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.

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

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

Conclusions
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).

References: