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Cardiolipin remodeling in diabetic heart

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ABSTRACT

Cardiolipin, a signature phospholipid of mitochondria, is predominantly present in the mitochondrial inner membrane and plays an important role in keeping optimal mitochondrial function. In addition to the cardiolipin content, the composition of four fatty acid chain is thought determine cardiolipin biological function. These acyl chains of cardiolipin are dynamically remodeled via tafazzin, monolysocardiolipin acyltransferase, and acyl-CoA lysocardiolipin acyltransferase especially in the heart under pathological conditions. The major species of cardiolipin in the normal heart, tetralinoleoyl cardiolipin, is dramatically decreased in the diabetic heart, but other species, typically those containing long fatty acyl chains, are increased. This remodeling of cardiolipin has detrimental effects on mitochondrial function and thereafter cardiac function. Approaches for manipulating cardiolipin acyl chains have been examined including via molecular biology and through supplementation of linoleic acid. The efficiency of cardiolipin remodeling and functional improvement is still under investigation.

1. Introduction

The synthesis of cardiolipin (CL) in the heart starts with cytidine-5′-diphosphate-1,2-diacyl-*sn*-glycerol and phosphatidic acid, involving four sequential reactions catalyzed by cytidinediphosphatediacylglycerol synthetase, phosphatidylglycerolphosphate synthase (PGPS), phosphatidylglycerolphosphate phosphatases, and CL synthase (CLS). Once CL is synthesized, its fatty acyl chains undergo extensive remodeling catalyzed by calcium-independent phospholipase A_2 ($iPLA_2$), tafazzin, monolysocardiolipin acyltransferase (MLCL AT), and/or acyl-CoA:lysocardiolipin acyltrasferase (ALCAT). CL synthesis and acyl chain remodeling occur exclusively in mitochondria.

It is well known that CL is important for optimal mitochondrial function including (1) optimal activities of respiratory chain complexes and ADP-ATP translocase (Beyer and Nuscher, 1996), which are involved in ATP production as well as reactive oxygen species (ROS) formation; (2) cytochrome *c* anchoring to the out leaflet of the inner mitochondrial membrane (Ott et al., 2002), which is associated with mitochondria-initiated cell death; (3) maintenance of mitochondrial inner membrane fluidity and osmotic stability (Lewis and McElhaney, 2009), which is associated with opening of mitochondrial permeability transition pores and mitochondria-gated cell death; and (4) regulation of mitofusion (Li et al., 2012) and mitochondrial protein import (Jiang et al., 2000), which are associated with mitochondrial biogenesis. Thus, CL deficiency and/or improper remodeling of CL species directly impair mitochondrial function.

Cardiac myocytes are filled with highly organized contractile apparatuses (e.g., sarcomeres) composed of thin actin filaments, thick myosin filaments, and highly packed mitochondria that supply ATP. The myocytes consume vast amounts of ATP to keep the cardiac muscle contraction. Thus cardiac myocytes have a very high mitochondrial density, comprising about 35% of the cytoplasmic volume in mice (Barth et al., 1992). Cardiac myocytes occupy 75% of the myocardial structural space, but count only one third of the cell population because of their large size (Weber and Brilla, 1991). It is obvious that CL is a very important component for cardiac myocytes and not surprised that CL was first isolated from beef heart (Eichberg and Burnham, 1970).

2. Cardiolipin remodeling during heart development

Cardiac CL is dynamically remodeled during postnatal development. Total CL content is gradually increased from postnatal day 1 (about 2 nmol/mg protein) to day 35 (about 15–20 nmol/mg) (Kiebish et al., 2012). At day 35, myocardial CL content and species profile are present as those in adult. Approximately 60% CL molecular species contain four linoleic acids (18:2) (i.e., tetra18:2 CL) in mouse heart. The majority of the rest of CL is composed of at least one longer acyl chain than 18 carbon atoms such as docosahexaenoic acid (22:6).

The profile of CL molecular species at postnatal day 1 displays several abundant species including 18:2–18:2–18:2–18:2,

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18:3–18:2–18:2–18:2, 18:2–18:2–18:2–18:1, 18:2–18:2–18:2–20:3, 18:2–18:2–18:1–20:3, 18:2–18:2–18:2–20:2, 18:2–18:2–18:2–20:4, 18:2–18:1–16:1–22:6, 18:2–18:2–18:1–16:1, 18:2–18:2–18:2–16:0, and 18:2–18:2–18:2–16:1 (He et al., 2013; Kiebish et al., 2012). The CL species containing longer acyl chain than 18 carbon atoms are increased till day 7 and the shorter chain species are significantly decreased accordingly (Kiebish et al., 2012). From day 14 to day 35, the CL species containing longer fatty acyl chains are significantly decreased and tetra18:2 CL is present as the only predominant species (Kiebish et al., 2012).

The reduction of tetra18:2 CL content is always associated with dysfunctional heart, including diabetes (Han et al., 2005), heart failure (Sparagna et al., 2007), and ischemia reperfusion injury (Paradies et al., 2004; Lesnefsky et al., 2001). It is widely accepted that tetra18:2 CL is the fully functional CL species (Zachman et al., 2010). It is believed (never confirmed yet) that the content of tetra18:2 CL, other than the total CL, determines the mitochondrial function, thereafter cardiac function (Sparagna et al., 2007; Schlame, 2008). Total CL content may be important in the neonatal heart, at least in certain degree, since tetra18:2 CL is not the predominant species at that developing stage, instead it is only one of the several abundant species. On the other hand, the different profile of CL molecular species in the neonatal heart from that in adult may reflect the importance of tetra18:2 CL to optimize cardiac function since neonatal heart does not contract as strong as that in adult. Both cardiac myocyte and mitochondria undergo maturation process during the postnatal development. It has been reported that mitochondria control cardiac myocyte differentiation during embryonic development (Drenckhahn, 2011; Hom et al., 2011). Based on CL remodeling during cardiac development, it is reasonable to propose that CL is one of the factors in controlling mitochondrial maturation.

3. Cardiolipin remodeling in diabetic heart

3.1. Metabolism in diabetic heart

Diabetes is a metabolic disease characterized with increased blood sugar and/or glycosuria. It is caused by either insulin deficiency (type I) or inefficiency (type II). Cardiovascular complication, typically diabetic cardiomyopathy, is the major cause for diabetic patient mortality. Under normal physiology conditions, the heart consumes multiple fuel substrates for ATP production including fatty acids, ketones, glucose, and amino acids (Avogaro et al., 1990). However, oxidation of fatty acid in the diabetic heart is augmented while glucose utilization is decreased (Lopaschuk et al., 2010). The two reverse processes of triacylglycerol synthesis and fatty acids oxidation dynamically occur at separate organelles (i.e., endoplasmic reticulum and mitochondria). Cardiolipin synthesis and remodeling are carried out in the same organelle as fatty acid oxidation (i.e., mitochondria). There are contact sites between endoplasmic reticulum and mitochondria, which facilitate lipid transferring (Kornmann and Walter, 2010). The processes of cardiolipin and triacylglycerol syntheses involve several common substrates which include acyl-CoA, lysophosphatidic acid, and phosphatidic acid. Though these two synthetic processes are compartmented separately, the enhanced fatty acid metabolism in the diabetic heart may directly affect cardiolipin synthesis and remodeling (Shi and Burn, 2004).

3.2. Ubiquitous presence of altered cardiolipin profile in diabetic myocardium

Depletion of cardiac tetra18:2 CL occurs at the very early stages of type I diabetic mouse model induced by streptozotocin (Han et al., 2005, 2007). CL species are extensively

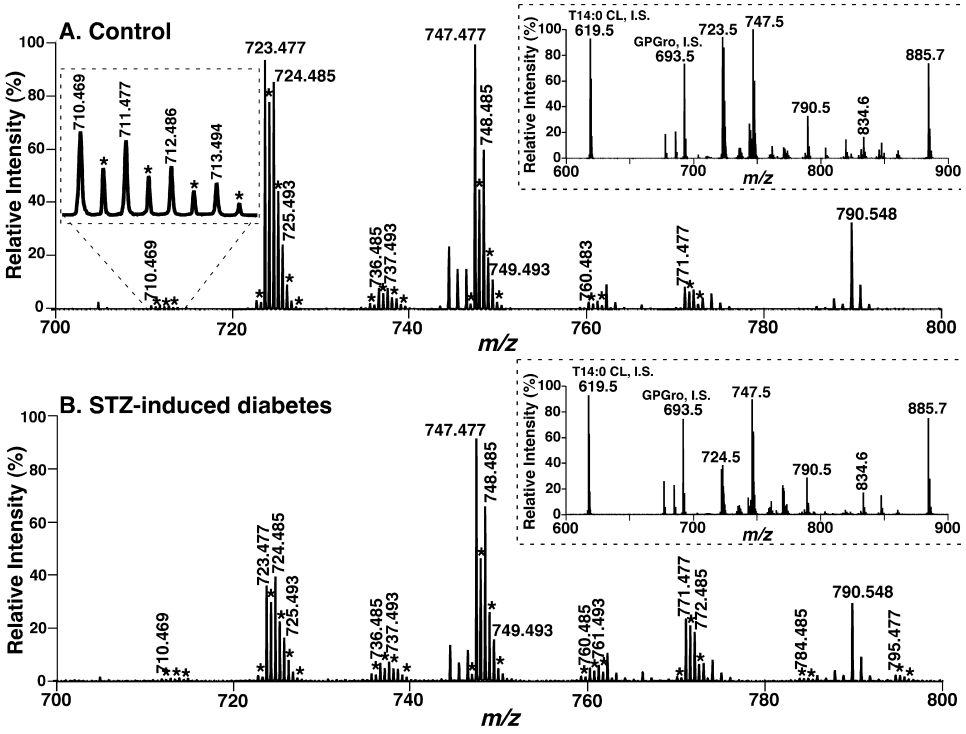

Fig. 1. Represent spectra displaying cardiolipin remodeled in diabetic mouse heart.
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