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REVIEW ARTICLE

Skeletal muscle regeneration is modulated by inflammation☆

Q12 Q1 Wenjun Yang, Ping Hu*

State Key Laboratory of Cell Biology, Center of Excellence in Molecular and Cell Biology, Shanghai Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences, 320 Yueyang Road, Shanghai, 200031, China

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Abstract Skeletal muscle regeneration is a complex process orchestrated by multiple steps. Recent findings indicate that inflammatory responses could play central roles in bridging initial muscle injury responses and timely muscle injury reparation. The various types of immune cells and cytokines have crucial roles in muscle regeneration process. In this review, we briefly summarise the functions of acute inflammation in muscle regeneration.
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Muscle injury and muscle stem cells in muscle regeneration

Skeletal muscle is the most abundant tissue in human body, which accounts for about 40% of the body mass. Under normal conditions, the turnover rate of adult skeletal muscle is about 1–2% of myonuclei per week [1]. Muscle is susceptible for various injuries in daily life, such as the mechanical trauma, thermal stress, myotoxic agents, ischaemia, neurological damage and other pathogenic conditions. The most common cause of muscle injury is mechanical trauma [2]. It destroys the integrity of the myofibre plasma membrane and basal lamina, leading to the influx of extracellular calcium [3] which eventually leads to the degradation of muscle proteins and necrosis [4]. Then, the muscle degeneration was further promoted by the swelling and haematoma formation [5], as the

☆ **The translational potential of this article:** Immune system is closely relevant to the muscle regeneration. Understanding the mechanisms of inflammation in muscle regeneration is therefore Q13 critical for the development of effective regenerative, and therapeutic strategies in muscular disorders. This review provides information for muscle regeneration research regarding the effects of inflammation on muscle regeneration.

* Corresponding author. State Key Laboratory of Cell Biology, Center of Excellence in Molecular and Cell Biology, Shanghai Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences, 320 Yueyang Road, Shanghai, 200031, China
E-mail address: hup@sibcb.ac.cn (P. Hu).

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consequence of the activation of acute inflammation. After the initial muscle degeneration, muscle regeneration mediated by muscle stem cells is switched on. The injured myofibres can be regenerated, and the muscle functions such as contraction force, metabolism can be restored.

Muscle stem cells (satellite cells) are the major contributor to muscle regeneration. They were discovered by Alexander Mauro in 1961 [6]. These cells are located in a membrane-enclosed niche between the sarcolemma (plasma membrane) and the basal lamina surrounding the myofibres. Muscle stem cells remain quiescent under normal conditions [7,8]. In response to exercise, muscle growth, trauma or other stimuli, muscle stem cells are activated to enter the cell cycle, proliferated briefly and further differentiated to new myotubes or fuse to the damaged myofibres to repair muscle injury. After activation and proliferation, part of the muscle stem cells can return to quiescence and replenish the *in vivo* stem cell pool to prepare for the next regeneration process [9,10].

The mechanism to activate muscle stem cells and promote muscle stem cell proliferation and differentiation in a timely manner remains to be explored. Understanding the mechanism will greatly facilitate the development of regenerative treatment for muscle injury and muscle degenerative diseases.

Acute inflammation bridges the conversion from muscle necrosis stage to regeneration stage

The process of muscle regeneration can be divided to several stages: necrosis of the injured muscle cell, activation of muscle stem cells, proliferation of the activated muscle stem cells, differentiation of the muscle stem cells, maturation of the newly formed muscle fibres and the remodelling of muscle fibres. Acute inflammation and immune cells play critical roles in almost all stages of muscle regeneration.

At the early stage of muscle regeneration, the injured muscle cells undergo necrosis in response to trauma. Upon muscle injury, the membranes of muscle fibres are damaged and the cellular contents and chemotactic factors are released to the extracellular space, which in turn induces the infiltration of many types of immune cells [11]. The infiltrated immune cells, such as mast cells and neutrophils, can help clearing the damaged myofibres at the injury site. Meanwhile, they can also secrete various types of cytokines to recruit more immune cells like macrophages. These immune cells can trigger on a cascade of cellular responses to regulate muscle stem cell activation, proliferation and differentiation. They serve as important mediators to orchestrate muscle regeneration.

The first wave of immune cells: complement system, mast cells and neutrophils

The major events of early stage of muscle regeneration after injury include muscle fibre necrosis, lesion enlargement and debris clearance. The activation and infiltration of the first wave of immune cells occur at the early stage of muscle regeneration. The early event of muscle repair is characterised by the necrosis of the damaged fibres after trauma. The immune system was activated by the cell debris and the cell content leakage from the damaged fibres at the muscle lesion site.

The complement system serves as the first sensor of the muscle injury. The complement system, which represents the first defence line of innate immunity, is activated immediately within seconds after injury [12]. It is made up of a collection of nine major complement proteins found in the bloodstream allowing a rapid immune response against an antigen [13,14]. The activation of complement system in the injured muscle leads to infiltration of neutrophils and macrophages to the lesion site [15]. The complement C3 and C4 are two of complement proteins. Their cleavage products C3a and C4a are upregulated in the serum of population with prolonged exercises, revealing the involvement of the complement-mediated inflammation in the early stage of muscle injury [16].

Mast cells are large, ovoid cells of haematopoietic lineage that circulate in the blood and mature after entering peripheral tissues, with a centrally located nucleus and numerous large, intensely basophilic granules [17]. Mast cell degranulation is one of the earliest innate immune system responses involved in muscle damage and repair that leads to the consequent inflammatory events. Mast cell degranulation is often observed in areas surrounding injured myofibres. Upon muscle injury, the resident mast cells in skeletal muscle are rapidly activated. After activation, master cells degranulate and release proinflammatory cytokines, such as tumour necrosis factor-α (TNF-α), interleukin (IL)-1 and histamine to recruit more mast cells, neutrophils and other immune cells to the injury site [18,19]. As the result, more mast cells and neutrophils infiltrated to the lesion to further promote inflammation [20].

Neutrophils are one of the most important immune cell types in the first wave of the proinflammatory phase following muscle injury. Like mast cells, the resident neutrophils in skeletal muscles can be activated immediately after the muscle injury and release the proinflammatory cytokines including TNF-α, IFN-γ and IL-1β [21,22]. The peripheral neutrophils can be further recruited by proinflammatory cytokines secreted by resident neutrophils and mast cells. This mechanism allows rapid infiltration of the large amount of neutrophils to the extracellular space around the damaged fibres within two hours. The number of the infiltrated neutrophils peaks in 6—24 hours after injury and declines rapidly 72—96 hours after injury [23].

Neutrophils can release a variety of factors such as cytokines, enzymes and oxidative factors to facilitate the clearance of the necrotic muscles [24—26]. The removal of the fibre debris facilitates the progress of muscle regeneration. The infiltrated neutrophils at the injury site produce IL-1 and IL-8 to induce the macrophage infiltration to the lesion [27]. The infiltration of macrophages can further improve the muscle injury repair as described in the following.

Neutrophils are the major source of reactive oxygen species after injury as well [28]. The neutrophil-derived reactive oxygen species has been shown to contribute to the muscle fibre degradation and vascular alterations

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