamoto et al., 1994). Evidence also supports the hypothesis that inflammatory processes may occur in the early stages of AD (Schuitemaker et al., 2009; Veerhuis et al., 2003; Engelhart et al., 2004). In conclusion, due to its role in inflammation, resistin may contribute to AD pathogenesis. However, because evidence is limited, future studies are necessary to clarify the contribution of resistin to AD.

2.6.2. Depressive mood

Previous study results showed disturbances in adipokine secretion play a role in the pathogenesis and clinical outcome of mental disorders in psychiatric patients, particularly affecting their mood (Wędrychowicz et al., 2014).

Recently, researchers suggested an association between inflammatory agents produced by adipose tissue and risk of depression (Shelton and Miller, 2011). In some studies, a positive correlation between resistin concentration in the blood and atypical, melancholic subtypes of major depressive disorders was reported (Weber-Hamann et al., 2006). This association may be related to the reduction in intrasynaptic concentration of monoamines by resistin *via* inhibition of norepinephrine and dopamine release in the hypothalamus (Brunetti et al., 2004). The involvement of resistin in the pathogenesis of bipolar disorders (BDs) has been suggested. Insulin resistance is an important etiological factor in BDs. Resistin activates enzymes involved in gluconeogenesis and increases glycogenolysis, thereby contributing to hepatic insulin resistance by decreasing the expression of GLUT4. In a recent study, increased resistin levels were reported in patients with BD, however, the specific role of resistin in the pathogenesis of this illness remains unknown (Yumru et al., 2007).

2.7. Correlation between resistin and physical exercise and training

The improvements obtained by physical exercise and training are well established. Different studies indicated an inverse association between physical activity and low-grade inflammation (Jones et al., 2009; Lavie et al., 2019; Van Pelt et al., 2017; Pinto et al., 2012). Lower levels of inflammatory markers have been observed in individuals who reported performing frequent moderate-intensity physical activity (Beavers et al., 2010). Both aerobic training (AT) and resistance training (RT) have been shown important for improving inflammatory profiles (Nassis et al., 2005). Nimmo et al. concluded the most significant improvements in the inflammatory profile are probably achieved with a combination of high-intensity AT and RT (Nimmo et al., 2013). Training intensity and frequency have been shown to affect inflammation markers in a dose-dependent manner (Fatouros et al., 2009).

In a recent study, how combined aerobic RT in healthy men can improve the levels of inflammation markers was investigated (Ihalainen et al., 2018). The effects of 24 weeks of combined AT and RT performed on the same day or on different days on inflammation markers were analysed. The plasma hs-CRP, IL-6, MCP-1, TNF-α, and adipocytokines resistin, adiponectin, and leptin levels were analysed. Training significantly reduced circulating hs-CRP, leptin, and resistin levels in both

training groups. Significant correlations were observed between changes in abdominal fat mass and corresponding changes in MCP-1, leptin, adiponectin, and resistin levels.

In another study, high-intensity training induced an improvement of inflammation biomarkers and insulin resistance, with a reduction of IL-1b, IL-6, TNF-α, IFN-γ, leptin, and resistin (associated with decreased insulin, C-peptide, and HOMA-IR) and an increase of IL-4, IL-10, and adiponectin, thus indicating that exercise exerts anti-inflammatory and insulin-sensitising effects (Balducci et al., 2010).

The previous above-mentioned studies included young and healthy men and postmenopausal women. In addition, exercise and training were shown to aid in the prevention of CVD and enhanced glucose uptake in adolescents and children.

Jones T.E. et al. investigated the role of long-term exercise training on hormones associated with appetite (leptin, ghrelin, and PYY) and insulin sensitivity (adiponectin and resistin) in overweight adolescents, particularly with respect to concomitant changes in these hormones that might occur during exercise training. Study subjects participated in eight months of supervised exercise sessions. Decreased percent body fat, concentrations of triglycerides and resistin and increased concentration of PYY in response to long-term exercise training were observed. Pre- and post-training leptin concentrations correlated with pre- and post-training percent body fat and pre- and post-training triglyceride concentrations. The change in triglycerides correlated with the change in resistin (Jones et al., 2009).

Ying Cai et al. hypothesized the anti-atherogenic effects of exercise were related to miR-492-mediated downregulation of resistin and repair of endothelial injury. The authors previously found that swimming exercises increased the expression of PPARγ in the liver and myocardium of ApoE-/- mice, which suppressed the development of aortic plaques, and the underlying mechanism may be related to improved IR in peripheral tissues of mice. In the recent study, swimming exercises over a 12-week period increased the miR-492 expression and decreased resistin levels in the aortic endothelium of ApoE-/- and C57BL/6 J mice. Additionally, swimming exercises alleviated AS due to weight loss and decreased levels of lipids, free fatty acids, glucose, and insulin. In combination with their previous data that miR-492 negatively regulates the expression of resistin in insulin-resistant HUVECs, swimming exercises inhibited the progression of AS possibly by upregulating the expression of miR-492, downregulating resistin expression, modulating the glucose and lipid metabolism, alleviating endothelial IR, and repairing endothelial injury (Cai et al., 2018).

Another research group investigated how physical activity was associated with decreased adiposity-related inflammation in adults (Vella et al., 2017). Whether this association is independent of central obesity is unknown, however, understanding the mechanisms associated with reducing cardiometabolic disease risk through physical activity is important. In the study, whether the association of physical activity and obesity-related inflammatory markers were independent of central adiposity was examined. The mean (range) age of participants was 64.7 years (55–84 years) and 50% were female. After adjusting for age and sex, compared to the lowest quartile, inflammatory markers in the highest quartile of moderate-to-vigorous physical activity were 16% higher for adiponectin and 30%, 26%, and 9% lower for leptin, IL-6, and resistin, respectively ($p < 0.05$ for all). In linear regression analysis adjusted for demographics, dyslipidaemia, hypertension, diabetes, smoking, glomerular filtration rate, renin, and aldosterone, each standard deviation increment of moderate-to-vigorous physical activity was associated with significantly higher levels of adiponectin ($\beta = 0.04$) and lower levels of leptin ($\beta = -0.06$), IL-6 ($\beta = -0.08$), and resistin ($\beta = -0.05$, $p < 0.05$ for all). The association with leptin, IL-6, and resistin was independent of total and central adiposity ($p < 0.05$), whereas the association between moderate-to-vigorous physical activity and adiponectin was attenuated by central adiposity ($p > 0.05$). Significant interactions were not observed based on race/ethnicity or sex. The authors concluded that moderate-to-vigorous physical activity was associated with a more favourable profile of inflammatory markers, independent of relevant cardiometabolic disease risk factors including central obesity.

In another study, 60 overweight/obese patients with DM2 were evaluated (Kadoglou et al., 2007). All subjects were inactive and reported engaging in no systemic (more than one time per week) sport activities before the study. Patients in the exercise group underwent a16-week aerobic exercise training program consisting of four 45–60 min sessions per week (50–85% maximum oxygen consumption; VO_2max). Aerobic exercise consisted mainly of cycling, calisthenics involving upper and lower limbs, and walking or running on a treadmill. Moreover, subjects in the exercise group were encouraged to increase daily physical activities (*e.g.*, brisk walking). Control subjects were instructed to maintain their habitual activities. The study results indicated that exercise training, without weight loss, decreases resistin and inflammatory cytokines in patients with DM2.

In a previous study, the risk of elevated serum resistin concentrations were lower in subjects who spent more than 20 min/day engaging in physical activity during their leisure time; the risk was higher in subjects with a more sedentary lifestyle (Marcelino-Rodríguez et al., 2017).

Another research group searched electronic databases (MEDLINE, EMBASE, and Cochrane Controlled Trials Registry) and references in relevant papers for articles published from 1966–2013. The authors selected studies in which the effects of exercise intervention on inflammatory markers/cytokines and adipokines in adult patients with DM2 were evaluated. Weighted mean differences of exercise on outcomes were derived using fixed or random effect models; factors influencing heterogeneity were identified using meta-regression analysis. The results obtained were based on meta-analysis of 14 randomized controlled trials (824 patients). Exercise was associated with a significant change in CRP = -0.66 mg/L (95% CI, -1.09 to -0.23 mg/L; -14% from baseline) and IL-6 = -0.88 pg/mL (95% CI, -1.44 to -0.32 pg/mL; -18% from baseline) but did not alter adiponectin or resistin levels; an aerobic exercise program was associated with a significant change in leptin = -3.72 ng/mL (95% CI, -6.26 to -1.18 ng/mL; -24% from baseline). Regarding IL-6, exercise was more effective in subjects who stayed longer in the program and performed more sessions during the study period ($p = 0.001$). The authors concluded that exercise decreases inflammatory cytokine (CRP and IL-6) in patients with DM2. Exercise could be a therapeutic option for improving abnormalities in inflammation levels in patients with diabetes (Hayashino et al., 2014).

In another study, the effects of six-week aerobic exercise on chemerin and resistin concentration in menopausal and postmenopausal women diagnosed with hypertension were examined. The study subjects were 50–55 years of age and lived in Amol, Iran. Twenty volunteers provided their personal consent and filled out a health questionnaire. The subjects were randomly and equally assigned to the experimental or control group ($n = 10$ per group). The experimental group performed a 6-week AT program from 8 to 10 am every day. Endurance exercise decreased chemerin ($t = 10.41$, $p < 0.000$) and resistin ($t = 2.42$, $p < 0.051$) levels, indicating a decline of inflammation and CVD. Based on the study results regarding the anti-inflammatory effects of exercise, training plays an important role in reducing inflammatory indices in humans, and endurance training can be a good method to manage inflammation and cardiovascular risk factors (Aghapour and Farzanegi, 2013).

In a 2007 study, the separate and combined effects of a 1-year exercise and diet intervention on several adipokines, adiponectin, IL-6, IL-8, TNF, MCP-1, hepatocyte growth factor, nerve growth factor, CRP, and resistin were examined. In a randomized, controlled, multifactorial trial on the effects of long-term changes in diet and exercise, a significant reduction in body weight and fat mass was observed. Alteration in leptin and plasminogen activator inhibitor-1 (PAI-1) concentrations were previously reported in the study. During the study, 188 males with several risk factors for diabetes and CVD were randomly allocated to

four groups: diet, exercise, combined diet and exercise, and control.

The plasma adiponectin concentrations remained unchanged, however, BMI and fat mass decreased after dietary changes and an increase in physical activity. In the control group, adiponectin concentrations were reduced. When analysed based on the factorial design, only diet intervention had a significant positive effect on plasma adiponectin relative to control, and this effect was largely due to changes in fat mass. After adjusting for change in percent body fat, significant positive effects on TNF were observed in all three intervention groups; minor changes were observed for the other adipokines. The authors concluded that diet intervention had a significant positive effect on adiponectin concentrations and mainly due to a reduction in fat mass (Rokling-Andersen et al., 2007).

3. Resistin and aging

Aging is a complex and multifactorial biological process defined as an age-dependent or age-progressive (gradual) decline in intrinsic physiological function after maturity, leading to an increase in age-specific mortality rate or disability. With aging, an increased prevalence and a clustering of metabolic abnormalities has been observed. These abnormalities include obesity, dyslipidaemia, hypertension, and insulin resistance, DM2, also known as MetS (Haffner, 2006; Kwon et al., 2006), leading to the increased risk for cardiovascular diseases (Gabriely and Barzilai, 2001).

In particular, adipocytes modulate the activity of pre-adipocytes, endothelial cells, and monocytes/macrophages due to increased production of pro-inflammatory cytokines (IL-6, IL-10, IL-8, IL-1β, THF-α), hormones (leptin, adiponectin, resistin), nonesterified free fatty acids (NEFA), PAI-1, and angiotensinogen. This leads to the phenomenon known as inflammaging, which is thought to mediate many aspects of aging (Franceschi et al., 2001).

Therefore, adipose tissue and its age-associated redistribution (Arai et al., 2011; Zamboni et al., 2005; Prentice and Jebb, 2001) could play a role in inflammaging by affecting adipokines.

In this complex picture of age-related dysmetabolic alterations, resistin levels also show an age-related increase. In elderly subjects, resistin is increased in all situations of inflammaging.

Therefore, resistin cannot be considered exclusively as a molecule involved in a single disease process, but as a molecule acting in different physiological functions (Filková et al., 2009; Codoñer-Franch and Alonso-Iglesias, 2015; Patel et al., 2004; Aruna et al., 2008).

The role of resistin in different pathologies has not been yet elucidated, thus, several molecular effects of resistin could play a major role in disease pathophysiology and determining clinical outcomes. In cancer, for example, resistin has been shown in several *in vitro* studies to exert pro-inflammatory effects mediated by TLR4 receptor-mediated stimulation of the NF-kB pathway (Tarkowski et al., 2010; Howe et al., 2013). In other studies, resistin regulated the production of MMPs and modulated the secretion of VEGF, which plays a central role in neoangiogenesis and metastasis (Mu et al., 2006; Di Simone et al., 2006).

In several studies, centenarians' offspring showed a significant survival advantage and lower risk of developing the most significant age-related diseases. Therefore, these subjects represent one of the best models for studying the familial component of human longevity.

The offspring of long-lived parents had a lower prevalence of MetS and retain improved glucose tolerance and enhanced insulin sensitivity (Rozing et al., 2009; Wijsman et al., 2012; Barzilai et al., 2003) compared with age-matched controls (Ostan et al., 2013). In the study by Ostan R et al, the offspring of centenarians, who were characterized by a “healthier” aging (Terry et al., 2004; Atzmon et al., 2004; Vitale et al., 2012; Gentilini et al., 2013), showed a different prevalence of MetS, along with distinct regulation of circulating adipokines, cytokines, and metabolic mediators, compared with age-matched offspring of non-long-lived parents. In addition, this group of researchers evaluated whether MetS-affected offspring of centenarians displayed features of this metabolic/pro-inflammatory syndrome and a specific regulation of circulating adipokines, cytokines, and metabolic mediators, to identify a phenotype that could influence their overall health status. These observations suggested that a protective phenotype against MetS and insulin resistance could be inherited from long-lived parents and be relevant for healthy aging. In addition, although the prevalence of MetS was similar both in the offspring of centenarians and controls, MetS-affected offspring of centenarians appeared healthier, more functionally fit, and had lower resistin levels. The results showed that in the presence of MetS, offspring of centenarians have a significantly lower prevalence of several important age-related diseases such as prior cardiovascular events, hypertension, hypercholesterolemia, and renal insufficiency than the offspring of non-long-lived parents. In particular, MetS-affected offspring of centenarians had lower levels of HDL cholesterol and higher levels of LDL cholesterol; differences in total cholesterol, triglycerides, insulin, glycemia, and HOMA index were not observed between the two groups. MetS-affected offspring of centenarians had lower levels of resistin compared with MetS-affected controls; no differences in other inflammatory parameters (CRP, fibrinogen, PAI-1, serum amyloid A protein, IL-6, and TNF-α, TGF-β1), adiponectin, leptin, IGF-1, leptin/adiponectin, and resistin/IGF-1 ratio was found. In controls, resistin was positively associated with waist circumference; however, no association was found in the offspring of centenarians. Conversely, the offspring of non-long-lived parents may have a different cellular composition, with a higher proportion of infiltrating macrophages and a greater predisposition to produce pro-inflammatory molecules such as resistin, thus explaining the increased prevalence of cardiovascular events, hypertension, and hypercholesterolemia.

In a previous study, a preserved whole-body insulin sensitivity was observed in healthy centenarians (Paolisso et al., 1996) and recently, subjects with familial predisposition for healthy longevity showed better glucose tolerance and higher whole-body insulin sensitivity when compared with a control group similar in age, sex, and body composition (Rozing et al., 2009; Wijsman et al., 2012).

Moreover, adiponectin levels were significantly higher in subjects $\geq$95 years of age and in their offspring compared with controls, indicating inherited factors play a role in determining adiponectin levels (Atzmon et al., 2008). In a recent study, the high levels of several adipokines were inherited by offspring from their parents (Al-Daghri et al., 2011).

4. Conclusions

Based on the current evidence, high levels of resistin are involved in many chronic diseases affecting the elderly. However, resistin is probably not the main cause of age-related disorders, playing a synergistical role with inflammaging in the onset and progression of comorbidities. Accumulating observations indicate that resistin may exacerbate clinical conditions, triggering the failure to thrive status in subjects with higher comorbidity and pre-existing disability. Further studies on resistin could aid in understanding the complexity resistin in the onset of several clinical conditions, such as obesity, DM2, MetS, cardiovascular risk, and cancer, and their complications.

Moreover, evidence on the offspring of centenarians have provided the ground for hypothesizing an intertwined role among resistin, aging and longevity.

In keeping with that, resistin has been recently included among the putative hallmarks of aging, due to its mediator role on inflammation, mitochondrial dysfunction, apoptosis and dysfunctional cell proliferation and reduced adipose tissue activity (Cardoso et al., 2018). In addition, from a molecular perspective, specific genetic mechanisms are likely involved in the fine regulation of the complex adipokine network and IGF-1 pathway, including intracellular resistin signalling that converges in the activation of NF-κB and MAPK pathways.

In conclusion, based on the available literature, the understanding

of the role of resistin in aging and frailty, based on an accumulation of small deficits, ultimately responsible for clinically relevant malfunctioning, represents a challenging field that might identify this molecular mediator as a diagnostic and prognostic tool useful for understanding co-morbidities and, potentially, the biology of aging.

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