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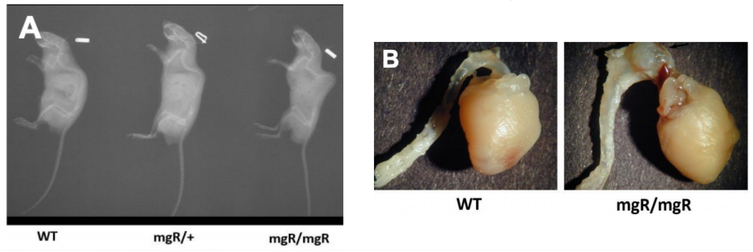
Introduction

Marfan Syndrome is an inherited autosomal dominant connective tissue disorder that is caused by a mutation within the Fibrillin-1 gene which encodes for the Fibrillin protein[3]. Common manifestations of Marfan Syndrome include thoracic aortic dilation, ectopia lentis, skeletal deformities, and chronic obstructive pulmonary disease (COPD) within the lungs[3]. Patients with Marfan Syndrome have higher concentrations of reactive oxygen species (ROS) in blood plasma[5]. This increase in ROS has been linked to the formation of aortic dilation within patients with Marfan Syndrome[6]. ROS created during oxidative stress can lead to increased cell damage and death through redox reactions involving DNA, RNA, and proteins[4]. Increased ROS concentration within the lungs has also been linked to the pathophysiology of COPD. This being said, the pathophysiology of Marfan Syndrome and its relation to lung involvement is underexplored. Superoxide Dismutases (SODs) are antioxidant enzymes that catalyze the reaction which turns superoxide radicals into oxygen gas and hydrogen peroxide[2]. Manganese-containing SOD (MnSOD) is a specific SOD located in the mitochondrial matrix where it protects the mitochondria from oxidative stress and is part of the apoptosis signaling pathway[4]. The aim of this study is to determine the activity of SOD1 and MnSOD in relation to the oxidative stress that is caused by the deficiency of Fibrillin protein. It is hypothesized that the mutation of Fibrillin-1 causes oxidative stress in the lung tissue, often causing COPD, thus it is expected that there would be less SOD activity in tissues from mice with Marfan syndrome.

Methods

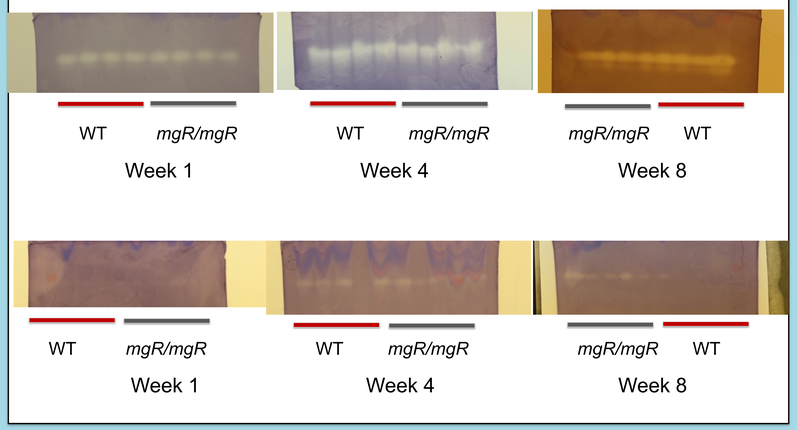
- Using the murine model of Marfan syndrome *Fbn1*$^{mgR/mgR}$, mice with a hypomorphic mutation in the Fibrillin-1 gene were sacrificed at 1, 4, and 8 weeks[1]
- Lung tissue of 8 mice (4 Marfan, 4 wild-type) from each time point were extracted and analyzed for SOD concentration through protein assay
- Native Polyacrylamide Electrophoresis was performed for each time point with equal amounts of protein – SOD1 and MnSOD
- Components of the gel - nitroblue tetrazolium (NBT) was used to create stained oxygen radicals and allow us to visualize the SOD activity by creating negative clearance bands[4]
- Bands, SOD activities, were analyzed and quantified using NIH ImageJ software

Fbn1$^{mgR/mgR}$ Mice Display Characteristics of Marfan Syndrome

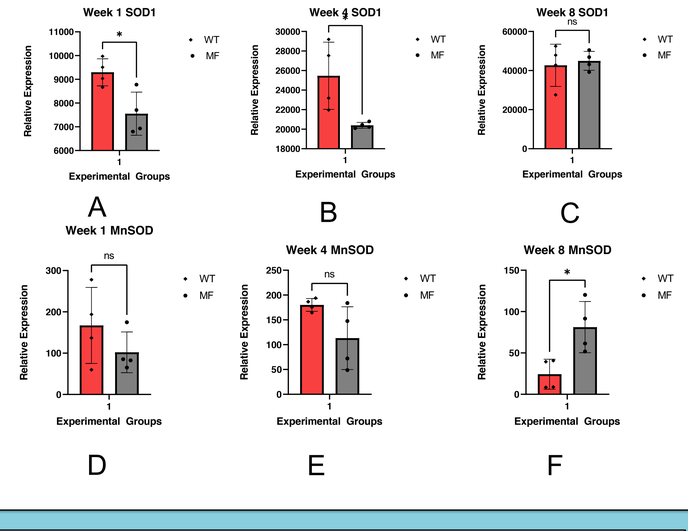


Homozygous mice, *Fbn1*$^{mgR/mgR}$ (mgR/mgR) have a hypomorphic mutation which leads to a 20% expression of normal Fibrillin-1 protein. Two common Marfan phenotypes, kyphosis (A) and thoracic aortic aneurysms (B), are shown.

SOD1 (top) and MnSOD (bottom) Native Gels



Results



The relative expression for SOD1 and MnSOD proteins in Marfan mice were compared to that of wild-type mice at week 1, 4, and 8. In weeks 1 and 4 (A, B), SOD1 proteins in wild-type mice are significantly more active (p=0.0173; p=0.0260). MnSOD proteins show more activity in Marfan mice at week 8 (F) (p=0.0193). Graphs C, D, and E show no statistical significance in difference of expression.

Conclusion and Future Directions

- SOD1 activity is generally decreased in lung tissue from mice with Marfan syndrome
  - Based on the results, this indicates that Marfan mice have a decreased ability to metabolize ROS into safer byproducts, consistent with the hypothesis
- Higher SOD activity in mice at 8 weeks suggests a possible compensation for oxidative stress
- In a future experiment, heterozygous mouse tissue would also be measured for SOD1 and MnSOD activity

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