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Review article

Myocardial triacylglycerol metabolism

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ABSTRACT

Myocardial triacylglycerol (TAG) constitutes a highly dynamic fatty acid (FA) storage pool that can be used for an energy reserve in the cardiomyocyte. However, derangements in myocardial TAG metabolism and accumulation are commonly associated with cardiac disease, suggesting an important role of intramyocardial TAG turnover in the regulation of cardiac function. In cardiomyocytes, TAG is synthesized by acyltransferases and phosphatases at the sarcoplasmic reticulum and mitochondrial membrane and then packaged into cytosolic lipid droplets for temporary storage or into lipoproteins for secretion. A complex interplay among lipases, lipase regulatory proteins, and lipid droplet scaffold proteins leads to the controlled release of FAs from the cardiac TAG pool for subsequent mitochondrial β-oxidation and energy production. With the identification and characterization of proteins involved in myocardial TAG metabolism as well as the identification of the importance of cardiac TAG turnover, it is now evident that adequate regulation of myocardial TAG metabolism is critical for both cardiac energy metabolism and function. In this article, we review the current understanding of myocardial TAG metabolism and discuss the potential role of myocardial TAG turnover in cardiac health and disease. This article is part of a Special Issue entitled "Focus on Cardiac Metabolism".

Contents

1. Introduction

The beating heart has a very high energy demand and thus evolved to utilize a variety of carbon sources for ATP production [1,2]. Despite this relative metabolic flexibility, the adult healthy heart derives most of its energy from mitochondrial oxidation of fatty acids (FAs) [1,2]. FAs are supplied to cardiomyocytes via circulating triacylglycerol (TAG)-rich lipoproteins that are catabolized by lipoprotein lipase on the luminal surface of the coronary vascular endothelium [3] as well as albumin-bound FAs secreted from adipose tissue [4]. Following transport across the cardiomyocyte plasma membrane by protein carrier mechanisms or passive diffusion [4], FAs are made available for intracellular metabolism via conversion to fatty acyl-coenzyme A esters (FA-CoAs) (Fig. 1) [5]. The two major fates of these "activated" FAs are either direct delivery to mitochondria and subsequent oxidation or esterification to TAG for temporary storage in cytoplasmic lipid droplets

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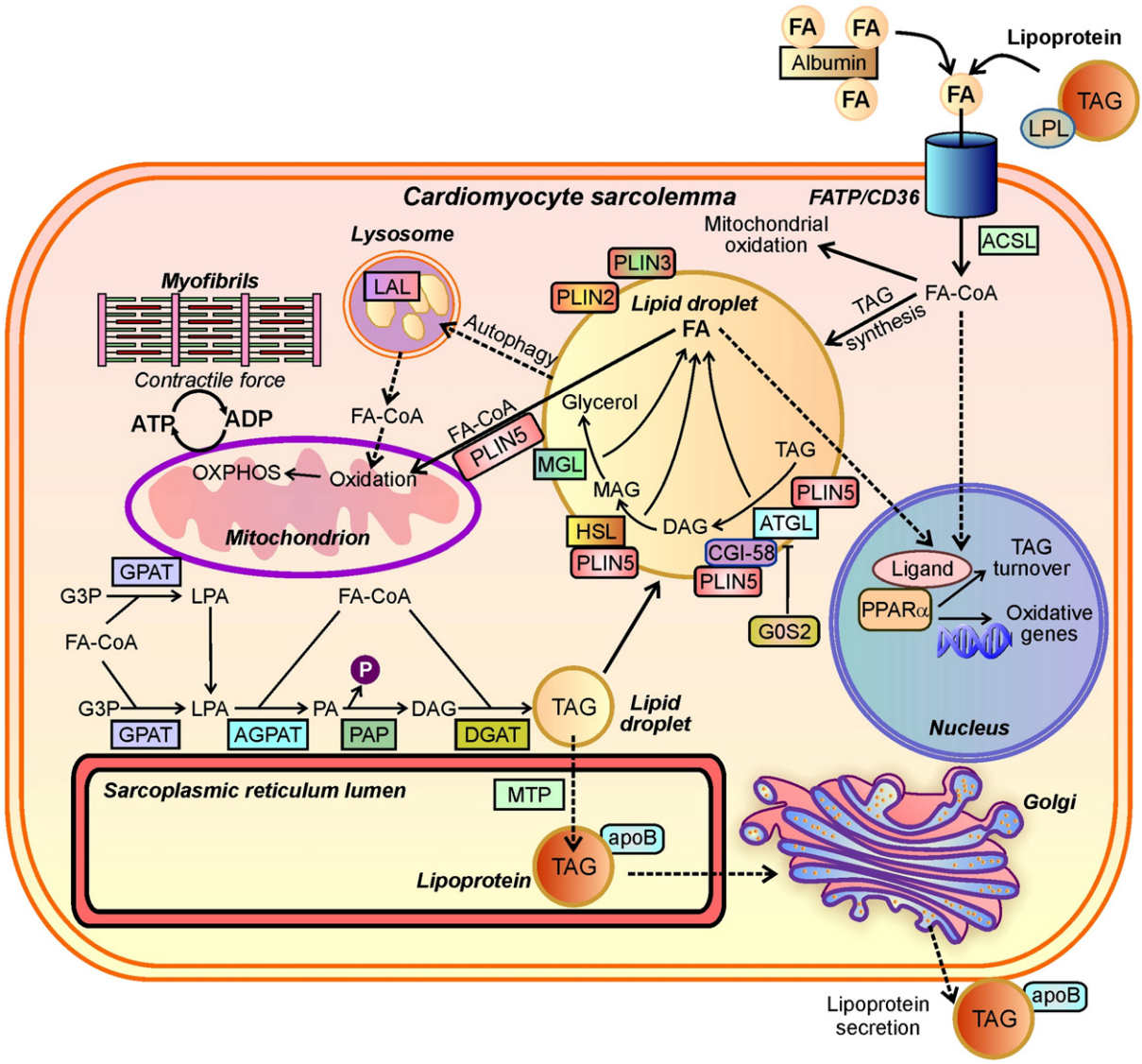

Fig. 1. Proteins involved in triacylglycerol (TAG) synthesis and catabolism in cardiomyocytes. Fatty acids (FA) are supplied to the cardiomyocyte as serum albumin-conjugated FA or in the form of TAG contained within lipoproteins (very-low-density lipoproteins and chylomicrons), which are hydrolyzed by lipoprotein lipase (LPL) in the coronary lumen. Released FA enter the cardiomyocyte mainly via FA transport proteins (FATP) or CD36 and are subsequently converted to fatty acyl-coenzyme A esters (FA-CoA) by long-chain acyl-CoA synthetases (ACSL). The major fates of these "activated" FA are mitochondrial oxidation or incorporation into TAG for temporary storage. TAG synthesis is initiated by glycerol-3-phosphate acyltransferases (GPAT) at the mitochondrial and sarcoplasmic reticulum membrane and then completed at the sarcoplasmic reticulum by *sn*-1-acyl-glycerol-3-phosphate acyltransferase (AGPAT), phosphatidic acid phosphatase (PAP), and *sn*-1,2-diacylglycerol acyltransferase (DGAT) reactions. The newly formed TAG is packaged into cytosolic lipid droplets, which are coated by scaffolding proteins from the perilipin (PLIN) family. TAG catabolism is performed by a cascade of lipolytic reactions that are initiated by adipose triglyceride lipase (ATGL) in conjunction with its coactivator protein, comparative gene identification-58 (CGI-58). In the currently proposed scheme, both ATGL and CGI-58 interact with each other and with individual perilipin-5 proteins at the lipid droplet surface to facilitate lipolysis. Contrary to CGI-58, G0S2 inhibits ATGL upon binding. Hormone-sensitive lipase (HSL) and monoacylglycerol lipase (MGL) complete the lipolytic cascade by hydrolyzing diacylglycerol (DAG) and monoacylglycerol (MAG), respectively. The FA released during TAG catabolism are mainly used for β-oxidation and subsequent energy (ATP) production via oxidative phosphorylation (OXPHOS) in mitochondria. FA transfer from lipid droplets to mitochondria may be regulated by PLIN5, which physically links these organelles. In addition to FA entering the cardiomyocyte, FA released by lipolysis are also suggested to provide ligands or their precursors for peroxisome proliferator-activated receptor α (PPARα), which stimulates the transcription of genes involved in FA oxidation and TAG turnover. Besides lipolysis at the lipid droplet, another potential pathway regulating TAG degradation in cardiomyocytes is TAG hydrolysis by lysosomal acid lipase (LAL) during the process of autophagy. In addition, TAG homeostasis is regulated by reverse TAG transport through lipoprotein secretion. In this process, TAG is catabolized and re-esterified by as yet unknown mechanisms and then packaged with the assistance of microsomal triglyceride transfer protein (MTP) into apolipoprotein B (apoB)-coated low-density lipoprotein particles that are secreted through the Golgi secretory pathway.

[1,2]. The lipid droplets are in close proximity to mitochondria and can be mobilized by lipid hydrolases in time of energetic need [6]. Synthesis and hydrolysis of myocardial TAG stores is a highly dynamic process that is tightly regulated and appears to contribute to proper cardiac metabolism and function. In agreement with this, deranged myocardial TAG metabolism and altered cardiac TAG content are associated with impaired heart function [7–14], supporting the important role that TAG metabolism plays in the regulation of cardiac function.

The utilization of proton magnetic resonance spectroscopy has allowed for the non-invasive analysis of myocardial TAG content in the beating human heart [15–18], revealing a substantial variability of myocardial TAG accumulation during both physiological and pathological conditions. For example, short-term (3-day) caloric restriction or 48 h fasting induced a marked increase in myocardial TAG content in healthy subjects [16,19], which is similar to observations in rodents [20,21]. Interestingly, this increase in myocardial TAG accumulation was paralleled by a decrease in diastolic function [19]. In contrast to caloric restriction or fasting, short-term consumption of a high fat diet (single high fat meal or 3-day high fat diet) did not lead to alterations in myocardial TAG content despite increased