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## Mitochondrial Abnormalities May Contribute to Skeletal Muscle Weakness and Poor Regeneration in Fukutin-Deficient Muscular Dystrophy Mice

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The dystrophin-glycoprotein complex (DGC) provides a link between extracellular and intracellular structures of the muscle cell. We have previously demonstrated that muscle-specific deletion of the fukutin gene [*Myf5/Fktn* KO mice (KO)] causes DGC disruption. KO mice present moderate to severe muscular dystrophy characterized by muscle weakness and delayed regeneration following muscle injury. The objective of this study was to determine the extent to which mitochondrial dysfunction contributes to the muscle weakness and delayed regeneration in these mice. We hypothesized that mitochondrial dysfunction contributes to muscle weakness in KO mice and that improving mitochondrial content would benefit muscle regeneration following muscle injury. We administered daily injections of saline or AICAR (500mg/d/kg), an agent previously shown to improve mitochondrial quality in dystrophic muscle, to both KO (saline n = 9, AICAR n = 6) and littermate (LM) control (saline n = 9, AICAR n = 8) mice. Two weeks after onset of treatment, the left hindlimbs (anterior and posterior compartments) of all mice were injured with cardiotoxin to induce muscle regeneration, while the right hind limbs served as contralateral uninjured controls. Mice were sacrificed 2 weeks post-injury. Body mass and gastrocnemius mass normalized to body mass was 21% and 13% lower in KO mice compared to LM controls (body mass:  $P < 0.001$ , gastrocnemius:  $P < 0.002$ ). Pre-injury peak isometric torque about the ankle joint was 38% lower in KO mice compared to LM ( $P = 0.044$ ). Interestingly, muscle strength was not fully recovered in any group of mice 2 weeks post-injury, but AICAR-treated mice had 25% greater muscle strength following injury compared to salinetreated mice, independent of genotype ( $P = 0.036$ ). Mitochondrial respiration of injured and uninjured permeabilized fibers was also assessed 2 weeks post-injury. Mitochondrial respiration was 23% lower in KO mice compared to LM mice, independent of treatment and injury ( $P = 0.023$ ). Further analysis is required to determine if this is due to lower mitochondrial content or mitochondrial dysfunction. While there was no effect of AICAR on mitochondrial respiration, AICAR-treated mice had ~14% greater levels of COXIV protein content compared to salinetreated mice, independent of genotype and injury ( $P = 0.015$ ). This suggests a longer duration of AICAR treatment may be necessary for gains in mitochondrial protein contents to be realized in terms of mitochondrial respiration. In conclusion, this data suggests that fukutin deficiency is associated with mitochondrial abnormalities that may contribute to skeletal muscle weakness and poor regeneration. AICAR treatment may facilitate strength recovery following muscle injury, although it is unclear the extent to which AICAR affects mitochondrial function following injury.