The Human TAZ Gene Complements Mitochondrial Dysfunction in the Yeast taz1Δ Mutant

IMPLICATIONS FOR BARTH SYNDROME

Barth syndrome is a genetic disorder that is caused by different mutations in the TAZ gene G4.5. The yeast gene TAZ1 is highly homologous to human TAZ, and the taz1Δ mutant has phospholipid defects similar to those observed in Barth syndrome cells, including aberrant cardiolipin species and decreased cardiolipin levels. Subcellular fractionation studies revealed that Taz1p is localized exclusively in mitochondria, which supports the theory that tafazzins are involved in cardiolipin remodeling. Because cardiolipin plays an important role in respiratory function, we measured the energy transformation and osmotic properties of isolated mitochondria from the taz1Δ mutant. Energy coupling in taz1Δ mitochondria was dependent on the rate of oxidative phosphorylation, as coupling was diminished when NADH was used as a respiratory substrate but was unaffected when ethanol was the substrate. Membrane stability was compromised in taz1Δ mitochondria exposed to increased temperature and hypotonic conditions. Mitochondria from taz1Δ also displayed decreased swelling in response to ATP, which induces the yeast mitochondrial unspecific channel, and to alamethicin, a membrane-disrupting agent. Coupling was measured in taz1Δ cells containing different splice variants of the human TAZ gene. Only the variant that restores wild-type cardiolipin synthesis (lacking exon 5) restored coupling in hypotonic conditions and at elevated temperature. These findings may shed light on the mitochondrial deficiencies observed in Barth syndrome.

Barth syndrome is a severe X-chromosome linked genetic disorder characterized by cardiac and skeletal myopathy, neutropenia, abnormal mitochondria, and increased levels of 3-methylglutaconic acid in the urine (1–3). The disorder is often associated with growth retardation and has a high rate of mortality in childhood because of cardiac failure or sepsis arising from agranulocytosis. The lipid composition of cells from patients with Barth syndrome showed a dramatic decrease in cardiolipin (CL)1 levels and reduced incorporation of linoleic acid (18:2) into CL and its precursor phosphatidylglycerol (4). In addition, tetratalinoleoyl-CL (L₄-CL), the most predominant CL species in mitochondria from normal skeletal and heart muscle, is almost completely absent in Barth syndrome, whereas the concentration and the fatty acyl patterns of other phospholipids are normal (5–7). Sequence analysis of the gene responsible for Barth syndrome, G4.5, suggested that it encodes a putative acyltransferase involved in phospholipid biosynthesis (8). More recent findings indicate that the TAZ gene encodes a transacylase (9). These studies suggest that the TAZ gene is involved in CL remodeling.

The yeast open reading frame YFR140w (TAZ1) is highly homologous to G4.5, and the yeast Saccharomyces cerevisiae taz1Δ mutant has defects similar to those found in Barth syndrome fibroblasts, including reduced CL levels and decreased CL species containing unsaturated fatty acids (10, 11). In addition, the putative intermediate of CL remodeling, monolysocardiolipin, accumulates in the taz1Δ mutant (10, 11). Therefore, the taz1Δ mutant provides an excellent model to study CL remodeling and Barth syndrome.

CL, the unique dimeric phospholipid in the mitochondrial inner membrane of eukaryotic cells, plays an important role in mitochondrial function (12–14). CL is more unsaturated than the other membrane phospholipids. The origin of the CL-specific acyl pattern is not understood and could potentially be explained by substrate preference in CL de novo synthesis or by remodeling of newly synthesized molecules through a deacylation-reacylation cycle (15). The accumulation of monolysocardiolipin in the taz1Δ mutant supports the latter possibility. The prediction that tafazzins are involved in CL remodeling strongly suggests that Taz1p is a mitochondrial protein. The subcellular localization of Taz1p in this study shows that the yeast tafazzin is exclusively localized in mitochondria.

Previous studies have shown that CL is essential for optimal performance of the mitochondrial energetic machinery and the stability of the mitochondrial membrane in unfavorable conditions (13, 14). Because CL plays an important role in bioenergetic coupling, we hypothesized that the taz1Δ mutant may exhibit bioenergetic defects. To this end, we characterized the energy transformation and osmotic properties of mitochondria from the taz1Δ mutant and show in this study that the mutant is defective in all parameters tested. These defects are complemented by expression of the human TAZ gene cDNA, specifically the variant lacking exon 5 (11). These studies have implications for understanding the cellular defects in Barth syndrome.

EXPERIMENTAL PROCEDURES

Yeast Strains—The S. cerevisiae strains used in this work are FGY3 (wild type, MATα, ura3Δ–52, lys2–52, lys2–801, ade2Δ–101, trp1Δ–1, his3Δ200, leu2–Δ1), ZGY1 (isogenic with FGY3 except for taz1Δ::KanMX4),
and FGY2 (isoionic with FGY3 except for erd1::URA3) (16). The yeast taz1Δ strains in the W303 background containing splice variants of the human TAZ gene are described elsewhere (11).

The entire open reading frame of TAZ1 was replaced by a KanMX marker using a PCR-mediated one-step gene replacement strategy (17). The KanMX cassette was amplified from pRS400 using primers Kan1 (ATGCTTCTTATAGGAGTG-
TCCTAGAAGAGGAGGATGAATTAGGAAAGCTAGCTGACGTCGAG-
gac) and Kan2 (CTAACTAGCTACCCCTCTTGGTTAAAACCTTCGAGG-
GCAGAAACTTTTTCGATGAGTACCTG), consisting of 50-nucleotide and 48-nucleotide sequences identical to the TAZ1 flanking regions at the 5′ ends (capital letters) and 19 nucleotides of sequences specific for the amplification of the KanMX marker gene at the 3′ ends (small letters) of each primer. The PCR product was purified and transformed into strain FGY3 (16), and transformants were selected on G418-containing agar plates. The presence of a KanMX module instead of TAZ1 was verified by PCR analysis using primers specific for this module, namely kanC (TGATTTTTGTGACGCGCTATAA) and kanB (CTQGAATGTGACGCGCTAT) in combination with primers specific for the flanking regions of TAZ1, TazB (GGAGCTACTTCTTTCACGC-
catt) and TazC (GACATATACCCTTCAAGAACACTC) (data not shown). To confirm the disruption by Southern blot analysis, genomic DNA was extracted from wild type and putative taz1Δ mutant cells constructed as described above, and approximately 50 μg of genomic DNA from both strains were digested overnight with NdeI and resolved on agarose (0.8%) gel, which was hybridized with a radiolabeled riboprobe complementary to the region upstream of the TAZ1 coding sequence (data not shown).

Cloning and Expression of Taz1p-his in taz1Δ—The TAZ1 DNA sequence containing a C-terminal His tag was amplified from W303 genomic DNA using a KpnI-tagged forward primer 5′-GTT ACC ATG TCT TTT AGG GAT GTC CTA G-3′ and a Sall-tagged reverse primer 5′-GTT ACC ATG ATG ATG ATG ATG ATC ATC CTT ACC TTG-3′ and cloned into the KpnI and SalI sites of pYPGK18 (11). Integrity of the insert was verified by DNA sequencing. This construct was transformed into taz1Δ and expressed as described previously (11). For cardiolipin analysis, spheroplasts were prepared using zymoloyase according to Franzussof et al. (18) and lysed by sonication in distilled water.

Subcellular Localization of Taz1p—Spheroplasts from taz1Δ cells expressing Taz1p-his were prepared using zymoloyase according to Franzussof et al. (18) and lysed in 50 mM potassium phosphate buffer, pH 7.0, containing 0.6 M sorbitol, 1 mM EDTA, and 1 mM KCl. A postnuclear supernatant was produced by centrifugation of the homogenate at 600 × g for 10 min at 4 °C, and this was centrifuged at 25,000 × g for 30 min at 4 °C. The resulting organelle pellet was dissolved in 1 ml of the same buffer used for spheroplast lysis and subjected to equilibrium density gradient centrifugation in a linear Nycoenz gradient as described (19). Immunoblot analysis of total homogenate, organelle pellet, cytosol, and gradient fractions was performed using a polyclonal His tag antibody (BD Biosciences). Citrate synthase, NADPH-dependent cytochrome c reductase, and phosphoglucosomerase were used as markers for mitochondria, endoplasmic reticulum, and cytosol, respectively. The activities of the marker enzymes were determined as described previously (20, 21).

Results

Subcellular Localization of Taz1p—Because tafazzins are involved in the remodeling of the mitochondrial phospholipid cardiolipin, their most likely location is in the mitochondria. However, this has never been shown experimentally. To determine the subcellular localization of the yeast enzyme Taz1p, we transformed taz1Δ with a construct encoding a C-terminally His-tagged Taz1p, Taz1p-his, enabling immunological detection of the expressed protein. Expression of Taz1p-his in taz1Δ restored growth on glycerol/ethanol plates at 37 °C and completely normalized the cardiolipin profile (not shown) as was previously shown for the untagged Taz1p (11). This demonstrates that the his-tag does not interfere with the localization and function of Taz1p. Initial analysis of the subcellular distribution of the expressed protein in this transformant showed that Taz1p-his is exclusively present in the particulate fraction (Fig. 1A). To determine the exact subcellular localization of Taz1p, the organelle fraction was loaded on a Nycoenz density gradient. When we analyzed the gradient fractions by immunoblot analysis using an anti-His antibody, the pattern of the
immunoreactive material exactly corresponded to that of the mitochondrial marker enzyme citrate synthase, confirming the mitochondrial localization of Taz1p (Fig. 1, B and C).

Defective Energetic Coupling in taz1Δ Mitochondria—Barth syndrome is characterized by abnormal mitochondrial morphology with impaired oxidative phosphorylation (1, 23). To understand the effect of the taz1Δ mutation on mitochondrial bioenergetics, energetic coupling was measured in taz1Δ mitochondria. Previous studies showed that the absence of CL leads to a decrease in energetic coupling during fast respiration driven by NADH as substrate, suggesting that CL is essential for the enhanced coupling of accelerated oxidative phosphorylation (14). The rate of oxidative phosphorylation was modulated using NADH and ethanol as respiration substrates. In yeast mitochondria, the external respiratory substrate NADH was shown to provide the maximal capacity of energy transformation because of a higher activity of NADH dehydrogenase compared with other substrate dehydrogenases (24, 25). As seen in Tables I and II, the state 3 respiration rate is about 1.5-fold higher with NADH than with ethanol as substrate, and the uncoupled respiration rate is higher than the state 3 respiration rate. NADH-oxidizing mitochondria from the taz1Δ mutant showed an increased state 4 respiration rate and decreased ADP/oxygen and respiratory control ratios compared with the isogenic wild type. With ethanol as the substrate, taz1Δ mitochondria showed only moderate decreases in respiratory control ratio, whereas the ADP/oxygen ratio was similar to that of the wild type.

Defective Osmotic Stability in taz1Δ Mitochondria—The dynamics of mitochondrial matrix volume play an important role in the regulation of mitochondrial metabolism. Low amplitude swelling and shrinkage cycles of mitochondria are associated with changes in the respiration state (26). Many metabolic parameters, including respiratory rates, the redox state of cytochromes, and the ADP/O ratio are strongly affected by mitochondrial volume (27). Although low amplitude swelling and shrinking cycles are normal responses to physiological changes, high-amplitude swelling leads to irreversible damage of the mitochondrial membrane (27).

We wished to determine whether the taz1Δ mutation affected the response of mitochondria to altered tonicity. This was assessed by measuring the effects of tonicity on state 3-state 4 transition. The inner membrane of intact mitochondria is relatively impermeable to protons. However, in damaged mitochondria, the inner membrane permits protons to leak back to the matrix, enabling electron transport to continue without concomitant phosphorylation of ADP to ATP. These conditions of uncoupling can be detected by the absence of a transition from state 3 to state 4. Oxidative phosphorylation was measured in taz1Δ mitochondria in hypotonic (0.3 M mannitol) and isotonic (0.6 M mannitol) media. Mitochondria were added to 0.15 mg of protein/ml (Mit), ADP was added to 0.2 mM (ADP), and FCCP was added to 5.9 μM (FCCP). The figure shown is typical of five experiments.

![FIG. 2. Defective oxidative phosphorylation of taz1Δ mutant mitochondria in hypotonic conditions.](http://www.jbc.org/content/56/1/44396/F2)
Wild type mitochondria were also coupled in hypotonic conditions. In contrast, taz1Δ/H9004 mitochondria exhibited a barely discernible state 3-state 4 transition in hypotonic conditions. Furthermore, following the addition of ADP, subsequent addition of the uncoupler FCCP to taz1Δ/H9004 mitochondria induced only a slight increase in state 4 respiration. In crd1Δ/H9004 mitochondria, which are completely deficient in CL, addition of uncoupler FCCP did not increase the respiration rate in state 4. These data indicated that mitochondria from taz1Δ mutant cells were uncoupled in hypotonic conditions.

To determine the effect of mutation on swelling and shrinking, taz1Δ mitochondria were subjected to strongly hypotonic conditions (24-fold decrease in tonicity) followed by partial restoration of tonicity (to 0.1M) with the addition of sucrose. Mitochondrial volume kinetics were monitored by following the change in apparent absorbance at 540 nm (22). As seen in Fig. 3, upon the addition of sucrose mitochondria from wild type, crd1Δ, and taz1Δ cells all exhibited a fast, immediate shrinkage. However, only wild type mitochondria maintained continuous shrinkage for 5 min. In contrast, taz1Δ mitochondria shrunk for only about 2 min and then gradually swelled. In crd1Δ mitochondria, shrinkage induced by the addition of sucrose lasted for less than 1 min and was followed by resumption of swelling. Therefore, taz1Δ mitochondria exhibited reduced shrinkage ability after hypotonic exposure to a degree intermediate between crd1Δ and wild type.

Swelling of the mutant mitochondria was further assessed by increasing the permeability of the mitochondrial membrane in isotonic conditions. This was achieved by opening of the yeast mitochondrial unspecific channel with ATP or by permeabilization of the mitochondria with the pore forming antibiotic alamethicin. Mitochondrial swelling was monitored by the absorbance of mitochondrial suspensions at 540 nm (22). Taz1Δ mitochondria exhibited defective swelling in response to ATP (Fig. 4) and to alamethicin (Fig. 5) as the change in optical density was less than in wild type mitochondria. These data indicate that the stretch capacity of the taz1Δ mitochondrial membrane is reduced.

Effect of Temperature on taz1Δ Mitochondria—Oxygen consumption in mitochondria from the taz1Δ mutant was measured at 25 °C and 40 °C. At 25 °C, the respiration of mutant

![Figure 3](http://www.jbc.org/)

**FIG. 3.** Defective shrinkage of hypotonically swollen taz1Δ mitochondria. Mitochondria from wild type (WT), crd1Δ, and taz1Δ cells (0.4 mg of protein/ml) were suspended in the basic reaction medium containing isotonic (0.6 M) or hypotonic (0.025 M) mannitol, and absorbance at 540 nm was monitored. Shrinkage of swollen mitochondria was induced by the addition of concentrated sucrose to 0.18 M. The figure shown is typical of five experiments.

![Figure 4](http://www.jbc.org/)

**FIG. 4.** Defective ATP-induced swelling in taz1Δ mitochondria. Mitochondria from wild type (WT), crd1Δ, and taz1Δ cells (0.4 mg of protein/ml) were added to the basic reaction medium supplemented with 0.5 mM P, and 2 mM NADH. The arrow indicates the addition of 2 mM ATP. Absorbance was monitored at 540 nm. The figure shown is typical of five experiments.

![Figure 5](http://www.jbc.org/)

**FIG. 5.** Defective alamethicin-induced swelling of taz1Δ mitochondria. Mitochondria from wild type (WT), crd1Δ, and taz1Δ cells (0.4 mg of protein/ml) were added to the basic reaction medium supplemented with 2 mM NADH. The arrow indicates the addition of 2 mM alamethicin. Absorbance was monitored at 540 nm. The figure shown is typical of five experiments.

![Figure 6](http://www.jbc.org/)

**FIG. 6.** Effect of temperature on taz1Δ respiration. Respiration in mitochondria from wild type (WT), crd1Δ, and taz1Δ cells was measured at 25 °C or 40 °C as described under “Experimental Procedures.” Mitochondria were added to 0.11 mg of protein/ml (mt), ADP to 0.2 mM (ADP) and FCCP to 5.9 μM. The figure shown is typical of five experiments.
mitochondria was relatively well coupled, and the state 3-state 4 transition in the mutant was similar to that of the wild type (Fig. 6). However, at 40 °C, taz1Δ mitochondria did not exhibit a state 3-state 4 transition. The addition of the uncoupler FCCP did not induce an obvious increase in the oxygen consumption rate in taz1Δ in contrast to wild type, in which coupling was apparent even at 40 °C. Therefore, similar to the mitochondria from the crd1Δ mutant, the mitochondria from the taz1Δ mutant were completely uncoupled at high temperature.

Exposure of wild type mitochondria to elevated temperature (40 °C) induced a slight swelling as indicated by a decrease in absorbance at 540 nm (Fig. 7). In the taz1Δ mutant, the extent of mitochondrial swelling was more pronounced than in wild type cells although less than that observed in the crd1Δ mutant (Fig. 7). This may explain the diminished energetic coupling in mitochondria from both taz1Δ and crd1Δ mutants exposed to elevated temperature (Fig. 6).

**FIG. 7.** Effect of temperature on swelling of taz1 mitochondria. Mitochondria from wild type (WT), crd1Δ, and taz1Δ cells (0.4 mg of protein/ml) were added to the basic reaction medium. Absorbance was monitored at 540 nm. For each sample, the top line indicates $A_{540}$ at room temperature (25 °C). The bottom line indicates $A_{540}$ after the same sample was bathed at 40 °C for 3 min. The figure is typical of five experiments.

**FIG. 8.** Energetic coupling in mitochondria from taz1Δ cells expressing the human TAZ gene. Mitochondria were prepared from WT, taz1Δ, and taz1Δ cells expressing the yeast TAZ gene (YTAZ), the human TAZ gene deleted for exon 5 or 7 (HTAZ-ex5 or HTAZ-ex7), the full-length human TAZ gene (HTAZ-full), or empty vector (plasmid). Coupling was measured as described in the legend to Fig. 1 in isotonic (A) and hypotonic (B) conditions, and at elevated temperature (C). The arrows pointing up indicate the addition of mitochondria (0.15 mg/ml at 25 °C or 0.11 mg/ml 40 °C). The figure is typical of three experiments.
blot analysis using an anti-human TAZ antibody (results not shown). This strongly suggests that the lack of complementation observed in some splice variants is caused by the inability of the proteins to exert their function in CL remodeling, not by defective targeting to the mitochondria.

**DISCUSSION**

The pathogenesis of Barth syndrome is not well understood, although alterations in mitochondrial ultrastructure and the respiratory chain have been identified (1, 28). Especially puzzling is the fact that the severity of symptoms is not strongly correlated with the nature of the TAZ gene mutation (1, 2), indicating that the phenotype is dependent on multiple factors not yet identified.

The yeast tat1Δ mutant provides an excellent model system in which to study the defects in Barth syndrome. This mutant has CL defects similar to those found in Barth syndrome fibroblasts, including reduced CL levels and decreased CL species containing unsaturated fatty acids (10). In this study, we determined the subcellular localization of Taz1p and characterized tat1Δ mitochondrial function with the ultimate goal of shedding light on the physiological defects in Barth syndrome.

Although mitochondrial localization of tafazzins might be expected because of the exclusive presence of CL in mitochondria, this has never been demonstrated experimentally. Our results show that yeast TAZ1, the orthologue of the human TAZ gene, encodes a mitochondrial protein, which supports the hypothesis that tafazzins are involved in the remodeling of CL.

The current study shows that tat1Δ mitochondria are defective with respect to bioenergetic coupling, membrane stability during elevated temperature and osmotic stress, and swelling in response to two different agents, ATP and alamethicin. In all parameters, the defect in tat1Δ was less severe than observed in crd1Δ, which is totally CL-deficient (16). The tat1Δ mutant has reduced total CL, decreased unsaturated fatty acids in CL, and increased monolysoc-CL. Any or all of these CL defects could be responsible for the observed deficiencies in mitochondrial function.

In Barth syndrome, the concentrations of cytochromes c1 + c, b, and a3 in the mitochondrial respiratory chain are diminished to 29, 47, and 64% of average control values (28), respectively. Moderately diminished respiratory rates for all substrates were also apparent in isolated intact skeletal muscle mitochondria (28). Energetic uncoupling, defective mitochondrial stability, and decreased resistance to osmotic and temperature stress that we report here in the tat1Δ mutant are consistent with the bioenergetic defects in Barth syndrome.

At least 12 possible mRNA splice variants may be produced from the human TAZ gene. Vaz et al. (11) reported that only the splice variant lacking exon 5 complemented the defective growth phenotype and altered the CL profile of the yeast tat1Δ mutant. Consistent with this, we found that only the variant lacking the exon 5 sequence restored the tat1Δ mutant mitochondrial coupling in hypotonic conditions and at elevated temperature in the tat1Δ mutant, further supporting the link between CL deficiency and mitochondrial dysfunction. Complementation of mitochondrial dysfunction in the yeast tat1Δ mutant by the human TAZ cDNA illustrates the highly conserved function of the corresponding gene and underscores the power of the yeast model for understanding Barth syndrome.

The pleiotropic defects associated with the tat1Δ mutation may help to explain the varying degrees of severity observed in Barth syndrome. For example, because tat1Δ mitochondria are hypersensitive to osmotic alterations, it is likely that the mutant phenotype would be exacerbated by mutations in genes that affect osmotic stress. The identification of synthetic lethal mutations in the tat1Δ background may shed light on this question. These experiments are in progress.

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