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Barth syndrome: a genetic ailment with a lipid component and bioenergetic ramifications

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Summary

In eukaryotes, membranes are structural components that are necessary for compartmentalization of function. Membranes consist of a lipid bilayer with a multitude of proteins on or in this sandwich. Nevertheless, membranes are not solely structural in function but also serve as basis for cellular signaling and metabolism. Membranes vary with respect to their lipid composition, protein:lipid ratio, thickness, carbohydrate content, etc., and hence their functions are not necessarily identical in the different compartments. In the mitochondrial inner membrane (mtIM), as in its bacterial ancestor, a special phospholipid is present. Cardiolipin (CL) is a phospholipid consisting of four hydrophobic tails. It is essential for the assembly of the electron transfer system (ETS) and its components, and hence CL is required for efficient mitochondrial bioenergetics. Mutations in CL remodeling enzyme encoded by the *TAFAZZIN* gene are associated with a syndrome first identified by Dutch scientist Peter Barth, hence the name Barth Syndrome. Here, we review recent research on this devastating syndrome focusing on CL biosynthesis and remodeling and relationship between the phospholipid component and mitochondrial bioenergetics.

1. Definition

Barth syndrome (BTHS) is a rare X-linked inherited disease that mainly affects males. It is caused by different mutations in the *TAFAZZIN* (*TAZ*) gene (Figure 1) [1]. BTHS was first described in 1983 by Dr. Peter Barth, a pediatric neurologist, who noticed a high infant mortality rate among males in a large pedigree of a family in his native the Netherlands. The deaths were linked to heart failure or sepsis [2]. The condition showed an X-linked recessive inheritance pattern, and was primarily characterized by dilated cardiomyopathy, skeletal myopathy, and neutropenia [2-4]. Barth was interested in pursuing the underlying cause of this disease and he observed abnormalities in the electron transfer system (ETS) in a patient's sample [2]. This was consistent with a previous discovery of an X-linked case of cardiomyopathy by Neustein in 1979, who also noticed mitochondrial abnormalities [5]. In 1991, Richard Kelley illustrated that organic aciduria, especially 3-methylglutaconic aciduria, is another feature found in individuals with this syndrome [3]. The prevalence of BTHS has been estimated to be 1 in 300 000–400 000 births. However, recent studies approximate the incidence to be around 1 case per million males. BTHS manifests mainly in infancy, as 90 % of patients with BTHS show symptoms of cardiomyopathy and neutropenia at less than 1 year old. The diagnosis of BTHS can be challenging, as 50 % of individuals are diagnosed after 1 year of age [6].

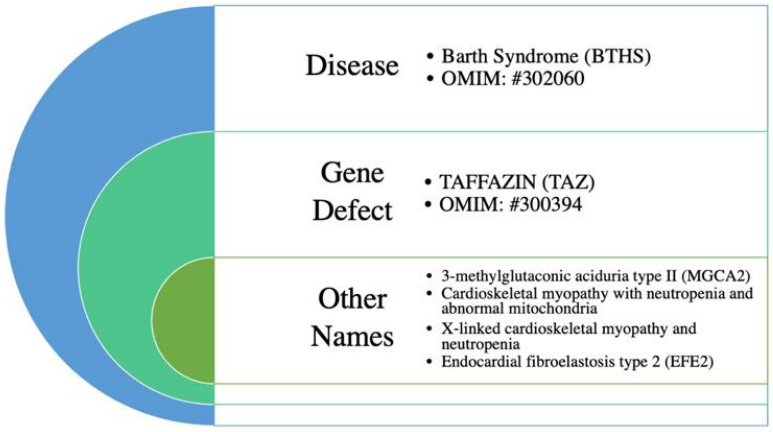

Figure 1. The disease card. Barth syndrome (BTHS) and its other used names, defective gene and Online Mendelian Inheritance in Man (OMIM) identification numbers.

2. Etiology

The primary cause of Barth Syndrome is a genetic mutation in the *TAZ* gene, which is located in the long *q* arm of chromosome X, most specifically in the Xq28 region [7, 8]. The *TAZ* gene spans 11 kbp and consists of 11 exons with a highly conserved sequence; the first two exons are non-coding [1, 7]. Over 160 mutations have been detected and identified in all different exons of the *TAZ* gene [9]. The majority of these are missense mutations and small insertion-deletion mutations. However, a small fraction of patients exhibited large exon deletions, and even in one case, a whole gene deletion was reported [4, 8].

Barth Syndrome follows an X-linked recessive inheritance pattern. According to the Barth Syndrome Foundation and data collected by the human *TAZ* gene mutation and variation database [10], roughly 13 % of males carry *de novo* mutations, which were not

identified in the maternal DNA of somatic cells [4]. However, gonadal mosaicism has been recorded, which raises the likelihood that unaffected mothers who do not carry any mutations in the TAZ gene in their somatic DNA would pass the mutation through gametes that contain a defective gene. It is still possible for females to show symptoms of BTHS [4, 8]. This was recorded in a female who had two different defective genes, the first had a large deletion of exons 1-5, and the second was a ring form with a large deletion of the long arm that included the Xq28 region of the chromosome. Skewed X-inactivation can cause females to show symptoms of BTHS with a variation in severity [4]. It has been suggested that a post-inactivation selection mechanism might happen causing ETS abnormalities or other damaging effects in different cell types [4, 8].

TAZ gene encodes for Tafazzin protein which is a phospholipid acyltransferase [11] required for the remodeling of cardiolipin (CL) [12]. CL (diphosphatidylglycerol) is a dimeric phospholipid (Figure 2) that is highly abundant in the mitochondrial inner membrane (mtIM) [13]. In fact, CL is the only phospholipid specific to mitochondria, making up about 15–20 % of the total phospholipids in the mtIM [13]. It assumes essential roles in the structure, function and physiology of mitochondria. It is implicated in mitochondrial dynamics [14-16], autophagy [17], mitophagy [18], apoptosis [19], mitochondrial DNA replication [20] and mitochondrial bioenergetics and metabolism [21-23]. Moreover, CL is required for cristae organization and biogenesis [24], as well as for lipid-protein interaction particularly with proteins involved in oxidative phosphorylation such as respiratory Complexes I, III, IV, and ATP synthase [25].

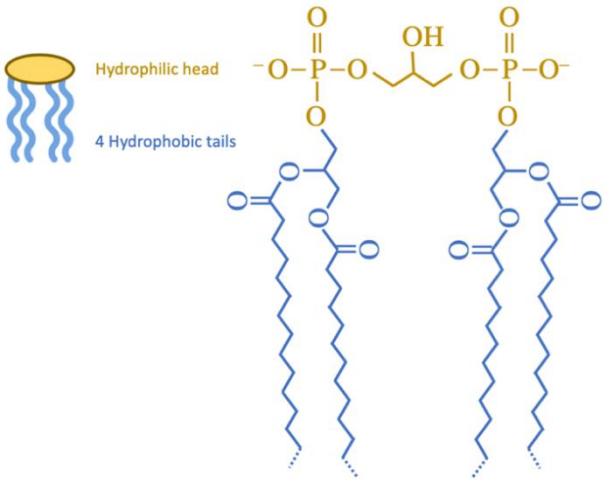

Figure 2. Structure of CL. A cartoon (left) and molecular (right) structures of CL show a wide hydrophilic head composed of two phosphates and four hydrophobic tails with varying chain lengths (dotted bonds). The structure is effectively a diphosphatidylglycerol.

2.1. Properties and biosynthesis of CL

CL is a double phosphatide linked to a glycerol moiety (Figure 2). Depending on the cell and tissue types, CL may contain several acyl chain configurations [6]. For instance, CL with four linoleoyl species (L_4-CL or tetra linoleoyl CL) is normally abundant in highly oxidative tissues such as cardiac and skeletal muscles accounting for up to 70-80 % of total CL [4].

The biosynthesis of CL (Figure 3) is exclusively located to the mitochondria without the involvement of the endoplasmic reticulum. This multistep synthesis starts in the mtIM after the import of phosphatidic acid (PA) from the endoplasmic reticulum. The enzymatic

activation of PA produces cytidine diphosphate-diacylglycerol (CDP-DAG), in a reaction catalyzed by CDP-DAG synthase (CDS). CDP-DAG is then converted to phosphatidylglycerol phosphate (PGP) by condensing with glycerol 3-phosphate (Gp). This step, which is catalyzed by PGP synthase (PGPS), is the committed step in synthesizing CL. Phosphatidylglycerol phosphate phosphatase (PGPP) then dephosphorylates PGP producing phosphatidylglycerol (PG), which ultimately condenses with another CDP-DAG molecule via CL synthase (CLS), a protein found in the inner leaflet of the mtIM facing the matrix, generating nascent (premature) CL [26, 27].

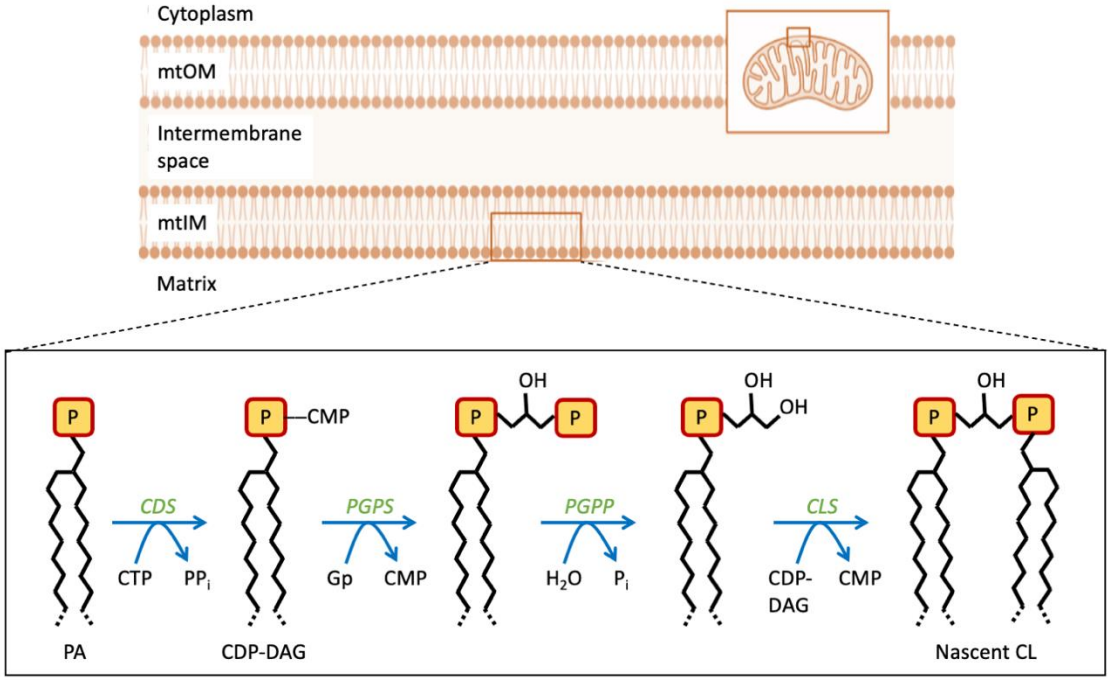

Figure 3. *De novo* biosynthesis of CL. The pathway of CL generation occurs in the mitochondrial inner membrane facing the mitochondrial matrix where a sequence of four enzymes converts phosphatidic acid to nascent CL molecule. Note that the tails of CL are arbitrary and do not reflect the actual length of the acyl chains which vary. CDS, CDP-DAG synthase; CLS, CL synthase; CMP, cytidine monophosphate; Gp, glycerol 3-phosphate; PGPP, phosphatidylglycerol phosphate phosphatase; PGPS, phosphatidylglycerol phosphate synthase; P_i, inorganic phosphate; mtIM, mitochondrial inner membrane; mtOM, mitochondrial outer membrane.

Nascent cardiolipin is then remodeled by exchanging its fatty acyl moieties (Figure 4). Remodeling (Figure 4) starts by the iacylation of one acyl group by several phospholipases of the PLA_2 family [28, 29] producing monolysocardiolipin (MLCL). Tafazzin is a coenzyme A-independent acyltransferase that reacylates MLCL to form the mature CL molecule [30, 31]. It is noteworthy that Tafazzin is not the only CL remodeling enzyme as other coenzyme A-dependent acyltransferases can also acylate MLCL [32]. The addition of a fourth acyl group to MLCL is catalyzed by two acyltransferases (MLCLAT1 and ALCAT1) to produce the remodeled, mature L_4-CL with four acyl groups. Disruption of CL remodeling can result in transforming MLCL into dilysocardiolipin (DLCL) by PLA_2 followed by the degradation of CL [26]. Mutations in the *TAZ* gene results in a reduction in the formation of mature forms of CL such as L_4-CL and an increase in the intermediate

species with different acyl compositions (MLCL) [33]. This disrupts and increases the ratio of MLCL to L_4-CL [4, 8]. In fact, analysis of L_4-CL content in fibroblasts is a specific biochemical approach to detect this disorder [6]. In BTHS, MLCL accumulates due to impaired Tafazzin activity, which leads to abnormal mitochondrial structure with inefficient oxidative phosphorylation [22, 34-36]. Interestingly, research on *Saccharomyces cerevisiae* implies that CL remodeling does not alter mitochondrial oxidative phosphorylation nor mitochondrial morphology. As Tafazzin lacks fatty acyl chain specificity, the only defining factor for acyl chain composition is the lipids of the surrounding environment, which makes CL remodeling tissue specific. The results even suggest that there is no difference in functionality between remodeled and unremodeled CL, and that using a PLA_2 inhibitor such as bromoenol lactone can partially correct the ratio between MLCL and CL [37].

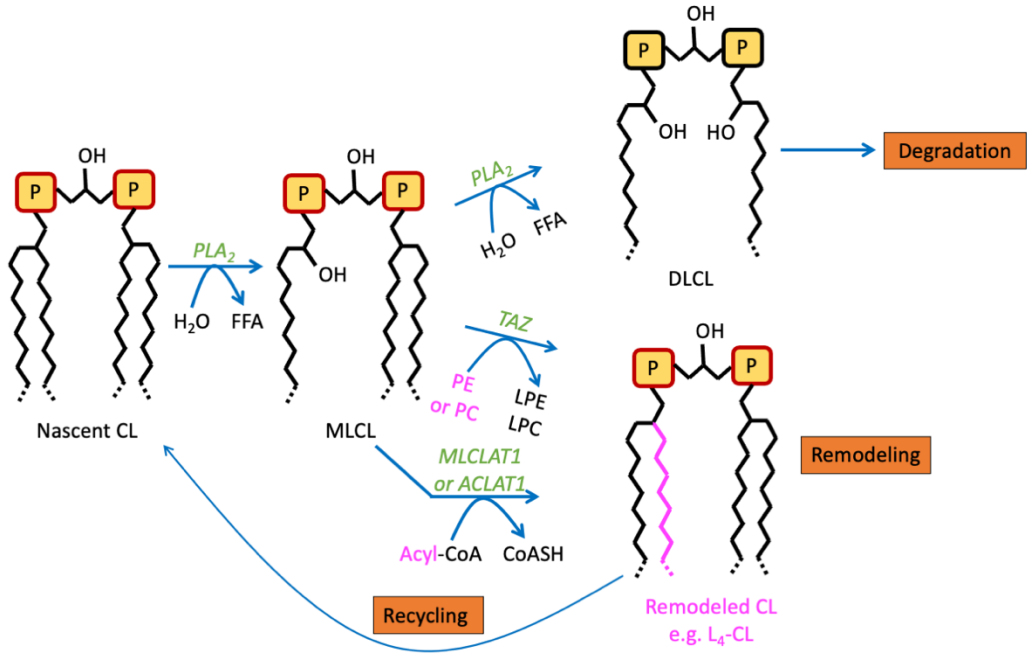

Figure 4. Remodeling of CL. Nascent CL is remodeled by the removal of its fatty acyl chains by phospholipase 2A (PLA_2) and reinsertion of new fatty acyl moieties by different acylating enzymes including Tafazzin, to produce L_4-CL (remodeling process). Lyso-CL that is generated after the action of PLA_2 and left unremodeled is later degraded (degradation process). Remodeled CL can also be recycled back to the original nascent CL structure (Recycling process). note that the tails of CL are arbitrary and do not reflect the actual length or unsaturation of the acyl chains which vary. ACLAT1, Acyl-CoA:lysocardiolipin acyltransferase 1; FFA, free fatty acid; L_4-CL or tetra linoleoyl CL; LPC, lysophosphatidylcholine; LPE, lysophosphatidylethanolamine; MLCL, monolyso-CL; MLCLAT1, MLCL acyltransferase 1; PLA_2, phospholipase A2; TAZ, Tafazzin.

2.2. CL and bioenergetics

Respiratory complexes reside in the mtIM and carry electrons from NADH or succinate ultimately to molecular oxygen, while pumping protons in the process. Reentry of protons down their concentration gradient results in a concomitant generation of ATP via ATP synthase. CL is both highly acidic and hydrophobic enabling it to interact favorably with the respiratory complexes embedded in the mtIM. Such an interaction is required for the optimal function of these proteins [38-40]. CL has been shown to interact with all components of the ETS. Indeed, specific binding sites for CL were observed in Complexes I, III and IV, which are required for the electron transfer from NADH to oxygen [41-43]. Other *in vitro* studies have demonstrated strict dependence of respiratory Complex IV and ATP synthase on CL [44, 45]. Multiple molecules of CL were present in Complexes III and IV and the removal of these molecules led to the dissociation of the subunits and the loss of activity, indicating an essential role of CL in maintenance of structure and function of respiratory complexes [41]. Using molecular dynamics simulation and resolving of the crystal structure, CL was shown to spontaneously locate near the catalytic site of Complex III [46]. CL is found buried in the crevices of integral membrane proteins of the ETS, between the transmembrane helices [43]. According to ultrastructural data one or more CL molecules associate with each complex (Table 1). Those CL molecules are thought to glue complexes together and are required for their full functionality, including proton translocation [41, 42].

Table 1. CL molecules in the solved crystal or cryo-EM structures of the respiratory complexes.

Complex	Species	CL molecules	Refs.
CI (NADH dehydrogenase)	ovine heart	4	[47]
CII (succinate dehydrogenase)	*E. coli*	1	[48]
CIII (cytochrome *c* oxidoreductase)	*S. cerevisiae*	1	[42, 49]
CIV (cytochrome *c* oxidase)	bovine heart	2	[50]

In vivo, respiratory complexes are rarely present as represented in biochemistry books, as individual entities; they are organized into supercomplexes termed respirasomes [51-56]. There are multiple conformations and compositions of respirasomes depending on the origin of mitochondria among other things [56, 57]. The main function of respirasomes was initially thought to increase substrate channeling and efficiency of electron transfer. However, recent research found that the substrate binding sites are far from each other, and that the term “channeling” is not very accurate since an actual tunnel running through the supercomplex is not present. Nevertheless, respirasomes (the dynamic interaction between Complexes I, III, and IV) are essential for the stability of the cristae, in addition to minimizing the distances that the substrates, ubiquinone and cytochrome *c* must diffuse between the complexes. [58-60]. There seems to be an increasing consensus that the major benefit of supercomplexes is to minimize electron leak to oxygen (i.e. superoxide formation), which is consistent with mitochondrial oxidative stress being a primary component of BTHS pathophysiology and Tafazzin/CL deficiency [61-63]. CL has been found to be instrumental in the formation

and proper functioning of these supercomplexes [39, 64-66]. The tight binding of CL to Complex IV is important for the formation of Complex III and Complex IV tetramers [65]. Moreover, CL was demonstrated to be involved in the supramolecular organization of ATP synthase, carnitine palmitoyl-transferase, creatine phosphokinase, and other mtIM proteins [26, 67]. Additionally, CL was also shown to be required for the optimal function and stabilization of many different other enzymes and proteins residing in the mtIM that have important functions in mitochondrial bioenergetics, including adenine nucleotide translocase [68], the mitochondrial phosphate carrier [69], di- and tricarboxylate transporters [70, 71], as well as other proteins [43]. CL is therefore essential for the assembly of higher order mitochondrial complexes and supercomplexes.

Not only is CL involved as a structural component in supercomplexes, but also seems to interact actively in their function. Since the headgroup of CL is fully titratable, it can act as a proton trap for the proteins involved in oxidative phosphorylation. In other words, CL can be used as a reservoir for protons to be pumped by Complexes I, II, and IV, and for supplying protons for ATP synthase [72-74]. Data suggest that using proton trapping CL may aggregate respiratory complexes and restrict their pumped protons within its headgroup to be translocated directly through ATP synthase without much changing the bulk pH [72]. Also, data indicate that cytochrome *c* is adsorbed on CL-containing membranes owing to its positive charge and this helps in the transfer of electrons through the ETS [75]. Interestingly, CL can also bind to Complex I inducing global conformational changes, which modulate the accessibility of its substrate, ubiquinone. This links the structural aspects of binding CL within the membrane with functionality of Complex I [76].

As a specific lipid in the mtIM, CL is involved in cristae structure formation [77]. Indeed, proton trapping by CL was used to explain CL involvement in cristae formation. In a study on giant unilamellar vesicles, proton trapping by CL in the intermembrane space resulted in a charge neutralization in the outer leaflet of the mtIM and therefore to area reduction when compared to the inner leaflet, leading to the creation of cristae-like invaginations [78].

In all, the functions of CL in mitochondria are diverse and multifaceted, rendering a pivotal role for this unusual lipid in mitochondrial bioenergetics which depend strongly on CL [41, 46, 79]. Mutations in the *TAZ* gene can result in decreased mitochondrial enzymatic activity, especially the respiration rate, resulting in the formation of reactive oxygen species (ROS) due to the inability to transfer electrons through the ETS [61], thus lowering the optimum ATP production. This decrease in ATP synthesis is counteracted and compensated by increased mitochondrial content [19] and hypertrophic cardiomyopathy [80]. The high ROS levels in cardiomyocytes affect metabolism, sarcomerogenesis and contractile activity in muscles [63]. High ROS levels result in the activation of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) which in turn phosphorylates and activates ryanodine receptor 2 (RyR2), with a concomitant release of Ca^{2+} from the sarcoplasmic reticulum into the cytoplasm. The constant abnormal activation of CaMKII and Ca^{2+} mishandling result in elevating Ca^{2+} in *TAZ* mutant cardiomyocytes, which in turn impairs the relaxation of the heart and can lead to cardiac arrhythmias [62].

It is also worth noting that the precise impact of altered CL composition and Tafazzin deficiency on bioenergetics is still an area of active investigation and appears to be more complex than overt ETS dysfunction [37, 81]. For instance, mitochondria from *TAZ* knockdown (TAZ^{KD}) mice were found to have 40-60 % lower fatty acid and pyruvate oxidation capacity than wild type mitochondria, which was counteracted by an increase in glutamate oxidation rates. The availability of coenzyme A was also found to be impaired and limited in TAZ^{KD} mitochondria, and exogenous CoA increased pyruvate and palmitoylcarnitine oxidation capacities, suggesting that there is dysregulation in the intermediary metabolism of CoA rather than a defect in ETS [37]. In summary, studying the role(s) of different CL species and the enzymes responsible for making them on mitochondrial bioenergetics is still active and the results are being constantly debated, making this an active field of research.

3. Clinical manifestations

BTHS is a devastating disease which manifests in several organs and organ systems. The following table (Table 2) represents a summary of clinical manifestations, both major and minor, of this disease in a multitude of human systems.

Table 2. Clinical manifestations of Barth syndrome [4].

Systems	Major (Signs/Symptoms)	Minor (Signs/Symptoms)
cardiovascular	• dilated Cardiomyopathy • left ventricular non-compaction • prolonged corrected QT interval	• endocardial fibroelastosis • ventricular arrhythmia/sudden cardiac death • undulating cardiomyopathy • hypertrophic cardiomyopathy (rarely)
hematological & infectious	• neutropenia • recurrent aphthous ulcers & sore gums • perianal dermatitis	• recurrent bacterial infections • septicemia
neuromuscular	• delayed motor milestones • exercise intolerance • abnormal fatigability • proximal myopathy	
neurological	• mild learning disabilities • attention deficits	• strokes (cardiac embolism)
endocrine and metabolic	• 3-methylglutaconic aciduria • constitutional bone delay with delayed bone age • delayed puberty	• hypercholesterolemia • hypoglycemia • lactic acidosis (often accompanies cardiac failure) • osteopenia
dysmorphic features	• deep-set eyes • large ears (older boys) • full cheeks	

4. Diagnosis

The clinical diagnosis of BTHS had been based on the triad of neutropenia, cardiomyopathy, and high levels of 3-methylglutaconic acid (3-MGA) in urine and plasma. Cardiomyopathy is present in approximately 70 % of patients with BTHS, and many BTHS patients have a 5– to 20–fold increase in 3-MGA levels. However, some BTHS patients with cardiomyopathy were not diagnosed with BTHS even though they exhibited other clinical manifestations such as muscle weakness and growth delay, because these patients had normal 3-MGA levels in urine. Therefore, measuring 3-MGA as a tool for diagnosing BTHS is insufficient.

Measurement of the ration of MLCL to CL ratio in dried blood spot specimens is a better tool for the diagnosis of BTHS. It is critical to measure the ratio because many BTHS patients have normal levels of CL but an elevated MLCL:CL ratio. Thus, measuring the MLCL:CL ratio is considered a sensitive and 100 % specific test for the diagnosis of BTHS. Once elevated MLCL:CL ratio has been detected, sequencing the *TAZ* gene and detecting any mutations is considered as a final confirmatory test for the diagnosis of BTHS [36].

5. Disease management

Many BTHS patients show responsiveness to drugs that are usually used to manage standard heart failure, including beta blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, vasodilators, anticoagulants, digoxin and diuretics [82]. It is recommended to observe BTHS patients for any signs of ventricular arrhythmia or other symptoms such as syncope. Such findings would require additional testing and new treatment plans to manage the condition pharmacologically with antiarrhythmic medication (Class I – Class V). In some cases, the placement of an implantable cardioverter-defibrillator should be considered [36].

Cardiac transplantation is another treatment protocol that has shown good results in general, even though it carries high pre-operative risks. In some boys with severe cardiac dysfunction, left ventricular assist devices have been used to aid them until a heart donor can be found. Using an assist device has major risks including infection caused by neutropenia, and strokes caused by clots forming in the chambers of the heart [4].

Neutropenia is usually treated with subcutaneous granulocyte colony-stimulating factor (G-CSF). The dose and frequency of the G-CSF injection varies depending on the severity of neutropenia, drug responses, and infections. The goal of using G-CSF is to increase the average count of neutrophils rather than cure neutropenia or normalize the neutrophil count. This treatment approach has resulted in noticeable improvements, as it reduces bacterial infections, lethargy, and mouth ulcers [4]. Neutropenia can also be managed with prophylactic antibiotics along with the G-CSF injections, which lower the risk of serious infections [83].

Oral supplements are also given to BTHS patients as an additional approach to manage the disease and its symptoms. Some patients have low levels of mineral ions such as potassium and magnesium, as well as low levels of vitamins. This creates a deficiency that can be improved by multivitamins and minerals supplements. Arginine and amino

acid supplementation can also be given to the patients to enhance their growth. Cornstarch is an important nutritional supplement to prevent hypoglycemia and when given before bedtime, it slows the breakdown of protein in the muscle during the night. Physiotherapy and resistance exercise training are two ways to improve the function of cardiac muscle in addition to skeletal muscle [36].

Many promising experimental therapeutic strategies to treat or even cure Barth syndrome are in progress, including lipid replacement therapy, which is the use of oral supplements containing cellular phospholipids and antioxidants to treat various lipid deficiencies and syndromes [84]. These oral supplements are protected against oxidative damage during storage, ingestion, digestion, and absorption by the introduction of antioxidants, and they are protected from chemical enzymatic activity and bile by using protective molecules, such as fructooligosaccharides, to bind to phospholipid micelles non-covalently [36, 85, 86]. In skin fibroblasts derived from BTHS patients, the addition of linoleic acid to the growth medium showed increased levels of L_4-CL indicating a potential therapeutic effect of linoleic acid supplementation [87]. In another study, the administration of exogenous CL using CL nanodisks on *TAZ*^{KD} HL60 cells showed increased intracellular CL levels [88]. However, the administration of CL nanodisks into *TAZ*^{KD} mice with intraperitoneal injections did not change or improve their CL profile [89].

Elamipretide, also known as Bendavia [90], is a synthetic lipophilic tetrapeptide experimental drug with the potential to treat Barth Syndrome. Elamipretide has the ability to penetrate cellular and mitochondrial membranes by diffusion where it gets associated with ionic phospholipids, especially cardiolipin in the mtIM. This peptide-lipid interaction stabilizes ETS complexes and results in increased ATP synthesis [91]. There are only a few clinical trials to test the efficacy and tolerability of elamipretide. The initial results are promising, as they showed actual improvement in ATP synthesis and positive effects on the left ventricular volumes [92]. However, further studies and tests are required to ensure the safety of this product on the long term. Moreover, *TAZ* gene replacement therapy, mitochondria-targeted antioxidants, induced pluripotent stem cells [7] have been used as possible treatment strategies.

TAZ gene replacement therapy is another promising therapeutic strategy. In *TAZ*^{KD} mice, three different AAV9 vectors were tested and compared on BTHS mouse neonates to determine the optimal promoter for the expression of *TAZ*, and to investigate the effects of this treatment on the subjects of the study. The three promoters were found to improve muscle strength, cardiac function, ETS activity, and mitochondrial structure indicating a viable potential therapeutic avenue for human patients [93].

Since mitochondrial ROS production is increased in BTHS patients, the use of a mitochondrially-targeted antioxidant, Mito-TEMPO, was examined in *TAZ*^{KD} cardiomyocytes. Cells treated with this antioxidant showed a decrease in the production of ROS, and increased production of ATP indicating amelioration of the phenotype [61].

In addition to the pharmacological and surgical treatment of the disease, a team of different specialists consisting of psychologists, speech and language therapists, educational support workers, as well as others, are needed for achieving a top-level management of the disease [1].

6. Conclusions and future directions

Barth syndrome is a rare X-linked disease where the *TAZ* gene is mutated rendering the protein product, Tafazzin, nonfunctional. Tafazzin is responsible for the CL remodeling, specific to the mtIM. CL was found to be associated with different mitochondrial proteins, especially those involved in oxidative phosphorylation and electron transfer pathway complexes. CL stabilizes these complexes and proteins which enhances ATP production and maintains the whole mitochondrial membrane. Barth syndrome patients struggle from cardiomyopathy, myopathy, neutropenia, and other symptoms as a result of this mutation. Currently a known cure or a complete treatment for Barth syndrome is lacking. However, multiple strides have been made in disease management using varying techniques and treatment plans. Clinical studies and basic mitochondrial research are ongoing to find a way to cure Barth syndrome using novel drugs, gene therapy, lipid replacement therapy, and others.

Abbreviations

3-MGA	3-methylglutaconic acid
BTHS	Barth syndrome
CaMKII	Ca^{2+}/calmodulin-dependent protein kinase II
CDP-DAG	cytidine diphosphate-diacylglycerol
CLS	CL synthase
CDS	CDP-DAG synthase
CL	cardiolipin
DLCL	dilyso-CL
ETS	electron transfer system
FFA	free fatty acid
Gp	glycerol 3-phosphate
G-CSF	granulocyte colony-stimulating factor
L_4-CL	tetra linoleoyl CL
LPC	lysophosphatidylcholine
LPE	lysophosphatidylethanolamine
MLCL	monolyso-CL
mtIM	mitochondrial inner membrane
PA	phosphatidic acid
PC	phosphatidylcholine
PE	phosphatidylethanolamine
PGP	phosphatidylglycerol phosphate
PFPP	phosphatidylglycerol phosphate phosphatase
PFPS	phosphatidylglycerol phosphate synthase
PLA_2	phospholipase A2
ROS	reactive oxygen species
RyR2	ryanodine receptor 2
TAZ	*TAFAZZIN* gene
TAZ^{KD}	*TAFAZZIN* gene knockdown

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