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CANCER CENTER

Background

85% of children diagnosed with cancer are expected to survive their diagnosis. Cancer and chemotherapy contribute to poorer health outcomes. Despite the high survival rate there is minimal research on the influence of pediatric chemotherapy on musculoskeletal physiology. Given that vincristine is a commonly prescribed chemotherapeutic in pediatric populations, the aim of the current research was to investigate the musculoskeletal consequences associated with vincristine in pediatric mice.

Methods

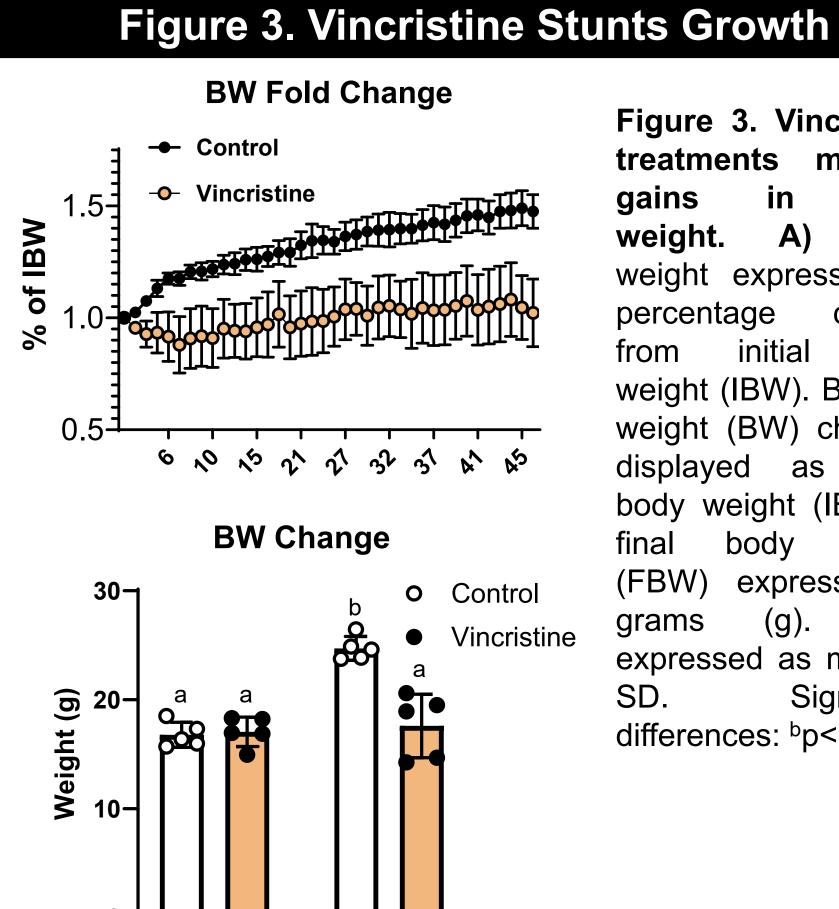
In vitro atrophy and oxygen consumption rate was assessed by exposing C2C12 myotubes with Vincristine was administered (1.5 mg/kg/2x weekly, i.p.) to 4-week-old male C57BL/6J mice. Body mass was monitored daily. Vehicle (n=5) and experimental mice (n=5) were culled after 35 days. Skeletal muscle mass was measured at the completion of the study. Ex vivo muscle function testing was completed. Muscle protein expression was measured via western blotting, and gene expression via qPCR...

Figure 1. Vincristine Reduces Myotube Diameter **Vincristine Figure** cells promotes myotube atrophy. A&B) Representative

images of myotubes exposed to Vincristine. C) Myotube diameter of C2C12 myotubes cocultured with GL261 cells expressed as µm. Data expressed as mean ± SD. Significant differences: bp<0.05.

Figure 2. Vincristine Reduces OCR in Myotubes **C2C12 Mytotube: Oxygen Consumption Rate** 1500-Control Vincristine 1000-20 Time (minutes)

Figure 2. Vincristine (50 pM) Reduces Oxygen Consumption Rate in C2C12 Myotubes. Seahorse analysis of OXPHOS in C2C12 Myotubes. Incubated for 24 hours prior experiment in XF assay medium supplemented with 5 mM glucose and 2 mM glutamine and consecutively injected with oligomycin (1 µM), FCCP (1.5 μ M), antimycin (1 μ M) and rotenone (1 μ M). Continuous OCR values (pmoles/min/µg protein) are shown. Mean ± SD. OCR normalized to protein content (BCA). bp<0.05



IBW

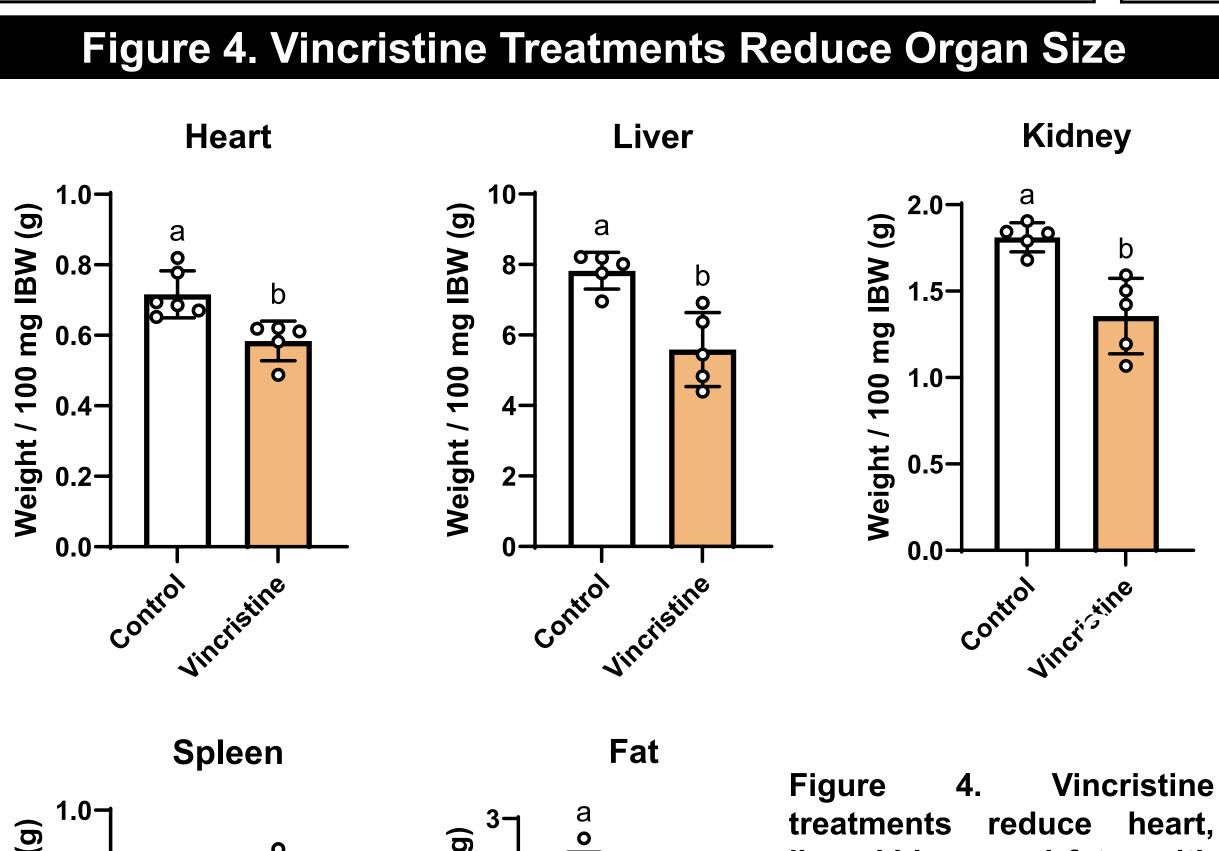
FBW

Figure 3. Vincristine treatments mitigate gains body weight. A) Body weight expressed as percentage change body from weight (IBW). B) Body weight (BW) changes displayed initial as body weight (IBW) to weight (FBW) expressed in grams (g). Data expressed as mean ± SD. Significant differences: bp<0.05.

shifts

glycolytic

Data



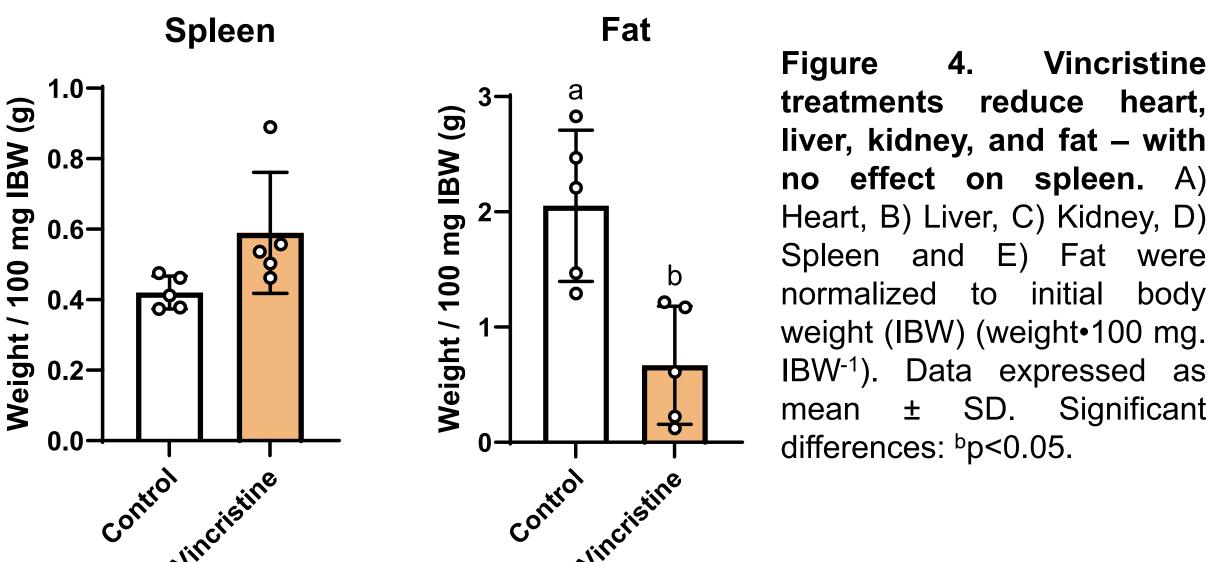


Figure 5. Vincristine impedes muscle growth and reduces muscular force **GSN** TA Quad **Ex Vivo** 100 200-Weight A 100-

Figure 5. Vincristine treatments reduces skeletal muscle weight and ex vivo force. A) Gastrocnemius, B) Quadriceps, C) Tibialis Anterior muscle weights were normalized to initial body weight (IBW) (weight/100 mg IBW). D) EDL peak ex vivo force measured at 150Hz. Ex vivo force expressed as kN/m². Data expressed as mean ± SD. Significant differences: bp<0.05.

Figure 6. Vincristine treatments shift towards glycolytic fiber type. Contro

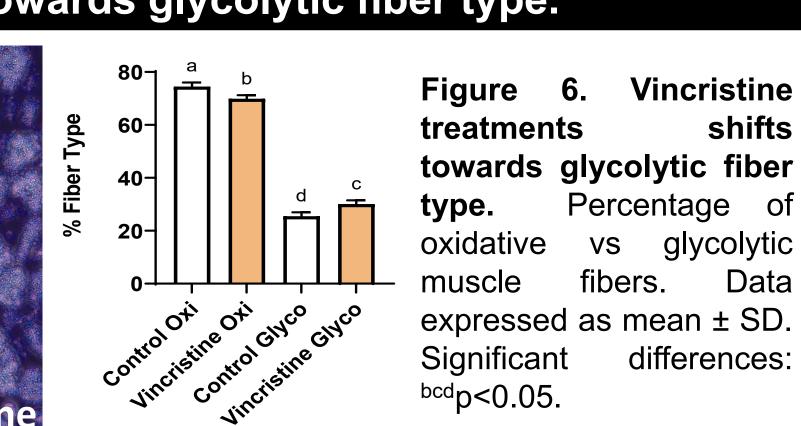


Figure 7. Vincristine Treatments Increase Protein Degradation and PGC1- α protein expression

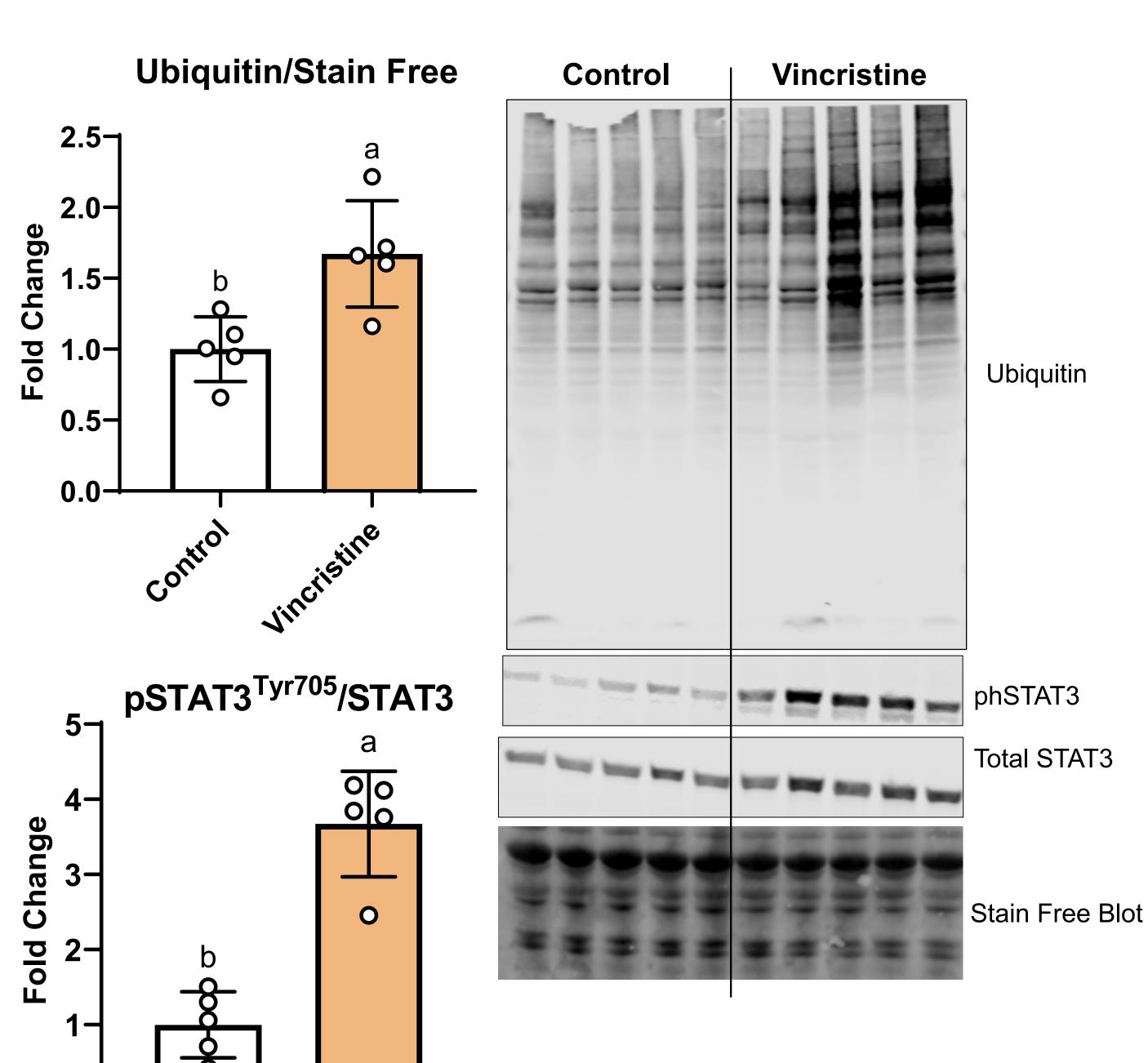


Figure 7. Vincristine treatments increase protein degradation and phosphorylation of STAT3. Protein expression via Western **blotting of** A) Ubiquitin, B) phospho-STAT3^{TYR705}. H) Representative Western Blot. Data expressed as mean ± SD. Significant differences: bp<0.05.

Fat were

Significant

body

initial

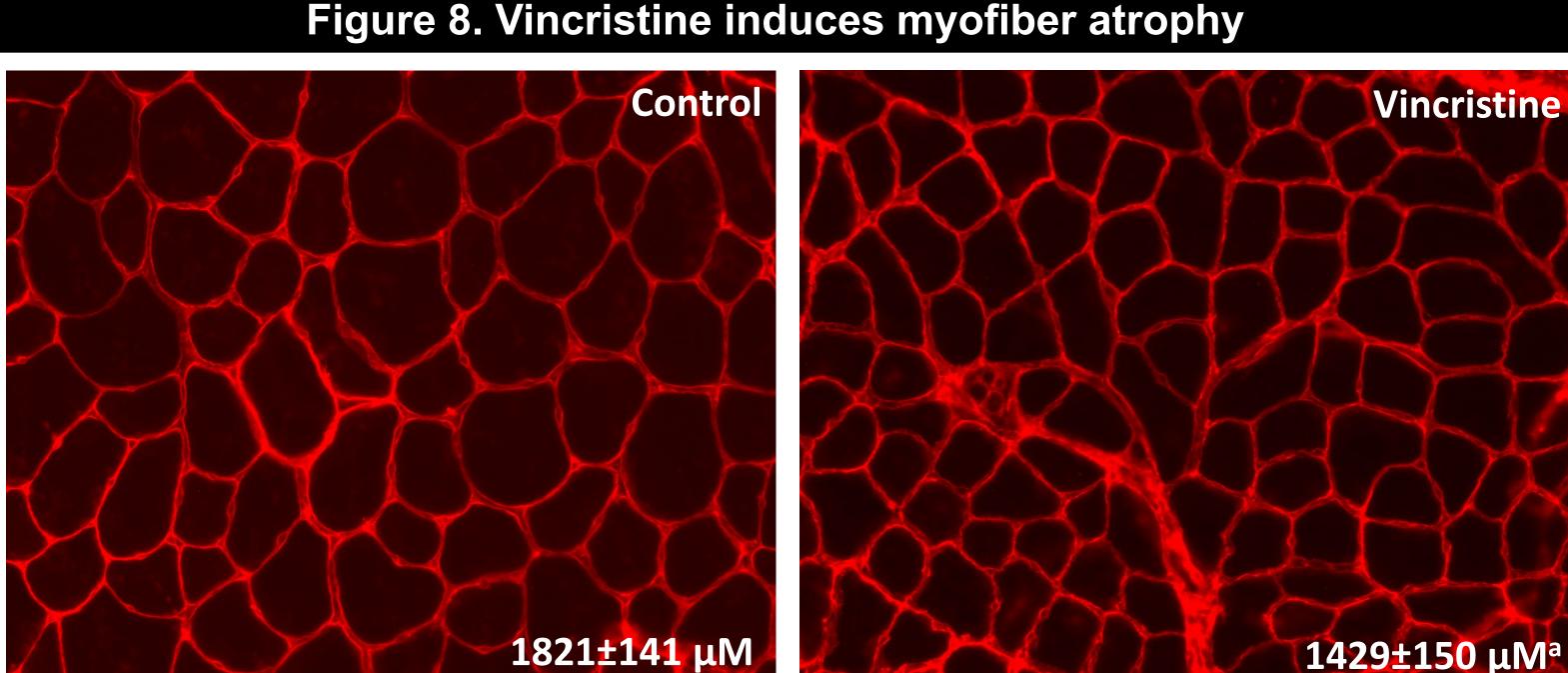


Figure 8. Vincristine treatments reduces myofiber cross sectional area. Average cross-sectional area (CSA) of myofibers is expressed as micrometer per squared meter (µm²); Representative image of myofiber cross sectional area for control and vincristine. Data expressed as mean ± SD. Significant differences: ^ap<0.05.

Figure 9. Vincristine treatments yield divergent E3 ligase expression and downregulate PGC1-α gene expression

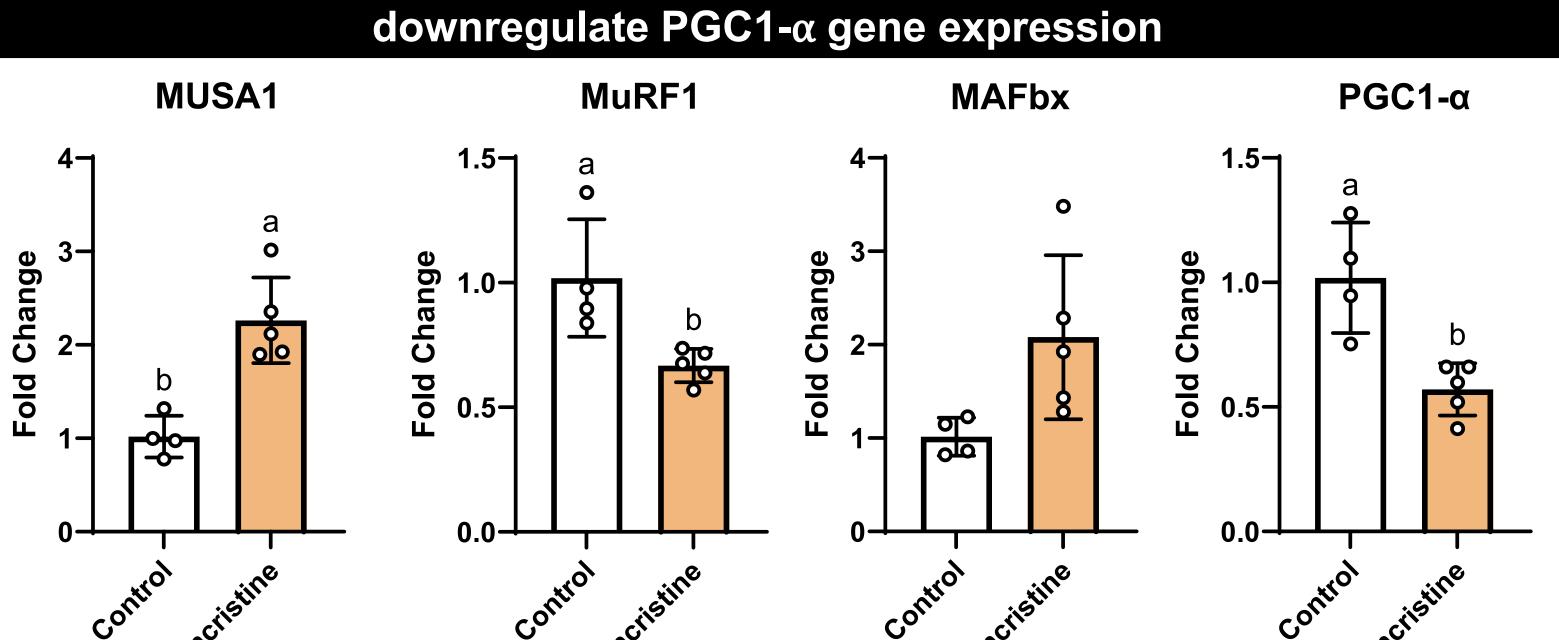


Figure 9. Vincristine treatments yield divergent muscle-specific ubiquitin ligases gene expression and downregulates PGC1-α gene expression.. Gene expression (via qPCR) of A) MUSA1, B) MuRF1, C) MAFbx, and PGC1-α in quadriceps muscle. Gene expression expressed as arbitrary unit. Data expressed as mean ± SD. Significant differences: bp<0.05.