Perspective

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"Know Diabetes by Heart": role of adipocyte-cardiomyocyte communications

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Abstract: Cardiovascular disease is the leading cause of morbidity in patients with diabetes mellitus. In 2019, the American Heart Association and the American Diabetes Association (along with industry leaders) launched the groundbreaking collaborative initiative "Know Diabetes by Heart™" to reduce cardiovascular deaths in type 2 diabetic patients. The molecular basis linking diabetes with cardiovascular complications has not yet been fully defined. Recent clinical and experimental studies strongly suggest that adipocyte dysfunction and subsequent pathological communications between adipocyte and cardiomyocytes play important roles in diabetic cardiac injury. This perspective article will review recent development concerning adipocyte-cardiomyocyte communications, and identify the most critical questions remain to be answered in this filed.

Keywords: adipocyte; cardiomyocyte; diabetes; myocardial ischemia.

Cardiovascular disease is the leading cause of death for people with type 2 diabetes [1]. Obesity, hyperglycemia, and hyperlipidemia are the most common metabolic disorders identified in diabetes and are established cardiovascular risk factors. However, recent large-scale clinical trials failed to demonstrate cardiovascular mortality benefit from strict glycemic control in diabetic patients [2]. Novel strategies capable of protecting diabetic cardiomyocytes from exacerbated post-myocardial infarction (MI) remodeling and heart failure are urgently needed.

Research in the past decade has increased understanding of the role adipocytes play in health and disease [3]. Three distinct but inter-related pathways mediating adipocytes-cardiomyocytes communicate have been recognized (Figure 1). Classically, the role of the adipocyte has been energy storage. In adult humans, adipocytes are the most effective cell type in the storage and (upon demand) release of energy. In the postprandial state, adipocytes esterify non-esterified fatty acids and take up glucose. During fasting, adipocytes hydrolyze triacylglycerols. Adipocyte metabolic function is tightly regulated by the balance between lipogenesis and lipolysis. Maintaining normal plasma glucose and fatty acid levels is particularly important to the cardiomyocyte, as it is the most energy consuming cell type. Under pathological conditions, the equilibrium between lipogenesis and lipolysis is disrupted. Unrestrained adipocyte lipolysis results in increased fatty acid release, leading to hyperlipidemia and hyperglycemia, two major metabolic phenotypes of type 2 diabetes. Adipocyte-derived glucose and lipid are the traditional "messengers" mediating communication between adipocytes and cardiomyocytes. Normal, controlled glucose/lipid release by adipocytes maintains cardiac energy supply, whereas uncontrolled pathologic glucose/lipid release by adipocytes contributes to ischemic heart injury and heart failure (Figure 1A).

Adipocyte endocrine signaling is the second most important adipocyte-cardiomyocyte communication pathway. Adipocytes release proteins, signaling lipids, and metabolites (collectively known as adipokines), all of which are involved in an extensive network of inter-organ communication. Since adipose tissue can represent up to 50% of total body weight, it is therefore considered a significant endocrine organ with profound systemic influence. Among all currently recognized adipokines, leptin, and adiponectin are most extensively investigated for their roles in type 2 diabetic and diabetic cardiovascular complications [4]. Plasma leptin is significantly increased in type 2 diabetes. Hyperleptinemia is a risk factor for diabetic cardiovascular complications. However, the role of adiponectin in type 2 diabetes and cardiovascular complications is markedly more complex [5]. Numerous epidemiological studies demonstrate that plasma adiponectin is

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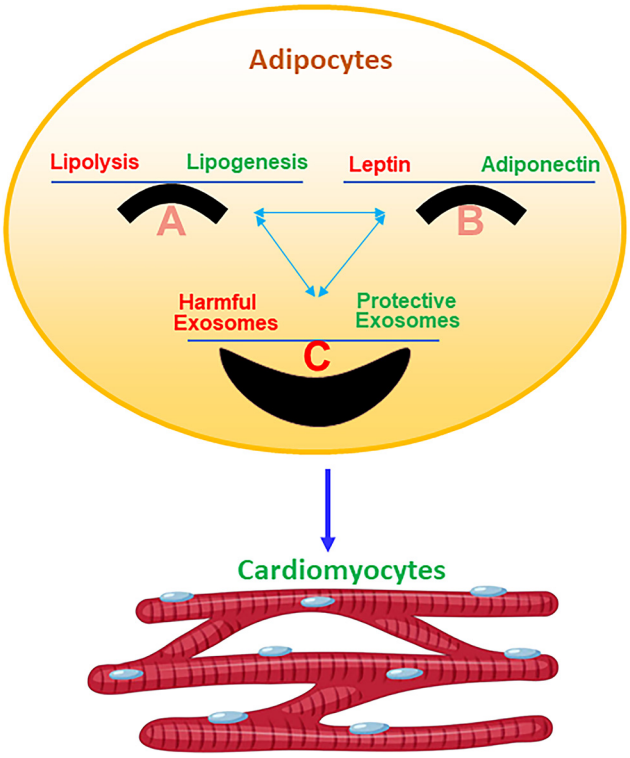

Figure 1: Adipocytes "watch" and "talk" to cardiomyocytes through three balanced systems and their interaction, remotely regulating heart function.

significantly reduced (rather than increased) in obesity and type 2 diabetic patients. Clinical observations show that reduced adiponectin levels correlate with increased risk of cardiovascular disease, a relationship that persists even after adjustment for diabetes, dyslipidemia, hypertension, smoking, and BMI. Consistently low plasma adiponectin concentration after acute MI is predictive of future adverse cardiac events, and post-MI plasma adiponectin levels correlated positively with myocardial salvage index and ejection fraction recovery [5]. The causative role of adiponectin deficiency in type 2 diabetes and diabetic cardiac injury has been established in animal models. We were the one of the two groups that first independently reported that adiponectin deficiency significantly increases myocardial ischemia/reperfusion injury and post-MI remodeling [6–8]. Two evolutionarily acquired specific adiponectin receptors (AdipoR1 and AdipoR2) have been cloned. They belong to a new family of membrane receptors (PAQR) predicted to contain seven transmembrane domains similar to G-protein-coupled receptors (GPCRs), but structurally and topologically distinct. Adiponectin can also bind with T-cadherin, in an interaction tethering adiponectin to the cell surface, but without transmembrane signaling (as T-cadherin lacks an intracellular domain). Activation of AdipoR1 (primarily expressed in muscular cells) and AdipoR2 (primarily expressed in hepatocytes) by adiponectin increases glucose and free fatty acid utilization, stimulates mitochondrial biogenesis, and inhibits inflammatory response [9]. It is now generally accepted that balanced production of leptin and adiponectin is critical in the maintenance of healthy heart function. In contrast, pathological disturbance of this balance significantly contributes to cardiovascular complications (Figure 1B). However, many questions remain. In particular, how adipocytes regulate production of leptin and adiponectin and maintain a normal balance during physiologic conditions, and how this balance is disturbed during pathological conditions, remains unknown.

It should be noted that, while the cardioprotective effects of adiponectin in acute myocardial ischemic injury are well-recognized, adiponectin's role in chronic heart failure is controversial. Despite clear experimental evidence demonstrating adiponectin deficiency significantly exacerbates heart failure progression, several clinical observations demonstrate hyperadiponectinemia is associated with poor cardiac function and increased mortality in these patient populations. In this regard, we have recently demonstrated that AdipoR1 is a direct substrate of GRK2, a molecule significantly upregulated in failing cardiomyocytes. GRK2 phosphorylates AdipoR1 at multiple serine sites, blocking AdipoR1 mediated cardioprotective signaling [10]. These results demonstrate that augmented adiponectin production in advanced heart failure patients is likely a compensatory mechanism due to the development of 'adiponectin resistance' similar to hyperinsulinemia during insulin resistance [11].

While there is clear evidence that metabolites and adipokines travel through the conventional diffusion process and regulate remote organ function, many recent studies reveal strong evidence for additional mechanisms of transport, particularly extracellular vesicles. Several types of extracellular vesicles exist, but exosomes (a 30–150 nm particle of endosome origin) are the most extensively investigated [12]. Despite their discovery decades ago, exosomes have only recently been identified to play an important role in inter-cellular and inter-organ communication. Recent studies demonstrate that the adipocyte is a major source of exosomes, particularly those containing miRNA in circulation. In adipocyte specific dicer deficiency mice, there is a substantial reduction in circulating exosomal microRNAs [13]. More importantly, substantial evidence supports the critical role of dysfunctional adipocyte exosomes in promoting remote organ pathologic remodeling (i.e. liver, skeletal muscle, and cancer) during diabetes. The regulatory functions of

adipocyte-derived exosomes upon cardiovascular systems have been recently recognized. Exosomes from PPARγ function-inhibited adipocytes attenuate cardiac hypertrophy [14], whereas exosomes from diabetic animals exacerbate atherosclerosis. Finally, we recently demonstrated for the first time that diabetes causes adipocyte exosome dysfunction, switching adipocytes-derived exosome phenotype from protective to harmful [15]. Specifically, adipocyte exosomes from non-diabetic adipocytes carry protective signaling from adipocytes to cardiomyocytes, significantly attenuating post-MI injury. In contrast, adipocyte-derived exosomes from diabetic animals exacerbate MI/R injury, evidenced by decreased cardiac function, larger infarct size, and increased apoptotic death. Mechanistic investigation identified miR-130b-3p as a common molecule significantly increased in diabetic human serum exosomes, high fat diet-fed animal serum exosomes, high fat diet adipocyte-derived exosomes, and high glucose/high lipid-challenged non-diabetic adipocyte released exosomes. *In vitro* and *in vivo* experiments revealed that miR-130b-3p suppresses multiple anti-apoptotic/cardioprotective molecules (including AMPK, Birc6, and Ucp3) in cardiomyocytes, exacerbating post-MI injury in the diabetic heart [15]. Collectively, accumulating evidence suggests that exosome production is the third function mediating adipocyte-cardiomyocyte communications (Figure 1C). Healthy adipocytes release cytoprotective exosomes, protecting cardiomyocytes from pathological injury. In contrast, exosomes from diabetic adipocytes are enriched with cytotoxic molecules, mediating pathological communication between adipocytes and cardiomyocytes. However, multiple critical questions remain to be answered. Molecules present in non-diabetic adipocyte-derived exosomes that are cardioprotective need to be identified. How diabetes causes the phenotypic switch, and whether blocking the switch may protect against diabetic post-MI remodeling remains unknown. Finally, whether diabetic cardiomyocytes (recipient cells) may have an altered response to adipocyte-derived exosomes needs to be clarified.

In summary, as the heart is the organ "knowing" (sensing) diabetes, and adipocyte is the "culprit" of obesity-induced diabetes, complete understanding of the molecular mechanisms mediating the adverse communication between diabetic adipocytes and diabetic cardiomyocytes may lead to the discovery of novel effective therapies against diabetic cardiac injury.

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References

1. Baena-Diez JM, Penafiel J, Subirana I, Ramos R, Elosua R, Marin-Ibanez A, et al. Risk of cause-specific death in individuals with diabetes: a competing risks analysis. Diabetes Care 2016;39:1987–95.
2. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–72.
3. Scherer PE. The many secret lives of adipocytes: implications for diabetes. Diabetologia 2019;62:223–32.
4. Fortuno A, Rodriguez A, Gomez-Ambrosi J, Fruhbeck G, Diez J. Adipose tissue as an endocrine organ: role of leptin and adiponectin in the pathogenesis of cardiovascular diseases. J Physiol Biochem 2003;59:51–60.
5. Goldstein BJ, Scalia RG, Ma XL. Protective vascular and myocardial effects of adiponectin. Nat Clin Pract Cardiovasc Med 2009;6:27–35.
6. Tao L, Gao E, Jiao X, Yuan Y, Li S, Christopher TA, et al. Adiponectin cardioprotection after myocardial ischemia/reperfusion involves the reduction of oxidative/nitrative stress. Circulation 2007;115:1408–16.
7. Tao L, Gao E, Jiao XY, Christopher TA, Lopez BL, Koch WJ, et al. Cardioprotective effects of adiponectin in ischemia/reperfusion injury and its mechanisms. Circulation 2005;112(2 Suppl):182–3.
8. Shibata R, Sato K, Pimentel DR, Takemura Y, Kihara S, Ohashi K, et al. Adiponectin protects against myocardial ischemia-reperfusion injury through AMPK- and COX-2-dependent mechanisms. Nat Med 2005;11:1096–103.
9. Lau WB, Tao L, Wang Y, Li R, Ma XL. Systemic adiponectin malfunction as a risk factor for cardiovascular disease. Antioxidants Redox Signal 2011;15:1863–73.
10. Wang Y, Gao E, Lau WB, Wang Y, Liu G, Li JJ, et al. G-protein-coupled receptor kinase 2-mediated desensitization of adiponectin receptor 1 in failing heart. Circulation 2015;131:1392–404.

11. Wang Y, Ma XL, Lau WB. Cardiovascular adiponectin resistance: the critical role of adiponectin receptor modification. Trends Endocrinol Metabol 2017;28:519–30.
12. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. Science 2020;367:eaau6977.
13. Thomou T, Mori MA, Dreyfuss JM, Konishi M, Sakaguchi M, Wolfrum C, et al. Adipose-derived circulating miRNAs regulate gene expression in other tissues. Nature 2017;542:450–5.
14. Fang X, Stroud MJ, Ouyang K, Fang L, Zhang J, Dalton ND, et al. Adipocyte-specific loss of PPARgamma attenuates cardiac hypertrophy. JCI Insight 2016;1:e89908.
15. Gan L, Xie D, Liu J, Lau WB, Christopher TA, Lopez B, et al. Small extracellular microvesicles mediated pathological communications between dysfunctional adipocytes and cardiomyocytes as a novel mechanisms exacerbating ischemia/reperfusion injury in diabetic mice. Circulation 2020;141:968–83.