Exercise and skeletal muscle regeneration

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Abstract  Skeletal muscle injury is generally caused by stimuli, such as intense resistance training, eccentric muscle contraction, muscle strain and bruising. Injured skeletal muscles are repaired within several weeks after injury, because skeletal muscle has a remarkable capacity for muscle regeneration. Cellular and molecular events underlying the regenerative processes are mainly regulated by myogenic stem cells and inflammatory cells. The aim of this review is to summarize the current understanding of the cellular and molecular mechanisms responsible for muscle regeneration. In this review, focus will be given to the critical roles of satellite cells and macrophages during muscle regeneration. In addition, the satellite cell responses to exercise are also discussed.

Keywords: muscle regeneration, satellite cell, macrophage, myokine

Introduction

Skeletal muscle is the largest organ in the human body, comprising about 40-50% of body mass. Postnatal growth and regeneration of skeletal muscle is mediated by satellite cells. The cells are a quiescent population of myogenic stem cells that reside between the basal lamina and plasmalemma (plasma membrane), and are rapidly activated in response to appropriate stimuli1,2). Satellite cells are activated in response to injury; they then proliferate, differentiate, and fuse to repair or replace damaged myofibers. Skeletal muscle regeneration is a coordinated process, in which several factors are sequentially activated to maintain and preserve muscle structure and function.

Inflammation is clearly a critical component of muscle physiology and it is an important phase in the regenerative process. At the early phase of muscle regeneration, injury of myofibers results in rapid necrosis, due to an influx of extracellular calcium which induces proteolysis of the myofibers3,4). The presence of necrotic fibers activates a defined inflammatory response that is characterized by the sequential invasion of muscle by specific inflammatory cell populations5). Neutrophils are the first inflammatory cells that infiltrate the site of muscle injury, followed by macrophage invasion5). Macrophages are the predominant inflammatory cell type within the injured area. They play a direct role not only in removing tissue debris, but also in the activation of satellite cell-mediated muscle repair and regeneration6,7).
Satellite cells in response to exercise

Resistance and endurance exercise training enhances the satellite cell pool in humans and animals\(^{21,22}\). Furthermore, the authors also demonstrated that increases in the satellite cell pool of skeletal muscle, following endurance training, depend on the intensity rather than duration of exercise\(^{21}\). However, it is not fully clear which factors can induce increases in proliferative potential of satellite cells by exercise training.

Skeletal muscle has been acknowledged as a cytokine-producing organ during muscular exercise, so-called myokines\(^{23}\). To date, the list of identified myokines comprises IL-6, IL-7, IL-8, IL-15, LIF, FGF 21, and brain-derived neurotrophic factor (BDNF)\(^{23}\). Some myokines have the potential to affect satellite cell proliferation. Previous research showed that dramatic increases in plasma IL-6 and LIF were observed after endurance exercise. It is important to note that IL-6 or LIF knock-out mice underwent a blunted hypertrophic response compared with wild-type mice following compensatory hypertrophy\(^{24,25}\). Increases in the number of satellite cells are necessary for full skeletal muscle growth and hypertrophy\(^{1,26}\). It was confirmed that IL-6 may induce a dose-dependent increase in the proliferative potential of satellite cells through activation of janus kinase (JAK)/signal transducer and activator of transcription 3 (STAT3)/Cyclin D1 pathway (Kurosaka and Machida, unpublished data). In addition, LIF could induce satellite cell proliferation in culture through activation of the STAT3 signaling pathway\(^{16}\). IL-6 or LIF binds to the receptors, STAT3 is phosphorylated by activated JAK, STAT3 homo- or heterodimers are formed, and then are translocated to the nucleus where the transcription of downstream target genes is activated by binding to specific DNA elements in their promoter regions\(^{27}\). Once in the nucleus, p-STAT3 promotes the transcription of downstream genes, such as Cyclin D1, that are associated with the cell cycle\(^{28}\).

The role of macrophages in muscle regeneration

Neutrophils are the first inflammatory cells that infiltrate the site of muscle injury, followed by macrophage invasion\(^9\). Neutrophils rapidly release high concentrations of free radicals and proteases. These factors promote the

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**Fig. 1** Schematic representation of the molecular events regulating muscle regeneration

platelet-derived growth factor (PDGF-AA and PDGF-BB)\(^{17}\), IL-4\(^{18}\), and stromal cell-derived factor-1 (SDF-1)\(^{19}\). These factors are not only secreted from myofibers, but are also secreted from inflammatory cells, myocyte nuclei, the vasculature and satellite cells themselves\(^{1,20}\). The specific microenvironment of satellite cells, known as the ‘niche’, plays an important role in normal muscle regeneration.
removal of cellular debris and the secretion of proinflammatory cytokines that stimulate the homing of macrophages, further promoting tissue inflammation. Macrophages are recruited by chemotactic factors, including monocyte chemoattractant protein 1 (MCP-1), fractalkine (CX3CL1), and urokinase-type plasminogen activator (uPA), for circulating monocytes on the damaged site. Chazaud et al. (2009) showed that myogenic cells secrete chemotactic factors for monocytes. Resident macrophages also secrete MCP-1, which helps to recruit both neighboring resident macrophages and circulating monocytes.

Several findings suggest that macrophages play a direct role not only in removing tissue debris, but also in the activation of satellite cell-mediated muscle repair and regeneration. How do macrophages play distinct roles and even opposite functions during muscle regeneration? It is generally known that two distinct macrophage populations, including pro-inflammatory macrophage (also called M1) and anti-inflammatory macrophage (also called M2), exist. Macrophage phenotypes have been characterized based on distinct functional properties, surface markers, and the cytokine profile. M1 macrophages are the first to reach damaged muscle following muscle damage. M1 macrophages are characterized by expressing CD68 and lacking a CD163 cell surface marker (Fig. 1). Also, M1 macrophages strongly express IL-12 and IL-23, whereas they weakly express IL-10. They produce copious amounts of pro-inflammatory cytokines, such as TNF-alpha and IL-1-beta, and are responsible for the phagocytosis of necrotic muscle fibers. Phagocytosis of necrotic debris switches the phenotype of M1 macrophages into M2 macrophages. M2 macrophages express CD68 but lack CD68 on their surface. They also strongly express IL-10 and weakly express IL-12 and IL-23. M2 macrophages regulate the secretion of growth factors to regulate satellite cells. In vitro, M1 macrophages stimulate myoblast proliferation, whereas M2 macrophages stimulate their differentiation. Thus, macrophages are involved in both phases of skeletal muscle regeneration: first, inflammation and cleansing of necrosis, and then myogenic differentiation and tissue repair.

Conclusions

Muscle satellite cells and macrophages play critical roles in skeletal muscle regeneration. Exercise could improve several functions of satellite cells. Thus, understanding the molecular mechanisms by which satellite cells and macrophages regulate muscle regeneration could lead to new physical therapeutic strategies to promote muscle regeneration.

Conflict of interest

There is no conflict of interest.

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