The Antioxidant N-Acetylcysteine Rescues Myocardial Noncompaction in a Mouse Model of Barth Syndrome

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Introduction

Barth syndrome is a rare X-linked disorder caused by mutations in the transacylase tafazzin, leading to abnormalities in its target, the signature mitochondrial phospholipid cardiolipin. Patients develop a cardiomyopathy (CM), whose hallmark is noncompaction, but may die *in utero*. The disease can be modeled in a doxycycline-inducible transgenic tafazzin knockdown (TAZKD) mouse: prenatal TAZKD leads to a developmental myocardial patterning defect (noncompaction), while postnatal TAZKD leads to clinical CM. The pathogenesis of this CM is not known.

Objectives

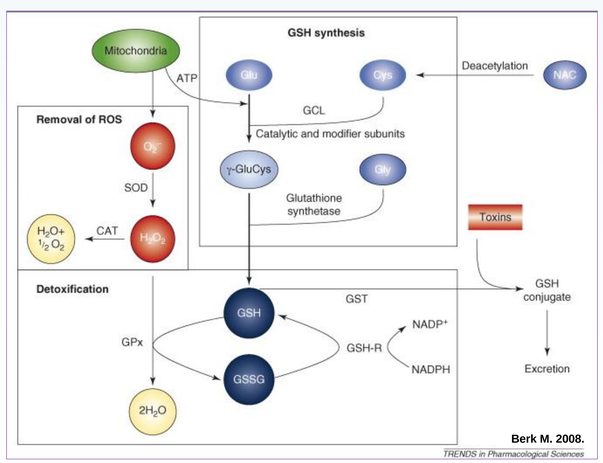
To supply initial proof-of-principle that reactive oxygen species (ROS) underlies noncompaction *in vivo*.

Methods

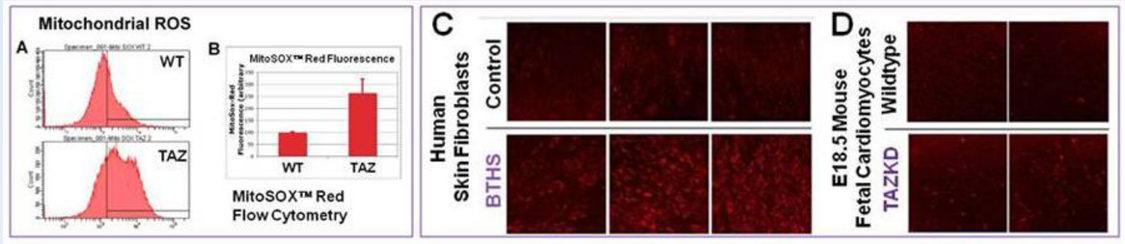
We assayed ROS in several model systems: *TAZ*-knockout mouse embryoid bodies; skin fibroblasts from Barth syndrome patients; and E18.5 TAZKD mouse ventricular cardiomyocytes. Tafazzin knockdown *in vivo* was induced in mouse embryos by feeding doxycycline to pregnant dams. To reduce ROS *in vivo*, we fed N-acetylcysteine (NAC) to mice throughout pregnancy in drinking water (500 mg/kg/day). Hearts were harvested for histology from newborn pups on the day of birth.

NAC as Therapy

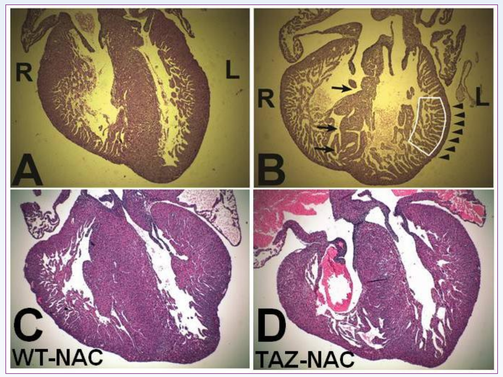
NAC increases glutathione reserves, acting as an antioxidant.

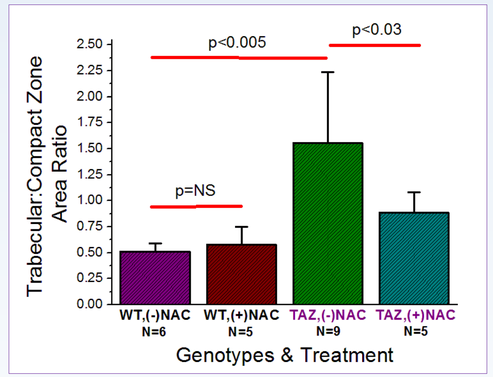


Results



ROS appeared elevated in tafazzin-deficient cells *(TAZ*-knockout cells [A,B], patient skin fibroblasts [C], and TAZKD fetal cardiocytes [D]).





NAC-treated TAZKD hearts showed partial rescue of noncompaction CM: less prominent trabeculations and a thicker compact zone (D vs. arrowheads in B), and a well-formed ventricular septum (D vs. arrows in B). Analysis of the trabecular and compact zones of wildtype (WT) and NAC-treated mice showed clear improvement in the extent of noncompaction (E).

Conclusions

Improvement with NAC suggests ROS underlies the noncompaction CM in Barth syndrome, and modulation of ROS shows promise as an *in vivo* treatment.

References:

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