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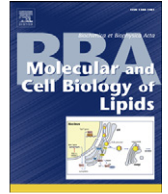

Review

Cardiolipin remodeling and the function of tafazzin ☆

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ABSTRACT

Cardiolipin, the specific phospholipid of mitochondria, is involved in the biogenesis, the dynamics, and the supramolecular organization of mitochondrial membranes. Cardiolipin acquires a characteristic composition of fatty acids by post-synthetic remodeling, a process that is crucial for cardiolipin homeostasis and function. The remodeling of cardiolipin depends on the activity of tafazzin, a non-specific phospholipid–lysophospholipid transacylase. This review article discusses recent findings that suggest a novel function of tafazzin in mitochondrial membranes. By shuffling fatty acids between molecular species, tafazzin transforms the lipid composition and by doing so supports changes in the membrane conformation, specifically the generation of membrane curvature. Tafazzin activity is critical for the differentiation of cardiomyocytes, in which the characteristic cristae-rich morphology of cardiac mitochondria evolves. This article is part of a Special Issue entitled Phospholipids and Phospholipid Metabolism.

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1. Introduction

Around 1980, Peter Barth, a pediatric neurologist in Amsterdam, recognized a clinical pattern presenting with cardiomyopathy, skeletal muscle weakness, and neutropenia, and established the X-linked inherited nature of the syndrome. He also demonstrated, by measuring the activities of respiratory enzymes and by studying electron micrographs, that the disease has a profound impact on structure and function of mitochondria [1]. More than a decade later, the locus of Barth syndrome mutations was identified and named “tafazzin” after a comic character from Italian television [2]. Soon after, the emerging field of bioinformatics enabled sequence alignment algorithms that revealed similarities between tafazzin and acyltransferases, which provided the first hint that tafazzin may be involved in the metabolism of mitochondrial lipids [3]. This idea was confirmed in 2000 by Peter Vreken, also from Amsterdam, who showed that tafazzin affected specifically the incorporation of fatty acids into cardiolipin [4]. Tetralinoleoyl-cardiolipin was subsequently identified as the molecular species that is most dependent on tafazzin activity [5]. The mechanism of Barth syndrome has since become an intense field of research, which has provided unexpected insight into the function of phospholipids in mitochondrial membranes, and specifically the function of cardiolipin.

2. Remodeling of cardiolipin

In most tissues, cardiolipin contains only one or two dominant acyl residues, which promotes structural uniformity and molecular symmetry among its molecular species [6]. The acyl groups of cardiolipin are typically dominated by unsaturated chains. The characteristic species composition of cardiolipin is the result of post-synthetic modification, a process commonly referred to as “remodeling” [7]. Remodeling is initiated by the removal of one acyl group, which yields monolyso-cardiolipin. In yeast, a cardiolipin-specific phospholipase has been identified and demonstrated to shape the acyl composition of cardiolipin [8]. In mammals and flies, circumstantial evidence has implicated calcium-independent phospholipase A_2 in cardiolipin hydrolysis [9,10]. However, it is not clear whether cardiolipin hydrolysis is an obligatory step in cardiolipin remodeling because monolyso-cardiolipin can also be formed by tafazzin.

Three enzymes have been implicated in the re-acylation of monolyso-cardiolipin, namely monolyso-cardiolipin acyltransferase (MLCLAT) [11], acyl-CoA:lysocardiolipin acyltransferase (ALCAT) [12], and tafazzin [13]. MLCLAT is in fact a truncated version of the trifunctional enzyme that catalyzes 3 steps in beta oxidation [14]. The purified protein has some acyltransferase activity, although its specific activity is low. Alterations in the MLCLAT expression level affect the incorporation of [^{14}C]linoleic acid into cardiolipin [14]. However, more work is necessary to establish the biological function and indeed the native activity of the truncated trifunctional enzyme.

ALCAT, on the other hand is a bona fide lysophospholipid:acyl-CoA acyltransferase that can react with a number of lysophospholipid species [15]. Thus, the specificity of this enzyme for lyso-cardiolipins is only in its name. ALCAT is localized in mitochondria-associated membranes that play an active role in cellular lipid metabolism [16]. ALCAT over-expression decreases the concentration of cardiolipin and modestly increases the proportion of polyunsaturated fatty acids in cardiolipin. ALCAT over-expression also causes oxidative stress, mitochondrial fragmentation, and loss of mitochondrial DNA

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apparently via modulation of the expression of MFN2, a protein that tethers the endoplasmic reticulum to mitochondria [17]. Hence, there is strong evidence for a role of ALCAT in the interaction between mitochondria and mitochondria-associated membranes, and specifically the lipid metabolism of these membranes. ALCAT is up-regulated in response to oxidative stress and diet-induced obesity, two conditions in which oxidation-sensitive polyunsaturated species of cardiolipin may theoretically be involved [16]. However, the function of ALCAT in cardiolipin remodeling has not been clearly explained.

It is important in that regard to define the term "cardiolipin remodeling". Many alterations of mitochondrial structure and function may affect the species composition of cardiolipin, but I will apply the term "cardiolipin remodeling" strictly to those chemical reactions that actually generate the normal species pattern of cardiolipin. Despite of their names, the substrate specificity and indeed the function of MLCLAT and ALCAT remain to be defined. Neither the inactivation of MLCLAT nor the inactivation of ALCAT has any measurable effect on the cardiolipin composition of *Drosophila* [18]. In contrast, tafazzin is absolutely essential to sustain the normal fatty acid composition and the normal concentration of cardiolipin in yeast, flies, and mammals [18–21]. In humans, mutations of the tafazzin gene cause Barth syndrome, which underscores not only the significance of tafazzin but also that of cardiolipin remodeling [4,5].

3. Expression and targeting of tafazzin

Homologues of tafazzin occur throughout the eukaryotic kingdom, including animals, fungi, plants, and protists [22]. In yeast and flies, tafazzin is targeted to the mitochondrial compartment and this is presumably true for other organisms as well [23–26]. The targeting signal however is not associated with either the N or the C terminus [25]. In mitochondria, tafazzin binds to the outer face of the inner membrane or to the inner face of the outer membrane and can thus be regarded as a resident of the intermembrane space [25]. The alkali extraction profile of tafazzin suggests that its association with the membrane relies on hydrophobic interactions, although a specific transmembrane domain could not be identified [25]. Tafazzin sequences contain a conserved hydrophobic segment near the N terminus (Fig. 1), but this segment is probably not the membrane binding domain because it is more accessible to proteases than other parts of the protein [25]. Based on protease susceptibility, a model was proposed for the membrane topology of tafazzin [25]. However, this model does not account for protein–protein interactions that, just like protein–lipid interactions, may shield tafazzin from proteases. Such interactions may be important for the topology of tafazzin because most of the enzyme is associated with protein complexes ranging in size from 10^5 to 10^6 Da [25–27]. The composition of these complexes has not been characterized and the direct binding partners of tafazzin have not been identified. Yet, the significance of the association of tafazzin with protein complexes is evident because impairment of tafazzin assembly may cause the loss of tafazzin function [28].

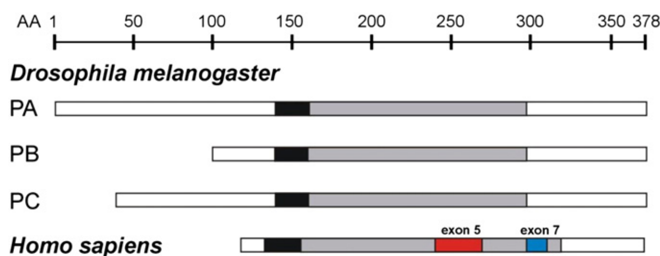


Fig. 1. Tafazzin isoforms are expressed by alternative splicing. The schematic shows the alignment of amino acid (AA) sequences of the predicted tafazzin isoforms from humans and flies (from Ref. [26]). *Drosophila* tafazzins differ by their N-terminal sequences. Human tafazzins differ by the presence or absence of exons 5 and 7, respectively. Conserved hydrophobic segments are shown in black.

When tafazzin was first described in humans, it was recognized that alternative splicing of its gene can produce a number of different mRNAs [2]. These include the full-length isoform as well as species that are missing exon 5, exon 7, or both (Fig. 1). However, only one of these isoforms, the one that is missing exon 5 (Δexon5), was found to be functional in complementation analyses carried out in yeast [29]. Not surprisingly, the Δexon 5 variant is the principle product of tafazzin expression in humans [30,31]. If Δexon 5 is functional and is the major isoform, why does exon 5 exist at all? We have shown that full-length human tafazzin can complement tafazzin deletion in *Drosophila*, which contradicts the observation made in yeast, and we have demonstrated a small difference between the alkali extraction profiles of the full-length and the Δexon5 isoforms [26]. We have also some unpublished data suggesting that both isoforms are present as endogenous proteins in human cells. Since exon 5 is present in humans and primates only [30], the question arises as to why full-length tafazzin is required in these highly developed species.

In *Drosophila*, the tafazzin gene also expresses different isoforms, but in *Drosophila* this has implications for the intracellular targeting (Fig. 1). Tafazzin-A, the most abundant isoform, is targeted to mitochondria. In contrast, tafazzin-B associates with a variety of intracellular compartments, including mitochondria, the endoplasmic reticulum, and the Golgi apparatus [26]. Tafazzin-A, tafazzin-B, and the two human isoforms carry the same enzymatic activity, which will be discussed in the following section.

4. Enzymatic function of tafazzin

Tafazzin is a transacylase that catalyzes the transfer of an acyl group from a phospholipid (PL) to a lysophospholipid (LPL) [13]:

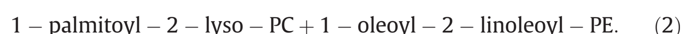
$$PL_1 + LPL_2 \rightarrow LPL_1 + PL_2. \quad (1)$$

The catalytic mechanism has not been studied but distant sequence homologies to acyltransferases, including the presence of the HX_4D motif, make it conceivable that tafazzin acts in a manner similar to those enzymes, which involves a ternary complex as catalytic intermediate. This was discussed in more detail in an earlier review article [7]. Little new information has been added to this topic since.

Although our first study in isolated mitochondria suggested some acyl specificity of tafazzin, subsequent experiments with the purified recombinant enzyme showed that it reacts with a wide spectrum of phospholipid species. Tafazzin activity has been demonstrated with cardiolipin, phosphatidic acid, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidylserine, and their lyso-analogs, carrying acyl groups with 7–19 carbon atoms and 0–3 double bonds [26,32,33]. Hence, it is probably safe to extrapolate these data inferring that tafazzin reacts with all PL/LPL species. Furthermore, the enzyme does not distinguish between acyl groups in *sn*-1 and *sn*-2 position. Positional promiscuity of tafazzin has been established by comparing the substrates 1-monolyso-cardiolipin with 2-monolyso-cardiolipin [32] and by comparing positional isomers of 18:0–18:1-phosphatidylcholine [33].

The absence of specificity has important implications. For instance, when tafazzin catalyzes the transacylation of 1-palmitoyl-2-linoleoyl-PC and 1-oleoyl-2-lyso-PE, there are two possible outcomes:

1-palmitoyl-2-linoleoyl-PC + 1-oleoyl-2-lyso-PE →



1 – palmitoyl – 2 – lyso – PC + 1 – oleoyl – 2 – linoleoyl – PE. (2)

1-palmitoyl-2-linoleoyl-PC + 1-oleoyl-2-lyso-PE →

1 – lyso – 2 – linoleoyl – PC + 1 – oleoyl – 2 – palmitoyl – PE. (3)

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