Supplemental Information:

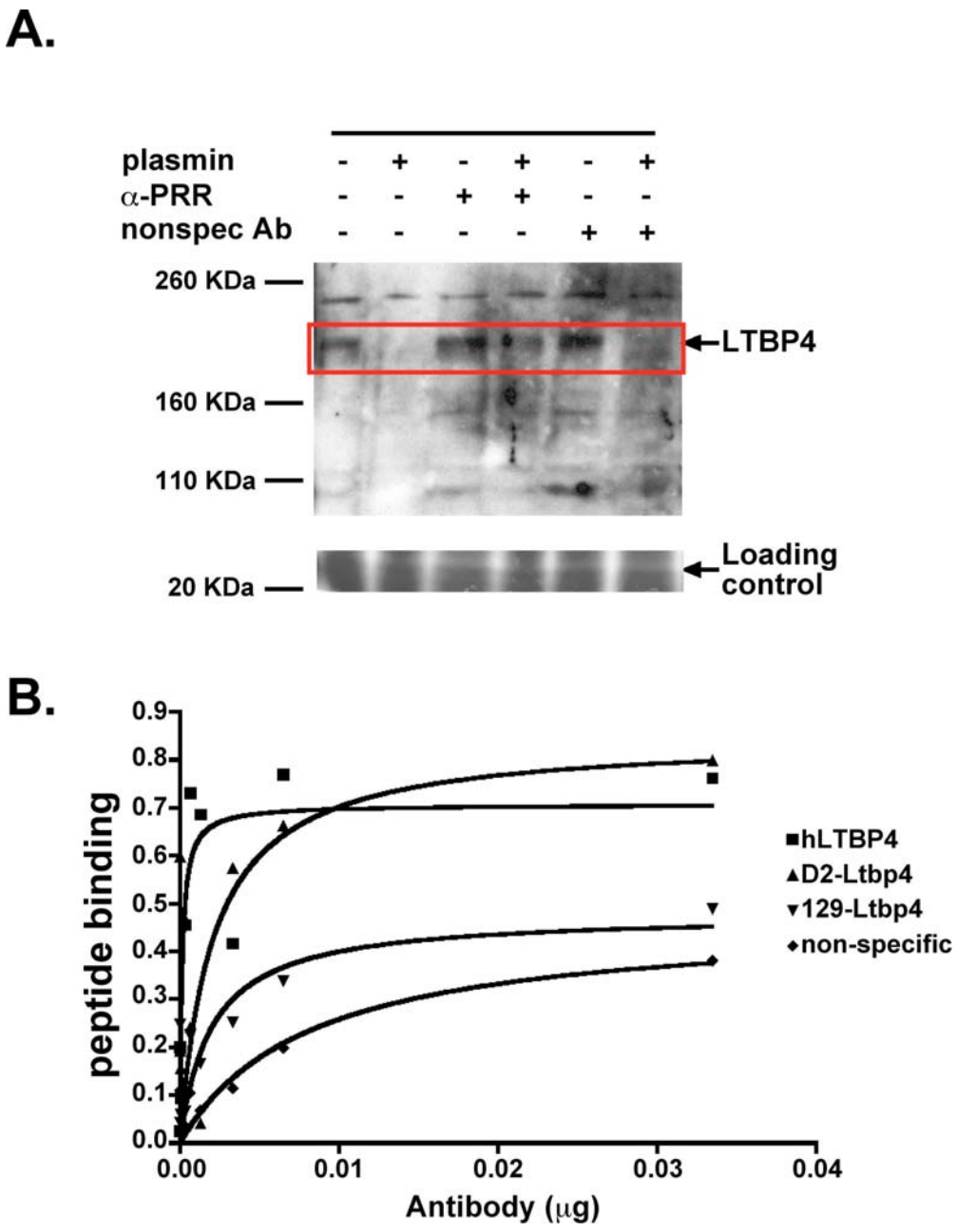

Fig S1. LTBP4 cleavage is specifically blocked by the anti-PRR antibody. A. Anti-PRR antibody was generated against the human LTBP4 PRR hinge region and was used in the in vitro proteolysis assay. The anti-PRR antibody specifically protects against human LTBP4 proteolysis. The nonspecific antibody does not protect from proteolysis. **B.** ELISA assays showed enhanced binding of the anti-PRR antibody to the human LTBP4 peptide.

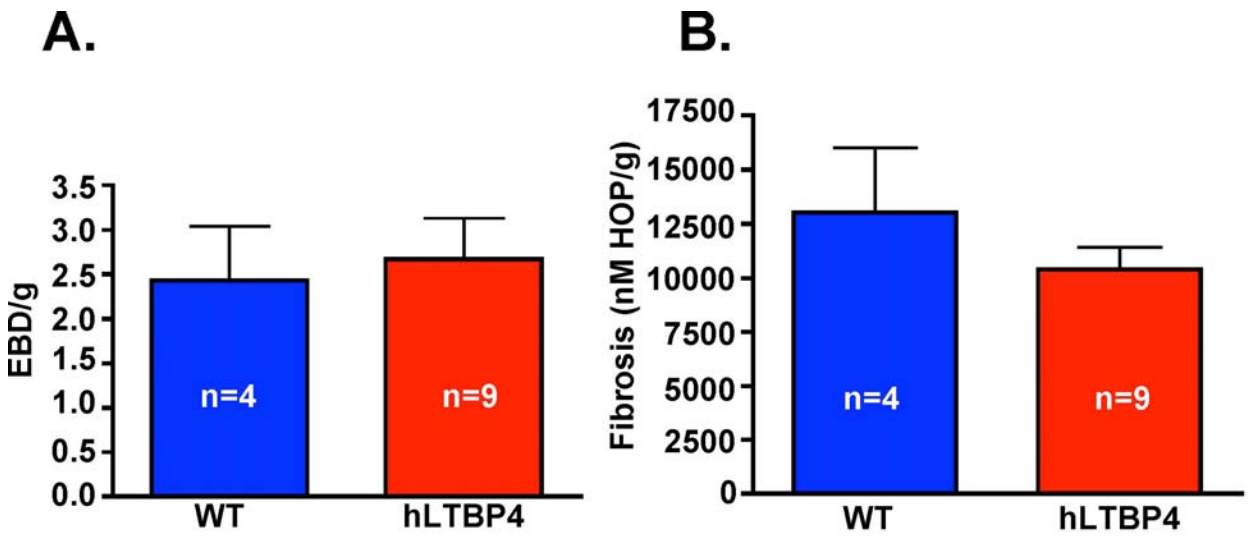

Fig S2. The BAC transgene does not alter membrane leak and fibrosis. Evans blue dye and fibrosis is not altered by the presence of the hLTBP4 BAC transgene in the wildtype background.

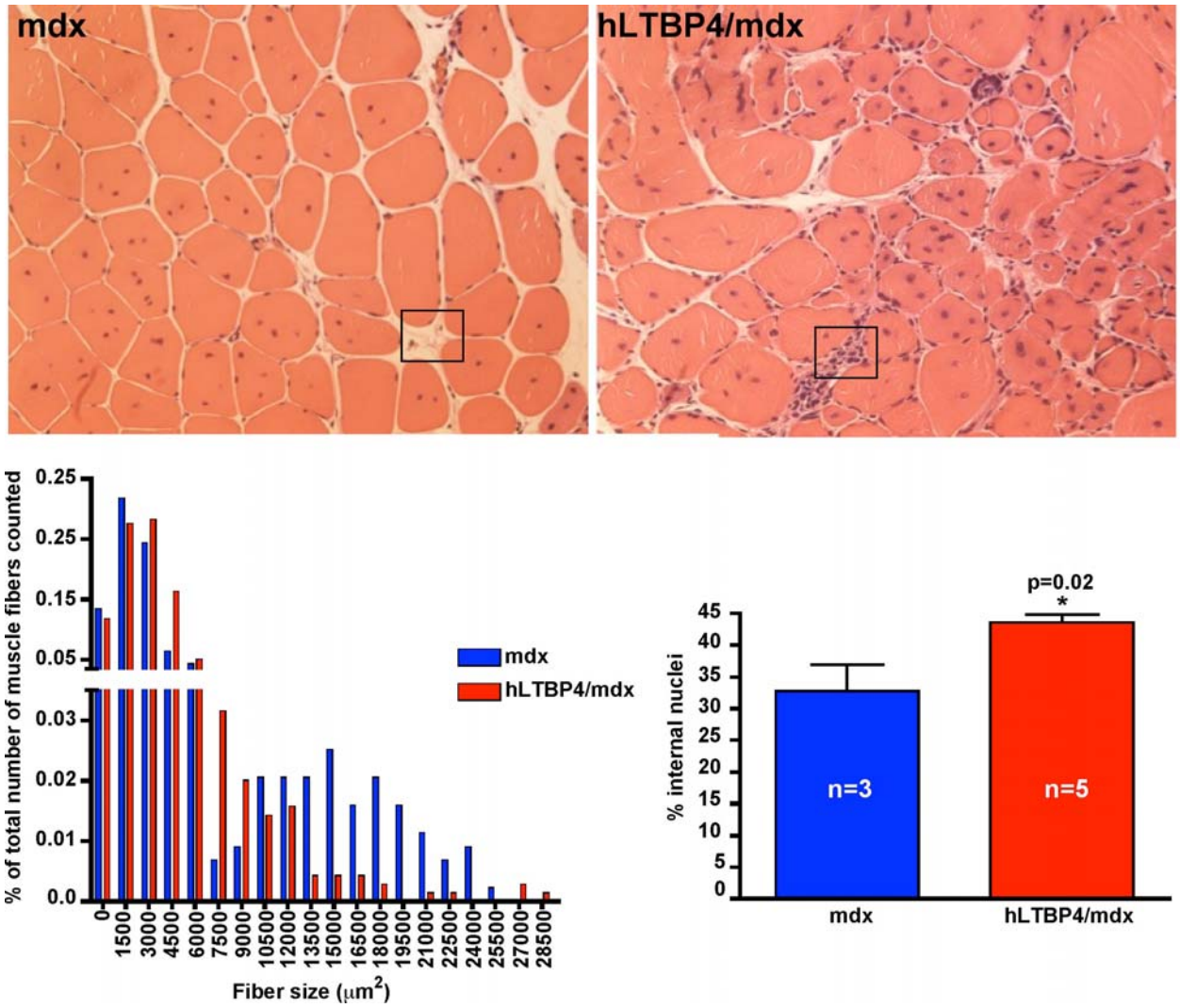

Fig S3. Human LTBP4 (hLTBP4) expression intensifies *mdx* muscle pathology. The *hLTBP4* BAC transgene was crossed into *mdx* mice and littermates were compared. **A.** Representative histopathology in *mdx* (left) versus *hLTBP4/mdx* mice (right). H&E staining showed elevated mononuclear cell infiltrate (compare boxed areas), fibrosis, and significantly more centralized nuclei in *hLTBP4*/*mdx* mice compared to *mdx* littermate controls. *hLTBP4/mdx* mice had fewer large myofibers (left panel) and an increase in centrally nucleated fibers (right panel).

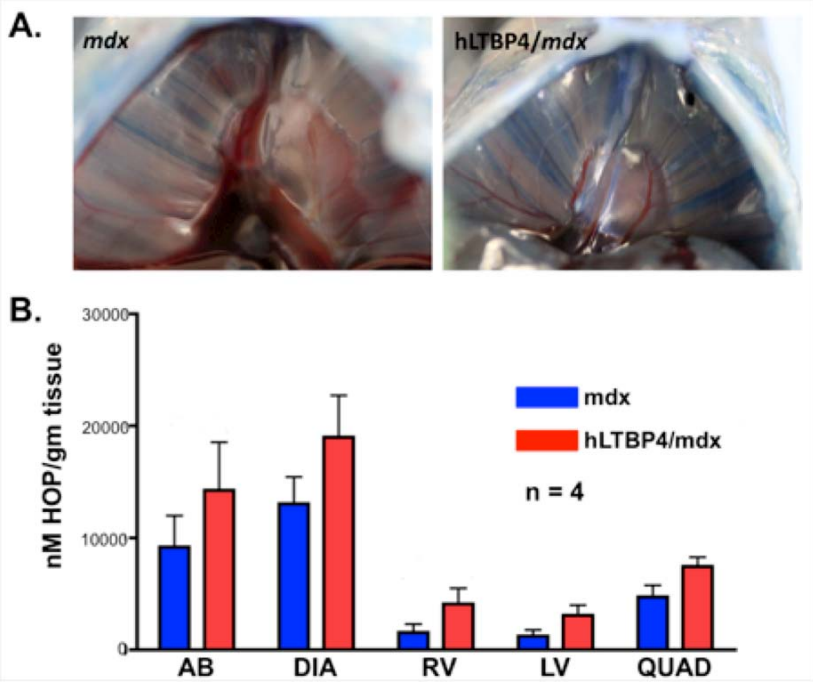

Fig S4. Multiple muscles are worsened by the hLTBP4 transgene in the *mdx* mouse. Increased Evans blue dye uptake and increased hydroxyproline content in *hLTBP4/mdx* mice compared to *mdx* mice. **A.** A representative diaphragm muscles from *mdx* and *hLTBP4/mdx* littermates; there is increased visible dye uptake (seen as blue areas) in the *hLTBP4/mdx* diaphragm muscles. **B.** Hydroxyproline content is increased in multiple muscle groups in *hLTBP4/mdx* muscles compared to *mdx* muscles.

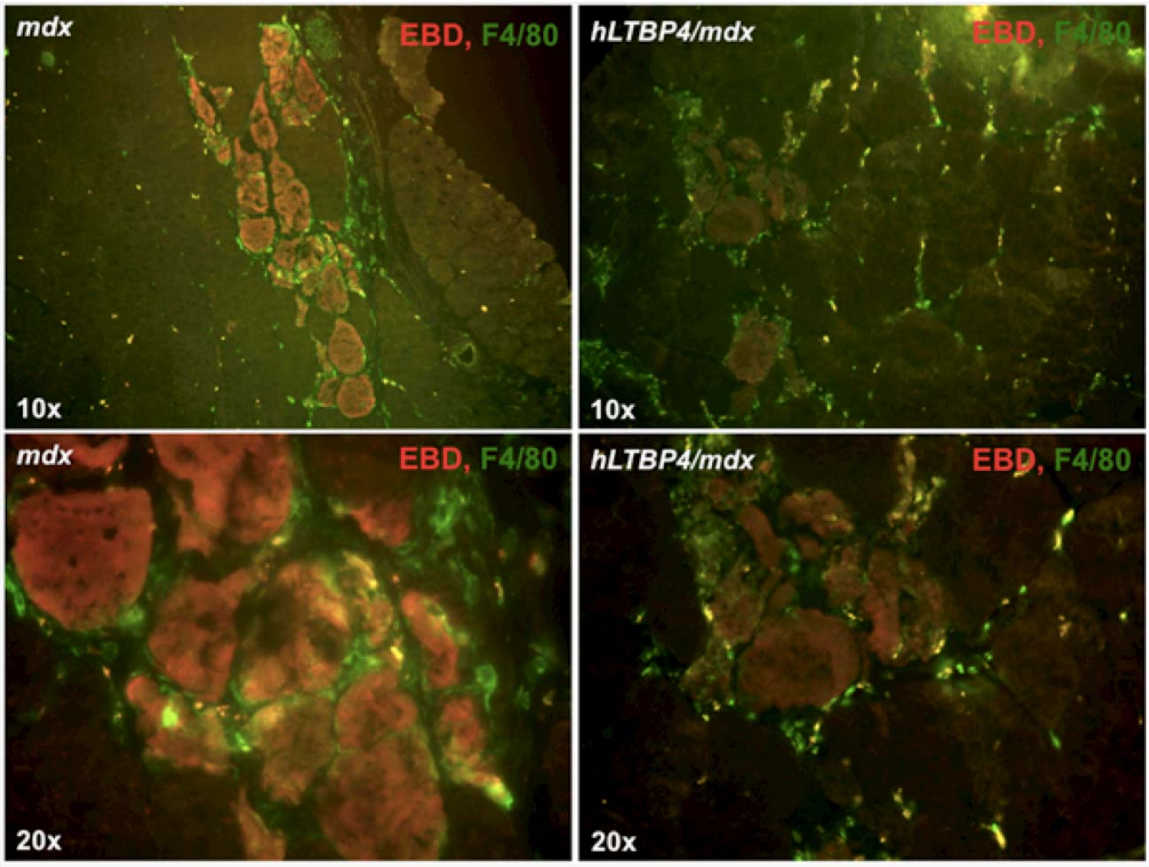

Fig S5. Increased macrophage infiltration in hLTBP4/mdx muscle. F4/80 staining (green) was used to identify activated macrophages. The distribution of F4/80 staining in *mdx* muscle was largely restricted to Evans blue dye positive areas (seen as red) where green cells clustered at the edges of dye positive fibers. In contrast, F4/80-positive cells were distributed throughout *hLTBP4/mdx* muscle in addition to being found near dye-positive cells.