IGF-1 isoforms and skeletal muscle regeneration

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The remarkable potential of lower vertebrates to rebuild adult organs and tissues contrasts with relatively poor regenerative capacity in mammals, which respond by rapid fibrosis and scarring. To improve the mechanisms at work in the mammalian response to damage or disease, we used a local acting isoform of Insulin-like growth factor-I (IGF-1).

When expressed specifically in skeletal muscles of transgenic mice, mIGF-1 induces hypertrophy and maintains tissue integrity during ageing, enhances healing following injury or exercise, and counters muscle decline in neurodegenerative disease and chronic heart failure, attenuating muscle loss by activation of stem cell-mediated repair mechanisms. After cardiotoxin-induced damage, regenerating mIGF-1 transgenic muscles rapidly downregulated markers of inflammation, suggesting that resolution of the inflammatory response is an important component of efficient regeneration. This is documented by repression of specific inflammatory cytokines and the NFkB pathway by mIGF-1 in damaged muscle and the increased regenerative capacity of mice lacking a functional NFkB pathway specifically in skeletal muscle.

Through alternate promoter usage and differential splicing, the single-copy IGF-1 gene is transcribed into several additional isoforms, which can either perform an endocrine function or act locally. Especially in light of the beneficial effects of the mIGF-1 isoform and its potential for clinic interventions, it is crucial to understand the differences between other naturally occurring IGF-1 variants. When over-expressed exclusively in skeletal muscle, none of the transgenic lines carrying the different IGF-1 isoforms showed a change in whole body weight or the weight of distal organs, such as heart, spleen or kidney. Interestingly, all but one isoform induced significant hypertrophy of myofibers. However, analysis of gene expression and phosphoprotein profiles reveal substantial differences in responses at the molecular level, suggesting that IGF-1 isoforms control more subtle aspects of muscle physiology as well. These and more recent results will be discussed.