Diabetic cardiomyopathy: is resistin a culprit?

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Abstract: Cardiovascular disease, including heart failure (HF), is the major cause of death in patients with diabetes. A contributing factor to the occurrence of HF in such patients is the development of diabetic cardiomyopathy. Recent evidence demonstrates that perturbations associated with adipokines secretion and signaling result in lusitropic and inotropic defects in diabetic cardiomyopathy. This perspective editorial will discuss the central role of resistin, a recently discovered adipokine, in the maladaptive cardiac phenotype seen in diabetic hearts. Given the pleiotropic effects of resistin, strategies targeting the control of resistin levels may constitute a potentially viable therapeutic utility in patients with diabetes and diabetes-induced cardiovascular diseases.

Keywords: Diabetic cardiomyopathy; resistin; heart failure (HF); resistin therapy; fibrosis marker; diabetes

Diabetic cardiomyopathy: pathology and causes

Obesity, insulin resistance and their frequent complication of type 2 diabetes mellitus (T2DM) are major risk factors of cardiac dysfunction and heart failure (HF). The epidemic rise, in particular of T2DM, is alarming, especially considering the increased incidence of insulin resistance and diabetes in young adults and children (1,2). Cardiovascular disease, including HF, is the major cause of death in diabetic patients. A prominent contributing factor to HF in these patients is the development of diabetic cardiomyopathy (3)—a clinical myocardial condition distinguished by ventricular dysfunction that occurs independently of coronary artery disease (CAD) and hypertension. However, many diabetes-related comorbidities are now known to adversely affect the heart as diabetes progresses, including coronary atherosclerosis and microangiopathy, hypertension, autonomic dysfunction and neuro-hormonal abnormalities (4,5). The Framingham Heart Study was the first to quantify the increased risk of congestive HF experienced by patients with diabetes. Diabetic men have twice the risk of age-matched controls, and diabetic women experience a fivefold increased risk, which could not be explained by obesity, hyperlipidemia, hypertension or CAD (6). This observation was further confirmed by Rubler *et al*. who found fibrosis, hypertrophy, remodeling and other evidence of congestive HF in four diabetic patients without clinically significant CAD (3). Subsequently, extensive clinical data supported the concept of a diabetic cardiomyopathy in humans, and animal studies in both type 1 diabetes mellitus (T1DM) and T2DM models also demonstrate cardiac dysfunction worsened by diabetes (7-9). Diabetic cardiomyopathy usually manifests with diastolic dysfunction preceding systolic dysfunction, and has been observed in the context of both T1DM and T2DM. The development of diabetic cardiomyopathy and the cellular and molecular perturbations associated with the pathology are complex and multifactorial (7-9). Although considerable progress has been made, the molecular etiologies of diabetic cardiomyopathy remain poorly understood. Recently, a novel paradigm for the role of adipokines secretion and signaling in cardiac metabolism and function has emerged. Resistin, a newly discovered adipokine, has been proposed to be a link between obesity, insulin resistance and diabetes (10).

Resistin: a regulator of metabolism and insulin homeostasis

Resistin, a novel cysteine-rich hormone secreted by rodent fat cells, was found to impair glucose metabolism and insulin action in mouse models of obesity and cultured adipocytes, and immuno-neutralization of resistin improved insulin action in mice with diet-induced obesity (10). Overexpression of resistin in metabolically healthy mice led to insulin resistance and dyregulated lipid metabolism with increased accumulation of triglycerides and cholesterol (11,12). Plasma resistin levels were increased in db/db, ob/ob and diet-induced obese mice (10), while resistin mRNA levels in adipose tissue of obese rodents were often found to be decreased (13). Notably, mice lacking resistin have improved glucose tolerance compared with wildtype controls both in diet-induced obesity (14) and in ob/ob mice (15), suggesting a role for resistin in insulin resistance and hyperglycemia associated with obesity. Loss-of function and gain-of-function studies have demonstrated that resistin modulates glucose metabolism through inhibition of AMP-activated protein kinase and increased expression of gluconeogenic enzymes in the liver (14-16). However, other studies suggest that resistin may also act centrally to regulate glucose homeostasis (17,18). Resistin is also believed to be a target of the anti-diabetic drug thiazolidinedione (TZD) as TZD treatment suppressed resistin expression in 3T3-L1 adipocytes and in white adipose tissues of mice fed a high fat diet (10). Collectively, these findings provide evidence that resistin may function as a significant contributor to the development of diabetes.

However, the pathophysiological role of resistin in humans has been questioned because the human homologue of resistin is only 59% identical to mouse resistin at the amino acid level and the source of resistin appears to differ between humans and mice (10,19). Unlike mice, resistin in humans is undetectable in adipocytes but highly expressed in macrophages. However, emerging evidence suggests that cardiovascular disease is accompanied by changes in resistin levels. Elevated levels of resistin were observed in the serum of obese and T2DM patients and increasing plasma resistin concentrations were therefore considered to be a predictor of poor prognosis in patients with cardiovascular disease.

Cardiac actions of resistin

Resistin's role in cardiac function in the diabetic heart is currently obscure. Resistin was shown to impair glucose transport in isolated mouse cardiomyocytes (20) and to be up-regulated by cyclic stretch and aorta-caval shut (21), suggesting resistin may affect cardiac function in animal models. A variety of cardiovascular effects of resistin were reported since its discovery in 2001; such as the induction of endothelial dysfunction and the promotion of ischemia-reperfusion (I/R) myocardial injury (22-24). However, the latter finding is controversial with at least one study showing a protective effect of resistin against myocardial I/R injury and another showing worsening of myocardial I/R injury by resistin. Other lines of evidence from our laboratory and others (25) strongly indicate that hyper-resistinemia may contribute to the impairment of cardiac contractility and development of diabetic cardiac dysfunction. We have demonstrated that cardiac tissues from T1DM mice and T2DM humans and rats express elevated levels of resistin (26). We have shown that adenoviral overexpression of resistin induces hypertrophy, contractile dysfunction with impaired Ca^{2+} handling (27), and insulin resistance in isolated rat cardiomyocytes (28). We have subsequently shown that long-term cardiac specific overexpression of resistin *in vivo* using adeno-associated virus serotype 9 significantly decreased left ventricular contractility and induced a complex phenotype of oxidative stress, fibrosis, apoptosis and myocardial remodeling in normal rats, producing a phenotype resembling diabetic cardiomyopathy (29). In addition, recombinant human resistin was shown to exacerbate cardiac I/R injury, and stimulates TNF-α secretion and upregulates cardiac injury markers such as atrial natriuretic peptide, brain natriuretic peptide and creatine kinase through an NF-κB signaling pathway (24). We have also observed that transgenic mice overexpressing human resistin develop cardiac hypertrophy and myocardial fibrosis (unpublished observations).

Furthermore, by using several animal models of cardiac hypertrophy and failure and measuring cardiac tissue levels of resistin, we were able to demonstrate that animal models of cardiac hypertrophy that is associated with fibrosis (diabetes, pressure overload and HF) demonstrate elevated tissue levels of resistin compared to non-fibrosing hypertrophy (volume overload) where resistin is minimally or not elevated (30). We also demonstrated that chronic ischemia is likely to explain these differences. Using animal models of myocardial infarction, we demonstrated that resistin is expressed locally in the infarct area as opposed to the remote area (30). Thus, we propose resistin as a simple indicator of cardiac fibrosis and chronic ischemic damage. Linking resistin to cardiac fibrosis is of particular prognostic

and therapeutic interest since (I) serum resistin is elevated in hypertrophic and diabetic cardiomyopathies, conditions in which myocardial fibrosis is emerging as a predictor of arrhythmias and as a potential criterion for device therapy; and (II) the deposition of collagen and its gradual organization into irreversible fibrosis are histological hallmarks of diabetic cardiomyopathy (31). Over time, fibrosis manifests as myocardial stiffness with impairment of relaxation, i.e., diastolic dysfunction, which is one of the earliest observable cardiac changes in diabetic patients, and often presents initially without any other clinical sign of heart disease. Echocardiography of asymptomatic diabetic patients often reveals subclinical hypertrophy and impaired relaxation, even before the onset of clinically significant fibrosis (32).

We were also able to demonstrate that in cardiac tissue from animals with pressure-overload and volume overload, resistin inversely correlates with mRNA levels of angiotensin II receptor type 1. Therefore, resistin is a potential circulating second messenger that indicates neurohormonal stress on the heart. To establish this relationship, we exposed adult rat cardiac myocytes and fibroblasts to neurohormonal stimuli and this resulted in increased resistin expression (30). Thus, resistin can serve to modulate neurohormonal activity on cardiac tissue in conditions like HF, diabetes and hypertension, especially high-renin hypertension, and can be used as a predictor and indicator of response to therapy aimed at neurohormonal blockade, which varies between patients in these conditions. This is of particular interest as hyperresistinemia is associated with hypertension in patients with T2DM but not non-diabetic subjects (33), while hypertension and neuro-hormonal abnormalities constitute major diabetes-related comorbidities with nearly 80% of T2DM patients developing hypertension (34).

Resistin and human cardiovascular diseases

At the clinical level, several clinical and epidemiological studies linked high resistin levels with development of cardiovascular dysfunction, such as CAD, myocardial infarction, hypertension, and left ventricular hypertrophy, indicating that elevated resistin's function may be a major contributor to increased heart disease morbidity. For example, plasma resistin levels are elevated in female patients with coronary heart disease (35). What role resistin plays in the disease process is not known although in patients with atherothrombotic strokes, plasma resistin levels

are associated with elevated risk of 5-year mortality (36). Serum resistin concentrations have also been shown to be elevated in patients with HF with levels positively related to the severity of HF according to New York Heart Association functional classification (37). In addition, survivors of myocardial infarction displayed elevated levels of resistin and increased plasma resistin level was observed in the serum of obese (38) and T2DM patients (39). Although these studies do not indicate cause and effect relationships, increasing plasma resistin concentrations appear to be a predictor of poor prognosis in patients with cardiovascular disease. TZD treatment resulted in decreased plasma resistin levels in patients with T2DM (40), suggesting resistin plays an important role in the etiology of insulin resistance and diabetes; however, others have failed to show any association with insulin resistance (41,42).

A European case–control study of 26,490 healthy individuals found a relative risk of 2.09 for the development of myocardial infarction in those in the highest quartile of resistin (43). Other studies also reported higher resistin level in patients with acute myocardial infarction and the increase was more prominent in patients with diabetes than in those without (44), while higher plasma resistin levels were demonstrated to be a predictor of the presence and severity of CAD (45) and of all-cause mortality in patients with acute myocardial infarction (46). Recent reports from large cohorts studies (the Health ABC Study which included 2,902 subjects, the Framingham Offspring Study which included 2,739 subjects and the Heart and Soul Study of American veterans with known CAD) assessed the connection between resistin and incident HF and found an increased risk for HF hospitalization with elevated baseline resistin (47,48), and a significantly higher risk of HF and all-cause mortality in those in the highest quartile of resistin level (49). These studies clearly suggest a pivotal role of resistin in heart disease.

Resistin-targeted therapy: perspectives

Although there are currently no treatments developed specifically for the prevention or management of diabetic cardiomyopathy, there are few potential considerations, which warrant further investigation though, that support resistin inhibition as an efficient strategy for clinical translation in diabetes and diabetes-related complications. (I) Antagonism of the renin-angiotensin-aldosterone system with angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs) and

aldosterone antagonists has proven beneficial at preventing or slowing the progression of myocardial dysfunction associated with the diabetic cardiomyopathy. ACE inhibitors and aldosterone antagonists have been shown to prevent hypertrophy and inhibit collagen deposition and myocardial fibrosis (50-52). Candesartan, an ARB, has been shown to reduce collagen synthesis and promote its degradation in asymptomatic diabetic patients, leading to an improvement in echocardiographic parameters of diastolic dysfunction (50). Given our findings that resistin may function as a potential circulating second messenger following neurohormonal stress, it is conceivable to suggest that therapy aimed at neurohormonal blockade may evoke their beneficial effects through attenuation of resistin levels and as such, decreasing resistin levels may constitute a new therapeutic strategy to improve diabetes-induced cardiac dysfunction; (II) resistin is also regulated by the peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist TZDs. TZD treatment reduced plasma resistin levels in human patients with T2DM (40), and suppressed resistin expression in 3T3-L1 adipocytes and in the white adipose tissue of mice fed a high-fat diet (10), with a concomitant increase in insulin sensitivity in the heart and other tissues, suggesting that TZDs' resistin lowering effects may lead to improvement in resistin-evoked cardiac remodeling; however, TZDs are contraindicated in HF patients classified as New York Heart Association class III and above. In addition, TZDs caused weight gain secondary to hyperphagia in a number of patients by lowering leptin levels (53); (III) sarco/endoplasmic Ca^{2+}-ATPase (Serca2a) level and activity are compromised in diabetic hearts, adversely affecting cardiac function. We have demonstrated that myocardial-targeted restoration of Serca2a improved mechanical as well as energetic function of the diabetic hearts (54), and interestingly downregulated resistin expression in these hearts (26). Therefore, measures that underlie resistin repression through Serca2a genetic correction (through vector-based gene transfer) or pharmacological activation may emerge as a potential objective in the treatment of diabetes-induced HF; (IV) as discussed earlier resistin impairs lipid metabolism in mice and promotes dyslipidemia (11,12) which constitutes a hallmark contributor to diabetic cardiomyopathy (8). Resistin inhibition as a potentially effective therapy in severe type of dyslipidemia, such as familial hypercholesterolemia and atherogenic dyslipidemia, is being considered (55). In this regard, many cholesterol lowering drugs belonging to the class of the 3-hydroxy-3-methylglutaryl-coenzyme A

(HMG-CoA) reductase inhibitors, i.e., statins, have been tested for their ability to reduce resistin levels in patients with T2DM (56). A recently discovered effect of resistin demonstrates that resistin treatment increases proprotein convertase subtilisin/kexin type 9 (PCSK9) by enhancing gene expression and posttranscriptional stabilization of the protein, leading to downregulation of the low-density lipoprotein receptor (LDLR) (57). PCSK9 is known to regulate cholesterol homeostasis via enhancement of hepatic LDLR lysosomal degradation (58), strongly suggesting that resistin induction of PCSK9 results in an elevated level of serum LDL, a significant risk factor for atherosclerotic cardiovascular disease. This point raises the possibility that PCSK9 stimulation by resistin may blunt the response to statins, since they work by upregulating LDLR (57). Interestingly, resistin treatment of PCSK9-knockout mice also showed significant reduction in LDLR expression (57), suggesting that resistin may bind directly to the receptor targeting it to lysosomal degradation in a PCSK9-independent mechanism (59). Although statins may be an effective strategy to regulate cholesterol metabolism, therapeutic strategies controlling resistin levels may be more efficient as the benefits of resistin inhibition extend beyond diabetes-regulated cardiac function owing to the fact that resistin is involved in many other cardio- and non-cardiovascular diabetes comorbidities such as inflammation, angiogenesis, endothelial dysfunction and fatty liver disease.

In conclusion, animal models and clinical data speak to a central role of resistin in the maladaptive cardiac phenotype seen in diabetic hearts. Given the pleiotropic effects of resistin, strategies targeting the control of serum as well as tissue-specific resistin levels, is a potential and viable therapeutic utility in patients with diabetes and diabetes-induced cardiovascular diseases.

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Footnote

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