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Minireview

Barth syndrome, a human disorder of cardiolipin metabolism

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Abstract **Barth syndrome is an X-linked recessive disease caused by mutations in the tafazzin gene. Patients have reduced concentration and altered composition of cardiolipin, the specific mitochondrial phospholipid, and they have variable clinical findings, often including heart failure, myopathy, neutropenia, and growth retardation. This article provides an overview of the molecular basis of Barth syndrome. It is argued that tafazzin, a phospholipid acyltransferase, is involved in acyl-specific remodeling of cardiolipin, which promotes structural uniformity and molecular symmetry among the cardiolipin molecular species. Inhibition of this pathway leads to changes in mitochondrial architecture and function.**

Keywords: Cardiomyopathy; Fatty acid; Mitochondrial disease; Phospholipids; Skeletal muscle; Tafazzin

1. Introduction

About a quarter of a century ago, Peter Barth and his colleagues described a Dutch family with a three-generation history of infantile cardiomyopathy, in which abnormal mitochondria were implicated [1,2]. The disorder showed an X-linked recessive inheritance pattern and was similar in many aspects to a mitochondrial cardiomyopathy that was found two years earlier in another pedigree by Neustein et al. [3]. Since then, more cases have been identified in regions far apart, such as Australia [4], Europe [5], Japan [6], and North America [7], but the incidence is still unknown due to the lack of suitable demographic data.

The classical presentation of this cardiomyopathy, which today is known as Barth syndrome (MIM 302060), also includes skeletal muscle weakness, neutropenia, and growth retardation [2,7]. Furthermore, two metabolic abnormalities are typically present, namely elevated urinary excretion of 3-methylglutaconic acid and hypocholesterolemia [7]. A mild cognitive phenotype has been described as well [8]. However, there is considerable variability in the age of onset, the expression of symptoms, and the progression of the disease. The majority of patients registered with the Barth Syndrome Foundation (www.barthsyndrome.org) are children, although this is likely to change as the improved overall care reduces infant and childhood mortality.

The current patient population covers a wide range of individuals from those who have severe debilitating disease to those who are nearly asymptomatic. The characteristic symptoms of Barth syndrome (cardiomyopathy, skeletal myopathy, neutropenia, growth retardation) are not consistently present in every patient and the clinical situation may change as patients grow older. Nevertheless, the most serious finding is usually cardiomyopathy, presenting either as biventricular dilatation or as left-ventricular non-compaction [9]. Sudden episodes of cardiac deterioration are common and are often followed by unexplained remissions. This obscure clinical pattern has led many to refer to Barth syndrome as a "mystery disease". It has also made it challenging for physicians to establish the correct diagnosis in Barth patients.

About 10 years after the first description of Barth syndrome, the locus for the disease was mapped to the distal portion of Xq28 [4,10] and mutations were eventually identified in G4.5 [11], a gene that is ubiquitously expressed in human tissues [12]. This gene has the potential to form several proteins because 3 of its 11 exons may undergo differential splicing [11]. Since the G4.5 protein products have been named tafazzins, in reference to a comic Italian television character [11], G4.5 is now commonly referred to as the tafazzin gene. Many different mutations have been identified in this gene over the past decade, yet no clear correlation has emerged between the genotypes and the various phenotypes that patients present with [6,9,13–15].

Although the nucleotide sequence and transcriptional organization of the tafazzin gene suggest that it may express up to twelve different mRNA species [11], only four species have actually been found in human tissues [16,17]. These include the full-length mRNA as well as three shorter mRNAs in which either exon 5, or exon 7, or both exon 5 and exon 7, are missing. The corresponding proteins range from 28.5 to 33.5 kDa in size (248–292 amino acids).

Homologs of human tafazzin are present in the genomes of many diverse eukaryotes, such as yeast, roundworm, fruit fly, and mammals to name a few. These tafazzins form a subgroup within a large superfamily of proteins with known and putative acyltransferase function [18]. Since the known members of this superfamily use lysophospholipid substrates, it has been postulated that tafazzins are acyltransferases involved in phospholipid metabolism.

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2. Involvement of phospholipids in Barth syndrome

The first evidence for a role of tafazzin in phospholipid metabolism was provided by Peter Vreken and colleagues who showed that fibroblast cultures from Barth patients contain less cardiolipin than control cultures [19]. Cardiolipin is a dimeric phospholipid (Fig. 1) that is specifically localized in mitochondria [20]. Since the rate of cardiolipin synthesis was not affected in Barth fibroblasts, the authors suspected that the low concentration of cardiolipin was caused by increased degradation [19]. Under normal conditions, cardiolipin is degraded to monolysocardiolipin and then converted back into cardiolipin in order to exchange its fatty acids [21]. In Barth fibroblasts, the deacylation–reacylation cycle seemed to be impaired because the incorporation of linoleic acid into cardiolipin was reduced [19]. This observation in conjunction with the low cardiolipin level suggested a decline in the rate of reacylation relative to the rate of deacylation. Several years later, the idea of insufficient reacylation was corroborated when monolysocardiolipin was shown to accumulate in Barth patients [22] and in tafazzin-deficient yeast [23].

Involvement of acyl remodeling was also inferred from the analysis of cardiolipin species in Barth patients [24]. Interestingly, only a single molecular species, namely tetralinoleoyl–cardiolipin, was missing in the patients, whereas other cardiolipins were either unaffected or even increased. Tetralinoleoyl–cardiolipin is the dominant species in heart and skeletal muscle, where the defect was originally discovered [24]. However, tetralinoleoyl–cardiolipin was also deficient in platelets [24–26], fibroblasts [27], and granulocytes [28]. Because platelet samples are readily available from patients, it was possible to investigate the specificity of the cardiolipin defect for Barth syndrome and to explore its potential diagnostic utility [25]. Tetralinoleoyl–cardiolipin deficiency was shown to be a specific marker of Barth syndrome, distinguishing this disease from related cardiomyopathies and skeletal muscle disorders. As a result, the platelet test for cardiolipin is now being used in the work-up of patients in whom Barth syndrome is considered as a differential diagnosis [25,26].

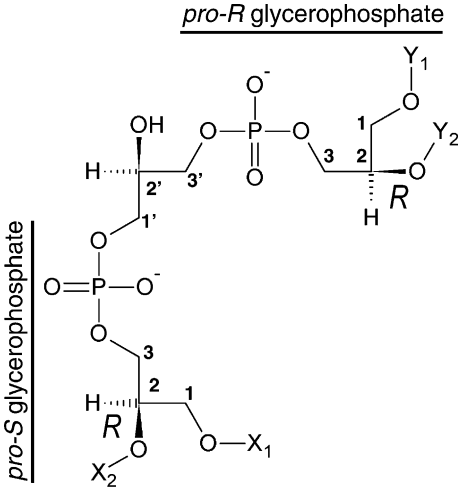

Fig. 1. Structure of cardiolipin. The molecule consists of two *sn*-glycero-3-phosphate moieties linked by a glycerol group. Four acyl groups (X_1, X_2, Y_1, Y_2) are attached to the glycerophosphates. Both glycerophosphates carry obligate chiral centers in *R* conformation. The central glycerol carries a prochiral center (if $X_1 = Y_1$ and $X_2 = Y_2$) or a true chiral center (if $X_1 \neq Y_1$ or $X_2 \neq Y_2$). As a result, the two glycerophosphates occupy different stereochemical positions [36].

Besides the change in cardiolipin composition, there is a consistent decrease in the total concentration of cardiolipin not only in heart [22,24,25] and skeletal muscle [24,25], but also in platelets [24–26], granulocytes [28], lymphocytes [22], cultured lymphoblasts [22,25] and cultured fibroblasts [19,25,27]. In contrast, the concentration of other phospholipids does not seem to change significantly [19,25]; but this does not imply that the effects of Barth syndrome are strictly confined to cardiolipin. For instance, in heart biopsies from Barth patients, the molecular compositions of phosphatidylcholine and phosphatidylethanolamine are altered due to an increase in linoleoyl-containing species, in particular 1-palmitoyl-2-linoleoyl-phosphatidylcholine and 1-stearoyl-2-linoleoyl-phosphatidylethanolamine, at the expense of the corresponding arachidonoyl-containing species [22,25]. The molecular composition of phosphatidylcholine is also altered in lymphoblasts [29]. These changes, albeit small in comparison to cardiolipin, may nevertheless be relevant and they may in fact be related to the metabolism of cardiolipin, which will be discussed in Section 4.

3. Abnormal molecular species of cardiolipin

The specific lack of tetralinoleoyl–cardiolipin created the idea that Barth syndrome is simply caused by inadequate incorporation of linoleic acid; thus supplementation with linoleic acid was proposed as a treatment [30]. However, it soon became clear that tafazzin mutations also alter the cardiolipin composition of lymphoblasts, in which tetralinoleoyl–cardiolipin is not present [31]. Likewise, the molecular pattern of cardiolipin is affected by deletion of the tafazzin gene in yeast, although linoleic acid is not present in yeast cardiolipin [23,32]. Therefore, a different paradigm is needed to explain why tafazzin mutations change the molecular composition of cardiolipin.

To recognize the essential nature of the tafazzin effect, it is informative to compare the cardiolipin composition of tafazzin mutants in humans [24,31], yeast [23,32], and fruit flies [33]. In all three examples, mutations cause a diversification of the cardiolipin pattern, i.e. the pattern changes from one that is dominated by a few major molecular species to one that contains multiple minor species. It appears that structural uniformity, or the selection of a limited number of molecular species, is an important feature of normal cardiolipin. Indeed, structural uniformity was found among cardiolipins from diverse eukaryotic organisms despite their differences in fatty acid composition [34]. Only one or two kinds of fatty acids are usually selected for the assembly of cardiolipins. For instance, in many mammalian tissues, cardiolipin has a strong preference for linoleic acid [24], in bivalves it is docosahexaenoic acid [35], and in *Drosophila* it is both linoleic and palmitoleic acid [34].

What is the function of the selective incorporation of fatty acids into cardiolipin and why may the absence of such selectivity be a disadvantage? While a convincing answer to this question has yet to be found, we would like to discuss the structural implications of random cardiolipin acylation, which seems to take place in patients with Barth syndrome. As shown in Fig. 1, each acyl residue of cardiolipin is attached to a ster-

eochemically unique hydroxyl group. The uniqueness of each ester site is related to the prochirality of the central glycerol, which makes one glycerophosphate *pro-S* (1′-linked) and the other one *pro-R* (3′-linked) [36]. As a result, there are four distinguishable sites, namely *sn*-1′-(1-glycerol), *sn*-1′-(2-glycerol), *sn*-3′-(1-glycerol), and *sn*-3′-(2-glycerol). This implies that N^4 positional permutations are possible in a cardiolipin with N types of fatty acids. For example, 625 cardiolipin species could occur in yeast that contains five fatty acids, and 38 416 cardiolipin species could occur in humans with fourteen fatty acids. Thus, Barth patients contain a nearly infinite variety of cardiolipin species generated by random acyl substitution. In contrast, normal individuals and normal eukaryotic organisms contain only a limited number of cardiolipin species due to the strong selection of specific fatty acids.

We have identified three different scenarios for the assembly of cardiolipin species, which are based on the selective incorporation of one, two, or three types of fatty acids (Fig. 2) [34]. If one fatty acid is selected, such as in many mammalian tissues, only a single molecular species becomes the dominant component of cardiolipin (Fig. 2A). If two fatty acids are selected, such as in fruit flies, 16 molecular species emerge (Fig. 2B). If three fatty acids are selected, such as in the sea urchin *A. punctulata*, one would expect a total of 81 molecular species. However, positional specificity among the three fatty acids limits the number of molecular species to four (Fig. 2C). Fatty acid specificity of cardiolipin not only creates structural uniformity, it also increases the degree of molecular symmetry, i.e. the formation of molecular species with identical 1,2-diacylglycerol moieties [34]. When the process of fatty acid selection is impaired, like in patients with Barth syndrome, mostly asymmetric cardiolipin species are formed, in which the prochiral carbon atom of the central glycerol group becomes a true chiral center. The significance of cardiolipin chirality has not been studied, but several ideas about the role of molecular symmetry in cardiolipin have been discussed in a previous article [34].

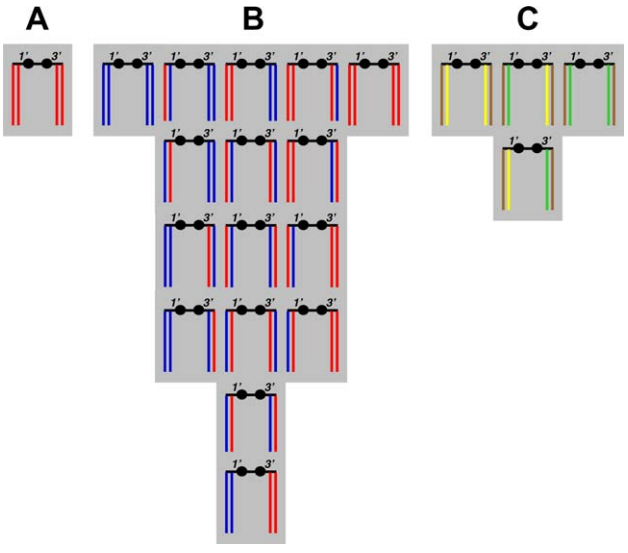

Fig. 2. Molecular species of cardiolipin in different organisms. Each species is presented as a drawing, in which color-coded acyl groups are attached to the following carbon atoms (from left to right): *sn*-1′-(1-glycerol), *sn*-1′-(2-glycerol), *sn*-3′-(2-glycerol), and *sn*-3′-(1-glycerol). (A) Cardiolipin from human heart. (B) Cardiolipin from *D. melanogaster*. (C) Cardiolipin from *A. punctulata*. See Ref. [34] for experimental data. Color code: blue, palmitoelic acid (16:1); yellow, oleic acid (18:1); red, linoleic acid (18:2); green, docosadienoic acid (20:2); brown, docosapentaenoic acid (20:5).

4. The role of tafazzin

What is the mechanism by which cardiolipin acquires a specific fatty acid profile? Like many other phospholipids, cardiolipin undergoes remodeling of its acyl moieties after de novo formation. This remodeling consists of a deacylation–reacylation cycle [21], similar to the classical Lands pathway [37]. However, in contrast to the Lands pathway that uses acyl-coenzyme A as substrate, cardiolipin remodeling was shown to use acyl groups from other phospholipids [31]. In rat liver mitochondria, this transacylation is highly specific for linoleoyl residues, which supports the idea that transacylation is the critical step in shaping the fatty acid profile of cardiolipin. Deacylation of cardiolipin, which is also essential for remodeling, appears to have no acyl specificity [31].

The enzymes involved in cardiolipin remodeling have remained obscure for many years. Two acyl-CoA dependent enzymes have been identified, which are capable to reacylate monolysocardiolipin in vitro, but they do not have any strong acyl specificity [38,39]. Tafazzin was implicated in cardiolipin remodeling because mutations in the tafazzin gene cause an increase of monolysocardiolipin, a decrease of cardiolipin, and a change of the cardiolipin composition [22–25]. These effects were reversible by tafazzin expression in the Δ*taz* yeast strain [32], strongly suggesting that tafazzin catalyzes the reacylation of monolysocardiolipin. In light of the proposed transacylation mechanism of cardiolipin remodeling [31], the question arises whether tafazzin is in fact a transacylase.

Tafazzin belongs to a protein superfamily, of which several members transfer activated fatty acids to glycero-3-phosphate either from acyl-coenzyme A or from acyl–acyl–carrier protein, another phosphopantetheine based coenzyme [18]. While these activities are consistent with an acyltransferase function, they do not specifically suggest a transacylation mechanism. However, tafazzins form a distinct subgroup within the superfamily, so their specific catalytic function can not be inferred from alignment analysis alone. There are now several lines of evidence to suggest that tafazzin has indeed transacylase activity. First of all, tafazzin deficiency is associated with a significant decrease of the phospholipid transacylation rate in lymphoblast mitochondria [31]. Second, yeast tafazzin was shown to catalyze reacylation of lysophosphatidylcholine in the absence of acyl-coenzyme A [40], a reaction for which transacylation is a likely mechanism. Third, we recently expressed *Drosophila* tafazzin in Sf9 insect cells and showed that it can exchange fatty acids between cardiolipin and phosphatidylcholine in a reversible, acyl-specific manner (unpublished data).

Finally, the effect of tafazzin mutations on the species pattern of phosphatidylcholine is consistent with the idea that tafazzin transfers specific fatty acids from phosphatidylcholine to cardiolipin. In patients with Barth syndrome, the same fatty acids that fail to accumulate in cardiolipin, do accumulate in phosphatidylcholine [25,29], suggesting that acyl groups normally flow from phosphatidylcholine to cardiolipin. Fig. 3 illustrates the cardiolipin–phosphatidylcholine transacylation

pathway. It is important to note that transacylations are near-equilibrium reactions that can not be the underlying mechanism for unidirectional fatty acid transfer from one phospholipid to another, unless they are coupled to an irreversible reaction. The driving force of fatty acid transfer may be the hydrolysis of acyl-coenzyme A, if the cardiolipin–phosphatidylcholine transacylation is coupled on one end to the hydrolysis of cardiolipin and on the other end to the reacylation of lysophosphatidylcholine (Fig. 3).

5. Involvement of mitochondria

Barth syndrome was originally described as a mitochondrial disease because tissue biopsies contained mitochondria with abnormal ultrastructure and diminished respiratory function [2]. The involvement of mitochondria in Barth syndrome seems plausible from our current prospective because tafazzin, the mutated enzyme, is localized in mitochondria [40,41] and so is cardiolipin, its primary metabolic target [22–25]. Barth syndrome seems to be unique among mitochondrial diseases since cardiolipin deficiency is not commonly present in patients with MELAS, Leigh syndrome, cytochrome oxidase deficiency, and mitochondrial DNA deletions [42].

Cardiolipin is mostly found in the inner mitochondrial membrane, where it interacts with many of the proteins involved in oxidative phosphorylation [20]. The unusually strong binding of cardiolipin to a number of different proteins, makes it an essential factor for the tertiary and quarternary protein structure and, by extension, the supramolecular organization of the crista membrane. For instance, cardiolipin occupies critical positions in the crystal structure of respiratory complex III [43] and the ADP–ATP carrier [44]. Cardiolipin also promotes the formation of supercomplexes from individual components of the respiratory chain [45,46]. Not surprisingly, the supercomplex equilibrium is affected by disruption of the tafazzin gene, so in Δ*taz* yeast mitochondria, respiratory complexes tend to exist in the dissociated state [47]. Thus, Barth syndrome may potentially interfere with assembly and stability of the respiratory chain, although the role of cardiolipin in mitochondrial biogenesis is not very well established. Cardiolipin is synthesized at the matrix side of the inner membrane in rat liver mitochondria [48]. In contrast, tafazzin is localized in the outer membrane of yeast mitochondria with its predicted catalytic domain exposed to the intermembrane space [47]. This suggests that de novo formation and remodeling of cardiolipin may occur at different sites and it raises questions as to where cardiolipin is incorporated into the respiratory complexes and how protein import is coordinated with cardiolipin formation and remodeling.

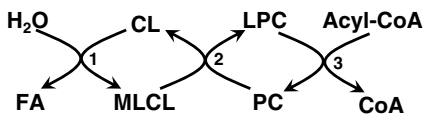

Fig. 3. Proposed mechanism of cardiolipin remodeling. (1) CL deacylation; (2) PC-CL transacylation (tafazzin reaction); (3) LPC reacylation. This pathway may reshuffle fatty acids due to the acyl specificity of the individual reactions. The net reaction of the pathway is: Acyl-CoA + $H_2O \rightarrow$ FA + CoA. *Abbreviations.* CL, cardiolipin; CoA, coenzyme A; FA, fatty acid; LPC, lysophosphatidylcholine; MLCL, monolysocardiolipin; PC, phosphatidylcholine.

Studies on Barth syndrome may provide unique insights into the role of cardiolipin in crista membrane assembly. Tissue biopsies from Barth patients contain mitochondria with bundles of stacked and compacted cristae that seem to be largely disconnected from the inner boundary membrane [49]. We found related abnormalities in flight muscle mitochondria of *Drosophila* with tafazzin mutation [33]. Electron tomography of abnormal cristae in Barth lymphoblasts showed a collapse of the intracrista space due to adhesion of the two opposing membranes (unpublished data). These structural changes suggest gross abnormalities in the assembly process, which will be dissected in future studies. Collapse of the intracrista space is probably incompatible with oxidative phosphorylation because this space is required for substrate diffusion and it supplies the protons for the electrochemical gradient.

Oxidative phosphorylation has been studied in lymphoblasts from Barth patients [29] and in tafazzin-deficient yeast [41]. There was a mild decrease in coupling efficiency, as shown by a decrease in state-3 respiration, an increase in state-4 respiration, and a decrease in the mitochondrial membrane potential. However, the overall ability to produce ATP was preserved, perhaps because of mitochondrial proliferation, which may compensate for the loss of mitochondrial function [29].

6. Pathogenesis of Barth syndrome

The current concept of Barth syndrome places cardiolipin at the center of the molecular pathogenesis. Cardiolipin deficiency is a plausible cause of mitochondrial dysfunction, which in turn may be the underlying mechanism for myopathy and heart failure. This idea is supported by our recent work in *Drosophila*, where tafazzin deletion leads to abnormal cardiolipin, abnormal mitochondria, and motor weakness of the indirect flight muscles [33]. However, many questions with regard to the pathogenesis of Barth syndrome, remain to be answered.

For instance, the clinical presentation of Barth syndrome is too sophisticated to be accounted for by a mere breakdown of energy metabolism. In several ways, Barth syndrome shows the pattern of a developmental disease that interferes with embryogenesis and the maturation of organ systems. This is specifically suggested by left-ventricular non-compaction in some newborns with Barth syndrome, a phenotype that is the result of impaired cardiac morphogenesis [6,9]. The variability in clinical presentation of Barth patients is also consistent with the idea that the syndrome is modulated by embryogenetic factors. The identification of these factors is one of the future challenges in Barth syndrome research.

While cardiolipin has been implicated in the etiology of Barth syndrome, it is not known whether it is the reduced concentration of cardiolipin or the altered composition of cardiolipin that is more important for the pathogenesis. Mitochondrial functions, such as respiration and osmotic stability, correlated with the cardiolipin content in yeast deletion mutants of tafazzin and cardiolipin synthase [41]. However, the yeast model has its own limitations with respect to the tissue-specific aspects of Barth syndrome. Interestingly, the cardiolipin concentration was almost normal in two cardiac biopsies from Barth patients with severe cardiomyopathy [25]. The same patients had drastic alterations in the pattern

of molecular species, suggesting that it is the composition of cardiolipin rather than its concentration that plays a role in the pathomechanism. Nevertheless, severe reductions in the cardiolipin content are likely to have consequences for mitochondrial function.

The cardiolipin defect may affect various cellular functions that involve mitochondria, such as oxidative phosphorylation or the initiation of apoptosis by cytochrome *c* release. Studies have demonstrated a loss of energy coupling efficiency in cellular models of Barth syndrome [29,41], but the effects are subtle and it is not clear whether insufficient ATP supply is a pathogenetic factor in Barth syndrome. It is conceivable though, that oxidative phosphorylation becomes exhausted in tissues like heart or skeletal muscle during periods of high energy demand. Apoptosis has also been studied in neutrophils [28] and lymphoblasts [22] of Barth patients, but no difference was found to the controls.

Furthermore, mitochondrial biogenesis may be affected in Barth syndrome. It is intriguing that some genetic diseases, in which mitochondrial biogenesis is likely involved, may present with Barth syndrome-like clinical features. This is true for a mutation in a putative component of the mitochondrial protein import system [50] and for a MELAS-type mutation of the mitochondrial DNA [51]. Barth syndrome may alter the growth of mitochondria and their intracellular distribution because the disease is expressed in tissues in which the mitochondrial network shows a high level of structural organization. In heart and skeletal muscle, mitochondria are arranged around the contractile apparatus in a crystal-like pattern [52], the formation of which may require an intact cardiolipin metabolism.

Finally, one has to consider the possibility that extramitochondrial functions are involved in the pathogenesis of Barth syndrome. Since the tafazzin gene produces several transcripts [16,17], they may be targeted to different intracellular compartments and they may be involved in more than one pathway. As of yet, no evidence exists for this scenario, but the presence of multiple tafazzin mRNA's requires an explanation.

In conclusion, Barth syndrome is a mitochondrial disorder caused by an inborn error of phospholipid metabolism. Tafazzin deficiency inhibits specifically the acyl remodeling of cardiolipin. As a result, mitochondria contain reduced levels of cardiolipin and the remaining cardiolipin lacks its characteristic acyl pattern. The exact consequences for mitochondrial function remain to be established, but they may include deficiencies in mitochondrial energy coupling and/or in mitochondrial biogenesis. Mitochondrial abnormalities in Barth syndrome compromise the development and function of certain tissues, such as muscle and heart, in which high energy turnover requires a strict structural organization of mitochondria both in terms of their morphology and their intracellular distribution.

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References

[1] Barth, P.G., van't Veer-Korthof, E.T., van Delden, L., van Dam, K., van der Harten, J.J. and Kuipers, J.R.G. (1981) An X-linked mitochondrial disease affecting cardiac muscle, skeletal muscle and neutrophil leucocytes in: Mitochondria and Muscular Diseases (Busch, H.F.M., Jennekens, F.G.I. and Scholte, H.R., Eds.), pp. 161–164, Mefar, Beeststerzwaag.

[2] Barth, P.G., Scholte, H.R., Berden, J.A., van der Klei-van Moorsel, J.M., Luyt-Houwen, I.E.M., van't Veer-Korthof, E.T., van der Harten, J.J. and Sobotka-Plojhar, M.A. (1983) An X-linked mitochondrial disease affecting cardiac muscle, skeletal muscle and neutrophil leucocytes. J. Neurol. Sci. 62, 327–355.

[3] Neustein, H.B., Lurie, P.R., Dahms, B. and Takahashi, M. (1979) An X-linked recessive cardiomyopathy with abnormal mitochondria. Pediatrics 64, 24–29.

[4] Ades, L.C., Gedeon, A.K., Wilson, M.J., Latham, M., Partington, M.W., Mulley, J.C., Nelson, J., Lui, K. and Sillence, D.O. (1993) Barth syndrome: clinical features and confirmation of gene localization to distal Xq28. Am. J. Med. Genet. 45, 327–334.

[5] Cantlay, A.M., Shokrollahi, K., Allen, J.T., Lunt, P.W., Newbury-Ecob, R.A. and Steward, C.G. (1999) Genetic analysis of the G4.5 gene in families with suspected Barth syndrome. J. Pediatr. 135, 311–315.

[6] Chen, R., Tsuji, T., Ichida, F., Bowles, K.R., Yu, X., Watanabe, S., Hirono, K., Tsubata, S., Hamamichi, Y., Ohta, J., Imai, Y., Bowles, N.E., Miyawaki, T. and Towbin, J.A. (2002) Mutation analysis of the G4.5 gene in patients with isolated left ventricular noncompaction. Mol. Genet. Metabol. 77, 319–325.

[7] Kelley, R.I., Cheatham, J.P., Clark, B.J., Nigro, M.A., Powell, B.R., Sherwood, G.W., Sladky, J.T. and Swisher, W.P. (1991) X-linked dilated cardiomyopathy with neutropenia, growth retardation, and 3-methylglutaconic aciduria. J. Pediatr. 119, 738–747.

[8] Mazzocco, M.M.M. and Kelley, R.I. (2001) Preliminary evidence for a cognitive phenotype in Barth syndrome. Am. J. Med. Genet. 102, 372–378.

[9] Ichida, F., Tsubata, S., Bowles, K.R., Haneda, N., Uese, K., Miyawaki, T., Dreyer, W.J., Messina, J., Li, H., Bowles, N.E. and Towbin, J.A. (2001) Novel gene mutation in patients with left ventricular noncompaction or Barth syndrome. Circulation 103, 1256–1263.

[10] Bolhuis, P.A., Hensels, G.W., Hulsebos, T.J.M., Baas, F. and Barth, P.G. (1991) Mapping of the locus for X-linked cardioskeletal myopathy with neutropenia and abnormal mitochondria (Barth syndrome) to Xq28. Am. J. Hum. Genet. 48, 481–485.

[11] Bione, S., D'Adamo, P., Maestrini, E., Gedeon, A.K., Bolhuis, P.A. and Toniolo, D. (1996) A novel X-linked gene, G4.5. is responsible for Barth syndrome. Nature Genet. 12, 385–389.

[12] Bione, S., Tamanini, F., Maestrini, E., Tribioli, C., Poustka, A., Torri, G., Rivella, S. and Toniolo, D. (1993) Transcriptional organization of a 450-kb region of the human X chromosome in Xq28. Proc. Natl. Acad. Sci. USA 90, 10977–10981.

[13] D'Adamo, P., Fassone, L., Gedeon, A., Janssen, E.A., Bione, S., Bolhuis, P.A., Barth, P.G., Wilson, M., Haan, E., Orstavik, K.H., Patton, M.A., Green, A.J., Zammarchi, E., Donati, M.A. and Toniolo, D. (1997) The X-linked gene G4.5 is responsible for different infantile dilated cardiomyopathies. Am. J. Hum. Genet. 61, 862–867.

[14] Bleyl, S.B., Mumford, B.R., Thompson, V., Carey, J.C., Pysher, T.J., Chin, T.K. and Ward, K. (1997) Neonatal, lethal noncompaction of the left ventricular myocardium is allelic with Barth syndrome. Am. J. Hum. Genet. 61, 868–872.

[15] Johnston, J., Kelley, R.I., Feigenbaum, A., Cox, G.F., Iyer, G.S., Funanage, V.L. and Proujansky, R. (1997) Mutation characterization and genotype-phenotype correlation in Barth syndrome. Am. J. Hum. Genet. 61, 1053–1058.

[16] Lu, B., Kelher, M.R., Lee, D.P., Lewin, T.M., Coleman, R.A., Choy, P.C. and Hatch, G.M. (2004) Complex expression pattern of the Barth syndrome gene product tafazzin in human cell lines and murine tissues. Biochem. Cell Biol. 82, 569–576.

[17] Gonzalez, I.L. (2005) Barth syndrome: TAZ gene mutations, mRNAs, and evolution. Am. J. Med. Genet. 134A, 409–414.

[18] Neuwald, A.F. (1997) Barth syndrome may be due to an acyltransferase deficiency. Curr. Biol. 7, R465–R466.

[19] Vreken, P., Valianpour, F., Nijtmans, L.G., Grivell, L.A., Plecko, B., Wanders, R.J.A. and Barth, P.G. (2000) Defective remodeling of cardiolipin and phosphatidylglycerol in Barth syndrome. Biochem. Biophys. Res. Commun. 279, 378–382.

[20] Schlame, M., Rua, D. and Greenberg, M.L. (2000) The biosynthesis and functional role of cardiolipin. Progr. Lipid Res. 39, 257–288.

[21] Schlame, M. and Rustow, B. (1990) Lysocardiolipin formation and reacylation in isolated rat liver mitochondria. Biochem. J. 272, 589–595.
[22] Valianpour, F., Mitsakos, V., Schlemmer, D., Towbin, J.A., Taylor, J.M., Ekert, P.G., Thorburn, D.R., Munnich, A., Wanders, R.J.A., Barth, P.G. and Vaz, F.M. (2005) Monolysocardiolipins accumulate in Barth syndrome but do not lead to enhanced apoptosis. J. Lipid Res. 46, 1182–1195.
[23] Gu, Z., Valianpour, F., Chen, S., Vaz, F.M., Hakkaart, G.A., Wanders, R.J.A. and Greenberg, M.L. (2004) Aberrant cardiolipin metabolism in the yeast taz1 mutant: a model for Barth syndrome. Mol. Microbiol. 51, 149–158.
[24] Schlame, M., Towbin, J.A., Heerdt, P.M., Jehle, R., DiMauro, S. and Blanck, T.J.J. (2002) Deficiency of tetralinoleoyl–cardiolipin in Barth syndrome. Ann. Neurol. 51, 634–637.
[25] Schlame, M., Kelley, R.I., Feigenbaum, A., Towbin, J.A., Heerdt, P.M., Schieble, T., Wanders, R.J.A., DiMauro, S. and Blanck, T.J.J. (2003) Phospholipid abnormalities in children with Barth syndrome. J. Am. Coll. Cardiol. 42, 1994–1999.
[26] Valianpour, F., Wanders, J.A., Barth, P.G., Overmars, H. and van Gennip, A.H. (2002) Quantitative and compositional study of cardiolipin in platelets by electrospray ionization mass spectrometry: application for the identification of Barth syndrome patients. Clin. Chem. 48, 1390–1397.
[27] Valianpour, F., Wanders, R.J.A., Overmars, H., Vreken, P., van Gennip, A.H., Baas, F., Plecko, B., Santer, R., Becker, K. and Barth, P.G. (2002) Cardiolipin deficiency in X-linked cardioskeletal myopathy and neutropenia (Barth syndrome, MIM 302060): A study in cultured skin fibroblasts. J. Pediatr. 141, 729–733.
[28] Kuijpers, T.W., Maianski, N.A., Tool, A.T.J., Becker, K., Plecko, B., Valianpour, F., Wanders, R.J.A., Pereira, R., van Hove, J., Verhoeven, A.J., Roos, D., Baas, F. and Barth, P.G. (2004) Neutrophils in Barth syndrome (BTHS) avidly bind annexin-V in the absence of apoptosis. Blood 103, 3915–3923.
[29] Xu, Y., Sutachan, J.J., Plesken, H., Kelley, R.I. and Schlame, M. (2005) Characterization of lymphoblast mitochondria from patients with Barth syndrome. Lab. Invest. 85, 823–830.
[30] Valianpour, F., Wanders, R.J.A., Overmars, H., Vaz, F.M., Barth, P.G. and van Gennip, A.H. (2003) Linoleic acid supplementation of Barth syndrome fibroblasts restores cardiolipin levels: implications for treatment. J. Lipid Res. 44, 560–566.
[31] Xu, Y., Kelley, R.I., Blanck, T.J.J. and Schlame, M. (2003) Remodeling of cardiolipin by phospholipid transacylation. J. Biol. Chem. 278, 51380–51385.
[32] Vaz, F.M., Houtkooper, R.H., Valianpour, F., Barth, P.G. and Wanders, R.J.A. (2003) Only one splice variant of the human TAZ gene encodes a functional protein with a role in cardiolipin metabolism. J. Biol. Chem. 278, 43089–43094.
[33] Xu, Y., Condell, M., Plesken, H., Edelman-Novemsky, I., Ma, J., Ren, M. and Schlame, M. (in press) A Drosophila model of Barth syndrome. Proc. Natl. Acad. Sci. USA.
[34] Schlame, M., Ren, M., Xu, Y., Greenberg, M.L. and Haller, I. (2005) Molecular symmetry in mitochondrial cardiolipins. Chem. Phys. Lipids 138, 38–49.
[35] Kraffe, E., Soudant, P., Marty, Y., Kervarec, N. and Jehan, P. (2002) Evidence of tetradocosahexaenoic cardiolipin in some marine bivalves. Lipids 37, 507–514.
[36] Powell, G.L. and Jacobus, J. (1974) The nonequivalence of the phosphorus atoms in cardiolipin. Biochemistry 13, 4024–4026.
[37] Lands, W.E.M. (1960) Metabolism of glycerolipids. II. The enzymatic acylation of lysolecithin. J. Biol. Chem. 235, 2233–2237.
[38] Taylor, W.A. and Hatch, G.M. (2003) Purification and characterization of monolysocardiolipin acyltransferase from pig liver mitochondria. J. Biol. Chem. 278, 12716–12721.
[39] Cao, J., Liu, Y., Lockwood, J., Burn, P. and Shi, Y. (2004) A novel cardiolipin-remodeling pathway revealed by a gene encoding an endoplasmic reticulum-associated acyl-CoA:lysocardiolipin acyltransferase (ALCAT1) in mouse. J. Biol. Chem. 279, 31727–31734.
[40] Testet, E., Laroche-Traineau, J., Noubhani, A., Coulon, D., Bunoust, O., Camougrand, N., Manon, S., Lessire, R. and Bessoule, J.-J. (2005) Ypr140wp, 'the yeast tafazzin', displays a mitochondrial lysophosphatidylcholine (lyso-PC) acyltransferase activity related to triacylglycerol and mitochondrial lipid synthesis. Biochem. J. 387, 617–626.
[41] Ma, L., Vaz, F.M., Gu, Z., Wanders, R.J.A. and Greenberg, M.L. (2004) The human TAZ gene complements mitochondrial dysfunction in the yeast taz1Δ mutant. Implications for Barth syndrome. J. Biol. Chem. 279, 44394–44399.
[42] Schlame, M., Shanske, S., Doty, S., Konig, T., Sculco, T., DiMauro, S. and Blanck, T.J.J. (1999) Microanalysis of cardiolipin in small biopsies including skeletal muscle from patients with mitochondrial disease. J. Lipid Res. 40, 1585–1592.
[43] Lange, C., Nett, J.H., Trumpower, B.L. and Hunte, C. (2001) Specific roles of protein–phospholipid interactions in the yeast cytochrome bc_1 complex structure. EMBO J. 20, 6591–6600.
[44] Pebay-Peyroula, E., Dahout-Gonzalez, C., Kahn, R., trezeguet, V., Lauquin, G.J. and Brandolin, G. (2003) Structure of mitochondrial ADP/ATP carrier in complex with carboxyatractyloside. Nature 426, 39–44.
[45] Zhang, M., Mileykovskaya, E. and Dowhan, W. (2002) Gluing the respiratory chain together. Cardiolipin is required for supercomplex formation in the inner mitochondrial membrane. J. Biol. Chem. 277, 43553–43556.
[46] Pfeiffer, K., Gohil, V., Stuart, R.A., Hunte, C., Brandt, U., Greenberg, M.L. and Schagger, H. (2003) Cardiolipin stabilizes respiratory chain supercomplexes. J. Biol. Chem. 278, 52873–52880.
[47] Brandner, K., Mick, D.U., Frazier, A.E., Taylor, R.D., Meisinger, C. and Rehling, P. (2005) Taz1, an outer mitochondrial membrane protein, affects stability and assembly of inner membrane protein complexes: Implications for Barth syndrome. Mol. Biol. Cell 16, 5202–5214.
[48] Schlame, M. and Haldar, D. (1993) Cardiolipin is synthesized on the matrix side of the inner membrane of rat liver mitochondria. J. Biol. Chem. 268, 74–79.
[49] Bissler, J.J., Tsoras, M., Goring, H.H.H., Hug, P., Chuck, G., Tombragel, E., McGraw, C., Schlotman, J., Ralston, M.A. and Hug, G. (2002) Infantile dilated X-linked cardiomyopathy, G4.5 mutations, altered lipids, and ultrastructural malformations of mitochondria in heart, liver, and skeletal muscle. Lab. Invest. 82, 335–344.
[50] Davey, K.M., Parboosingh, J.S., McLeod, D.R., Chan, A., Casey, R., Ferreira, P., Snyder, F.F., Bridge, P.J. and Bernier, F.P. (2006) Mutation of DNAJC19, a human homolog of yeast inner mitochondrial membrane co-chaperones, causes DCMA syndrome, a novel autosomal recessive Barth syndrome-like condition. J. Med. Gen. 43, 385–393.
[51] De Kremer, R.D., Paschini-Capra, A., Bacman, S., Argarana, C., Civallero, G., Kelley, R.I., Guelbert, N., Latini, A., Noher de Halac, I., Giner-Ayala, A., Johnston, J., Proujansky, R., Gonzalez, I., Depetris-Boldini, C., Oller-Ramirez, A., Angaroni, C., Theaux, R.A., Hliba, E. and Juaneda, E. (2001) Barth's syndrome-like disorder: a new phenotype with a maternally inherited A3243G substitution of mitochondrial DNA (MELAS mutation). Am. J. Med. Gen. 99, 83–93.
[52] Vendelin, M., Beraud, N., Guerrero, K., Andrienko, T., Kuznetsov, A.V., Olivares, J., Kay, L. and Saks, V.A. (2005) Mitochondrial regular arrangement in muscle cells: a "crystal-like" pattern. Am. J. Physiol. Cell Physiol. 288, C757–C767.