**BARTH SYNDROME:**

**CARDIOLIPIN ALTERATIONS LINKED TO TAFAZZIN MUTATIONS**

**LEADS TO APOPTOSIS AND MITOPHAGY ALTERATIONS**

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Tafazzin mutation reduces cardiolipin (CL), changes their acyl chain composition, impairs mitochondrial function, and causes dilated cardiomyopathy in Barth syndrome, a rare and often fatal X-linked genetic disorder accompanied by aciduria, neutropenia, and myocardial noncompaction. Tafazzin is a unique phospholipid transacylase that catalyzes the remodeling of cardiolipin, a mitochondrial phospholipid that exhibits « gluying » effects on the components of the respiratory chain that are ideally maintained at the right distance to assume maximal electron transport capabilities. Cardiolipin interacts with cytochrome *c* and affects the supramolecular organization of the ATP synthase in zone of high curvature of mitochondrial inner membrane for optimal respiratory activities.

However, the molecular mechanisms underlying the cause of mitochondrial dysfunction in Barth syndrome remain poorly understood. Taking into account recent findings, i.e. bioenergetic perturbations1, ROS production1, cell cycle dysregulation2, that accompagnied tafazzin gene mutations or knockdown experiments, we have focused on the effect of modified CL on mitochondrially driven apoptosis and mitophagic processes.

Using Barth syndrome patient-derived cells and HeLa cells in which tafazzin was knocked down, we show that cardiolipin is required for apoptosis. Cardiolipin provides an anchor and activating platform for caspase-8 translocation to, and embedding in, the mitochondrial membrane3.

Consistent with a key role of mitophagy in mitochondria quality control, impaired bioenergetic and oxidative stress linked to CL non-maturation lead to impaired mitophagy.

Together, these findings provide key insights on mitochondrial dysfunction in Barth syndrome, suggesting that pharmacological restoration of mitophagy may provide a novel treatment for this lethal condition.

1Gonzalvez F, D'Aurelio M, Boutant M, Moustapha A, Puech JP, Landes T, Arnauné-Pelloquin L, Vial G, Taleux N, Slomianny C, Wanders RJ, Houtkooper RH, Bellenguer P, Møller IM, Gottlieb E, Vaz FM, Manfredi G, Petit PX. [Barth syndrome: cellular compensation of mitochondrial dysfunction and apoptosis inhibition due to changes in cardiolipin remodeling linked to tafazzin (TAZ) gene mutation.](http://www.ncbi.nlm.nih.gov/pubmed/23523468) Biochim Biophys Acta. 2013 1832 (8): 1194-1206.

2He Q, Wang M, Harris N, Han X. [Tafazzin knockdown interrupts cell cycle progression in cultured neonatal ventricular fibroblasts.](http://www.ncbi.nlm.nih.gov/pubmed/23997105)Am J Physiol Heart Circ Physiol. 2013 1; 305(9): H1332-1343.

3Gonzalvez F, Schug ZT, Houtkooper RH, MacKenzie ED, Brooks DG, Wanders RJ, Petit PX, Vaz FM, Gottlieb E. [Cardiolipin provides an essential activating platform for caspase-8 on mitochondria.](http://www.ncbi.nlm.nih.gov/pubmed/19001123) J Cell Biol. 2008 183(4): 681-696.