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Review

Lipid metabolism and signaling in cardiac lipotoxicity☆

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ABSTRACT

The heart balances uptake, metabolism and oxidation of fatty acids (FAs) to maintain ATP production, membrane biosynthesis and lipid signaling. Under conditions where FA uptake outpaces FA oxidation and FA sequestration as triacylglycerols in lipid droplets, toxic FA metabolites such as ceramides, diacylglycerols, long-chain acyl-CoAs, and acylcarnitines can accumulate in cardiomyocytes and cause cardiomyopathy. Moreover, studies using mutant mice have shown that dysregulation of enzymes involved in triacylglycerol, phospholipid, and sphingolipid metabolism in the heart can lead to the excess deposition of toxic lipid species that adversely affect cardiomyocyte function. This review summarizes our current understanding of lipid uptake, metabolism and signaling pathways that have been implicated in the development of lipotoxic cardiomyopathy under conditions including obesity, diabetes, aging, and myocardial ischemia–reperfusion. This article is part of a Special Issue entitled: Heart Lipid Metabolism edited by G.D. Lopaschuk.

1. Introduction

Lipotoxicity is defined as the process where excess accumulation of lipids and over-activation of lipid signaling pathways trigger cellular distress and dysfunction, which may manifest as insulin resistance, defective mitochondria, energy starvation, and endoplasmic reticulum (ER) stress and may ultimately lead to apoptotic cell death or lipoapoptosis (Fig. 1) [1]. When this process occurs in cardiomyocytes, the consequences can be cardiac dysfunction and heart failure, which is also referred to as lipotoxic cardiomyopathy [1,2]. The archetypal conditions triggering a lipotoxic milieu within cardiomyocytes are metabolic disorders such as obesity, insulin resistance, and diabetes mellitus [3–6]. In addition, cardiac lipotoxicity has also been observed during other patho/physiological conditions, e.g. myocardial ischemia–reperfusion/infarction and aging [7–9]. Increased myocardial lipid deposition develops when cardiomyocyte fatty acid (FA) uptake outpaces FA oxidation, leading to an increased availability of FAs for non-oxidative metabolic pathways and accumulation of cardiotoxic FA metabolites [3]. In the case of obesity, insulin resistance, and diabetes the main culprit is excess FA delivery due to augmented dietary fat intake and adipose tissue lipolysis [10]. In addition, myocardial insulin resistance and impaired glucose utilization may further increase myocardial FA uptake and accumulation of toxic lipid species [11]. While insulin resistance is likely a key contributing factor to obesity and diabetes-induced lipotoxic cardiomyopathy by causing a shift in cardiac substrate utilization from glucose to FAs and concomitant FA overload, it is also a consequence of cardiac lipotoxicity since toxic FA metabolites can impair myocardial insulin signaling [12,13].

Due to its limited ability to synthesize FAs, the myocardium relies heavily on the uptake of FAs in the form of albumin-bound free FAs or lipoproteins – chylomicrons and very-low-density-lipoproteins – from the circulation to sustain cardiomyocyte lipid homeostasis and energy metabolism [14]. In fact, uptake of FAs is a major determinant of FA oxidation and therefore mitochondrial ATP production [15–17]. Although FAs are the principal energy substrate for the healthy adult heart, cardiomyocytes are omnivorous, deriving their ATP for contractile work from a variety of sources including glucose, lactate, and amino acids, allowing for metabolic flexibility to adjust substrate utilization to circulating substrate concentrations, work load, hormonal stimuli and oxygen supply [3,18,19]. In contrast, diseased hearts often have decreased metabolic flexibility, which can contribute to cardiac dysfunction and lipotoxic cardiomyopathy [19–21].

Abbreviations: ACSL1, long-chain acyl-CoA synthetase 1; ATGL, adipose triglyceride lipase; CerS5, ceramide synthase 5; CPT, carnitine palmitoyltransferase; DAG, diacylglycerol; DGAT, diacylglycerol acyltransferase; ER, endoplasmic reticulum; ERK, extracellular signal regulated kinase; FA, fatty acid; FABPpm, plasma membrane isoform of fatty acid binding protein; FoxO1, forkhead box protein O1; HSL, hormone-sensitive lipase; IκB, Inhibitor of NFκB; IKK, IκB kinase; JNK, c-Jun N-terminal kinase; $iPLA_2$, calcium-independent phospholipase A_2; LPA, lysophosphatidic acid; LPC, lysophosphatidylcholine; LPL, lipoprotein lipase; MAPK, mitogen activated protein kinase; MLK3, mixed lineage kinase-3; MFBD, milk fat-based high fat diet; NFκB, nuclear factor-κB; PGC1, peroxisome proliferator-activated receptor γ-coactivator 1; PIP2, phosphatidylinositol-4,5-bisphosphate; PKC, protein kinase C; PLC, phospholipase C; PP2A, protein phosphatase 2A; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; SAPK, stress activated protein kinase; S1P, sphingosine-1-phosphate; SPT, serine palmitoyltransferase; TAG, triacylglycerol; TNFα, tumor necrosis factor α; TLR4, toll-like receptor 4; VLDLR, very low density lipoprotein receptor.

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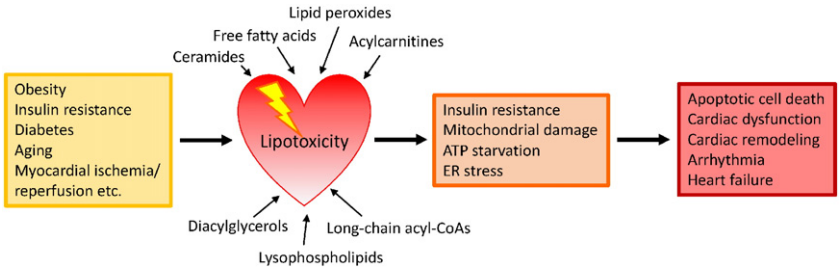

Fig. 1. Causes and consequences of cardiac lipotoxicity. Stressors including metabolic diseases, aging, and myocardial ischemia–reperfusion can lead to increased accumulation of lipids and lipid metabolites in the heart that have toxic effects on cardiomyocytes. Cardiac lipotoxicity can trigger cell stress and impair myocardial function.

To date, numerous rodent models have been generated and studied that were instrumental for the characterization of lipotoxic cardiomyopathy and using which lipid metabolic and signaling pathways were identified that mediate cardiomyocyte lipotoxicity (for a list of mouse models of cardiac lipotoxicity see Goldberg et al. [3]). In addition, it has also been revealed that the fruit fly can exhibit lipotoxic cardiomyopathy when fed a high fat diet, suggesting that the molecular mechanisms that lead to toxic lipid overload of the myocardium are evolutionarily conserved [22]. It has become evident that chronically increased accumulation of certain FA metabolites in cardiomyocytes and the ensuing pathological sequelae are sufficient to precipitate cardiac dysfunction in these animal models. The FA metabolites linked to cardiac lipotoxicity include ceramides, diacylglycerols (DAGs), long-chain acyl-CoAs, acylcarnitines, lysophospholipids, and triacylglycerols (TAG), although it is believed that the latter represents a marker of lipotoxicity rather than being directly cytotoxic (Fig. 2) [4,23]. Changes in FA uptake, storage, and/or oxidation in animal models of lipotoxic cardiomyopathy influence more than one lipid metabolism and signaling pathway, which renders it difficult to pinpoint a specific FA metabolite causative for cardiomyocyte dysfunction. It is unlikely to be the excess deposition of a single FA metabolite and over-activation of a single lipid signaling pathway, but rather a combination of these that triggers cardiac dysfunction in animal models of lipotoxic cardiomyopathy.

The etiology and functional relevance of cardiac lipotoxicity is less clear in the human heart when compared to animal models of lipotoxic cardiomyopathy. In this regard, the development of proton magnetic resonance spectroscopy for the noninvasive quantification of intramyocardial TAG in vivo was an important contribution towards the understanding of the relationship between increased cardiac lipid deposition and cardiac function in humans [24–27]. Using this technique, it has been demonstrated that increased myocardial TAG deposition is not only associated with but precedes cardiac dysfunction in humans with type 2 diabetes mellitus [28] and correlates with body mass index [29,30]. These findings indicate that there is a causative relationship between cardiac lipid accumulation and impaired myocardial contractility. Moreover, it has been suggested that cardiac steatosis and ensuing lipotoxic cardiomyopathy are widespread and clinically highly relevant given the global rise in the prevalence of obesity and metabolic complications [30].

It is currently poorly understood whether the cardiac accumulation of lipids other than TAGs, which are believed to contribute to cardiac

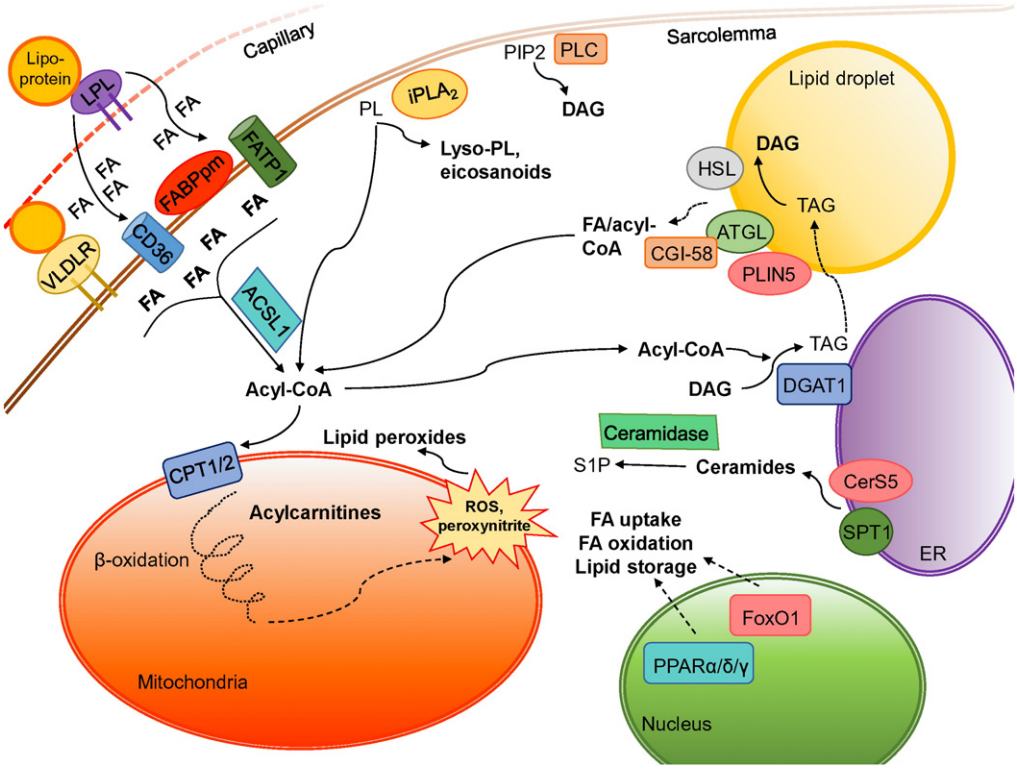

Fig. 2. Schematic representation of lipids and proteins involved in lipid uptake and metabolism that have been implicated in cardiac lipotoxicity. Excess FA delivery and uptake in cardiomyocytes, impaired or incomplete FA oxidation, lipid peroxidation, as well as ceramide, glycerolipid, and phospholipid metabolism have been linked to cardiac lipotoxicity. Lipid classes and metabolites that have been associated with lipotoxicity in the heart include long chain acyl-CoAs, FAs, acylcarnitines, lipid peroxides, ceramides and other sphingolipids, DAGs, lyso-PLs, and eicosanoids (highlighted in bold letters).