Human Resistin and Cardiovascular Disease

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Obesity has become a major worldwide health problem and is involved in multiple diseases, such as insulin resistance, type 2 diabetes, atherosclerosis and ischemic heart disease.¹⁾ Many studies have identified adipocytes or adipose tissue, which were traditionally well-known to have roles in heat insulation, mechanical protection and energy reservoir, and as an endocrine gland that secretes important hormones, cytokines, vasoactive substances and other peptides.^{2,3)} Adipocyte biology and systemic metabolism such as in the brain, liver, muscle, and lymphoid organs are influenced by adipocytes or adipose tissue.²⁾ Adipocytes or adipose tissue express and secrete many factors that are referred to as adipokines.²⁾ Adipokines have multiple roles, such as in energy homeostasis, glucose and lipid metabolism, thermogenesis control, reproduction, immunity, and cardiovascular function.⁴⁾ Since resistin was first described in 2001, many studies have examined the relationship between resistin and chronic diseases. Chang, *et al.* have indicated that the plasma resistin level is associated with plasma tumor necrosis factor (TNF)- α , epicardial fat volume and larger left atrial scar.⁵⁾ A high resistin level is an independent predictor for recurrence of atrial arrhythmia after catheter ablation for atrial fibrillation (AF). Here, we will outline the relationship between resistin and cardiovascular diseases.

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Resistin was discovered by Steppan, *et al.* as a small circulating mouse protein that was specifically expressed and secreted by adipocytes.⁶⁻⁸⁾ Human resistin is a 12.5 kDa cysteine-rich polypeptide (108 amino acids) and is the member of a small family of secreted proteins with hormone-like activity which are characterised by a unique spacing of 10-11 cysteine residues and known as resistin-like molecules (RELMs) or as FIZZ (found in inflammatory zone) proteins.^{6,9)} In humans, the primary source of circulating resistin is secretion by peripheral blood mononuclear cells (PBMCs), macrophages and bone marrow cells.¹⁰⁾ Resistin is also secreted by the pituitary gland, hypothalamus, gastrointestinal tract, goblet cells, adrenal glands and other tissues.^{7,10-13)} Inflammatory conditions are

associated with increased levels of circulating resistin.¹⁴⁾

Many studies have indicated that resistin was a major cause of atherosclerosis (ATS) and related cardiovascular diseases (CVD), such as heart failure (HF) and cardiac ischemic events.¹⁵⁻¹⁷⁾ Resistin also has an anorexic effect leading to a decrease of body mass and an increase of lipogenic enzymes and inflammatory cytokines in the liver¹⁸⁾ (Figure).

Thus far, mounting evidence indicates that resistin plays an important role in the genesis of atherosclerotic plaques which lead to focal damage in the blood vessels, promoting ischemic insults and increasing the risk of thrombosis.^{11,12)} In the case of hyper-resistinemia, reactive oxygen species (ROS) are increasingly produced, low-density lipoprotein (LDL) is accumulated in the intima of the vessel, and monocytes are recruited, which produce resistin and 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, and other mechanisms, which play a key role in altering leukocyte adhesion, endothelium permeability and vascular tone control, leading to an atherogenesis-promoting microenvironment.^{10,12)} Resistin mediates endothelial dysfunction by the release of endothelin-1 (ET-1), expression of vascular cell adhesion protein-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), vascular endothelial growth factor receptors (VEGFRs), matrix metalloproteinases (MMPs), and monocyte chemotactic protein-1 (MCP-1); resistin also reduced TNF receptor-associated factor 3 (TRAF3), a key inhibitor of CD40 signaling in endothelial cells.¹⁹⁻²¹⁾ Meanwhile, endothelial dysfunction increases the expression and production of resistin.²²⁾ Resistin can also increase lipid accumulation in macrophages, contributing to foam cell formation.^{12,23)}

There is growing evidence indicating that an increase in the circulating resistin level is associated with risk of HF. High serum resistin levels were observed in patients with HF and a high number of cardiac events.²⁴⁾ Several studies investigated the effects of resistin on cardiomyocyte function. Resistin directly impaired glucose uptake in cardiomyocytes by altering vesicle trafficking.²⁵⁾ Resistin expressed in diabetic hearts can promote cardiac hypertro-

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Figure. Overview of cardiovascular effects of resistin.

phy and depress myocyte contractility.²⁶⁾ In cultured rat neonatal cardiomyocytes, the expression of resistin was also increased by mechanical stretch.²⁷⁾ However, until now, whether human resistin has direct pathogenic effects on HF development and aggravation has not been tested.

Several experimental and clinical studies have highlighted a relationship between resistin and hypertension. In a clinical study, Zhang, *et al.* found that higher blood resistin levels were correlated with a raised risk for incidents of hypertension among women without diabetes.²⁸⁾ Although the precise mechanisms by which resistin affects blood pressure is not clear, several mechanisms have been proposed. Potential mechanisms linking resistin to hypertension include the vasoconstrictor property of resistin, promoting smooth muscle cell proliferation, and effects on the renin-angiotensin system (RAS).^{29,30)}

Although a specific receptor for human resistin has not been fully identified yet, considering that resistin is associated with various cardiovascular diseases, solving these obstacles one by one will provide insight into these molecules not only with respect to cardiovascular diseases but also metabolic and other disorders.

Disclosure

Conflicts of interest: None.

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