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Browning the Epicardial Adipose Tissues in Cardiovascular Regulation

Hui-Chen Ku and Ching-Feng Cheng*

Department of Pediatrics, Taipei Tzu Chi Hospital, Taipei, Taiwan

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***Corresponding author:** Ching-Feng Cheng, Department of Pediatrics, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, 289, Jianguo Road, Xindian District, New Taipei City, 23142, Taiwan

Abstract

Epicardial adipose tissue (EAT) is located between the myocardium and the visceral layer of pericardium. EAT is characterized by increased rate of fatty acid metabolism and increased expression of thermogenic genes. EAT and the myocardium share the same microcirculation, suggesting a close interaction between them. Under normal physiological conditions, EAT produces anti-inflammatory or anti-atherosclerotic cytokines to exert its cardioprotective effects. Although many clinical studies have found significant associations between increased EAT mass and coronary artery disease (CAD). There is no direct evidence that inflammatory EAT worsens CAD. This short review focuses on the emerging physiological and pathophysiological role of EAT and potential pre-clinical application of EAT re-browning for treatment of cardiovascular disease.

Keywords: Epicardial Adipose Tissue; Browning; Cardiovascular Disease

Abbreviations: EAT: Epicardial Adipose Tissue; CAD: Coronary Artery Disease; BAT: Brown Adipose Tissue; UCP1: Uncoupling Protein 1; PRDM16: PR Domain Containing 16; WAT: White Adipose Tissue; TAG: Triacylglycerol; FFA: Free Fatty Acid; SAT: Subcutaneous Adipose Tissue; ROS: Reactive Oxygen Species

Introduction

Epicardial Adipose Tissue (EAT) and Cardiac Function

Epicardial adipose tissue (EAT) is the fat depot located between the myocardium and the visceral layer of the pericardium and generally exists in the atrioventricular and interventricular grooves [1,2]. The role of EAT within the heart is complicated, but can be commonly distinguished by mechanical, thermogenic, metabolic, and endocrine/paracrine functions [3,4]. EAT functions mechanically to protect the coronary artery against the torsion induced by the arterial pulse wave and myocardial contraction [5]. In addition, the studies from Sacks et al. had suggested that EAT functions similarly to brown adipose tissue (BAT) and yield heat directly to the myocardium conferring a survival benefit by protecting the heart from ischemia or hypoxia [6]. Higher expression levels of BAT-specific genes, such as uncoupling protein 1 (UCP1), PR domain containing 16 (PRDM16) and PPAR-γ coactivator-1α (PGC-1α) were observed in human EAT than in other fat depots [6]. Whether EAT is a BAT or functions as a BAT-like fat depot needs further investigation [7].

Metabolically, EAT exhibits high rates of white adipose tissue (WAT) lipogenesis and lipolysis, acting as local triacylglycerol (TAG) store and as a buffer against toxic levels of FFA, in both myocardium and arteries [8]. EAT is abundant in saturated fatty acids and has the highest rate of free fatty acid (FFA) release and uptake of all fat depots [9,10]. It is widely known that the energy production in the heart is primarily generated by FFA oxidation, especially during the period of high demand [4,9]. EAT can produce several adipokines and inflammatory cytokines which generate potential interactions through apocrine or paracrine effect between EAT and myocardium [11,12]. Under normal physiological conditions, EAT produces anti-inflammatory or anti-atherosclerotic cytokines, such as adiponectin and adrenomedullin, to exert its cardioprotective effects [13,14]. Moreover, McAninch et al. had shown that EAT is a highly inflammatory tissue enriched with genes involved in coagulation, endothelial function, immune signaling and apoptosis compared to subcutaneous adipose tissue (SAT) [15].

EAT in the Pathogenesis of Heart Diseases

The increment of EAT causes additional mass on both ventricles that can enhance the cardiac work demands and left ventricular hypertrophy [16]. EAT thickness is positively correlated with myocardial fat and may regulate cardiomyocyte function [17]. EAT can release FFA into the bloodstream, perturbing vascular homeostasis and endothelial dysfunction, and causing

coronary artery disease (CAD) and hypoxia [18,19]. Increased lipid accumulation into cardiomyocytes may lead to cardiac steatosis. Several animal studies had shown that the harmful consequences of lipid overload accompanying obesity, such as diabetes and insulin resistance, that can cause cardiomyocyte apoptosis, cardiac fibrosis and impaired cardiac contractile function [20,21]. Hirata et al. had found that patients with advanced CAD have more inflammatory M1 macrophages but fewer anti-inflammatory M2 macrophages in EAT compared to subjects without CAD [22]. The transition of macrophages from M2 to M1 indicated the macrophage-regulated inflammation in epicardial fat. EAT in CAD patients showed increased expression of genes involved in oxidative stress and increased levels of reactive oxygen species (ROS) products than SAT [23]. Since higher oxidative stress could activate inflammatory signals in EAT and lead to the development and progression of CAD.

Browning EAT to Reduce cardiovascular Risk

A variety of studies indicate that increasing brown and/or beige adipose mass and activity is a practical target to ameliorate obesity and related cardiac disease [24,25]. The beneficial role of BAT from animal studies showed that its activation reduces hypercholesterolemia and prevents the development of atherosclerosis [26]. Dozio et al. had shown that EAT of patients with CAD is associated with a brown-to-white trans-differentiation characterized by decreased expression levels of thermogenic genes and upregulation of white adipogenesis [27]. This brown-to-white phenotypic transition is associated with a significant increase in ROS production in EAT [27]. Furthermore, transplantation of BAT improves body metabolism and the function of the heart and other WAT fat depots [28]. Therefore, it could be hypothesized that re-browning of EAT in obesity and CAD individuals may improve the hypoxic, inflammatory microenvironment disturbing the vasculature and causing coronary atherosclerosis.

Conclusion

The pharmaceutical treatment of EAT in cardiovascular diseases is still unclear. Although the strong clinical correlations exit, there is no direct proof that inflammatory EAT worsens CAD. Since mice have a limited amount of EAT, most of the studies on EAT have been performed in humans. The causative role of EAT in CAD has not been investigated. Therefore, the use of genetically-engineered animal models, such as animals which develop atherosclerosis, diabetes or hypercholesterolemia, would enlarge our understanding of the role of EAT in the cardio-metabolic diseases. The re-browning of EAT may be obtained using a variety of dietary, environmental and pharmacological approaches. Future pre-clinical trials should be designed to examine the effects of the proper interventions on the EAT prior to cardiac surgeries and establish the modern intervention to facilitate the browning of EAT for reducing the cardiovascular risk.

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