Review Article

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Crosstalk between adipose tissue and the heart: An update

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ABSTRACT

It is important to understand how different human organs coordinate and interact with each other. Since obesity and cardiac disease frequently coincide, the crosstalk between adipose tissues and heart has drawn attention. We appreciate that specific peptides/proteins, lipids, nucleic acids, and even organelles shuttle between the adipose tissues and heart. These bioactive components can profoundly affect the metabolism of cells in distal organs, including heart. Importantly, this process can be dysregulated under pathophysiological conditions. This also opens the door to efforts targeting these mediators as potential therapeutic strategies to treat patients who manifest diabetes and cardiovascular disease. Here, we summarize the recent progress toward a better understanding of how the adipose tissues and heart interact with each other.

Key words: adipose tissue, heart, crosstalk, obesity, cardiovascular disease

INTRODUCTION

Adipose tissue (AT) in human adults accounts for 20%–50% of the body mass and is considered to be the second largest organ after skin.[1] Excessive expansion of AT defines the various forms of obesity, depending on which fat pads absorb the bulk of the calories. The prevalence of obesity has been continuously rising in recent decades.[2] Obesity is well established as an independent risk factor for cardiovascular disease, and has a pronounced association with coronary artery disease, heart failure, and atrial fibrillation.[3] Therefore, it is of paramount importance to better understand the mechanistic basis for the tight correlations between AT dysfunction and cardiovascular pathophysiology. Here, we pay particular attention to the crosstalk between AT and heart, in which significant progress has been made recently.

The breakthrough discoveries of adiponectin and leptin have completely changed the view of AT as a simple energy reservoir to a highly active and complex endocrine organ. The secretory fingerprints of the various ATs are now much better defined and stretch from simple metabolites to a variety of bioactive molecules, including adipokines, inflammatory cytokines, lipids, carbohydrates, miRNA, and extracellular vesicles (EVs).[4-6] We review the potential impact of these mediators on the physiological or pathological functions of heart. We also need to focus on the functions of epicardial AT, a unique fat depot anatomically located adjacent to the myocardium. There is, in fact, emerging evidence for a reverse crosstalk from the heart to AT, which also deserves some discussion (Figure 1).

ADIPOKINES

Adipokines are factors mainly secreted by adipocytes. Since there is a significant amount of AT in the body, fairly large amounts of adipokines enter the blood circulation and coordinate the physiological state of the AT with the function of distal

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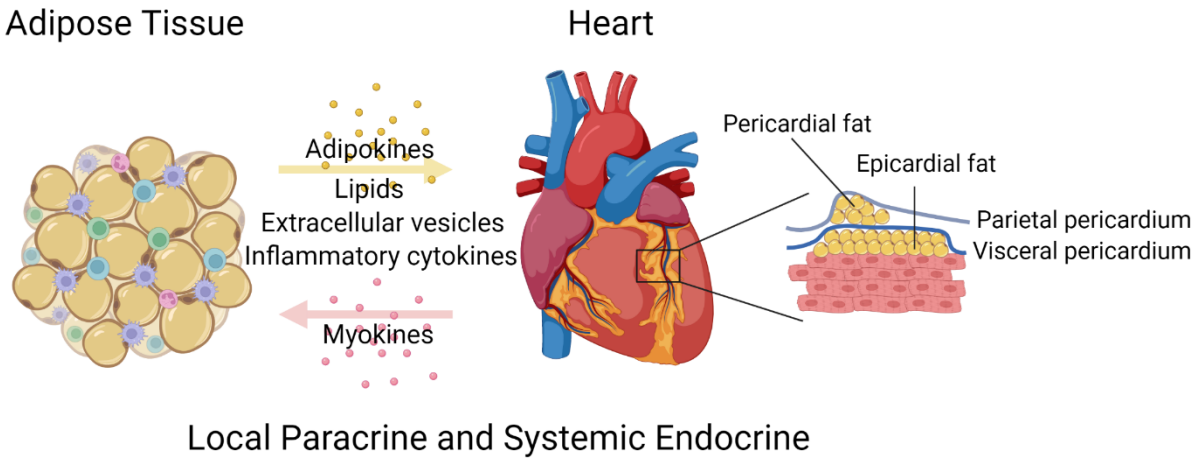

Figure 1: The crosstalk between adipose tissue and the heart.

organs as well as with the local microenvironment of the adipocyte. Depending on how loose a definition we use for the term adipokine, a fair number of these proteins have been reported. Here, we would only summarize the ones that exert a clear influence on cardiac function. These include adiponectin, leptin, resistin, and fibroblast growth factor (FGF) 21.

Adiponectin

Adiponectin, initially identified in 1995,[7] is a complex adipokine. Adiponectin exerts pleiotropic effects on multiple tissues, which includes the brain, heart, liver, kidneys, bone, blood vessels, pancreatic β-cells, and immune cells,[8,9] and is beneficial for healthspan and lifespan.[10] Low levels of adiponectin are tightly associated with increased incidence of cardiac diseases.[11] However, in the setting of high plasma adiponectin levels in the context of end-stage heart disease, it is associated with increased mortality. Further complicating the issue is the fact that adiponectin may have differential effects on patients with ischemic heart disease and heart failure as a function of ethnic background.[12–15]

Atherosclerosis is the main cause for myocardial infarction in man. In mice, adiponectin inhibits the inflammatory responses in immune cells, and therefore is tightly associated with reduced atherosclerosis.[16,17] Moreover, adiponectin deficiency further worsens and adiponectin administration attenuates ischemia/reperfusion (I/R)-induced cardiac injury.[18] In a murine model for cardiac hypertrophy, induced by pressure overload and angiotensin II infusion, adiponectin represses cardiac hypertrophy and remodeling.[19,20] Adiponectin exerts its effect on the heart mainly through binding with its receptors in the heart. There are three receptors for adiponectin, including AdipoR1, AdipoR2, and T-cadherin.[21,22] Multiple mouse studies show that T-cadherin plays a protective role in the progression of cardiac diseases. However, the detailed function of AdipoR1 and AdipoR2 in cardiomyocytes is still somewhat obscure. T-cadherin may be the main mediator for adiponectin's effect on cardiomyocytes, even though this receptor lacks a cytoplasmic signaling domain.[23] Adiponectin administration into T-cadherin-knockout mice has no beneficial effects on pressure overload-induced cardiac hypertrophy, indicating that the other two receptors, AdipoR1 and AdipoR2, do not play a major role in this process.[24]

Leptin

Discovered in 1994,[25] leptin is predominantly secreted by AT.[26] Leptin is a pleiotrophic hormone that can regulate food intake, energy expenditure, reproduction, hemostasis, angiogenesis, blood pressure, and immune responses8. Clinical observations have shown that hyperleptinemia is positively correlated with adverse cardiovascular disease outcome.[27] Plasma leptin is acutely increased in patients suffering from a myocardial infarction.[28] In fact, high plasma levels of leptin is an independent risk factor to predict the occurrence of cardiac death in patients with coronary artery disease.[29] In addition, high levels of leptin, independent of body mass index (BMI) and blood pressure, is linked to increased myocardial wall thickness.[30]

In rodent models with cardiac disease, the contributions of leptin and its receptors to the disease are quite complex. In atherosclerosis, leptin deficiency represses disease progression in ApoE-knockout mice,[31] but promotes atherosclerosis in low-density lipoprotein receptor (LDLR)-knockout mice.[32] Both ob/ob mice (leptin deficiency) and db/db mice (leptin receptor [LEPR] deficiency) manifest age-dependent progression of cardiac hypertrophy.[33,34] Particularly, cardiac diastolic and systolic function is impaired in db/db mice.[35,36] Acute deletion of LEPR

in adult cardiomyocytes leads to lethal heart failure[37] and worsens myocardial infarction-induced injury.[38] Interestingly, myocardial infarction in rats upon neutralizing leptin receptor with antibodies has no impact on the infarct size, but mitigates cardiac dysfunction and hypertrophy.[39] Either way, it seems that leptin–LEPR pathway is essential to maintain normal function of the heart. However, upon a pathological insult, overactivation of this pathway may compromise cardiac function.

How can both low and high leptin levels be associated with cardiac disease? Our recent observations on leptin action may provide some clues. Complete lack of leptin in mice and humans leads to morbid obesity, while hyperleptinemia is also associated with an obese phenotype.[40] These observations clearly imply that circulating leptin levels need to be maintained in a narrow range to sustain normal physiological functions: too much leptin is detrimental to cardiac function, while the complete lack of leptin is also harmful. We have to bear this in mind regarding various leptin-associated human diseases, including cardiac disease. In patients with very low or no circulating leptin levels, elevating its levels by supplementing exogenous leptin may be highly effective in preventing disease progression. However, in a conventional obese patient with high circulating leptin levels, reducing the leptin levels, by either genetic or pharmaceutical approaches, is beneficial toward achieving metabolic health.[41,42]

Resistin

Resistin was named because of its effect in inducing insulin resistance. It was identified independently by several laboratories.[43–45] In mice and humans, resistin exerts similar functions, even though it displays completely different expression patterns. In mice, resistin is mainly secreted by adipocytes, while in humans, it is largely derived from macrophages.[46] Resistin can bind to two receptors, the toll-like receptor 4 (TLR4) and adenylyl cyclase-associated protein 1 (CAP1), to promote inflammatory responses.[47,48] The function of resistin is diverse under different pathological conditions. Resistin protects the heart from I/R injury through activating the AKT pathway.[49] However, resistin also exacerbates pressure overload-induced heart failure due to activating a DNA damage response.[50]

Fibroblast growth factor 21

FGF21 is a unique member of the fibroblast growth factor family. It affects the cell metabolism rather than proliferation, a common function that the other members of the family exert.[51] FGF21 is a hepatokine, adipokine, and myokine, and has profound beneficial effects on obesity and type 2 diabetes.[52] It is also emerging as a crucial link between AT and the heart. FGF21 can repress cardiac hypertrophy and protect the heart from I/R injury.[53,54] Under regular physiological conditions, FGF21 is mainly secreted by the liver. However, under some pathophysiological conditions, FGF21 can be secreted by other tissues, including brown AT and even the heart itself. Ruan *et al.* establish a clear link between brown AT and heart with respect to FGF21. They demonstrate that in rodents, brown AT can secrete FGF21 into the circulation under hypertensive conditions. This FGF21 directly targets the heart to attenuate cardiac remodeling.[55] Moreover, it is possible that cardiomyocyte-derived FGF21 could constitute a feedback signal to AT. Serum concentrations of FGF21 are significantly elevated after myocardial infarction both clinically as well as in murine models.[56] Under these conditions, FGF21 may impact systemic glucose and lipid metabolism. As such, FGF21 constitutes a two-way communication axis between AT and the heart.

INFLAMMATORY CYTOKINES

Obesity is generally accompanied by subclinical but chronic inflammation, and the severity of type 2 diabetic state correlates well with the degree of inflammation.[57] In the diabetic state, the immune cells together with adipocytes produce a considerable number of inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, IL-1, IL-17, and IL-22.[58] This systemic inflammatory state can further worsen the progression of ischemic and hypertensive heart disease.[59] Meantime, cardiomyocytes and infiltrated immune cells in the damaged heart secrete considerable amounts of inflammatory cytokines as well,[60] which may also affect the function of AT. Therefore, the inflammatory response is an integral part in the crosstalk between AT and the heart.

LIPIDS

ATs are actively secreting, fatty acid-derived bioactive lipids. While some of the lipids are retained in AT, others enter the bloodstream and possess a broad effect on distal organs, including liver, heart, muscle, and pancreas.[61,62] Here, we highlight two kinds of lipids that may have direct effects on cardiac diseases.

Ceramides

Ceramides are produced either by hydrolysis of membrane-located sphingomyelin or by *de novo* synthesis.[63] Ceramide levels in human plasma have emerged as prognostic indicators of major adverse cardiovascular events.[63,64] In atherosclerotic plaques, ceramides are enriched. They may initiate the formation of lipoprotein aggregation[65] and impair the plaque stability.[66] Importantly, animal studies show that inhibiting the synthesis of ceramide alleviates

atherosclerosis.[67] Zhang *et al.* report that Hypoxia-inducible factor 2α (HIF2α) deficiency in adipocytes exacerbates western diet-induced atherosclerosis. Mechanistically, HIF2α initiates the transcription of alkaline ceramidase 2, which hydrolyzes ceramides. Therefore, HIF2α deficiency results in an elevation of ceramides and a worsening of atherosclerosis.[68] Moreover, ceramides play a detrimental role in heart failure. Heart biopsies reveal that high levels of ceramides accumulate in the failing myocardium as well.[69] This accumulation impairs cardiac function.[70] In contrast, decreasing the levels of ceramides improves myocardial infarction-induced heart failure.[69] In addition, our own studies have shown that adiponectin and its receptors enhance ceramide catabolism,[71] which is likely to be the basis for the cardioprotective effects of adiponectin.

Palmitoleate

Palmitoelate is a unique monosaturated fatty acid, in which the double bond is at position n-6. It was first identified as an adipose-derived bioactive lipid in Fabp4/5 double-knockout mice.[72] Intriguingly, palmitoleate is found in postprandial python plasma and can promote physiological heart growth.[73] Palmitoleate can also repress inflammatory responses, thereby attenuating the progression of atherosclerosis.[74]

EXTRACELLULAR VESICLES

EVs are cell-derived membranous structures which can be sorted into three subtypes, microvesicles, exosomes, and apoptotic bodies, according to their origins and the pathways that lead to their release.[75,76] Proteins, lipids, nucleic acid, and even submitochondrial particles can be packaged into EVs and then transported to other cells or organs.[77,78] Clinical studies have shown that some specific plasma EVs are correlated with a high incidence of myocardial infarction and mortality in obese patients with vascular diseases.[79–81] Here, we focus on the recent advances regarding the EV-mediated crosstalk between AT and heart.

In AT, adipocytes, immune cells, mesenchymal stem cells, and endothelial cells actively produce a large number of EVs, which affect the immune response, adipogenesis, thermogenesis, and adipokine release.[82] These EVs transport messages from ATs to distal organs, including heart, liver, skeleton muscle, pancreas, and brain. Importantly, several reports have directly demonstrated that AT-derived EVs play an important role in ischemic heart diseases. Lu *et al.* reveal that adipocytes from high fat diet (HFD) mice secrete miR-130b-3p-containing EVs, which exacerbate cardiac I/R injury.[83] Our lab recently reported that mitochondria-containing EVs derived from dysfunctional adipocytes can trigger a burst of reactive oxygen species (ROS) and a compensatory antioxidant response in cardiomyocytes that protects the heart from the damage triggered by an I/R insult.[84]

EVs can also be secreted by cells in the heart, including cardiomyocytes, endothelial cells, and fibroblasts.[85] Similarly, these EVs not only play a role locally, but also transport cargos to other organs such as AT. Lu *et al.* recently showed that EVs derived from the mouse heart upon an I/R insult can induce endoplasmic reticulum (ER) stress in adipocytes and impair their endocrine function.[86] Interestingly, we found that in adipocytes, caveolin 1 can effectively be replenished by EVs secreted by endothelial cells. Combined, all the observations highlight the very active communication between cardiovascular system and ATs.[87]

EPICARDIAL AT AND THE HEART

As a specific subtype of visceral fat, epicardial AT directly interacts with the myocardium and is located between epicardium and heart (Figure 1). Epicardial AT is completely absent in mice. However, in humans, it can account for 20% of the total ventricular weight,[88] covering 80% of the area of human heart,[89] even infiltrating into the myocardium.[90] Epicardial AT originates from the splanchnopleuric mesoderm as well as the heart itself.[91] The composition of epicardial AT is similar to that of the subcutaneous and other visceral fat tissues. Interestingly, the size of adipocytes in epicardial AT is comparatively smaller, probably due to a higher ratio of pre-adipocytes to mature adipocytes, which is not seen to the same extent in other fat pads.[92]

Clinical studies have shown that the volume of epicardial AT is highly associated with cardiac disease. The thickness of epicardial AT positively correlates with the degree of the metabolic syndrome[93] and has significant potential predicting a high risk to develop cardiovascular disease.[94] A higher volume of epicardial AT tends to impair the stability of plaques in atherosclerosis,[95,96] which leads to an increase in the events of ischemic heart disease. Besides, epicardial AT is a risk factor for ventricular hypertrophy, heart failure with preserved ejection fraction,[97] and atrial fibrillation.[98] All these clinical observations suggest that epicardial AT may be a driving force for cardiac diseases. However, the detailed mechanistic involvement of epicardial AT in the processes still needs to be worked out.

In contrast to its aforementioned role in cardiac disease, epicardial fat in humans may also exert some beneficial roles in preserving normal heart function based on a limited set of observations: (1) epicardial AT can protect the heart

from mechanical stress; (2) epicardial AT can serve as a local energy sink for cardiac muscle to protect against high levels of free fatty acids in coronary circulation;[99] (3) epicardial AT functions as a brown fat to defend the myocardium and coronary vessels against hypothermia;[100] and (4) epicardial AT provides the anatomical site for the ganglia innervating the myocardium.[101] However, due to the complete absence of epicardial fat in current existing mouse models, it is very difficult to clarify the exact role(s) of epicardial AT in heart function under normal physiological and pathological conditions. Nonhuman primate models may have to provide the necessary insights to unravel a direct functional involvement of epicardial AT in cardiovascular disease.

Beyond that, similar to the other fat depots, epicardial AT can secrete adipokines, EVs, and lipids to affect heart, and we appreciate that the heart can regulate the status of epicardial AT. Coronary atherosclerosis correlates well with a proinflammatory phenotype in epicardial AT.[102] Interestingly, although there is no epicardial AT around heart in normal mice, it can be induced after the mice are subjected to myocardial infarction,[103] thereby opening up the possibility to study its impact on the mouse heart. In addition, cardiac hormones, such as ANP and BNP, and cytokines secreted from heart can affect epicardial AT directly.

CONCLUSIONS AND PERSPECTIVES

Ample evidence supports the notion that an active crosstalk exists between AT and the heart via adipokines, cytokines, lipids, and EVs. Here, we provide a very high-level assessment of some of the mechanisms in place to mediate this crosstalk. Considering the high prevalence of obesity and cardiovascular disease, this area will receive more attention in the future, as many gaps persist. Once we identify the key players, they may not only serve as important biomarkers, but also have the potential to be targets for intervention to resolve aspects of various pathophysiological cardiac disease states.

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Conflict of Interest

None declared.

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