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Review

Nuclear positioning in skeletal muscle

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ABSTRACT

Skeletal muscle cells possess a unique cellular architecture designed to fulfill their contractile function. Muscle cells (also known as myofibers) result from the fusion of hundreds of myoblasts and grow into a fiber of several centimeters in length. Cellular structures gradually become organized during muscle development to raise a mature contractile cell. A hallmark of this singular cell architecture is the position of nuclei at the periphery of the myofiber, below the plasma membrane. Nuclei in myofibers are evenly distributed except in specialized regions like the neuromuscular or myotendinous junctions. Disruption of nuclear positioning results in hindered muscle contraction and occurs in a multitude of muscle disorders as well as in regenerative myofibers. We will explore in this review the step by step nuclear migrations during myogenesis for nuclei to reach their evenly distributed anchored position at the periphery.

Contents

1. Introduction

The skeletal muscle is a tissue that allies strength, flexibility and plasticity thanks to a highly ordered cellular structure [1]. This unique architecture is designed to serve the skeletal muscle's strenuous contractile function. Muscle biology may therefore be investigated through the prism of its cellular organization. The skeletal muscle is usually a tubular shaped organ that is subdivided into fiber shaped muscle fascicles. These are themselves composed of a bundle of muscle cells. The muscle cell, also known as myofiber, is the largest mammalian cell as it can span several centimeters in length. Its capacity to accomplish such size stems from the fusion of several hundreds of myoblasts at the beginning of myogenesis. Myoblasts exit the cell cycle prior to cell fusion to grow into a thick fiber filled with myofibrils. Myofibrils are intracellular contractile fibers built from sarcomeres joint end on end. One sarcomere unit is delineated on both sides by z-lines which serve as anchors for perpendicular actin filaments participating in the contraction process. Mid-way between two adjacent z-lines is the M-line. M standing for myosin, this line is an anchor for perpendicular myosin chains that overlap and intercalate in between actin filaments. Contraction of the sarcomere is therefore ruled by an actomyosin mechanism in which myosin heads pull on actin filaments. Sarcomeres are in the order of 2 μm in length and it is their cumulative contraction (from 200 to 250 serial sarcomeres per millimeter of fiber) that accomplishes overall muscle contraction and our ability to move within our environment [2].

To maximize contraction, the cytoplasm of myofibers is almost entirely occupied by myofibrils. The rest of the organelles is squeezed in between myofibrils or between myofibrils and the

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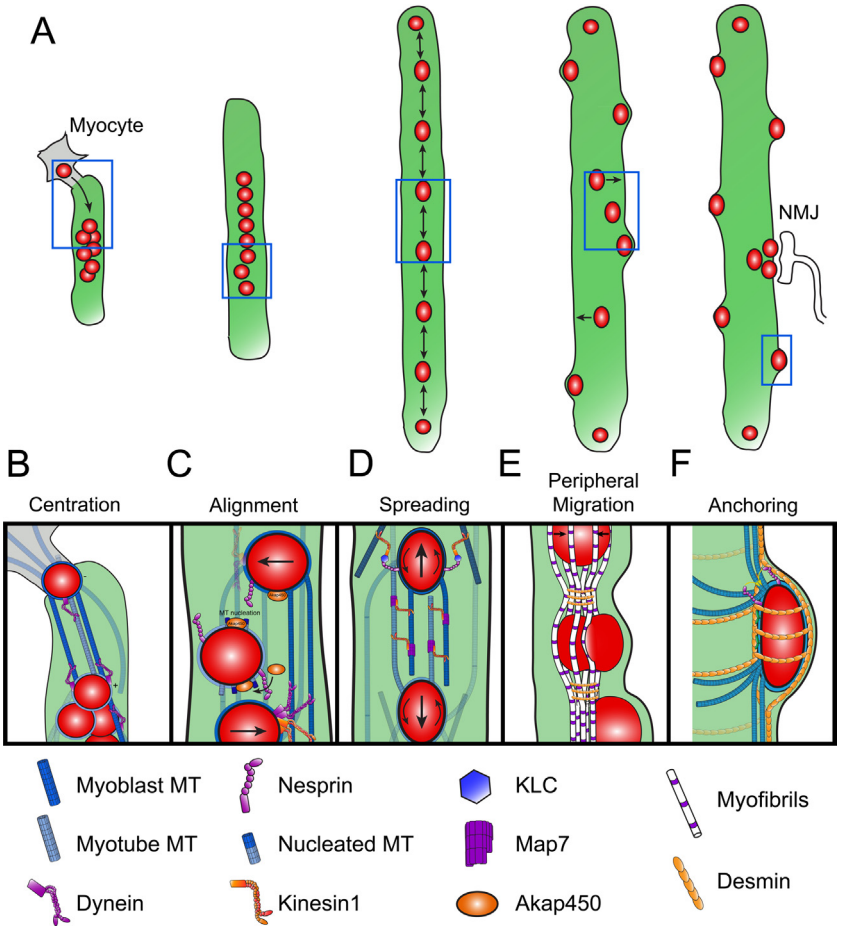

Fig. 1. (A) Nuclear movements during myogenesis. Blue rectangles represent zoomed illustrations of B–F. **(B) Centration.** Nucleus from newly fused myoblast is pulled toward the center of the myotube by dynein and microtubules. **(C) Alignment.** Nesprin-1α and PCM-1 recruit centrosomal and motor proteins to the NE. **(D) Spreading.** Kinesin-1 and Map7 attached to microtubules allow use the anti-parallel microtubular network to spread nuclei along the length of the myotube. Kinesin-1 and kinesin light chain (KLC) at the nuclear envelop walk towards the (+) end of surrounding microtubules to induce nuclear rotation. **(E) Peripheral migration.** Myofibril crosslinking, contraction and nuclear stiffness variations drive nuclear movement to the periphery. Myofibril crosslinking is mediated by desmin organization at the z-lines. **(F) Anchoring.** Nesprin organizes an astral microtubular network to anchor nuclei juste below the plasma membrane. Anchoring is reinforced by a desmin network.

plasma membrane. With an average diameter of 10 μm, nuclei are normally found at the periphery of the myofiber, just below the plasma membrane. Nuclear positioning at the periphery of myofibers is a hallmark of skeletal muscle although the function of this structural characteristic remains elusive. Nevertheless, peripheral anchoring of nuclei is not a straight forward process. Rather, each nucleus embarks on a journey of several hundreds of micrometers to reach its final position at the periphery of the cell [3]. Nuclear movement during myofiber maturation is a step by step process driven by different mechanisms that will be listed in this review. The first movement is termed centration and involves the migration of myonuclei from fused myoblasts to the center of the newly formed cell [4]. Once accumulated at the center, nuclei align on a central axis [5] and move longitudinally as the cell elongates into a fiber [6,7]. Nuclei then migrate from a central position to the cell periphery right below the plasma membrane where they become anchored (Fig. 1A). Thus, so far, 5 types of nuclear events have been described during muscle development: centration, alignment, spreading, peripheral movement and anchoring [3]. Nuclei are uniformly distributed along the myofiber apart from the neuromuscular junction (NMJ) and myotendinous junction (MTJ) where nuclei cluster [8,9]. The interplay between nuclei and their movement within a single cell is a unique feature of skeletal muscle in mammalian systems. The different types of movement sometimes implicate nuclei converging, spreading or moving independently. Such variation in the type of nuclear movements makes skeletal muscle a rich system to study nuclear migrations.

Nuclear movement in muscle involves the usual suspects. Forces on the nucleus must be generated to induce movement which is achieved by motor proteins that bind to the cytoskeleton and either push or pull the nucleus [8]. Certain nuclear migrations require the Linker of Nucleoskeleton and Cytoskeleton (LINC) complex although the full extent of the complex's role in all the 5 types of nuclear migrations remains to be elucidated. This complex is composed of KASH and SUN proteins and spans the nuclear envelope to link the nuclear lamina with the cytoskeleton in the cytoplasm [9]. KASH proteins (also known as Nesprins) exist in different isoforms capable of binding the various cytoskeletal families as well as motor proteins.

Nuclear mispositioning has previously been linked to muscle dysfunction [6,10]. Centrally located nuclei are routinely found in certain muscle disorders as well as muscle regeneration [11]. Most diseases exhibiting centrally located nuclei are caused by muscle wasting, a constant state of muscle degeneration/regeneration. However, certain myopathies are characterized by an accumulation of centrally located nuclei independent of muscle regeneration. These are found in diseases that affect key structural proteins such as plectin resulting in Epidermolysis Bullosa Simplex with Muscular Dystrophy EBS-MD [12] or the intermediate filament desmin which cause desminopathies [13]. The disease that epitomizes

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