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Human resistin in cardiovascular disease

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Abstract

An adipokine, resistin, was first discovered as a potential mediator of obesity related insulin resistance in rodents. However, the relevance of resistin in human obesity and insulin resistance has been challenged by the difference between human and rodent resistin and the controversies in human epidemiologic studies. Instead, recent human clinical studies and experiments support the idea that human resistin is an inflammatory mediator and a biomarker of cardiovascular diseases, especially in atherosclerosis and heart failure. Thus, we focused on the recent evidence of the role of human resistin in cardiovascular disease.

Key words: resistin, adipokine, inflammation, atherosclerosis, heart failure, cardiovascular disease

Resistin as an adipokine in rodent model

Prevalence of obesity is growing rapidly and it has become a major worldwide health problem because it is strongly associated with a number of diseases, including insulin resistance, type 2 diabetes, atherosclerosis and ischemic heart disease, that reduce life expectancy and together have huge economic and societal consequences (Ouchi *et al*., 2011). Adipocytes or adipose tissue have been considered to hold responsibility for development of such obesity-related disorders and became the target of tremendous studies to elucidate the mechanism of obesity-related disorders and the clues to cure or prevent those problems. These studies have identified adipocytes or adipose tissue, which were previously well-known for their essential role as energy storage depots, as an active endocrine gland that secretes important hormones, cytokines, vasoactive substances, and other peptides. Adipocytes or adipose tissue, thereby, influence local adipocyte biology as well as systemic metabolism at sites as diverse as brain, liver, muscle, B cells, gonads, lymphoid organs, and systemic vasculature as a regulator of food intake and nutrient metabolism, insulin sensitivity, stress responses, reproduction, bone growth, and

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inflammation (Kahn and Flier, 2000). These factors that are expressed and secreted by adipocytes or adipose tissue are collectively referred to as adipokines. A growing number of proteins have been identified as an adipokines since adipsin was identified as an adipokine by Cook *et al.* (1987) and TNF-alpha by Hotamisligil *et al.* (1993). Subsequently leptin was identified to be secreted by adipose tissue and to regulate food intake and energy expenditure in an endocrine manner by Zhang *et al.* (1994). Adiponectin was discovered as an adipokine that is decreased in obesity by Scherer *et al.* (1995), Hu *et al.* (1996) and Maeda *et al.* (1996), and many succeeding studies showed that it has protective role against several metabolic and cardiovascular disorders associated with obesity. It has been widely recognized that the abnormal expression of these factors strongly contributes the pathogenic processes of obesity related disorders (Ouchi *et al.*, 2011). Thus much attention has been paid to discovering new factors secreted by adipose tissue and identifying their role in obesity related metabolic dysfunction.

Resistin was discovered in this context in 2001 by three independent groups. Resistin is a 12 kDa cysteine-rich polypeptide and a member of a small family of secreted proteins characterized by a unique spacing of 10–11 cysteine residues and known as resistin-like molecules (RELMs) (Steppan *et al.*, 2001b) or as FIZZ (found in inflammatory zone) proteins and downregulated by antidiabetic thiazolidinedione drugs (Steppan *et al.*, 2001a). In rodents, resistin is secreted from white adipocytes (Kim *et al.*, 2001) and resistin levels are elevated in both diet-induced obesity and genetic mouse models of obesity (ob/ob) and diabetes (db/db). Administration of exogenous resistin or transgenic overexpression of it decreased insulin sensitivity while this effect was blocked by antibodies against resistin or resistin knock-out mice (Lazar, 2007). Resistin was observed to be in both trimer and hexamer in mice, with the smaller form (or possibly the monomer) being the most biologically active molecule (Patel *et al.*, 2004). Resistin also appears to have effects on lipid metabolism in mice. Total cholesterol and triglyceride concentrations were significantly higher, whereas the high-density lipoprotein cholesterol level was significantly lower in normal chow diet mice with adenovirus mediated resistin overexpression. Both low-density lipoprotein and very low-density lipoprotein were increased and conversely the expressions of genes involved in lipoprotein metabolism, such as low-density lipoprotein receptor and apolipoprotein AI in the liver, were decreased in the mice (Sato *et al.*, 2005). Adipokine resistin was therefore considered as a mediator of insulin resistance and metabolic dysfunction in rodents and most subsequent studies of resistin in animal models, but not all, support this notion that resistin is an adipokine regulator of insulin action (Arner, 2005).

Differences in human and rodent resistin

Human resistin is only 64% homologous and 59% identical with the rodent counterpart, the mouse resistin, at mRNA and amino acid level, respectively and this is less than most hormones conserved across species (Ghosh *et al.*, 2003). Yet, the genes are syntenic, with the gene encoding resistin (Retn) on mouse chromosome 8 being located at a similar distance from the insulin receptor gene as is the Retn gene on human chromosome 19 (Schwartz and Lazar, 2011). Unlike rodent resistin, human resistin is predominantly expressed in monocytes and macrophages, and its expression in human adipose tissue is predominantly mediated by stromal cells while the resistin levels decrease with thiazolidinedione treatment as in rodents (Savage *et al.*, 2001; Fain *et al.*, 2003; Patel *et al.*, 2003). The expres-

sion and secretion of resistin by human monocytes are remarkably augmented by pro-inflammatory stimuli, which increase circulating resistin concentration (Lu *et al*., 2002; Kaser *et al*., 2003; Lehrke *et al*., 2004). The lack of human resistin expression in adipocytes might be attributable to loss of a genomic binding site for peroxisome proliferator-activated receptor 5 (PPAR5) at enhancer region, which regulates the adipocyte-specific expression of the Retn gene in mice (Tomaru *et al*., 2009). The role of resistin in humans obesity and metabolic dysfunction is less certain. Clinical studies in humans have been conflicting, with some, but not all, studies identifying a significant correlation between resistin level and either obesity or insulin resistance (Heidemann *et al*., 2008; Chen *et al*., 2009; Schwartz and Lazar, 2011). It is unclear at present whether human resistin plays a similar role as rodent resistin, and if it does, how important human resistin is in the pathogenesis of the human insulin resistance (Yu and Ginsberg, 2005).

Human resistin in atherosclerosis and coronary artery disease

Evidences that support the pathological role of human resistin in development or progression of atherosclerosis and coronary artery disease can be grouped in two categories; 1) human clinical studies that show the association between various coronary artery diseases or it equivalents and either elevated circulating resistin level or local resistin expression; 2) in vitro experimental studies that demonstrated proatherogenic effects of resistin on endothelial cells, smooth muscle cells and monocytes or macrophages and in vivo animal studies that have shown the causal relationship between resistin and atherosclerosis progression. Several groups have investigated the association between circulating resistin levels and the development of coronary artery disease (CAD) in humans. The first landmark study was performed by Reilly and his colleagues in 2005 (Reilly *et al*., 2005). They showed that elevated resistin plasma level was correlated with coronary calcium score, a surrogate marker of atherosclerosis in asymptomatic healthy subjects. Subsequent studies supported this correlation in patients undergoing coronary angiography to diagnose angina pectoris (Ohmori *et al*., 2005; Pischon *et al*., 2005). Serum resistin levels showed a stepwise increase with the number of >50% stenosed coronary vessels in patients with stable CAD (Wang *et al*., 2009). Furthermore, resistin was an independent predictor of major adverse cardiovascular events, including cardiovascular death and myocardial infarction and restenosis in patients undergoing percutaneous coronary intervention (On *et al*., 2007; Krecki *et al*., 2011; Momiyama *et al*., 2011). In addition to these association between resistin and stable coronary artery diseases, elevated plasma resistin level was suggested to predict the development of myocardial infarction in a case–cohort study of 26,490 middle-aged subjects from the European Investigation into Cancer and Nutrition-Potsdam Study without history of MI or stroke with a relative risk of 2.09, adjusted for CRP (Weikert *et al*., 2008). Others have shown elevated levels of resistin in patients with acute coronary syndromes and its relationship with severe myocardial injury and poor prognosis (Lubos *et al*., 2007; Chu *et al*., 2008; Wang *et al*., 2009). High resistin level appears to be associated with poor outcome after atherothrombotic ischemic stroke, independently of other adverse predictors (Efstathiou *et al*., 2007). However, some studies have not detected an association between elevated circulating resistin level and either prevalence or outcome of CAD (Yaturu *et al*., 2006; Hoefle *et al*., 2007; Pilz *et al*., 2007; Piestrzeniewicz *et al*., 2008). The discrepancy between study results could be

related to differing demographics of the study groups, study design and patient selection criteria and also to non-standardized assay method.

Several in vitro studies were performed to test atherogenic effect of human resistin on endothelial cells, smooth muscle cells and monocytes or macrophages. Human resistin appears to promote endothelial cell activation in early studies. Human recombinant resistin increased the expression of pro-atherogenic molecule, ET-1, VCAM-1 and MCP-1 and down-regulated anti-atherogenic molecule TRAF-3, an inhibitor of CD40 ligand signaling in endothelial cells (Verma *et al.*, 2003). Human resistin was shown to induce adhesion molecule, ICAM-1 and VCAM-1 in endothelial cell and thereby increase monocyte-endothelial cell adhesion (Kawanami *et al.*, 2004; Cho *et al.*, 2011; Hsu *et al.*, 2011). Resistin was expressed by rat vascular smooth muscle cells and it was stimulated by hypoxia or cyclic mechanical stretch (Hung *et al.*, 2008; Wang *et al.*, 2010). Resistin promoted human vascular smooth muscle cell proliferation and migration (Calabro *et al.*, 2004; Jiang *et al.*, 2009). Human resistin was also expressed by macrophages infiltrated into atheromatous plaque (Jung *et al.*, 2006) and induced SR-A and CD36 expression and lipid accumulation in human macrophages, which suggests that resistin may act as a modulator for macrophage-to-foam cell transformation (Xu *et al.*, 2006; Lee *et al.*, 2009). Moreover, it was revealed that human resistin up-regulates inflammatory cytokine expression in monocytes/macrophages (Bokarewa *et al.*, 2005; Silswal *et al.*, 2005). In addition, resistin increased monocyte-endothelial cell adhesion by stimulating VLA-4 expression, a counterpart of VCAM-1, in monocytes (Cho *et al.*, 2011). Despite these studies, however, it has not been identified whether there is a causal-relationship between human resistin and either development or progression of atherosclerosis. In recent study using rabbit atherosclerosis model, human resistin promoted vascular inflammation and atherosclerosis progression mainly by increasing monocytes-endothelial cell adhesion by VLA-4 and VCAM-1 interaction, which was blocked by its inhibitor, CS-1 peptide (Cho *et al.*, 2011). This study also demonstrated that resistin increased both the size and vulnerability of atherosclerotic plaque by increasing macrophage infiltration, which can mechanistically explain the association between elevated resistin level and development of acute coronary syndrome in human clinical studies. Thus, animal and human studies have provided strong evidence that human resistin is a biomarker and a potential mediator of atherosclerosis and human coronary disease.

Human resistin in heart failure

Though the association between human resistin and heart failure has not been studies as much as its association with CAD, there are growing evidence that elevated circulating resistin level is associated with risk of heart failure development and aggravation. First, serum resistin level was shown to be higher in patients with heart failure and increased with advancing New York Heart Association functional class, in a case-control study (Takeishi *et al.*, 2007). In addition, the cardiac event rate was higher in patients with a high resistin level than in those with a normal level in these heart failure patients. More recently, the correlation between elevated resistin level and heart failure development has been supported by two large prospective cohort studies. A study analyzing data from 2,739 subjects in the Framingham Offspring Study followed up for 6 years, observed a 26% increase in heart failure risk (95% CI: 1–10%) with each 7.45 ng/mL increment in serum resistin level after adjusting for

known risks (Frankel *et al.*, 2009). Another study that analyzed 2,902 elderly persons without prevalent heart failure enrolled in the Health, Aging, and Body Composition (Health ABC) Study followed up for 9 years found an increased risk for heart-failure hospitalization with elevated baseline resistin (hazard ratio 1.15 per 10 ng/mL resistin), after adjustment for known risk factors (Butler *et al.*, 2009). Moreover, the Heart and Soul Study of American veterans with known stable coronary heart disease described that those with resistin levels in the highest quartile were at an increased risk of heart failure and death after adjustment for age, sex and race (Zhang *et al.*, 2011). However, further adjustments for obesity, hypertension, insulin resistance, dyslipidemia, and renal dysfunction eliminated these associations although these factors might themselves be dependent on resistin.

Several *in vitro* studies investigated the effects of resistin on cardiomyocyte function. Resistin directly impaired glucose uptake in cardiomyocytes by mechanisms that involve altered vesicle trafficking (Graveleau *et al.*, 2005). Resistin was expressed in diabetic hearts, promoted cardiac hypertrophy and depressed myocyte contractility (Kim *et al.*, 2008). Resistin expression was also enhanced by mechanical stretch in cultured rat neonatal cardiomyocytes (Wang *et al.*, 2007). However, not like the role of resistin in atherosclerosis progression, it has not been tested yet whether human resistin has direct pathogenic effects on heart failure development and aggravation and this should be the focus of much research in the future.

Conclusion and Prospective

Because of the difference between human and rodent resistin and conflicting results from human clinical studies there are strong debates on the role of human resistin in metabolic disorders. However, there is growing evidence from human clinical studies and experimental studies that resistin has pathogenic role in development and progression of atherosclerosis and CAD. More recently, large human studies support the association between elevated circulating resistin level and heart failure development and progression. For now, there are a lot of barriers including lack of standard resistin level measurement and limitation in using rodent animal model as a human alternative, which make it hard to clearly elucidate the role of human resistin in human disease. Furthermore, the specific receptor for human resistin has not been fully identified yet and this makes the experimental study more complicating. Solving these obstacles one by one will improve our understanding of the true role of human resistin not only in cardiovascular disease but also in metabolic disorders and so on.

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