Biomedicine & Pharmacotherapy 103 (2018) 463–472

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Bioenergetics mechanisms regulating muscle stem cell self-renewal commitment and function

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ARTICLE INFO

Keywords:
Adult muscle stem cell
Metabolic control
Cell fate

ABSTRACT

Muscle stem cells or satellite cells are crucial for muscle maintenance and repair. These cells are mitotically quiescent and uniformly express the transcription factor Pax7, intermittently entering the cell cycle to give rise to daughter myogenic precursors cells and fuse with neighboring myofibers or self-renew, replenishing the stem cell pool in adult skeletal muscle. Pivotal roles of muscle stem cells in muscle repair have been uncovered, but it still remains unclear how muscle stem cell self-renewal is molecularly regulated and how muscle stem cells maintain muscle tissue homeostasis. Defects in muscle stem cell regulation to maintain/return to quiescence and self-renew are observed in degenerative conditions such as aging and neuromuscular disease. Recent works has suggested the existence of metabolic regulation and mitochondrial alterations in muscle stem cells, influencing the self-renewal commitment and function. Here I present a brief overview of recent understanding of how metabolic reprogramming governs self-renewal commitment, which is essential for conservation of muscle satellite cell pools throughout life, as well as the implications for regenerative medicine.

1. Introduction

Muscle stem cells or satellite cells are stem cells required for muscle development, repair and tissue conservation. In adult muscle under normal conditions, these cells represent 3–5% of the overall amount of fiber nuclei [1]. The capacity to self-renew under normal physical conditions is essential to maintain the number of muscle stem cells to contribute toward repetitive muscle repair and to ensure the life-long preservation of contractile tissue. In response to muscle damage, such as injury, toxins, diseases or exercise, quiescent muscle stem cells (a state termed G_0) are activated and undergo a highly orchestrated activity with intense proliferation which gives rise to committed muscle precursors [2,3].

Recent work has observed that muscle stem cell activation can be regulated through metabolism. Thus, regulating metabolism may determine cell fate, and could be a successful strategy for understanding progressive muscle diseases and sarcopenia during aging [4,5,6,7]. The function of metabolism in adjusting cell commitment and function through transcription and post-transcriptional factors have been called “metabolic reprogramming” and represent a rising field of investigation [4,5,7].

My focus on this brief overview is to present recent understanding of the regulatory metabolic mechanisms governing muscle stem cell self-renewal commitment, which is essential for conservation of this cells as a stem cells pool throughout life, as well as implications for regenerative medicine and related cell therapies.

2. Cytoskeletal architecture and muscle stem cells

Skeletal muscle is one of the most dynamic and fascinating tissues with a complex structure. It’s attached to the bone and forms a distinct organ, including its cytoskeletal architecture, excitation-contraction coupling and energy metabolism. In this sense, Alexander Mauro [1] correctly predicted the origin and role of muscle stem cells, due their sub laminar location and intimate association with blood vessels and myofiber nuclei, as remnants of embryonic growth, organized to repeat this process following muscle damage [1] (Fig. 1). Current conclusions demonstrate that the activation of muscle stem cells during muscle regeneration is strongly influenced by the environment, such as nutrition and exercise [3,4,5,6].

Adult muscle satellite cells are characterized by the expression of paired domain transcription factor Pax7, which plays a key function in maintaining the quiescence and proliferation of progenitors, blocking premature differentiation and apoptotic cell death. The ablation of Pax7 allows muscle stem cells to assume different cell fates, confirming their critical function in conserving the myogenic identity [8,9]. In addition, other markers can be observed by microscopy and have been used as markers of muscle stem cells, such as paired domain transcription factor Pax3, characterized in embryonic myogenic progenitors during myofiber formation and mouse fetal development [8,9]; myogenic

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https://doi.org/10.1016/j.biopha.2018.04.036
Received 22 February 2018; Received in revised form 4 April 2018; Accepted 5 April 2018

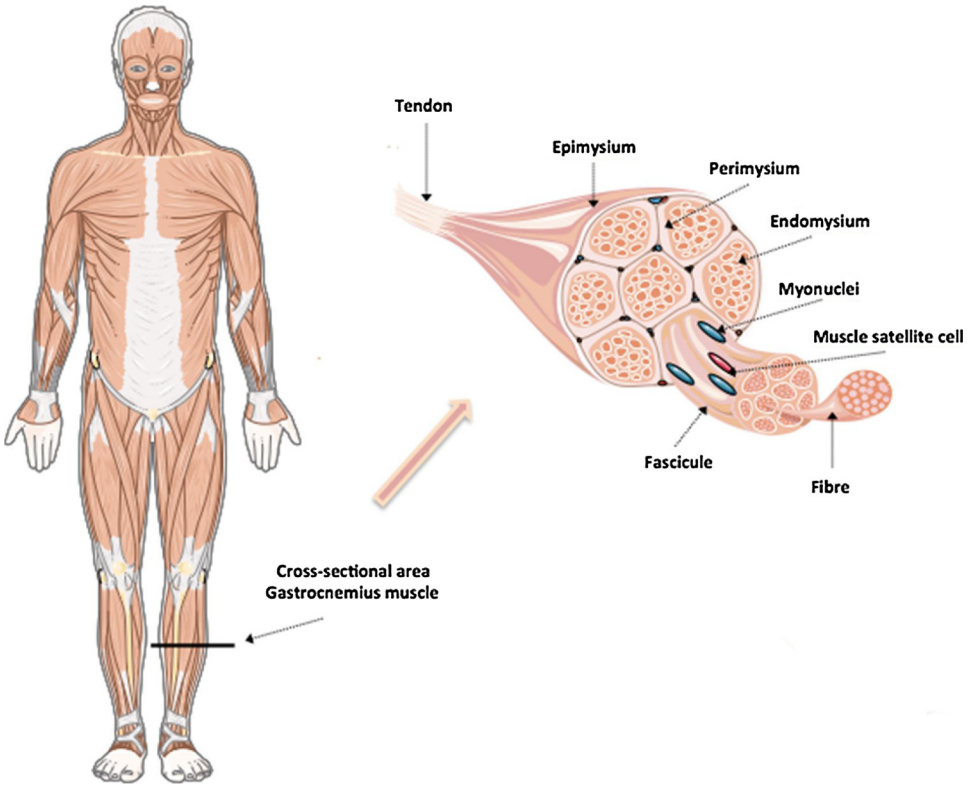

Fig. 1. Structural overview of the various domains of skeletal muscle structure and muscle cross-sectional area. Muscle tissue is one of the most plastic tissues of the body, being attached to bones by structural proteins and connective tissues fibers. Multiple bundles of cells called skeletal muscle fibers or fascicles are surrounded by perimysium, a type of connective tissue, which contains myonuclei arranged in clusters surrounded by a high density of subsarcolemmal mitochondria next to capillary branches. Muscle fibers are in turn composed of myofibrils or muscle fibrils that are basic units of a muscle cell, forming the basic machinery necessary for muscle contraction. Muscle stem cells or satellite cells are found between the basement membrane and the sarcolemma of muscle fibers. In adult myofibers, these cells expressing paired box 7 (Pax7) are normally quiescent and have high levels of active mitochondria, but that can be activated by metabolic and structural process to provide additional myonuclei for muscle maintenance, growth or repair. These cells are preferentially localized next to blood vessels that provide key bioenergetics resources needed for cell proliferation during activation, modulating the surrounding microenvironment of satellite cell and function [1,2].

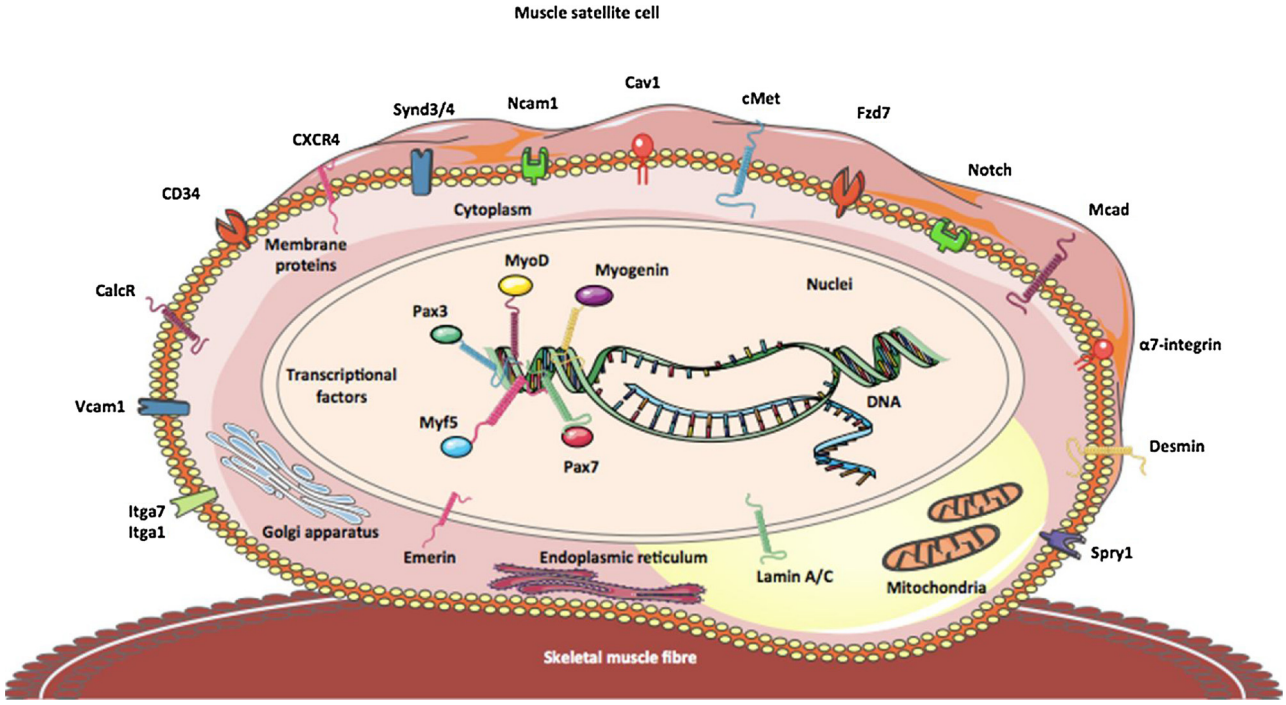

Fig. 2. Intracellular molecular markers and cell membrane surface for quiescence and activation muscle stem cells. The muscle stem cells can be identified by the specific intracellular expression of certain proteins, such as the transcription factors Pax7 and the nuclear membrane proteins lamin A/C and emerin, and specific markers located at the cell membrane surface such as syndecans 3 and 4 (Synd3/4), muscle M-cadherin (Mcad), calcitonin receptor (CalcR), C-X-C chemokine receptor type 4 (CXCR4), calveolin-1 (Cav1), α7- and β1-integrins (Itga7 and Itb1), neural cell adhesion molecule 1 (Ncam1), vascular cell adhesion molecule 1 (Vcam1) and CD34. The identification of these transcriptional factors improved the understanding of muscle stem cell function and commitment, furthering our ability to isolate muscle stem cell and modulate their behaviour in vivo to better control their quiescence and transition to activation state. With better purification methods and labelling for stem-cell-specific markers, several groups have developed cell-sorting techniques to prospectively isolate satellite cells, using a combination of positive selection for satellite cell surface markers and a negative selection for hematopoietic and fibrogenic lineages. Taken together, recent molecular and genetic studies of muscle stem cells are imperative to gain a holistic understanding of adult myogenesis and to enhance the regenerative capacity of damaged muscles. Adapted by Yin et al. [12].