EXPERIMENTAL CELL RESEARCH 316 (2010) 3050–3058

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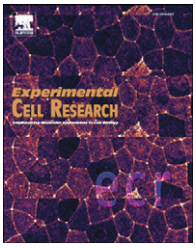

Review

Regulation and dysregulation of fibrosis in skeletal muscle

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ARTICLE INFORMATION

Article Chronology:
Received 21 May 2010
Accepted 30 May 2010
Available online 4 June 2010

Keywords:
Skeletal muscle
Fibrosis
Extracellular matrix remodeling
Muscle regeneration
Muscular dystrophy
Aging

ABSTRACT

In response to skeletal muscle injury, distinct cellular pathways are activated to repair the damaged tissue. Activation and restriction of these pathways must be temporally coordinated in a precise sequence as regeneration progresses if muscle integrity and homeostasis are to be restored. However, if tissue injury persists, as in severe muscular dystrophies, the repair process becomes uncontrolled leading to the substitution of myofibers by a non-functional mass of fibrotic tissue. In this review, we provide an overview of how muscle responds to damage and aging, with special emphasis on the cellular effectors and the regulatory and inflammatory pathways that can shift normal muscle repair to fibrosis development.

Contents

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doi:10.1016/j.yexcr.2010.05.035

Normal versus dysregulated muscle repair and fibrosis development

After injury of adult skeletal muscle, a series of well-coordinated events takes place that serve to repair the damaged tissue. These events are initiated immediately after injury by the release of growth factors and cytokines from both the injured blood vessels and infiltrating inflammatory cells. The cytokines further promote the migration, proliferation and survival of various cell types at the injury site, whereas the inflammatory cells are responsible for the phagocytosis of cell debris. The formation of new muscle fibers begins with the activation of normally quiescent satellite cells (muscle stem cells) which lie beneath the muscle basal lamina. Satellite cell activation is followed by extensive proliferation, commitment and differentiation of myoblasts at the edge of the injury. Finally, myoblasts will fuse either to themselves or to the damaged myofiber to form new myofibers. In normal muscle repair after an acute/moderate injury, the satellite cells use the basement membranes of necrotic fibers as a scaffold to ensure that the new muscle fibers maintain a similar position. Basement membrane components are also critical for guiding the formation of neuromuscular junctions, although eventually the basement membrane of the necrotic fiber is phagocytozed during the final stages of muscle regeneration. In parallel, muscle repair requires the migration and proliferation of fibroblasts which will produce increased levels of extracellular matrix (ECM) components which will be degraded as regeneration and growth of new myofibers proceeds. Angiogenesis is also required to establish a new vascular network at the site of injury. Finally, growth and maturation of newly formed muscle fibers occurs.

Perturbation of any of these stages can result in unsuccessful muscle regeneration, typically characterized by persistent myofiber degeneration, inflammation and fibrosis, which is essentially an excessive accumulation of ECM components (reviewed in [1,2]). The most recognized clinical consequences of defective muscle repair and fibrosis undoubtedly occur in the severe muscular dystrophies, where the primary defect leads to continuous cycles of myofiber degeneration and regeneration such that the muscle repair process is unable to replace the damaged muscle with new fibers. In many of the muscular dystrophies, the presence of inflammatory cells is sustained and necrotic muscle fiber basement membranes are phagocytozed before they are able to act as scaffolds for the seeding of new muscle fibers or guide innervation. Consequently, dystrophic muscle is characterized by abnormal muscle fiber arrangement. Similarly, the chronic persistence of damage and inflammatory cells in dystrophic muscle results in an excess of growth factors and cytokines. In addition to stimulating satellite cell functions, these molecules also induce the massive proliferation and activation of fibroblasts. With time, fibroblasts contribute to the formation of a permanent fibrotic tissue by producing an accumulation of fibrotic interstitial ECM components such as hyaluronic acid, fibronectin, proteoglycans and interstitial collagens [3–5]. Thus, fibrosis can be considered an aberrant or dysregulated tissue repair response that has severe consequences not only in hereditary myopathies but also in the aging process.

Extensive studies have identified a variety of different extracellular matrix proteins, growth factors, cytokines and their downstream signaling pathways, that orchestrate both muscle tissue homeostasis and the regeneration process. In this review, we summarize the results of functional *in vivo* studies that reveal the roles and activities of different fibrotic regulators which become prominent upon dysregulation of the muscle repair process during muscular dystrophy progression and in aged muscle.

Uncontrolled ECM remodeling may switch normal muscle repair to fibrosis development

The ECM surrounding skeletal muscle tissue plays an important role in maintaining the structure of the muscle and also in providing an environment in which the contractile muscle fibers can function. The external lamina of muscle fibers is made up of collagen IV, laminin and heparan sulfate proteoglycans; the interstitial matrix that surrounds them contains collagen I, III and V, fibronectin and perlecan [1–3]. In addition to providing physical stability and orientation, the ECM sequesters and presents heparin-binding growth factors such as hepatocyte growth factor (HGF) and fibroblast growth factor (FGF) to the fibers, as well as participates in signaling to the differentiated fibers through dystroglycan and sarcoglycan complexes [3].

Immediately after muscle injury, a hematoma is formed between the damaged myofibers, which is rapidly infiltrated by inflammatory cells, in particular phagocytic macrophages which clear myofiber debris and blood clot components. Fibrin and fibronectin extravasate from the circulation and cross-link to form a primary matrix, which provides a scaffold and anchorage site for both infiltrating cells and activated resident cells in addition to strengthening the nascent connective tissue against contractile forces [2,4]. At this time, activated fibroblasts synthesize a wide variety of growth factors and ECM components, including integrin ligands such as fibronectin, collagen I and III, and proteoglycans, in order to promote cell proliferation and migration and further expansion of the connective tissue. Although initially beneficial, the matrix deposition process becomes pathogenic if it continues uncontrolled, resulting in substantial remodeling of the muscle basal lamina and formation of permanent collagenous tissue surrounding the myofibers. In severe muscle pathologies such as Duchenne muscular dystrophy (DMD), it might ultimately lead to substitution of skeletal and cardiac muscle by fibrous tissue.

Control of muscle regeneration and fibrosis by specific ECM components

Analysis of individual components of the ECM after muscle injury in genetic knock out models or after pharmacological interference has provided important insight into the function of the ECM during muscle regeneration. Fibrinogen (and its end-product fibrin, referred to collectively by the term fibrin/ogen) has been found in injured skeletal muscle as a component of the provisional primary ECM. Mice with genetic loss of the fibrinolytic proteases uPA and plasmin (see also below) manifest defective fibrinolysis and accumulate fibrin after muscle injury and exhibit impaired muscle regeneration [6,7]. Muscle regeneration in these animals can be rescued by fibrin/ogen depletion, suggesting that excessive and persistent fibrin deposition is deleterious for myofiber repair. Fibrin also accumulates in the degenerating muscles of DMD patients and in the diaphragm of the mdx mouse model of DMD