

# Cytoprotective role of mitochondrial ATP-Binding Cassette Protein-2



NORTHWESTERN UNIVERSITY

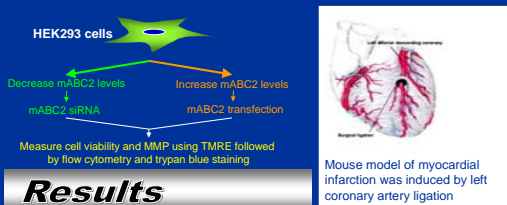
Rongxue Wu, Michael A. Burke, Tejaswitha J. Naik, Sathyamangla V. Prasad\*, Hossein Ardehali  
 Feinberg Cardiovascular Institute, Northwestern University, Chicago  
 \*Cleveland Clinic Foundation, Cleveland

## Introduction

Mitochondria are thought to play an important role in myocardial cell death in ischemic heart disease. We recently showed that mitochondrial ATP-binding cassette protein 1 (mABC1, a member of the ABC family of proteins) plays a role in protection against oxidative stress. Another member of this family, mABC2, shares sequence homology with mABC1, however, its function is not known. A yeast homolog of mABC2, Mdl1p, was recently shown to play a role in cellular resistance to oxidant stress. We hypothesized that mABC2 also plays a key role in protection of cells against oxidant stress.

## Methods

We modulated the levels of mABC2 in tissue culture via overexpression and RNA interference (siRNA). To assess the effects of overexpression and down regulation of mABC2, mitochondrial membrane potential (MMP) was measured by flow cytometry of tetramethylrhodamine ethyl ester (TMRE)-loaded cells.

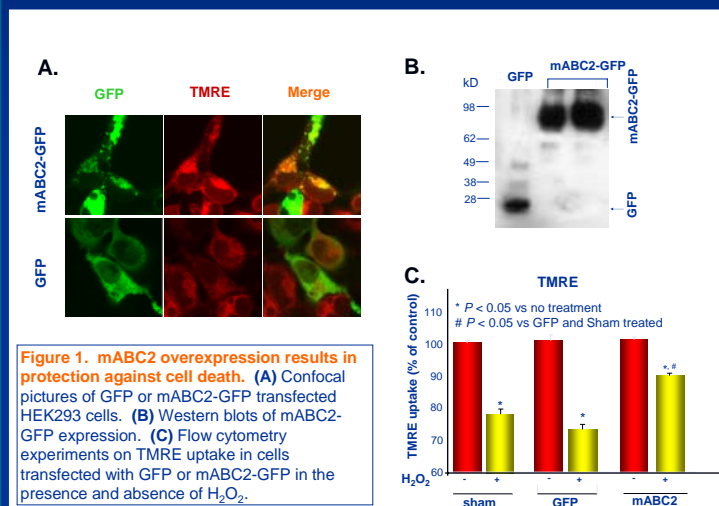


## Results

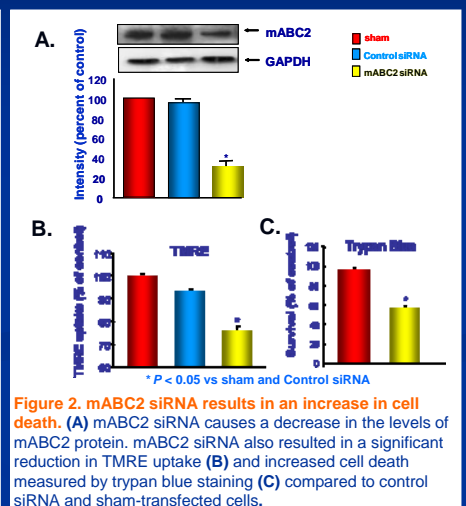
1. Downregulation of mABC2 protein results in an increase in cell death
2. Overexpression of mABC2 protects against H<sub>2</sub>O<sub>2</sub>-induced cell death
3. mABC2 is increased in ischemia.
4. mABC2 is increased in ischemic cardiomyopathy (CM)

## Conclusion

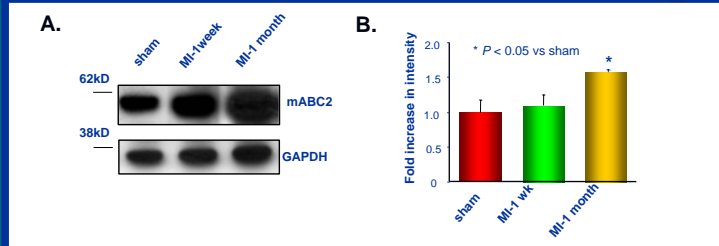
mABC2 is important for cell viability and protection against oxidant stress. These studies identify mABC2 as a novel target for cardioprotective therapeutics



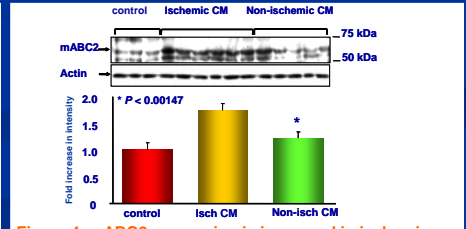
**Figure 1. mABC2 overexpression results in protection against cell death.** (A) Confocal pictures of GFP or mABC2-GFP transfected HEK293 cells. (B) Western blots of mABC2-GFP expression. (C) Flow cytometry experiments on TMRE uptake in cells transfected with GFP or mABC2-GFP in the presence and absence of H<sub>2</sub>O<sub>2</sub>.



**Figure 2. mABC2 siRNA results in an increase in cell death.** (A) mABC2 siRNA causes a decrease in the levels of mABC2 protein. mABC2 siRNA also resulted in a significant reduction in TMRE uptake (B) and increased cell death measured by trypan blue staining (C) compared to control siRNA and sham-transfected cells.



**Figure 3. mABC2 expression is increased in the hearts of mice subjected to coronary ligation.** (A) Western blot of mouse heart extracts from sham operated, one week and one month after MI. (B) Summary of Western blot results.



**Figure 4. mABC2 expression is increased in ischemic cardiomyopathy.** Western blot and summary of results from explanted heart samples. The levels of mABC2 were noted to be higher in patients with ischemic CM compared to control samples.