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# The physiopathologic interplay between stem cells and tissue niche in muscle regeneration and the role of IL-6 on muscle homeostasis and diseases

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ABSTRACT

Skeletal muscle is a complex, dynamic tissue characterized by an elevated plasticity. Although the adult muscle is mainly composed of multinucleated fibers with post mitotic nuclei, it retains a remarkable ability to regenerate in response to traumatic events. The regenerative potential of the adult skeletal muscle relies in the activity of satellite cells, mononucleated cells residing within the muscle in intimate association with myofibers. Satellite cells normally remain quiescent in their sublaminar position, sporadically entering the cell cycle to guarantee an efficient cellular turnover, by fusing with pre-existing myofibers, and to maintain the stem cell pool. However, after muscle injury satellite cells undergo an extensive increase of their activity in response to environmental stimuli, thereby participating to the regeneration of a functional muscle tissue. Nevertheless, regeneration is affected in several pathologic conditions and by a wide range of environmental signals that are highly variable, not only through time, but also depending on the physiological or pathological conditions of the musculature. Among these factors, the interleukin-6 (IL-6) plays a critical physiopathologic role on muscle homeostasis and diseases. The basis of muscle regeneration and the impact of IL-6 on the physiopathology of skeletal muscle will be discussed.

## 1. Introduction

Muscle regeneration is a highly coordinated program, which involves the activation of the muscle compartment of stem cells, namely satellite cells (SCs), as well as other precursor cells, whose activity is strictly dependent by environmental signals.

Mitotically quiescent satellite cells reside within an exclusive location underneath the basal lamina that surrounds muscle fibers; this niche is thought to protect and regulate their functions not only through cellular-mediated mechanisms but also by mechanical and biochemical inputs [1]. The hypothesis of a complex environment regulating stem cell behavior was proposed in 1978 by Schofield [2], who highlighted how the stemness potential is not only an intrinsic feature of the stem cells but might also be influenced by external stimuli. A tightly regulated interplay between stem cells and other resident cell types, as well as the intimate connection with structural components of the tissue niche, can be thus responsible for the maintenance of the stem cell pool under steady-state conditions and to guide stem cells activation and differentiation when regenerative signals are provided [3]. In the last years increasingly findings suggested that the stem cell biology may be more complex than originally postulated and that the comprehensive environment framing satellite cells in skeletal muscle could be an important determinant for their survival and diff ;erentiation [4]. Because niche factors and components normally control and sustain a physiological stem cell activity and maintenance, the loss of homeostatic input from the niche, as observed under pathological conditions, can deregulate stem cell physiology, critically affecting the ability of muscle tissue to efficiently regenerate and to regain the functional integrity after damage (Fig. 1). Thus, the stem cell niche is not only an anatomical compartment but a complex, integrated network of both cellular and acellular components that provide signals influencing stem cells and muscle homeostasis.

*Abbreviations:* IL-, interleukin; SC, satellite cell; ECM, extracellular matrix; MuSCs, muscle stem cells; ROS, reactive oxygen species; Treg, regulatory T cells; Pax7, Paired box protein 7; Myf5, myogenic factor 5; MyoD, myoblast determination protein; MRF, muscle regulatory factors; miRNA, microRNA; myomiR, muscle-specific miRNA; Lsd1, lysine-specific demethylase 1; FAPs, fibro-adipogenic progenitors; HGF, hepatocyte growth factor; bFGF, basic fibroblast growth factor; LM, laminin; sIL6R, soluble IL-6 receptor; Mac-1, M1 macrophages; Mac-2, M2 macrophages; TNFα, tumor necrosis factor alpha; Sema3A, semaphorin 3A; IGF-1, insulin-like growth factor-1; TGF-β, transforming growth factor; DMD, Duchenne muscular dystrophy; LIF, leukemia inhibitory factor; OSM, oncostatin M; CNTF, ciliary neurotrophic factor; SOCS3, suppressor of cytokine signaling; SHP2, SH2-domain containing protein tyrosine phosphatase 2; TC-PTP, T-cell protein tyrosine phosphatase; STAT3, signal transducer and activator of transcription 3

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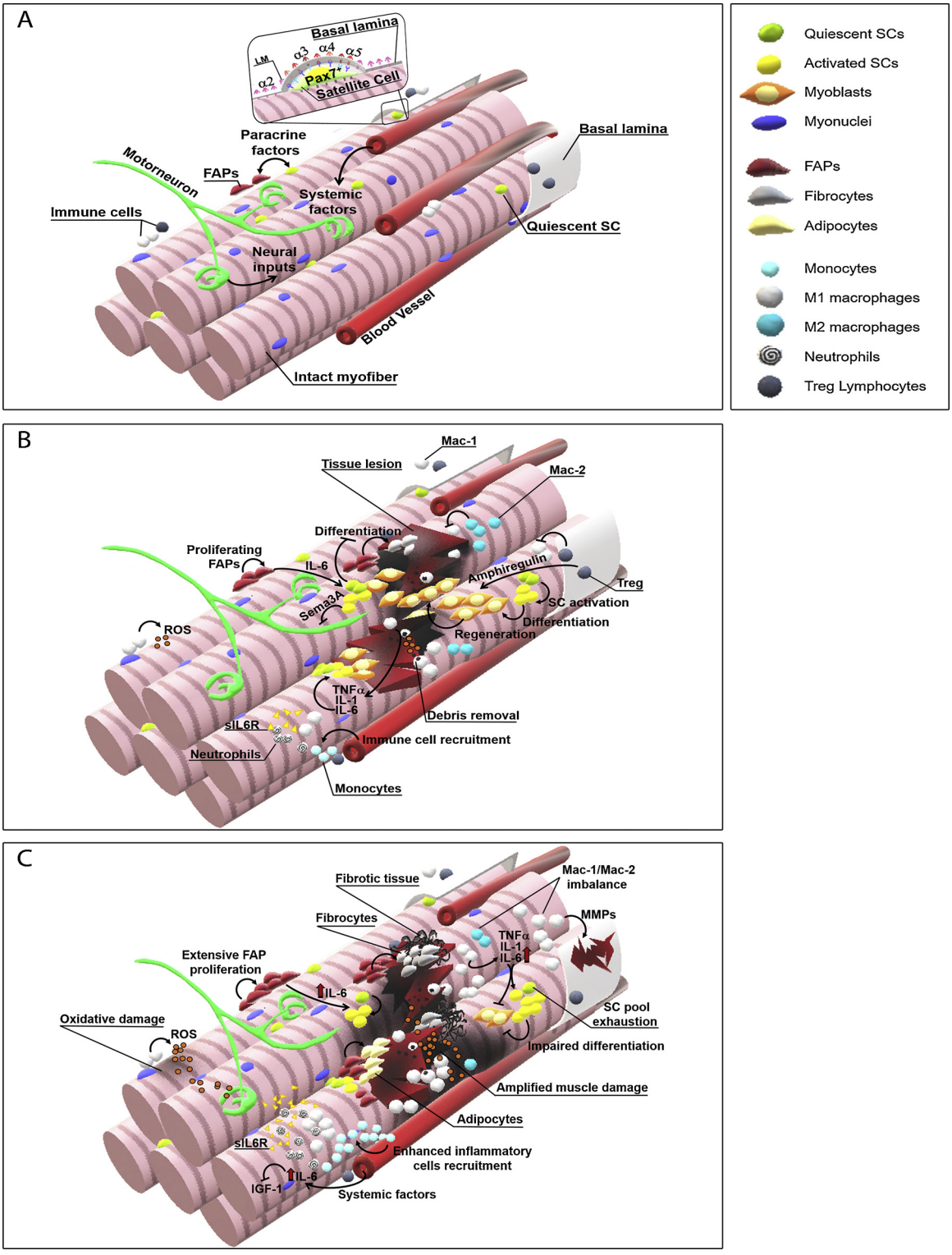


**Fig. 1.** Cell and molecular players involved in muscle regeneration.
(A) Tissue environment in healthy muscles includes satellite cells, non-myogenic progenitors (FAPs), resident immune cells innervation, ECM components, blood vessels and systemic factors. The functional interaction of these niche components contributes to the maintenance of tissue homeostasis. (B) A traumatic event involves a transient alteration of the muscle environment. Inflammatory cells, including neutrophils and macrophages, infiltrate the injured tissue and secrete a suite of mediators in a delicate balance between pro- and anti-inflammatory actions, critical to support muscle regeneration. Different growth factors and cytokines, including IL-6, induce the proliferation of satellite cells, which in turn differentiate and repair damaged myofibers. (C) Under pathologic conditions, such as DMD, detrimental changes in muscle niche alter the microenvironment, impinging muscle regeneration. Chronic inflammation leads to the excessive and prolonged production of inflammatory mediators, including IL-6, thereby affecting satellite cell behavior. On the other side FAPs prevail on satellite cells, leading to fatty and fibrotic tissue deposition. FAPs (Fibro-adipogenic progenitors); LM (Laminin); SC (Satellite cell); ROS (Reactive oxygen species); sIL6R (soluble IL-6 receptor); Mac-1 (M1 macrophages); Mac-2 (M2 macrophages); Treg (Regulatory T cell); TNFα (Tumor necrosis factor alpha); IL- (Interleukin); Sema3A (Semaphorin 3A); IGF-1 (Insulin-like growth factor-1).