

## Review

# Resistin and cardiovascular disorder

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Resistin belongs to a family of cysteine- rich secreted polypeptides produced by monocytes/macrophages. It is also regarded as a novel adipokine that has been suggested to play a role in the development of insulin resistance and obesity. In humans, inflammatory cells seem to be the major source of resistin. Resistin has been suggested to be an independent risk factor involved in the pathogenesis of numerous disorders. Cardiovascular complications account for significant morbidity and mortality. Moreover, resistin has been demonstrated to play a pivotal role in the pathogenesis of various vascular disorders such as atherosclerosis, hypertension, coronary artery disease and heart failure. Hence, the present review discussed the role of resistin in the pathogenesis of cardiovascular disorders.

**Key words:** Resistin, cardiovascular disorders, adipokine, cysteine, macrophages, monocytes.

## INTRODUCTION

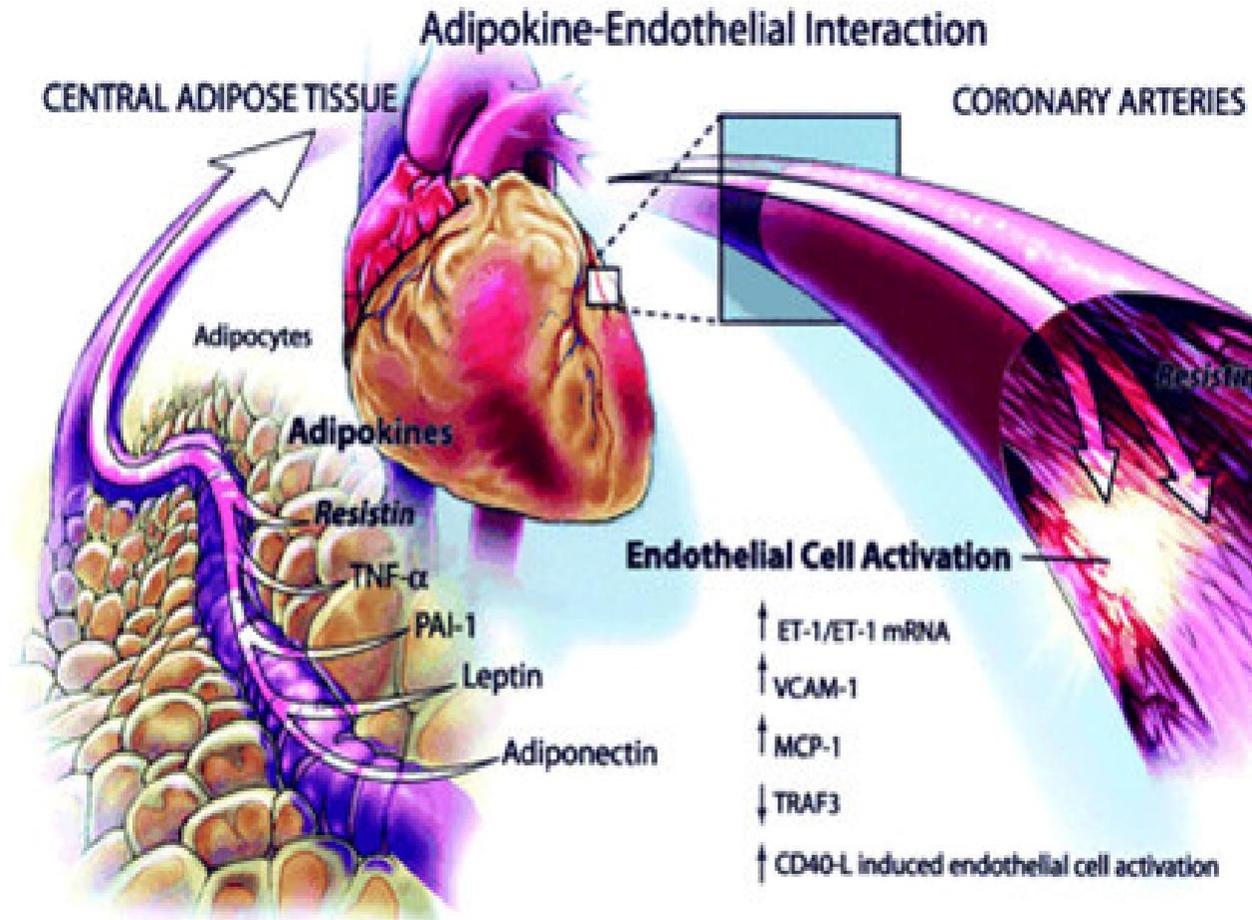
Resistin is a cysteine-rich protein that was discovered in 2001 (Mule and Cottone, 2010). Resistin is regarded as an important marker for obesity mediated insulin resistance and Type 2 diabetes mellitus (T2DM) (Reilly et al., 2005). However, resistin is expressed primarily in inflammatory cells (Kaser et al., 2003). Moreover in human monocytes the expression of resistin was markedly increased by treatment with endotoxin and proinflammatory cytokines (Kaser et al., 2003; Lu et al.,

2002). However, expression of resistin was found to be increased along with the maturation of monocytes into macrophage (Patel et al., 2003). In addition, resistin has been reported to augment the expression of adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM) and monocyte chemoattractant chemokine-1 (MCP) in endothelial cells *in vitro* (Verma et al., 2003; Kawanami et al., 2004). Pro-inflammatory cytokines, such as interleukin (IL) IL-1, IL-6, tumour necrosis factor-(TNF-) and also lipo-polysaccharides (LPS), increase resistin mRNA expression in human peripheral blood mononuclear cells *in vitro* (Kunnari et al., 2006). Resistin-induced expression and secretion of all of pro-inflammatory mediators involve the activation of nuclear transcription factor kappa B (NF- $\kappa$ B) by resistin (Barnes and Miner, 2009) through activation of protein kinase C (PKC), 1,4,5 inositol triphosphate (IP3) and the mobilization of intracellular calcium ( $Ca_2^+$ ) (Kaser et al., 2003). Further, it has been reported that resistin causes a marked increase in the generation of reactive oxygen species (ROS) and thereby decreases expression of endothelial nitric oxide synthase (eNOS) in endothelial cells (Kougias et al., 2005; Chen et al., 2010). Resistin has been reported to play a significant role in the progression of various disorders such as hypertension (Zhang et al., 2010), atherosclerosis (Verma et al., 2003), heart failure and hypertrophy (Nogueiras et al., 2010; Kim et al., 2008), inflammatory diseases like Rheumatoid

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Abbreviations: **T2DM**, Type 2 diabetes mellitus; **VCAM**, Vascular cell adhesion molecule-1; **MCP**, Monocyte chemoattractant chemokine-1; **TNF-**, Tumour necrotic factor-; **LPS**, Lipopolysaccharide; **IL**, Interleukins; **ROS**, Reactive oxygen species; **eNOS**, endothelial nitric oxide synthase; **ET-1**, Endothelin-1; **VLDL<sub>1</sub>**, Very low density lipoprotein; **LDL**, Low

phospholipase A2; **IRS-1**, Insulin receptor substrate-1; **MAPK**, Mitogen activated protein kinase; **MMP**, Matrix metalloproteinase; **VEGF**, Vascular endothelial growth factor; **VSMC**, Vascular smooth muscle cell; **SMC**, Smooth muscle cell; **RA**, Rheumatoid arthritis; **CRP**, C-reactive protein; **PKC**, Protein kinase C; **IP<sub>3</sub>**, 1, 4, 5 inositol triphosphate; **NF- $\kappa$ B**, Nuclear factor kappa B; **SOCS**, Suppressor of cytokine signalling-3.



**Figure1.** Shows the endothelial cell activation via interaction with various adipokines.

arthritis (RA) (Stofkova, 2010) and metabolic syndrome (Ukkola, 2002). Hence, the present review delineate with the pathophysiological role of resistin in the pathogenesis of various vascular disorders.

## RESISTIN AND CARDIOVASCULAR DISORDERS

### Resistin and hypertension

Cardiovascular disorders are the major cause of mortality and morbidity. Various studies indicate the role of resistin is in elevation of blood pressure (Dimitriadis et al., 2009; Zhang et al., 2010). Recombinant resistin has been noted to upregulate the expression of endothelin-1 (ET-1) and VCAM on human endothelial cells (Verma et al., 2003; Kawanami et al., 2004; Gomez-Ambrozi and Fruhbeck, 2005) as shown in Figure 1. Moreover, it was also reported to cause the proliferation of human aortic smooth muscle cells (SMC) (Kawanami et al., 2004). Various studies indicate that circulating resistin is associated with glomerular filtration rate in the early stages of essential hypertension (Zhang et al., 2009).

Moreover, resistin causes elevation in the level of IL's and C-reactive protein (CRP) (Kunnari et al., 2006; Tuttolomondo et al., 2010)

### Resistin and atherosclerosis

Resistin, 108-amino acid polypeptide (12.5 kDa) hormone was suggested to affect endothelial function and the migration of vascular smooth muscle cells (Calabro et al., 2004; Jung et al., 2006; Cohen and Horel, 2009), which are regarded as key pathophysiological mechanisms of atherosclerosis. Further, resistin has been noted to play a vital role in increasing the level of very low density lipoprotein (VLDL) and low density lipoprotein (LDL) in an obese person (Rizkalla et al., 2009; Xu et al., 2006; Burnett et al., 2005) which is directly atherogenic. Resistin induces increases in MCP-1 and sVCAM-1 expression in vascular endothelial cells which suggest a possible mechanism that contribute to atherogenesis (Verma et al., 2003; Kawanami et al., 2004; Calabro et al., 2004; Cohen and Horel, 2009). Recent reports indicate that resistin promotes proliferation of VSMC that

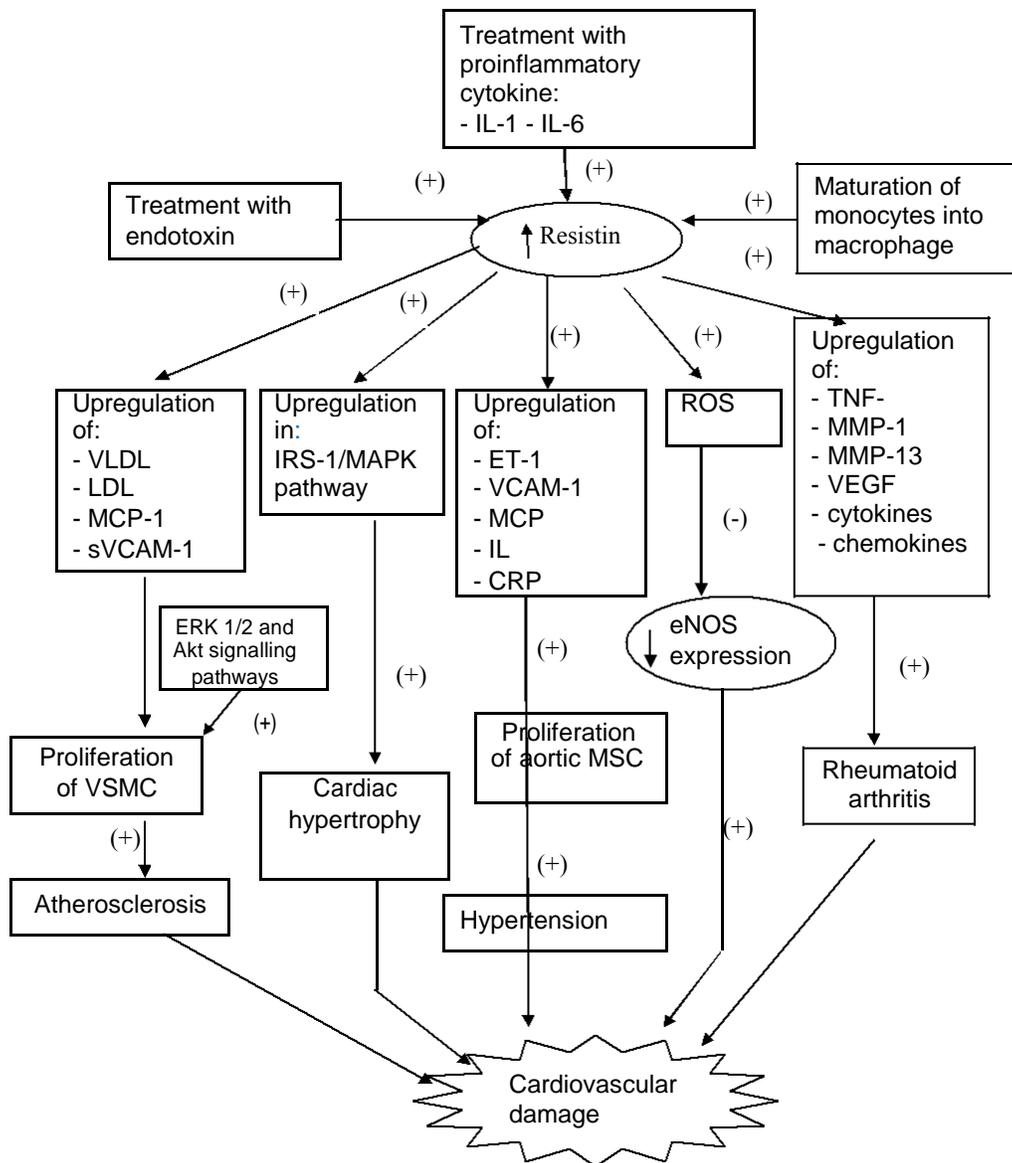


Figure 2. Mechanism by which Resistin-induces cardiovascular disorders. ET-1, Endothelin-1; MCP, Monocyte chemo attractant protein; VCAM, Vascular cell adhesion molecule; IRS, Insulin receptor substrate-1; eNOS, Endothelial nitric oxide synthase; TNF- , Tumour necrotic factor- ; MAPK, Mitogen activated protein kinase; ROS, Reactive oxygen species; IL, Interleukin; LPS, lipopolysaccharides; MSC, Smooth muscle cells; CRP, C-reactive protein; MMP, Matrix metalloproteinase; VEGF, Vascular endothelial growth factor; VLDL, Very low density lipoprotein; LDL, Low density lipoprotein; (+): triggering; (-): inhibition.

occurs through both ERK 1/2 and Akt signalling pathways (Calabro et al., 2004). Thus resistin is noted to enhance VSMC migration, which is a known component of athermanous plaque synthesis (Verma et al., 2003). Resistin promotes foam cell formation via dysregulation of scavenger receptors (SR-A) and ATP-binding cassette transporter- A1 (ABCA1) (Lee et al., 2009) through PPAR gamma. In atherosclerosis, increased level of resistin causes elevation of soluble TNF- receptor 2, IL-6 and lipoprotein-associated phospholipase A2 (Lp- PLA<sub>2</sub>)

(Reilly et al., 2005).

### Resistin and cardiac hypertrophy

Resistin over expression has been reported to alter cardiac contractility and promotes cardiac hypertrophy possibly via the insulin receptor substrate-1 and mitogen activated protein kinase (IRS-1/MAPK) pathway (Kim et al., 2008) as shown in Figure 2.

## RESISTIN AND INFLAMMATORY DISEASES

### Resistin and rheumatoid arthritis

Resistin, a secretory adipokine has been found to possess proinflammatory properties in humans and emerged as a promising inflammatory marker (Abdul Kader et al., 2010; Karmiris et al., 2007). Serum resistin levels were significantly increased in Rheumatoid Arthritis (RA) patients and correlated with inflammatory markers and TNF- suggesting that resistin may play a role in the rheumatoid inflammatory process (Migita et al., 2006). Moreover, resistin-treated human articular chondrocytes has been reported to increased the expression of cytokines, chemokines and matrix metalloproteinase 1 (MMP-1), MMP-13 (Stofkova, 2010; Zhang et al., 2010). Resistin has been noted to activate the local complement system that plays a vital role in the pathogenesis of RA (Grant et al., 2002). Moreover, various studies indicate that the administration of recombinant mouse resistin into the knee joints of healthy mice induces leucocyte infiltration and hyperplasia of the synovial and leads to RA (Bokarewa et al., 2005). In RA, synovitis and joint destruction occurs due to activation of vascular endothelial growth factor (VEGF), MMP-1 and MMP-13 by resistin (Choi et al., 2009; Stofkova, 2010).

## RESISTIN AND METABOLIC SYNDROME

Resistin has been reported to play a pivotal role in the progression of metabolic syndrome. Some recent genetic studies have demonstrated an association between resistin and insulin resistance and obesity (Ukkola, 2002). Various evidences elicited that there is 17% increase in the plasma resistin concentration in the individuals with the metabolic syndrome (Norata et al., 2007). Plasma resistin concentrations are correlated with chemokine markers of inflammation, such as MCP-1 which is reported to be a major culprit in the progression and the pathophysiology of the metabolic syndrome (Aquilantea et al., 2008).

### Resistin and diabetes

Resistin has been reported to impair insulin sensitivity. An increase in serum resistin levels has been shown to induce insulin resistance in several rat and mouse models (Rajala et al., 2003). Lazar and coworkers have recently shown that resistin increases the expression of SOCS (suppressor of cytokine signalling)-3, a known inhibitor of insulin signalling (Kusminski et al., 2005). Hence, the insulin-independent action of resistin on adipocytes could partly be mediated by SOCS-3, which could have a great impact on normal glucose homeostasis (Kusminski et al., 2005; Steppan et al., 2005).

## Conclusion

Hence, we concluded that resistin is one of the major mediators of cardiovascular disorders and other inflammatory disorder. Since no therapeutic interventions has been proven successful in the management of resistin mediated cardiovascular diseases. So, by having an idea about the signalling pathways mediated by resistin this can open a new vista for the development of therapeutic interventions,

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