Tafazzin in Mitochondrial Function, Development and Disease

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Tafazzin, an enzyme associated with the rare inherited x-linked disorder Barth Syndrome, is a nuclear encoded mitochondrial transacylase that is highly conserved across multiple species and plays an important role in mitochondrial function.

Keywords: Tafazzin ; mitochondria ; Barth syndrome ; rare X-linked genetic disease

1. Introduction

Mitochondria are ubiquitous essential cellular organelles that control mitochondrial respiration and adenosine triphosphate (ATP) generation through the metabolism of key substrates, thereby regulating cellular energy balance. Mitochondria are also unique among organelles in that they contain their own genome and translational apparatus that allows synthesis of a small set of essential proteins specific to the mitochondria. The mitochondrial proteome, however, is complex and includes many proteins that are encoded in the nuclear genome, synthesized in the cytoplasm and transported across the mitochondrial outer membrane, where they are sorted and transported to either the outer membrane, intermembrane space, inner membrane or mitochondrial matrix. Mitochondrial dysfunction is a common feature of many medical disorders, while primary mitochondrial disorders invariably affect multiple organ systems simultaneously. The role of mitochondria in development is poorly understood.

2. *Tafazzin* Is a Regulator of Mitochondrial Structure and Function

Ultrastructural abnormalities in mitochondria were noted in the original case report describing BTHS [1], and have been associated with defective mitochondrial Complex III function [2], but the nature of BTHS-mediated mitochondrial dysfunction has been complex and variable. In yeast, early reports indicated a defect in energy coupling and membrane stability [3], while studies in patient-derived lymphoblasts indicated abnormal proliferation, altered membrane potential and normal ATP formation, suggesting partial uncoupling and compensatory expansion of the mitochondrial compartment [4]. Changes in ultrastructure are also variable dependent upon model system and organ analyzed, and may be more prominent in differentiated rather than embryonic tissues. The effect has been hypothesized to be greater in mitochondria with higher cristae stacking density [5] and as heart mitochondria have twice the diameter and higher percentages of lamellated cristae (cristae increase surface area and allow for inner membrane cardiolipin assembly) than other organs, this may help explain why BTHS patients exhibit predominantly cardiovascular defects [6] Abnormal cardiolipin remodeling due to *Tafazzin* deficiency leads to destabilization of mitochondrial inner membrane complexes in yeast [7], disrupts respiratory super complex formation in patient lymphoblasts [8] and also interferes with super complex formation in human iPS cells [9]. Interestingly, despite alterations in cardiolipin profiles and disruption in mitochondrial respiratory super complexes, metabolic flux through the TCA cycle was not disrupted in patient skin fibroblasts [10]. In Drosophila flight muscles, the density of the F_1F_0 ATP synthase dimers in the inner mitochondrial membrane was reduced at high curvature areas and dimer rows were less extended and more scattered [11]. In mice containing a doxycycline inducible shRNA that knocks down *Tafazzin* expression, mitochondria developed a wide spectrum of mitochondrial abnormalities [12][13][14]. Both the morphological defects (i.e., mixture of swollen, honeycomb and widened/collapsed/absent cristae) and numbers of mitochondria are variable, as there are reports of increased, decreased and unchanged mitochondrial numbers, depending upon which stage, which organs and doxycycline concentration used. An extensive bioenergetic and lipidomic characterization of these mice revealed differential substrate utilization, and reduction in Complex III and V activities [15]. An independent assessment of mitochondrial function in the same line of mice and in human iPS cell-derived cardiomyocytes (iPSC-CMs) from BTHS patients indicated a tissue-specific reduction in Complex II succinate dehydrogenase activity [16]. A separate BTHS iPSC-CM study implicated a reduction in F_1F_0 ATP synthase specific activity and overall ATP reduction in cells cultured in galactose, to limit ATP generation from glycolysis [17]. Interestingly, basal

oxygen consumption rate is increased in BTHS iPSC-CMs, likely due to compensatory mechanisms, but total respiratory capacity is decreased [16][17]. *Tafazzin*-deficient mitochondria have been noted to generate increased ROS in yeast [18], in *Tafazzin* knockdown mice [16] and in human iPSC-CMs [17].

3. The Role of *Tafazzin* in Cellular Differentiation and Development

In vitro studies on cultured cells have suggested a role for *Tafazzin* in regulation of differentiation. BTHS iPSC-derived cardiomyocytes show irregular sarcomere organization but no difference in differentiation efficiency when cultured for 60 days [16] or when cultured on an un-patterned substrate [17]. This defect in sarcomere organization was only seen with a *Tafazzin* frameshift variant (c.517delG) but not a missense variant (c.328T > C), however, engineered tissue constructs generated from iPSC-CMs containing each variant demonstrated contractile dysfunction [17]. Targeted disruption of the endogenous *Tafazzin* locus in a C2C12 mouse myoblast cell line led to altered differentiation into myotubes [19].

The effect of *Tafazzin* loss of function on *in vivo* organismal development has been studied in a variety of model organisms. In zebrafish embryos, at 10 h post fertilization (hpf), *Tafazzin* is expressed ubiquitously with strongest expression in the head area, at 24 hpf is expressed highly in the head, eye and tail and by 30 hpf, becomes more restricted to the head, heart, eyes and region next to the yolk corresponding to endodermal tissue. At 51 hpf, *Tafazzin* mRNA becomes highly restricted to the zebrafish heart, although this intriguing tissue specificity has yet to be confirmed in mammals or in later mature hearts. Morpholino antisense oligonucleotide-directed knockdown of *Tafazzin* mRNA led to severe developmental abnormalities in a dose-dependent fashion. The most severely affected structures were in the heart and tail, with some eye abnormalities observed. Morphant embryos at 51 hpf developed marked edema with large pericardial effusions associated with dysmorphic, slowly beating hearts. The heart tube failed to loop, showing a profound effect on heart development. Co-injection of zebrafish *Tafazzin* mRNA containing a variant analogous to the human mutation G197R rescued bradycardia and tail abnormalities but continue to demonstrate heart failure [20].

In Drosophila, generation of *Tafazzin* null mutants by imprecise P-element excision upstream of the start codon in exon 1 was associated with abnormal cardiolipin remodeling and abnormal mitochondrial morphology as described above. Lifespan was unchanged, and heart rate was unchanged in pupae and locomotor activity was normal in larvae. Quantitative measurement of motor weakness in adult flies demonstrated reduced ability to climb against gravity [21]. The relatively mild effect of *Tafazzin* deletion on organism development in Drosophila is likely a reflection of the significant differences between the circulatory systems of insects and vertebrates.

In mice, an understanding of the role of *Tafazzin*, cardiolipin and mitochondria in organism development are each incompletely understood. For instance, it is unknown when *Tafazzin* mRNA or protein is initially present within mouse embryos, if there is differential expression levels and when mature cardiolipin is first detectable and within which organs. Similarly, although it is known that mouse embryonic heartbeat starts at five somites (around embryonic day E8) and that blood flow is initiated at seven somites (around embryonic day E8.25), it is unknown when and where the first mitochondria are developed [22][23]. Moreover, as the embryonic heart is thought to initially rely solely on anaerobic glycolysis prior to placental development establishing circulation and rising oxygen levels, it is thought that mitochondria (and hence *Tafazzin* function) are presumed to be required as the in utero heart transitions to using subsequent aerobic respiration and an increasing reliance upon mitochondrially generated ATP [24][25][26][27]. Until recently, generation of fertile chimeras containing knockout alleles have been unsuccessful, most likely due to profound effects on spermatogenesis [28]. Knockdown induced via doxycyline from the start of gestation resulted in prenatal loss from E12.5–13.5, associated with myocardial thinning, hypertrabeculation, noncompaction and defective ventricular septation. Diastolic dysfunction was also noted. The effect on cardiovascular morphogenesis was recapitulated when knockdown was induced at E7.5 and at E10.5 but not at E13.5 or E14.5, suggesting an important developmental window for *Tafazzin* function. *Tafazzin* knockdown was associated with reduced compact zone proliferation but no apoptosis. Some embryos survived gestation, but none survived to adulthood [14]. Mitochondrial and cardiolipin abnormalities were as described above. This report differed from the other mouse studies by administering doxycycline at a higher dose in the drinking water compared to the other studies that used doxycycline containing chow [12][13], which may explain why the same strain of mice receiving doxycycline in chow showed predominantly an adult phenotype. Doxycycline, however, is known to have inhibitory effects on mitochondrial morphology/function itself [29] and continual administration of doxycycline to mice has been shown to adversely affect both cardiac and neutrophil function [30]. Thus, it is challenging to discern from this model whether the effects observed are as a direct result of the reduction of *Tafazzin* function, or a consequence of doxycycline exposure on the mitochondria, or even a combination of both. Another limitation of this model is that it relies on reduced expression of a normal *Tafazzin* gene rather than expression of pathogenic *Tafazzin* variants seen in patients. At present it is not clear whether loss of *Tafazzin* globally or specifically in the developing heart (or specific heart lineages)

is responsible for the developmental and adult cardiac phenotypes observed. A recently developed *Tafazzin* conditional allele mouse line has enabled the study of both tissue specific and global deletion of *Tafazzin* [31]. Systemic deletion of *Tafazzin* in mice resulted in significant embryonic and perinatal lethality, while late embryonic deletion specifically in the heart resulted in adult onset dilated cardiomyopathy without any evidence of cardiac myocyte cell hypertrophy [32]. Systemic deletion also revealed that male *Tafazzin* knockout mice are sterile, as global loss inhibited germ cell meiosis as demonstrated by the reduced abundance of round spermatids and the near absence of elongated spermatids [31]. Although BTHS is thought to preferentially affect males, this result was unexpected and highlights the usefulness of transgenic mice approaches, as male infertility was not usually associated with BTHS. Further analysis of the embryonic phenotype or the tissue-specific contribution of *Tafazzin* to embryonic development using hematopoietic, testis, skeletal or early cardiac organ-restricted and lineage-specific deletion strategies has not yet been done, but is more than likely to be highly informative.

4. The Role of *Tafazzin* in Barth Syndrome, Non-Inherited Diseases and Potential Therapies in Development

The myriad of clinical features of BTHS have been well described [33][34]. The contribution of *Tafazzin* to mitochondrial dysfunction and subsequent muscle differentiation and dysfunction is easily understood given the enrichment of mitochondria in striated muscle tissue and the heightened energetic demands of muscle contraction. The contribution to left ventricular noncompaction can also be understood in this context as well, as the thickened left ventricle is the predominant chamber as it is responsible for pumping oxygenated blood throughout the entire body. The clinical impact of *Tafazzin* mutation on fetal loss and stillbirth has also been documented [35], although a clear effect on cardiovascular morphogenesis aside from noncompaction has not been described. Although the presence of cyclic neutropenia is also well documented in some BTHS patients, the mechanism causing this phenotype is poorly understood. Neutropenia makes it more difficult for the body to fight off foreign invaders such as bacteria and viruses, so affected individuals have an increased risk of recurrent infections. There is some evidence that apoptosis of myeloid precursors in the bone marrow results from *Tafazzin*-deficiency [36], but an explanation of why these cells are particularly susceptible has not been presented. Similarly, it is unclear why the high energy-requiring central nervous system is spared in BTHS, but not in many other mitochondrial diseases [37].

Reduction in mature and total cardiolipin has also been described in a spontaneously hypertensive rat model of heart failure, as well as adult human myocardial samples from patients with idiopathic dilated cardiomyopathy (IDCM) [38]. A subsequent follow up study found that the *Tafazzin* mRNA is reduced in both the hypertensive rat hearts and IDCM patient hearts but not control samples [39]. An analysis of pediatric cardiomyopathy samples demonstrated a similar reduction in mature and total cardiolpin in failing pediatric hearts but normal mitochondrial content and no change in *Tafazzin* expression, suggesting that other regulators of cardiolipin metabolism such as MLCL-AT may be important in the development of heart failure [40]. Increased *Tafazzin* expression has been associated with tumorigenicity of cervical cancer cells [41] and also with tumorigenesis and radiation response in rectal cancer [42]. Moreover, recent data has shown that *Tafazzin* can reduce stemness and increase differentiation of acute myeloid leukemia cells [43], although whether these are all primary or secondary effects upon cancer stem cells remains unknown.

Published therapeutic interventions for BTHS have focused on nutritional supplementation, reduction of oxidative stress and gene replacement therapy. The predominant mature cardiolipin in human hearts is tetralinoleoyl cardiolipin (L4CL) and BTHS patients show significant reduction in L4CL. Linoleic acid treatment of patient skin fibroblasts restores cardiolipin levels [44] and also partially improves BTHS iPSC-CM performance [17]. Scavenging of ROS in BTHS iPSC-CMs with mitoTEMPO also improved sarcomere organization and contractility [17], but scavenging of ROS *in vivo* through the use of mitochondrially targeted catalase in *Tafazzin*-deficient mice did not rescue cardiomyopathy [45]. Chemically modified RNA encoding *Tafazzin* was also able to rescue mitochondrial dysfunction in BTHS iPSC-CMs [17]. Adeno-associated viruse-9 (AAV9) mediated delivery of *Tafazzin* under the control of a myogenic-restricted desmin, a ubiquitously driven human cytomegalovirus immediate-early enhancer and promoter (CMV) or a native *Tafazzin* promoter each improved mitochondrial morphology, mitochondrial function, cardiac function and skeletal muscle performance in the *Tafazzin* knockdown mouse model [46]. In a separate study, AAV9-mediated delivery of *Tafazzin* under the control of the desmin promoter was able to normalize the proteomic profile of *Tafazzin*-deficient hearts [47]. AAV9-TAZ gene therapy was also able to restore mitochondrial morphology and function in BTHS patient fibroblasts [48]. AAV9-TAZ therapy administered to neonatal *Taz* KO mice was able to improve survival, reduce fibrosis, LV dilation and delay onset of cardiomyopathy when under the control of a *CMV* promoter but not a cardiomyocyte-restricted *cTNT* promoter, suggesting that the replacement of *Tafazzin* activity in skeletal muscle improves survival. It was also able to prevent the onset of cardiomyopathy and reverse established cardiomyopathy in *Tafazzin* myocardial conditional knockout mice when given at high doses [32].

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