Biological approaches to improve muscle healing after injuries

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Muscle injuries are among the most common and most frequently disabling injuries sustained by athletes. The inefficiency of the regeneration initiated in muscle shortly after injury is largely due to fibrosis (that is, scar tissue formation). We have identified growth factors that can improve muscle regeneration after injury, but we found that fibrosis still limits the degree of recovery. We demonstrated that transforming growth factor TGF-β1 plays a key role in skeletal muscle fibrosis and that the use of antifibrosis agents that inactivate TGF-β1 including decorin, relaxin, suramin, and gamma interferon, can reduce muscle fibrosis and significantly improve muscle healing after injury. Although we identified various agents that block the effect of TGF-β1 and reduce fibrosis in injured muscle, decorin’s unique ability to neutralize the fibrotic effect of TGF-β1 and enhance muscle regeneration makes this molecule particularly well-suited for use in efforts to improve muscle healing after injury. Although decorin’s effect on muscle regeneration may likely be a secondary effect to the reduction of fibrosis, we will present results showing a direct effect of decorin on muscle regeneration after laceration injury. We will show that decorin’s effect on muscle regeneration is mediated through its promotion of muscle cell differentiation by the up-regulation of myogenic genes, specifically p21, an important cyclin-dependent kinase inhibitor involved in muscle cell differentiation and muscle regeneration, and PGC-1α, a molecule that promotes the formation of slow-twitch muscle fibers. We will also present results showing that decorin not only neutralizes the effect of TGF-β1, but that it also down-regulates myostatin, a well known negative regulator of muscle mass, through a direct interaction with myostatin or through an up-regulation of follistatin, a well known antagonist of myostatin. Since decorin deficiency lead to impaired angiogenesis and decorin expression is induced in endothelial cells during angiogenesis, we believe that decorin may improve muscle healing through angiogenesis enhancement. We will present results showing that decorin influences the vascular supply in injured skeletal muscle and the healing process after injury. The experiments that will be presented in my talk should reveal not only the mechanism(s) by which decorin regulates muscle regeneration but also could lead to the development of new ways to promote the healing of injured or diseased muscle.