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Genetic ablation of 4E-BP1 and 4E-BP2 is associated with increased muscle mass, strength and protein synthesis in aged male-mice.

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Background. The mammalian target of rapamycin (mTOR) is a multiprotein complex linking nutrient availability to cell growth and proliferation as well as numerous cellular processes. However, the key downstream targets of mTOR and their respective importance in controlling skeletal muscle function are still poorly understood. eIF4E-Binding proteins (4E-BPs) are involved in the control of translation initiation by mTOR, and are described as strong candidates linking mTOR activity and metabolism. Deletion of 4E-BP1 and 4E-BP2 in mice leads to increased sensitivity to diet-induced obesity and insulin resistance (1). On the other hand, transgenic overexpression of 4E-BP1 protects mice against obesity (2, 3). The aim of this study was to characterize the effect of 4E-BP1 and 4E-BP2 deletion on skeletal muscle function and homeostasis in aged-mice.

Methods. 24-month old male and female wild-type (WT) and whole body 4E-BP1/4E-BP2 double knock-out (DKO) mice were used to measure forearm grip strength and wire screen holding time (n=5-6). Weight of the hindlimb muscles was measured after sacrifice. Protein synthesis was measured *ex-vivo* in EDL by incorporation of L-[U-¹⁴C] Phenylalanine in the presence or absence of leucine/insulin. Results were analyzed by student t-test or 2-way ANOVA. Bonferroni post-tests were used to compare replicate means by row. Results are expressed as mean±sem.

Results. Survival rate was identical in WT and DKO mice. In males, genetic ablation of 4E-BP1 and 4E-BP2 resulted in increased lean mass (liver and skeletal muscle mass, p<0.01). The increased muscle mass in DKO mice was associated with increased mean (100.0±6.1g vs. 66.6±4.8g, p<0.01) and maximal grip strength (128.9±8.5g vs. 95.2±11.7g, p=0.06). Protein synthesis as measured by ¹⁴C-Phe incorporation into proteins was higher in both basal (0.251±0.021nmol/mg prot/h vs. 0.124±0.021nmol/mg prot/h, p<0.05) and leucine/insulin stimulated conditions (0.313±0.011 nmol/mg prot/h vs. 0.189±0.053nmol/mg prot/h, p<0.05) in DKO skeletal muscle. No difference in body composition, muscle mass, grip strength or skeletal muscle protein synthesis was observed in female DKO as compared to WT.

Discussion. These results demonstrate that deletion of 4E-BPs might have beneficial effects on skeletal muscle mass and function in ageing mice. They also suggest that 4E-BP proteins are a gender-specific modulator of muscle homeostasis.

1. Le Bacquer, O. (2007) *The Journal of clinical investigation* **117**, 387-396
2. Tsai, S. (2015) *The Journal of clinical investigation* **125**, 2952-2964
3. Tsai, S. (2016) *Cell reports* **16**, 1903-1914