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Diverse Facets of Lipid Metabolism in Cardiac Pathology

Review Article

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Abstract

Myocardial lipid accumulation play significant role in the pathogenesis of heart failure. The disorders pertaining to diverse aspects of lipid metabolism manifest in the form of various types of cardiovascular diseases. Extensive studies are required to excavate the possibilities of various pharmacologic modulation of lipid metabolism in a failing heart and accompanying alterations in myocardial structure and function. The present review focuses on myriads of facets of lipid metabolism and associated myocardial pathology.

Keywords: lipid metabolism, cardiac pathology, cardiac metabolism, atherosclerosis

Abbreviations

Apo E: Apolipoprotein E; ATP: Adenosine triphosphate; AMPK: AMP activated protein kinase; ATGL: Adipose triglyceride lipase; ECM: Extracellular matrix; FA: Fatty acid; G0S2: G0/G1 switch 2; Glut 4: Glucose transporter type 4; IGF-1: Insulin-like growth factor I; LXR: Liver X receptor; MUFA: Monounsaturated fatty acid; mTOR: mechanistic target of rapamycin ; PPAR: Peroxisome proliferator-activated receptor gamma; ROS: Reactive oxygen species; SCD: Stearoyl-CoA desaturase; SREBP-1c: Sterol regulatory element binding protein-1c; TGF-ß: Transforming growth factor beta.

Introduction

Various types of cardiac stressors may cause considerable changes in myocardium in the form of tissue remodeling and cardiac hypertrophy ultimately leading to heart failure. Cardiac hypertrophy, though beneficial initially, becomes decompensatory and pathological, characterised by a metabolic shift in energy substrate utilization from fatty acids (FA) to glucose. While systemic metabolic disturbances contribute to cardiac dysfunction, chronic heart failure syndrome, though primarily a cardiac anomaly, may affect multiple organ systems in the long run, especially in the patients with high blood pressure, diabetes, obesity and hyperlipidemia [1].

Fatty acid metabolism and cardiac remodeling

An adult heart relies chiefly on fatty acid utilization for oxidative phosphorylation and ATP generation while the foetal heart prefers glucose as energy fuel, being in a relatively hypoxic environment. So after birth, there is increased expression of genes involved in fatty acid metabolism. However, adult heart is subjected to extensive cardiac remodelling in response to a variety of stressors that brings about a reprogramming of foetal genes resulting in the reduced expression of genes involved in fatty acid metabolism and relative increase in gene products involved in glucose metabolism [2]. Since the total number of ATP molecules generated during glycolysis is less than that produced during fatty acid oxidation, this altered substrate utilization during pathological remodeling results in overall reduced ATP production. Even in the absence of systemic metabolic disorders, such as diabetes or hyperlipidemia, alteration of cardiomyocyte lipid homeostasis contributes to the pathophysiological changes similar to those in diabetic cardiomyopathy [3].

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Cardiac steatosis amplifies the fibrotic effects of Angiotensin II through the activation of TGF-β signaling and increased ROS production [4]. High fat diet-induced murine cardiac remodeling has been shown to be prevented by successful metabolic alterations that include reduction of cardiac AMPK, Glut 4, hexokinase 2 and reduction of toxic lipid deposits and reactive oxygen species,thereby down regulating glucose metabolism and favoring lipid metabolism (beta oxidation pathway) [5]. The liver X receptors (LXRs) act as key cardiac transcriptional regulators of both glucose and lipid metabolism during the pathological cardiac hypertrophy. Cardiac LXRα protects against such cardiac dysfunction by augmenting glucose uptake and utilization [6]. Tissue inhibitor of metalloproteinase 3 (TIMP3) is an extracellular matrix (ECM) protein that regulates metabolic flexibility and oxidative stress response via apelin, another regulator of fatty acid oxidation, especially during episodes of increased cardiac stress [7]. G0/G1 switch 2 (G0S2) protein regulates cardiac lipolysis through direct inhibition of adipose triglyceride lipase (ATGL), the principal triacylglycerol hydrolase, thus modulating cardiac substrate utilization. Cardiac-specific G0S2 overexpression inhibits cardiac lipolysis leading to severe cardiac steatosis, less prone to fibrotic remodeling or cardiac dysfunction than hearts with a lipolytic defect due to ATGL-deficiency [8]. Ischemic cardiac damage causes upregulation of cardiac pro-inflammatory cytokines and lymphocytic invasion. Experimental myocardial infarction increases the number of regulatory T cells and adoptive transfer attenuates left ventricular remodeling [9, 10].

Fatty acids and atherosclerosis

Atherosclerosis refers to a chronic inflammatory disease of arterial wall that arises from an unbalanced lipid metabolism and a maladaptive inflammatory response and leads to the development of fibrotic plaques within the arterial walls, usually considered to be correlated to the uptake of oxidized low density lipoproteins [11]. The macrophages contribute to plaque development by internalizing both native and modified lipoproteins converting them into cholesterol-rich foam cells, thus disrupting normal macrophage cholesterol metabolism [12]. The lipid crystals represent one of the causative factors of plaque rupture as they mechanically stimulate adjacent extracellular matrix (ECM) in advanced atherosclerotic plaques causing vessel remodeling [13].

Cardiovascular diseases are linked to the increase in omega-6 and decrease in omega-3 fatty acid levels in blood and tissues and omega-3 fatty acid supplementation lowers high blood pressure [14]. Omega-3 fatty acids are known to attenuate atherosclerosis by favorably changing monocyte subsets and preventing monocyte recruitment to the sites of aortic lesions [15]. The enzyme lipoprotein lipase acts on triglyceride-rich lipoproteins producing remnant lipoprotein particles rich in cholesterol and apolipoprotein E (apo E). Apo E acts as the ligand for uptake of remnant lipoproteins via the LDL-receptor (remnant receptor) [16]. Dysbetalipoproteinemia or Fredrickson type III hyperlipidemia, linked to mutations in apolipoprotein E that disrupt the clearance of remnants of triglyceride-rich lipoproteins, is an extreme disorder of remnant metabolism and these remnant lipoproteins promote atherosclerosis [17].

The remnant-like particles, namely, Remnant Lipoprotein Cholesterol (RLP-C) and Remnant Lipoprotein Triglyceride (RLP-TG) are considered as the best risk predictor for coronary atherosclerosis and sudden cardiac death, respectively [18]. The elevated LDL-C level is the best known risk factor for coronary atherosclerosis [16].The anti-atherosclerosis effect of Corosolic acid, a pentacyclic triterpene acid, has been observed in apolipoprotein E-deficient mice, through regulation of the nuclear factor kappa B (NF-κB) signaling pathway and inhibition of monocyte chemoattractant protein-1 expression [19]. Insulin-like growth factor I (IGF-1) exhibits anti-atherosclerotic effects, reducing lipid oxidation and macrophage-derived foam cell formation via downregulation of 12/15-lipoxygenase [20].

Lipotoxicity and cardiac pathology

The metabolism of myocardial triacylglycerol stores are vital for normal myocardial functioning. While triacylglycerol synthesis detoxifies and recycles fatty acids to prevent lipotoxicity, lipolysis or triacylglycerol hydrolysis remobilizes fatty acids from endogenous store house. Lipotoxicity characterised by accumulation of increased levels of toxic metabolic intermediates is found in a failing heart, especially in diabetic and obese patients [1, 21-24]. Increased stores of triglycerides are noticeable in the heart of animals with obesity and diabetes as well as in obese and diabetic patients with cardiac dysfunction and heart failure [25]. Many studies highlight the significance of altered mitochondrial activity as a major contributor to cardiac dysfunction in diabetic cardiomyopathy. Such mitochondrial dysfunction involves altered cardiac substrate metabolism, lipotoxicity, impaired calcium handling, oxidative stress and mitochondrial uncoupling [26-28].

The ectopic myocardial lipid deposits may be an indication of progressive myocardial degradation during the progression of cardiac failure [1]. The development of diabetic cardiomyopathy is associated with lipotoxic injury caused by increased myocardial triglyceride content, myocardial steatosis and impaired left ventricular diastolic function [29-31]. Recent studies have revealed the role of mTOR in lipid homeostasis and that mTOR dysregulation may lead to abnormal lipid partitioning ie redistribution of triglycerides from adipocytes to nonadipose peripheral tissues and resulting lipotoxicity [32].

Recent studies showed that stearoyl-CoA desaturase (SCD), the rate-limiting enzyme in the biosynthesis of monounsaturated fatty acids (MUFA), can reprogram cardiac metabolism to improve cardiac function, signifying the role of SCD in the pathogenesis of lipotoxic cardiomyopathies [33]. SCD1 deficiency inhibits fatty acid beta oxidation and increases glucose utilization in the cardiac muscle by upregulating insulin signaling and decreasing FA availability and expression of FA oxidation genes [34]. SCD4, a cardiac-specific isoform of SCD, is specifically regulated by leptin and other dietary factors [35]. Clinical studies have also revealed high levels of circulating leptin, an adipokine in case of development of cardiac hypertrophy in obese people. Leptin plays a significant role in protecting the heart from cardiac lipotoxicity [36, 37]. The activation of the transcription factor Sterol Regulatory Element Binding Protein-1c (SREBP-1c) as well as the transcriptional coactivator peroxisome proliferator-activated receptor gamma (PPARγ) might be significant molecular switches regulating the event of lipotoxicity [1].

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Lipid metabolism based pharmacological intervention

Impaired calcium handling and intracellular calcium overload induced by chronic hypoxia plays a vital role in mediating myocardial injury. Trimetazidine, a well-known drug for angina pectoris, ameliorates such calcium imbalance through enhanced metabolic shift from lipid oxidation to glucose oxidation, thereby preventing hypoxic damage [38]. The pathogenesis of calcific aortic valve stenosis may be modulated by peroxisome proliferator-activated receptor-γ (PPAR-γ). Pioglitazone, an antidiabetic drug, is a PPAR-γ ligand that inhibits such valvular calcification and may be beneficial in preventing or slowing stenosis of aortic valves [39]. Resveratrol, a red wine polyphenol, exhibits cardioprotective effect against high fat diets due to its anti-atherogenic property and is a potential compound to be consumed for our healthy life-style [40].

Conclusion

The increased levels of toxic lipid intermediates in a failing heart is a suggestive of underlying impaired lipid metabolism. Further investigation is required to deal with the complex metabolic pathways and the role of huge diversity of intermediate metabolites. The area of cardiovascular lipidomics will help us to expand the horizon of pathophysiology of various cardiovascular diseases and provide novel therapeutic agents as well as preventive and diagnostic biomarkers.

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