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## Regeneration of skeletal muscle following eccentric injury

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### Abstract

Eccentric contraction-induced skeletal muscle injuries, can be included in what is clinically referred to as muscle strains, are among the most common injuries treated in the sports medicine setting. Although patients with mild injuries often fully recover to their pre-injury levels, patients who suffer moderate or severe injuries can have a persistent weakness and loss of function that is refractory to rehabilitation exercises and currently available therapeutic interventions. The objectives of this review are to describe the fundamental biophysics of force transmission in muscle and the mechanism of muscle strain injuries, as well as the cellular and molecular processes that underlie the repair and regeneration of injured muscle tissue. The review will also summarize how commonly used therapeutic modalities affect muscle regeneration, and opportunities to further improve our treatment of skeletal muscle strain injuries.

### Force Transmission and the Ultrastructure of Skeletal Muscle

Skeletal muscles consist of hundreds to thousands, and sometimes millions, of long, multinucleated fibers organized together by a highly ordered extracellular matrix (ECM). There are three general layers of ECM in muscles – the outermost layer is the epimysium, the intermediate layer is the perimysium and the inner most layer is the endomysium. The epimysium covers the surface of the muscle and has important roles in force transmission and insulation of the muscle <sup>1</sup>. Processes from the epimysium extend into muscle tissue and form the second layer of connective tissue, the perimysium. The perimysium contains blood vessels, nerves and lymphatic ducts, and structurally divides muscle fibers into functional groups called fascicles. The innermost layer of connective tissue is the endomysium. The endomysium is composed of two layers of mostly type I and type III collagen fibrils that fuse to form a sheet-like structure that inserts into the tendon <sup>2</sup>. The endomysium is important in gathering forces generated within the muscle and transmitting them to the tendon as well as laterally to other muscle fibers <sup>3</sup>. The endomysium is connected to a basement membrane that directly surrounds each muscle fiber and is composed mostly of type IV and VI collagen <sup>2</sup>. Unlike the fibrillar type I and type III collagen, type IV and VI collagen forms a mesh-like network that surrounds the muscle fiber <sup>4</sup>. An overview of the

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