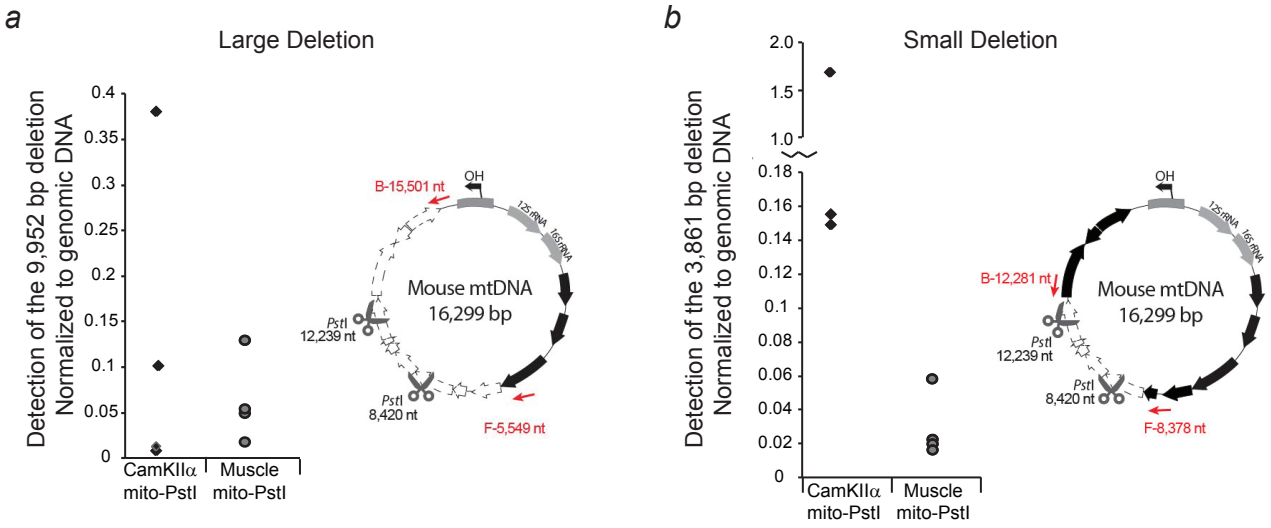
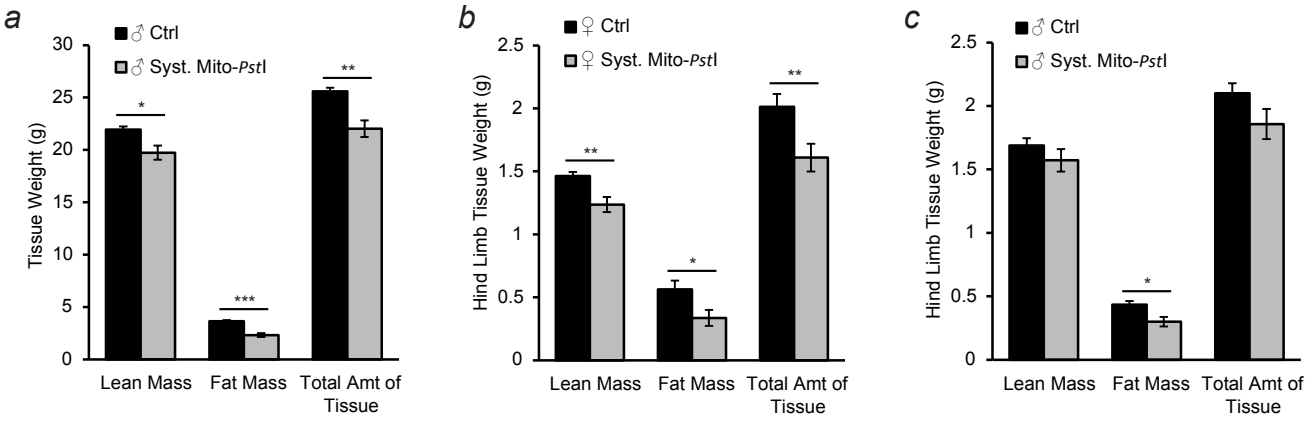
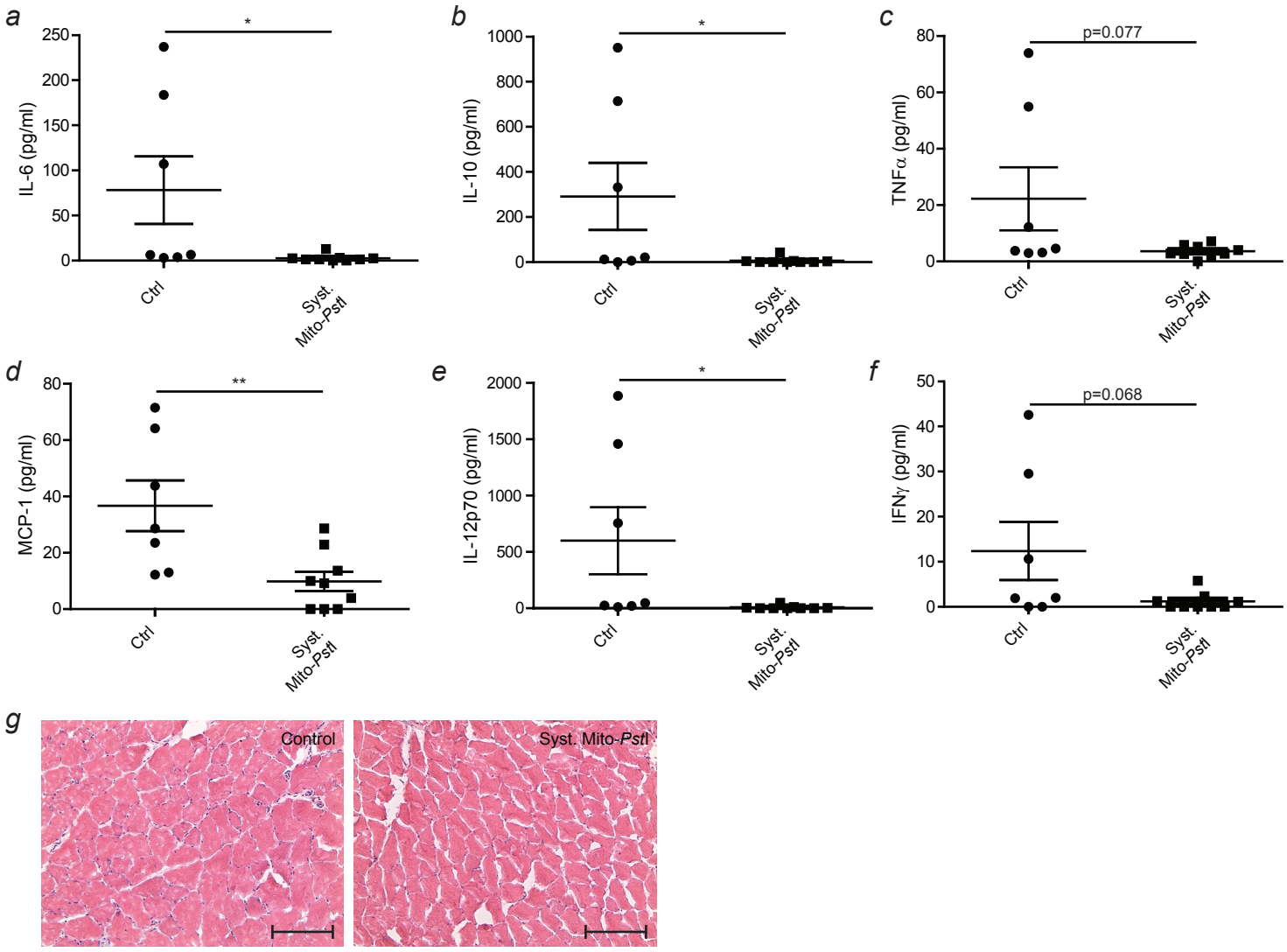


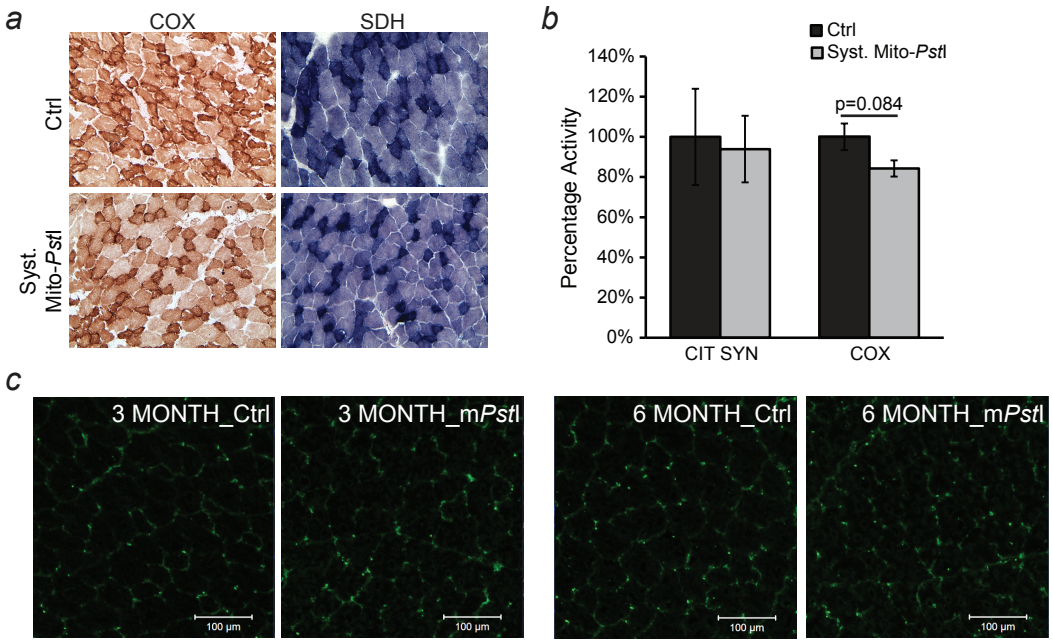
Supplementary figure S1. Systemic mito-*Pst*I mice have low levels of mtDNA deletions. ***a-b,*** Relative quantification of large (***a***) and small (***b***) deletions by quantitative PCR in skeletal muscle of the systemic mito-*Pst*I mice at 6 months of age, compared to levels in our previously reported CamKIIa-promoter induction model. Systemic mito-*Pst*I muscle harbored detectable deletion loads, but not at levels higher than those estimated to be 1%. Each symbol represents one animal. Red arrows indicate the primers used during qPCR.



Supplementary Figure S2. Tissue loss characterized in systemic mito-*Pst*I mice. ***a***, DEXA scan quantification (grams) of lean mass, fat mass, and total amount of tissue from 6 months old control and systemic mito-*Pst*I male mice (n=7~12 per group). ***b-c***, DEXA scan quantification (grams) of lean mass, fat mass, and total amount of tissue in the hind limb of 6 months old control and systemic mito-*Pst*I (***b***) female and (***c***) male mice (n=7~12 per group).



Supplementary Figure S3. Inflammatory cytokine levels in serum and histological staining of skeletal muscle from 6 month old mice. a-f, The cytokines (a-f, IL-12p70, TNFα, IFNγ, MCP-1, IL-10, IL-6) were measured using a BD Cytometric Bead Array Mouse Inflammation Kit, and data was analyzed using FCAP Array software. n=7 for Ctrl, and n=9 for Systemic Mito-*Pst*I. g, Representative H&E staining of quadriceps muscle from 6 months old mice. Data was presented as Mean±SEM (* =p<.05, ** = p<.01, *** = p<.001).



Supplementary Figure S4. Enzyme activity assay in skeletal muscle of 6 months old mice. a, Representative images of COX and Succinate dehydrogenase (SDH) activity staining of 6 months old control and systemic mito-***Pst***I mice (n=3 per group). b, Citrate synthase (CIT SYN) and Cytochrome c oxidase (COX) activity in quadriceps of 6 months old control and systemic mito-***Pst***I mice (n=5 per group). c, Immunohistochemical staining of 8-OHG/8-OHdG in frozen muscle sections from 3 and 6 months old control or systemic mito-PstI mice (n=3 per group). Values are presented as mean ± SEM (* =p<.05, ** = p<.01, *** = p<.001).