Myoferlin depletion induces DNA damage response and p53-dependent cell cycle arrest and apoptosis in colon cancer.

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INTRODUCTION

Colon cancer (COAD) is the second most common cancer in the world and leading cause of cancer related death. Although the cancer mortality rates have decreased some tumors remain resistant to therapy. Myoferlin a membrane protein involved in cell fusion was recently shown by our laboratory to be involved in mitochondrial structure and metabolism in pancreatic ductal adenocarcinoma. As no research had ever been performed on myoferlin in colon cancer, we decided to investigate the potential role of this protein in this particular cancer.

RESULTS

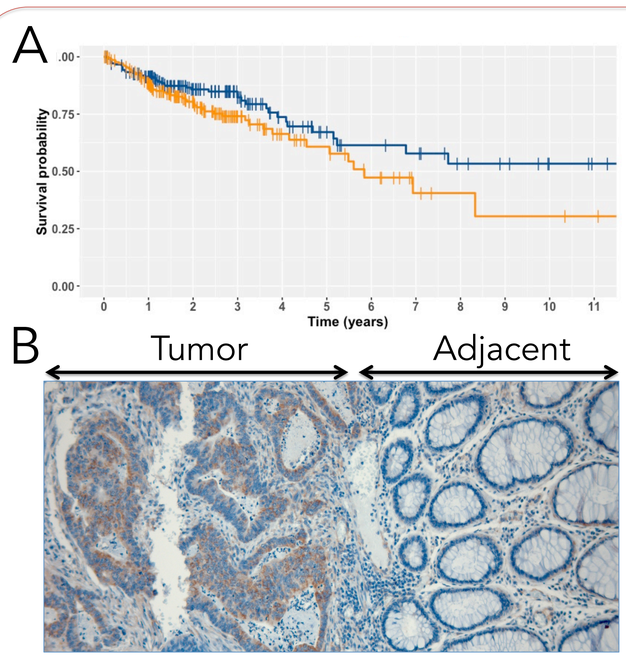


Figure 1A. *In COAD patients, high myoferlin expression is associated with low overall survival.*

Figure 1B. *In COAD patients, myoferlin expression is higher in tumor tissue in comparison to healthy adjacent tissue.*

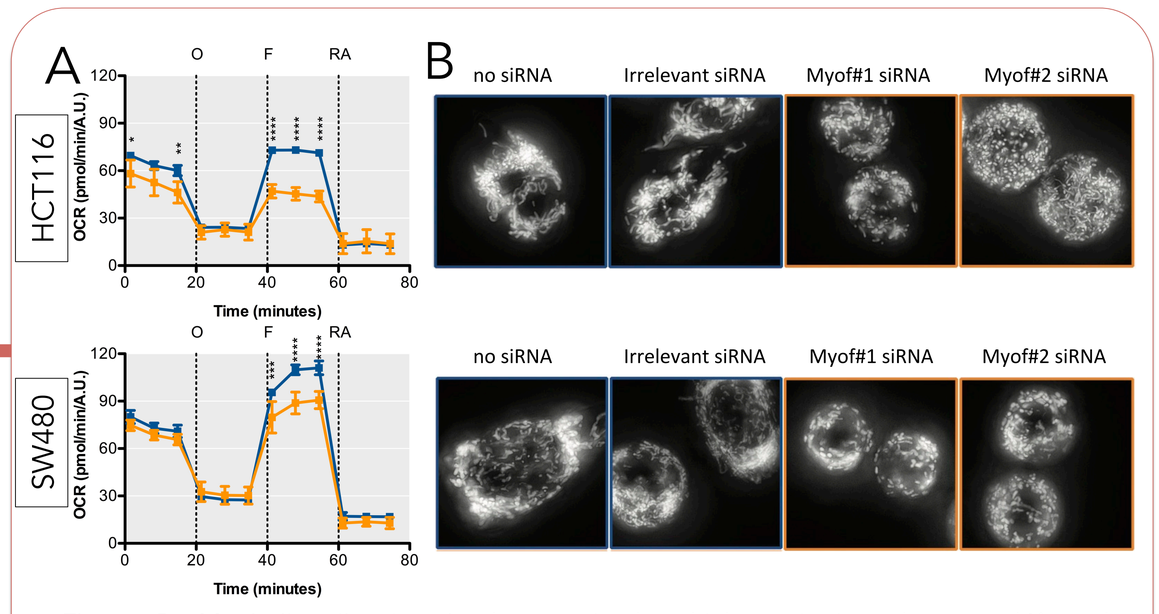


Figure 2. *Myoferlin silencing leads to mitochondrial respiration decrease (A) and mitochondrial fission (B) in HCT116 & SW480 cell lines.*

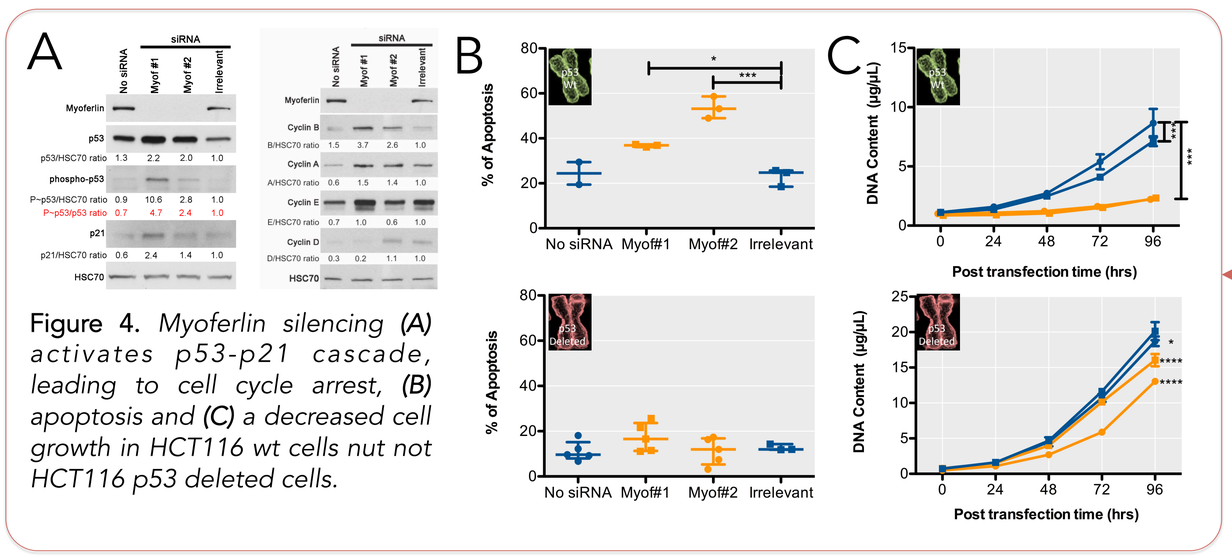


Figure 4. *Myoferlin silencing (A) activates p53-p21 cascade, leading to cell cycle arrest, (B) apoptosis and (C) a decreased cell growth in HCT116 wt cells nut not HCT116 p53 deleted cells.*

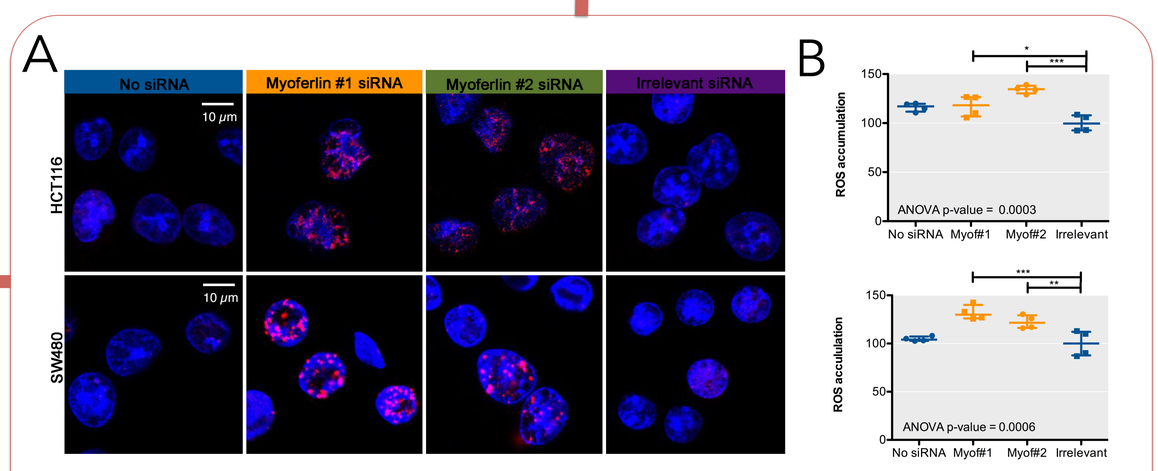


Figure 3. *Myoferlin depletion induces (A) DNA damage response and (B) mitochondrial ROS.*

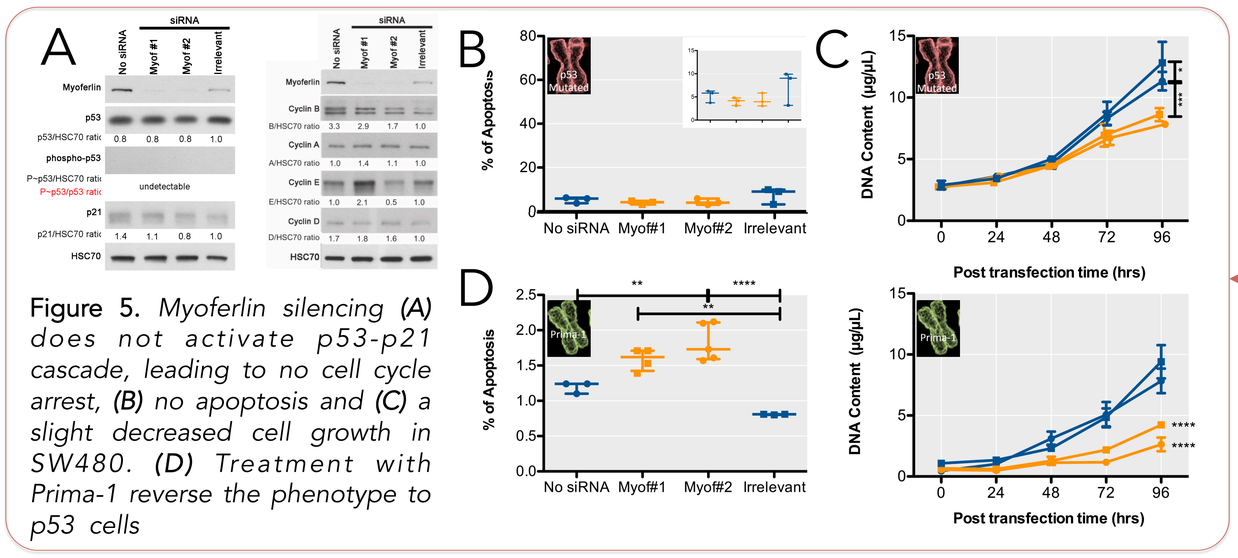


Figure 5. *Myoferlin silencing (A) does not activate p53-p21 cascade, leading to no cell cycle arrest, (B) no apoptosis and (C) a slight decreased cell growth in SW480. (D) Treatment with Prima-1 reverse the phenotype to p53 cells*

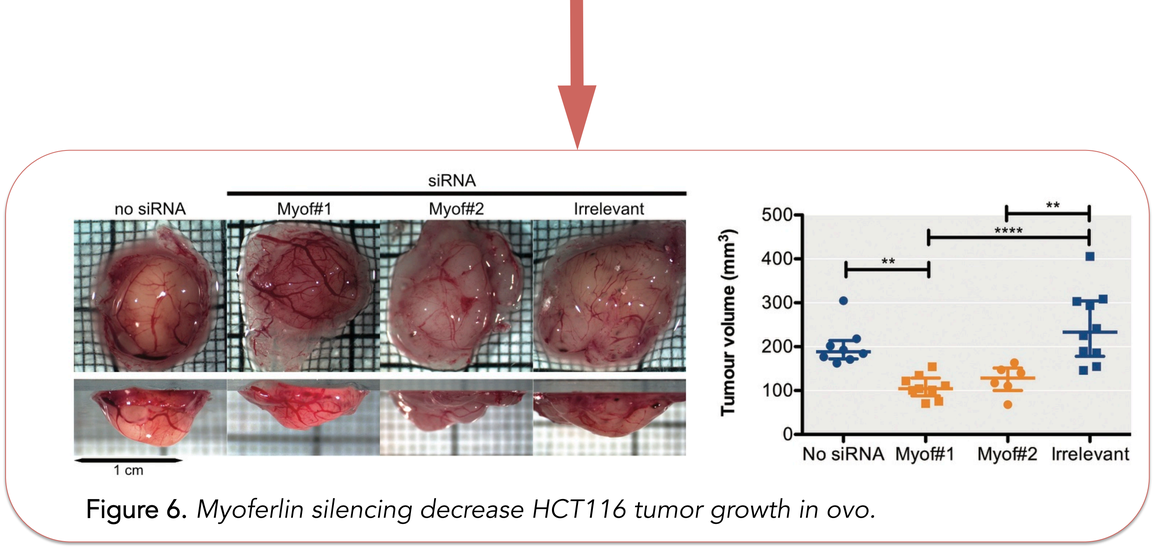
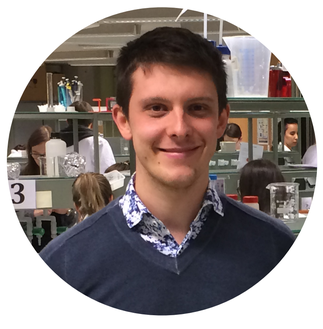


Figure 6. *Myoferlin silencing decrease HCT116 tumor growth in ovo.*

Conclusion & clinical relevance

Our results indicate that myoferlin expression is higher in colon cancer than in normal adjacent tissue and that is associated to poor survival. Myoferlin depletion leads to a mitochondrial respiration decrease and a mitochondrial fission inducing probably ROS production and subsequent DNA damages. Moreover, myoferlin silencing in p53 wild-type HCT116 cell line is leading to cell cycle arrest, apoptosis and important decrease in cell growth.

In conclusion, as apoptosis resistance is one of the most important resistance mechanism in COAD, myoferlin targetting could open up a new perspective in the development of new treatment for p53 WT patients.



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