

## Muscle hypertrophy and IGF-1 isoforms: is bigger better?

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Insulin like growth factor-1 (IGF-1) plays a central role in muscle hypertrophy and muscle wasting. IGF-1 exists as different isoforms due to different exon splicing (Shavlakadze *et al.*, 2005). IGF-1 isoforms that initiate from exon 1 are termed Class 1 (C1) isoforms, while isoforms that initiate from exon 2 are termed Class 2 (C2) isoforms. It has been proposed that different IGF-1 isoforms have different biological effects and may act through different signalling pathways. Previous studies show that over-expression of the Class 1 IGF-1 Ea (IGF-1:C1) causes skeletal muscle hypertrophy, slows the rate of myofibre atrophy following denervation and delays onset of necrosis in skeletal muscles of dystrophic *mdx* mice. Novel strains of non-dystrophic (normal) and *mdx* transgenic mice that over-express the Class 2 IGF-1 Ea (IGF-1:C2) isoform have muscle specific increase in total IGF-1 levels (~5 times higher compared to non-transgenic controls) and show more consistent muscle hypertrophy compared to the IGF-1:C1 mice.

Over-expression of the IGF-1:C2 resulted in a significant increase in quadriceps muscle mass in male and female IGF-1:C2 and *mdx*/IGF-1:C2 mice compared to their wild type littermates. Muscle hypertrophy in transgenic mice was more pronounced at 12 months of age compared to 3 months of age. Myofibre cross sectional area (CSA) was also examined in IGF-1:C2 and *mdx*/IGF-1:C2 mice. Average myofibre CSA was larger in IGF-1:C2 mice compared to the wild type littermates at both 3 and 12 months. In muscles from dystrophic *mdx*/IGF-1:C2 mice the average myofibre CSA was increased at 3 months but not at 12 months. The reduction in myofibre CSA in 12 month old *mdx*/IGF-1:C2 mice was due to myofibre splitting or branching. Diaphragm width was increased in 12 month but not in 3 month old male and female *mdx*/IGF-1:C2 mice. Despite the increased muscle mass, IGF-1:C2 did not increase specific force in muscles from non-dystrophic or *mdx* muscles and did not reduce myofibre necrosis in sedentary and treadmill exercised *mdx* mice. In adult (non-dystrophic and *mdx*) muscles, IGF-1:C2 over-expression does not coincide with the up-regulation of the Akt/mTOR signalling. However, striking activation of Akt signalling was observed in growing muscles of young 3 week old IGF-1:C2 mice. This study compared signalling activated by the C1 and C2 IGF-1 Ea isoforms and emphasized the impact of muscle growth. It also critically evaluated medically relevant scenarios where IGF-1 induced muscle hypertrophy might have beneficial effects.

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