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Muscle degeneration in rotator cuff tears

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Rotator cuff tears are among the most common injuries seen by orthopedic surgeons. Although small- and medium-sized tears do well after arthroscopic and open repair, large and massive tears have been shown to develop marked muscle atrophy and fatty infiltration within the rotator cuff muscles. These pathologic changes have been found to be independent predictors of failed surgical repair with poor functional outcomes. To understand the pathophysiology of rotator cuff disease, we must first develop an understanding of the changes that occur within the cuff muscles themselves. The purpose of this review is to summarize the molecular pathways behind muscular degeneration and emphasize new findings related to the clinical relevance of muscle atrophy and fatty infiltration seen with rotator cuff tears. Understanding these molecular pathways will help guide further research and treatment options that can aim to alter expression of these pathways and improve outcomes after surgical repair of massive rotator cuff tears.

Level of evidence: Review Article.

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Introduction

Rotator cuff tears (RCTs) are extremely common injuries and represent the most common muscle-tendon tear in patients. As the rotator cuff ages, it becomes susceptible to degenerative changes, which can lead to shoulder dysfunction. Rotator cuff repair oftentimes works well in patients with small- and medium-sized tears; however, large and massive tears have been shown to develop muscle atrophy and fatty infiltration within the cuff muscles. Clinically, both muscle atrophy and fatty infiltration are independent predictors of failed surgical repair with poor functional outcomes. Understanding the pathophysiology of rotator cuff disease begins with an understanding of the molecular, physical, and clinical changes that occur within the cuff muscles. Unlike tendon degeneration, which has been a focus of study for many years, relatively few studies have evaluated the degenerative processes that occur within the muscles after an RCT. This article will review the basic science and molecular pathways behind muscular degeneration and detail new findings related to the clinical relevance of muscle atrophy and fatty infiltration in the setting of RCTs.

Muscle structure and regulation of muscle size and atrophy

Myocytes and extracellular matrix

The harmful changes that occur after RCTs can be understood by examining the functional roles and molecular pathways that govern muscle cell structure. Muscle is

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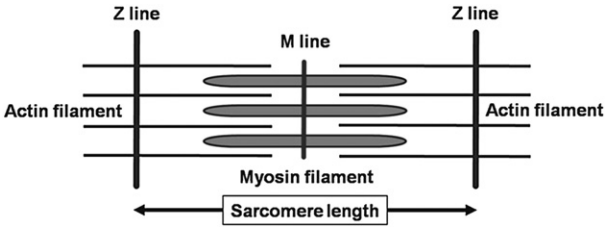

Figure 1 A sarcomere, the basic unit of a muscle cell. It is composed of multiple nuclei with myofibrils that are the contractile units of the muscle. Actin makes up the thin filament, and myosin make up the thick filament. (Reprinted with permission from Tomioka T, Minagawa H, Kijima H, Yamamoto N, Abe H, Maesani M, et al. Sarcomere length of torn rotator cuff muscle. J Shoulder Elbow Surg 2009;18:955-9. doi:10.1016/j.jse.2009.03.009.)

a unique and dynamic organ that is adaptive and responds to mechanical loads. It is dependent on a vast set of signaling pathways that include growth hormones, signal transduction pathways, and importantly, mechanical signals. Muscles respond to growth stimuli by increasing protein synthesis and developing a larger mass without a significant increase in myocyte number.

Unlike most other cells in the human body, the myocyte is a multinucleate cell that often contains over 100 nuclei in its mature state. Myocytes sit within an extracellular matrix of myofibrils, which are long chains of sarcomeres, to form myocyte contractile units (Fig. 1). In addition, there are a number of other cells, including fibroblasts, blood vessel endothelium cells, and muscle progenitor or stem cells (subtyped into satellite cells and muscle special cells), that form the body of the muscle. Muscle satellite cells, which are thought to be derived from pericytes,[16] have recently been found to be one of the primary progenitor cells in skeletal muscle; they merge into adjacent myocytes to replace dying myocyte nuclei.[80] Satellite cells can also form new myocytes, a process that is seen mainly in muscle development and regeneration.[12] Myofibers are connected to each other through the extracellular matrix (ECM), which has a central role in cell communication, transduction of mechanical force signals, and regulation of muscle differentiation, growth, repair, and remodeling. The ECM stores various growth factors and other bioactive molecules, including active and inactive proteases that can be released and activated by specific signal pathways that help modulate the changes seen in muscle.[46,69]

During the development of muscle atrophy, there is significant remodeling of the ECM that includes increased collagenous connective tissue (fibrosis). A group of zinc- or calcium-dependent proteinases, called matrix metalloproteinases (MMPs), is believed to play an important role of ECM remodeling in skeletal muscle. These enzymes alter protein expression within the cell to stimulate tissue remodeling.[2] Recent studies have shown significantly increased expression of MMP-2, MMP-9, and MMP-13 in muscle atrophy.[81,82] These MMPs have been implicated in tendon degeneration and tissue degradation in other disease states, and their roles in muscle changes have recently been evaluated. MMPs have been found to be involved in increasing atrophy in a rat and rabbit model of muscle atrophy.[4,19,49] MMP-2, MMP-9, and MMP-13 are thought to be involved in the transformation and morphogenesis of cells as well as degradation in both pathologic and non-pathologic states.[21,81] For example, Rodeo and colleagues[81] found that MMP-1, MMP-9, and MMP-13, of which MMP-1 and MMP-13 are collagenases, have increased expression in the supraspinatus tendon after it has been torn. Their presence indicates a cell-mediated tendon degradation that could possibly lead to the biomechanical instability seen in RCTs.[81]

Molecular regulation of muscle size and protein synthesis

Although new mature myocytes are rarely added to muscle, the muscle remains a dynamic structure that must respond to changes in daily demand and functional requirements. Regulation of muscle size is determined at the cellular level and is controlled by the magnitude of protein synthesis. These are complex and multifaceted pathways that are responsible for both protein synthesis and breakdown. Mechanical signals, growth hormones, insulin-like growth factor (IGF), and nuclear factor kappa B (NF-κB) have been implicated in regulating muscle size.[48] Alterations in these signal transduction pathways can either increase or decrease muscle size, dependent on the regulation of these pathways.

The majority of animal model studies evaluating muscle atrophy in RCTs have focused on muscle atrophy genes that alter the expression of protein degradation (Fig. 2). The ubiquitin-proteasome system is the primary regulator of protein breakdown that provides a mechanism for selective degradation of regulatory and structural proteins. Ubiquitin ligases are the key enzymes in this system.[47] It has been hypothesized that NF-κB has a central role in the development of muscle atrophy through three mechanisms[53]: (1) NF-κB can augment the expression of several proteins of the ubiquitin-proteasome system involved in the degradation of specific muscle proteins; (2) NF-κB can increase the expression of inflammation-related molecules that directly or indirectly promote muscle wasting; and (3) NF-κB can interfere with the process of myogenic differentiation that may be required for regeneration of atrophied skeletal muscles.[28]

NF-κB and forkhead transcription factor (FOXO) are responsible for the regulation and increased expression of atrophy-related proteins.[75,76] Two inducible E3 ubiquitin ligases, atrogin-1 (also known as MAFbx) and muscle ring finger protein 1 (MuRF1), have been identified as enzymes responsible for the degradation of the bulk of

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